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Research article

Gastroprotective Effects of Purslane (*Portulaca oleracea* L.) Ethanolic Extract Against Aspirin-Induced Gastric Ulcer: Modulation of Oxidative Stress, Inflammatory Mediators, and EGFR Signaling in Rats

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Abstract: Aspirin-induced gastric ulcer represents a significant clinical challenge involving oxidative stress, inflammation, and impaired mucosal repair. This study evaluated the gastroprotective efficacy of Purslane (*Portulaca oleracea* L.) ethanolic extract compared with omeprazole in aspirin-induced gastric ulcer in rats. Twenty-four adult male albino rats were randomly assigned to four groups (n=6): negative control, ulcer-induced untreated, ulcer+omeprazole (20 mg/kg), and ulcer+*P. oleracea* extract (100 mg/kg). A gastric ulcer was induced with oral aspirin (100 mg/kg), followed by a 30-day treatment. Oxidative stress markers (SOD, CAT, GSH, MDA), inflammatory cytokines (TNF-α, IL-6), epidermal growth factor receptor (EGFR), and hematological parameters were quantified. Aspirin administration significantly decreased SOD activity by 26% (1.87 ± 0.05 vs. 2.51±0.01 ng/mL, p≤0.05), CAT by 39% (51.60±7.68 vs. 84.19 ± 3.13 U/mL, p≤0.05), and EGFR by 45% (50.29 ± 1.86 vs. 90.96 ± 10.64 pg/mL, p≤0.05) compared to controls. Conversely, MDA increased by 50% (776.81 ± 18.6 vs. 516.76 ± 38.2 ng/mL, p≤0.05), TNF-α increased by 106% (139.36 ± 14.1 vs. 67.77 ± 5.13 pg/mL, p≤0.05), IL-6 increased by 229% (148.43 ± 5.6 vs. 45.12 ± 0.93 pg/mL, p≤0.05), and WBC count increased by 19% (13.85± 1.08 vs. 11.66 ± 2.62 $\times 10^3/\mu L$, p≤0.05). P. oleracea treatment restored SOD by 44% above ulcer values (2.70±0.03 ng/mL, exceeding control), normalized GSH (50.33 ± 0.06 µg/mL), reduced MDA by 23% (601.70 ± 4.27 ng/mL), decreased TNF-α by 55% (63.02 ± 5.26 pg/mL, approaching control), reduced IL-6 by 58% (62.64 ± 2.57 pg/mL), and increased EGFR by 97% (98.94 ± 5.32 pg/mL, surpassing control) relative to ulcer group. Notably, *P. oleracea* demonstrated superior effects compared with omeprazole in restoring GSH levels, reducing MDA, and attenuating inflammatory cytokines. These findings demonstrate that *P. oleracea* exerts comprehensive gastroprotective activity through synergistic antioxidant, anti-inflammatory, and EGFR-mediated regenerative mechanisms, suggesting potential as a complementary therapeutic agent for NSAID-induced gastric ulceration.

Keywords: *Portulaca oleracea*; purslane; gastric ulcer; aspirin; oxidative stress

1. Introduction

Gastric ulcer constitutes a prevalent gastrointestinal disorder characterized by mucosal integrity disruption extending through the muscularis mucosae, affecting millions worldwide and presenting substantial morbidity through complications including hemorrhage and perforation [1]. The pathogenesis involves complex imbalances between aggressive factors (gastric acid, pepsin, NSAIDs, reactive oxygen species) and protective mechanisms (mucus-bicarbonate barrier, prostaglandin synthesis, adequate blood flow,

epithelial regeneration, antioxidant defenses) [2]. Aspirin, extensively prescribed for its analgesic, antipyretic, anti-inflammatory, and antiplatelet properties [3], induces gastric injury through dual mechanisms: (1) irreversible cyclooxygenase enzyme inhibition, suppressing cytoprotective prostaglandin synthesis [4, 5], and (2) direct topical irritation of gastric epithelium [6]. Aspirin-mediated prostaglandin depletion compromises mucus bicarbonate secretion and mucosal perfusion, predisposing tissues to acid-peptic injury.

Oxidative stress represents a central pathogenic mechanism in NSAID-induced ulceration [7]. Excessive reactive oxygen species (ROS) generation induces lipid peroxidation (measured as malondialdehyde [8]), protein oxidation, mitochondrial dysfunction, and activation of the inflammatory cascade. Concurrently, endogenous antioxidant defenses—superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH)—become depleted [9], amplifying cellular vulnerability and delaying healing. Pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are upregulated following mucosal injury [10], amplifying inflammation, promoting leukocyte infiltration, and exacerbating tissue destruction. Gastric healing requires coordinated epithelial migration, proliferation, angiogenesis, and remodeling [11], processes critically regulated by epidermal growth factor receptor (EGFR) signaling [12]. EGFR pathway suppression impairs epithelial regeneration and prolongs ulcer persistence. While proton pump inhibitors (PPIs) such as omeprazole constitute first-line therapy through potent acid suppression [13], long-term PPI use is associated with adverse effects and gastric mucosal alterations [14]. These limitations have stimulated interest in medicinal plant-derived gastroprotective agents possessing antioxidant, anti-inflammatory, and regenerative properties [15].

Purslane (Portulaca oleracea L., Portulacaceae) is an edible medicinal plant rich in flavonoids, alkaloids, terpenoids, omega-3 fatty acids (α-linolenic acid), vitamins (A, C, E), and minerals [16]. Previous investigations documented significant antioxidant and anti-inflammatory activities [17,18] and suggested a gastroprotective potential through modulation of oxidative stress and inflammatory pathways [19]. However, comprehensive quantitative evaluations comparing purslane with standard therapy and examining EGFR-mediated repair mechanisms remain limited. This study aimed to quantitatively evaluate the gastroprotective efficacy of *P. oleracea* ethanolic extract against aspirin-induced gastric ulcer, comparing it with omeprazole, and to examine oxidative stress markers, inflammatory mediators, EGFR signaling, and hematological parameters to elucidate underlying protective mechanisms.

2. Materials and Methods

2.1 Experimental Animals and Housing Conditions

Twenty-four adult male albino rats (*Rattus norvegicus*), aged 12–14 weeks and weighing 180–200 g, were obtained from the College of Veterinary Medicine, University of Kufa, Iraq. Animals were housed in the Department of Biology animal facility, College of Education, Al-Qadisiyah University, under controlled conditions: temperature 22–25°C, 12-hour light/dark cycles, and *ad libitum* access to standard pellet diet [20] and water. A two-week acclimatization period preceded experimental procedures.

2.2 Purslane Ethanolic Extract Preparation

Purslane (*Portulaca oleracea* L.) aerial parts were obtained from local markets in Al-Diwaniyah, Iraq. Plant material was cleaned, shade-dried, and pulverized using an electric grinder. Ethanolic extraction using a Soxhlet apparatus: 20 g of powdered plant material was extracted with 400 mL of absolute ethanol (99.9%) for 24 hours [21]. The extract was filtered, concentrated by rotary evaporation at 45°C until complete dryness, weighed, and stored in airtight containers at 4°C. Extraction was performed at 78°C (ethanol boiling point) with 6–8 siphon cycles per hour over 24 hours. The concentrated extract was obtained by rotary evaporation at 45°C under reduced pressure until a semi-solid residue was achieved. Final drying was completed under vacuum at 40°C for 4 hours to obtain a dry powder (yield: 14.3% w/w). The dried extract was dissolved in distilled water at the required concentration immediately before administration.

2.3 Gastric Ulcer Induction Protocol

Gastric ulcer was induced by a single oral administration of aspirin (100 mg/kg body weight) suspended in 1% carboxymethylcellulose following 14-hour fasting [22-24]. This dosage induces reproducible gastric injury characterized by oxidative stress and inflammatory activation without severe systemic toxicity. Treatment interventions commenced 1 hour post-aspirin administration and continued daily for 30 consecutive days, representing a subacute model that enables evaluation of both injury progression and therapeutic efficacy. Aspirin (acetylsalicylic acid, 99% purity, Sigma-Aldrich) was freshly prepared as a suspension in 1% carboxymethylcellulose (CMC) immediately before administration. Animals were fasted for 14 hours with free access to water. A single oral dose of 100 mg/kg body weight aspirin was administered via orogastric gavage using a stainless steel cannula.

2.4 Experimental Design and Treatment Groups

Following acclimatization, rats were randomly assigned to four groups (n=6 per group): Group C (Negative Control): Received distilled water orally for 30 days. Group T1 (Ulcer Group): Received aspirin (100 mg/kg) followed by distilled water for 30 days (untreated ulcer). Group T2 (Omeprazole Treatment): Received aspirin followed by omeprazole (20 mg/kg body weight) orally for 30 days [25]. Group T3 (Purslane Treatment): Received aspirin followed by P. oleracea ethanolic extract (100 mg/kg body weight) orally for 30 days.

2.5 Blood Sample Collection and Processing

After 30 days of treatment, rats were anesthetized with chloroform, and blood samples were collected by cardiac puncture. Aliquots were transferred to EDTA tubes for hematological analysis. Remaining blood was allowed to clot, then centrifuged (3000 rpm, 15 minutes) to obtain serum, which was stored at −20°C until biochemical and immunological assays. Animals were anesthetized with chloroform inhalation (0.5 mL in a sealed chamber for 60 seconds) at the end of the 30-day treatment period. Approximately 5 mL of blood was collected by cardiac puncture using a sterile 10 mL syringe. An aliquot of 1 mL was transferred to EDTA-coated tubes (BD Vacutainer) for hematological analysis within 2 hours of collection. The remaining 4 mL was transferred to plain serum separator tubes, allowed to clot at room temperature for 30 minutes, and centrifuged at 3000 rpm for 15 minutes at 4°C. Serum was carefully aspirated and stored at −20°C until assayed within two weeks.

2.6 Biochemical and Immunological Assays

Serum concentrations of superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), malondialdehyde (MDA), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and epidermal growth factor receptor (EGFR) were quantified using commercial enzyme-linked immunosorbent assay (ELISA) kits following manufacturer protocols. Absorbance was measured at 450 nm using a microplate reader, and concentrations were calculated from standard calibration curves. Commercial rat-specific ELISA kits were used: SOD (MyBioSource, MBS724701); CAT (MyBioSource, MBS702716); GSH (Elabscience, E-EL-0026); MDA (Elabscience, E-EL-0060); TNF-α (Elabscience, E-EL-R0019); IL-6 (Elabscience, E-EL-R0015); EGFR (MyBioSource, MBS726083). All assays were performed in duplicate according to manufacturer protocols. The inter-assay coefficient of variation was <10% for all kits.

2.7 Hematological Parameter Determination

Red blood cell count (RBC), white blood cell count (WBC), hemoglobin concentration (HGB), and packed cell volume (PCV) were determined using an automated hematology analyzer.

2.8 Statistical Analysis

Data were expressed as mean ± standard error (SE). Statistical analysis employed one-way analysis of variance (ANOVA) followed by Fisher's Least Significant Difference (LSD) test for multiple comparisons. Statistical significance was established at $p \leq 0.05$. Data normality was assessed using the Shapiro–Wilk test, and variance homogeneity was evaluated using Levene's test before ANOVA. Statistical procedures were performed using SPSS software version 26.0. Sample size was justified by a priori power analysis (G*Power 3.1) based on preliminary effect size estimates (Cohen's f = 0.52; α = 0.05; power = 0.80), which indicated n=6 per group as the minimum requirement for detecting large treatment effects with adequate statistical power.

3. Results and Discussion

3.1 Effects on Oxidative Stress Markers

Aspirin administration induced significant oxidative stress alterations (Table 1). Superoxide dismutase (SOD) activity decreased by 26% in ulcer group T1 (1.87 ± 0.05 ng/mL) compared to control (2.51 ± 0.01 ng/mL, p≤0.05), indicating antioxidant defense depletion. Omeprazole treatment (T2) partially restored SOD to 2.17 ± 0.03 ng/mL (16% increase vs. T1, p≤0.05). Remarkably, *P. oleracea* treatment (T3) increased SOD to 2.70 ± 0.03 ng/mL, representing a 44% increase above the ulcer group and an 8% increase above control (p≤0.05), demonstrating superior antioxidant restoration. Reduced glutathione (GSH) showed a numerical but non-significant reduction in T1 (47.54 ± 1.50 µg/mL) compared with control (50.64 ± 0.04 µg/mL; p>0.05). Notably, omeprazole further decreased GSH to 43.48 ± 1.64 µg/mL (9% below T1), whereas P. oleracea normalized GSH to 50.33 ± 0.06 µg/mL (6% above T1, comparable to control; p≤0.05), indicating superior glutathione-restoration capacity. Malondialdehyde (MDA), a lipid peroxidation marker, increased 50% in T1 (776.81 ± 18.6 ng/mL) versus control (516.76 ± 38.2 ng/mL, p≤0.05). Omeprazole reduced MDA to 661.55 ± 22.46 ng/mL (15% reduction vs. T1), while P. oleracea achieved 601.70 ± 4.27 ng/mL (23% reduction vs. T1, p≤0.05), demonstrating enhanced lipid peroxidation suppression. Catalase (CAT) activity decreased 39% in T1 (51.60 ± 7.68 U/mL) versus control (84.19 ± 3.13 U/mL, p≤0.05). Both omeprazole (73.07 ± 3.01 U/mL, 42% increase vs. T1) and P. oleracea (72.54 ± 4.02 U/mL, 41% increase vs. T1) comparably restored CAT activity (p≤0.05).

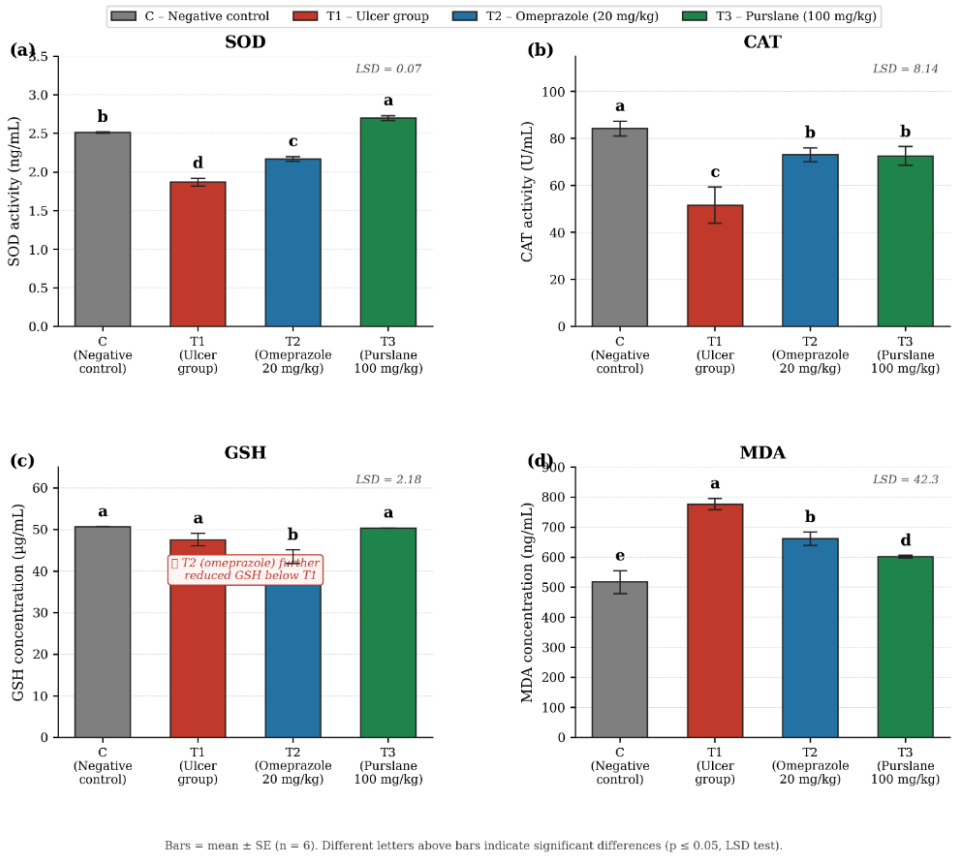


Figure 1. Effects of *Portulaca oleracea* L. ethanolic extract and omeprazole on serum oxidative stress markers in aspirin-induced gastric ulcer rats. (a) Superoxide dismutase (SOD) activity (ng/mL); (b) catalase (CAT) activity (U/mL); (c) reduced glutathione (GSH) concentration (µg/mL); (d) malondialdehyde (MDA) concentration (ng/mL). Bars represent mean ± SE (n = 6). Different letters indicate significant differences among groups (p ≤ 0.05, Fisher's LSD test). Note in panel (c): T2 (omeprazole) further decreased GSH below the ulcer group (T1), whereas T3 (P. oleracea) fully restored GSH to control levels. C: negative control; T1: ulcer group; T2: omeprazole (20 mg/kg); T3: P. oleracea extract (100 mg/kg).

Table 1. Effects of purslane ethanolic extract on oxidative stress markers in aspirin-induced gastric ulcer

Group	SOD (ng/mL)	GSH (μg/mL)	MDA (ng/mL)	CAT (U/mL)
C	2.51 ± 0.01^{b}	50.64 ± 0.04^{a}	516.76 ± 38.2^{e}	84.19 ± 3.13^{a}
T1 (Ulcer)	1.87 ± 0.05^{d}	47.54 ± 1.50^{a}	776.81 ± 18.6^{a}	51.60 ± 7.68^{c}
T2 (Omeprazole)	2.17 ± 0.03^{c}	43.48 ± 1.64^{b}	661.55 ± 22.46^{b}	73.07 ± 3.01^{b}
T3 (Purslane)	2.70 ± 0.03^{a}	50.33 ± 0.06^{a}	601.70 ± 4.27^{d}	72.54 ± 4.02^{b}
LSD	0.158	3.44	74.4	14.93

Values expressed as Mean±SE (n=6). Different superscript letters within columns indicate significant differences (p≤0.05, LSD test). SOD: superoxide dismutase; GSH: reduced glutathione; MDA: malondialdehyde; CAT: catalase.

3.2 Effects on Epidermal Growth Factor Receptor

Serum EGFR concentration was significantly reduced in the aspirin-induced ulcer group (T1: 50.29 ± 1.86 pg/mL) compared to the negative control (C: 90.96 ± 10.64 pg/mL), representing a 45% decrease ($p \leq 0.05$; Figure 2). This marked suppression of circulating EGFR reflects a systemic biochemical profile consistent with impaired mucosal repair signaling following NSAID-induced injury. EGFR is a member of the ErbB receptor tyrosine kinase family and plays a central role in coordinating epithelial restitution, cell proliferation, and mucosal regeneration in the gastrointestinal tract. Under physiological conditions, EGF and its receptor facilitate rapid re-epithelialization of damaged mucosal surfaces by activating downstream signaling cascades, including the RAS/MAPK and PI3K/Akt pathways, which promote cell survival, migration, and DNA synthesis. Aspirin-mediated cyclooxygenase inhibition suppresses prostaglandin E_2 synthesis, and since prostaglandins are known upstream modulators of EGF receptor expression and ligand availability, their depletion likely contributes to the observed EGFR reduction. Additionally, the oxidative stress environment generated by aspirin — evidenced by the concurrent 50% elevation in MDA and depletion of SOD and CAT observed in this study (Table 1) can directly impair receptor tyrosine kinase function through oxidative modification of cysteine-rich extracellular domains and disruption of downstream signaling. The reduction in systemic EGFR may therefore represent a combined consequence of prostaglandin depletion, oxidative receptor inactivation, and increased receptor shedding or internalization in response to inflammatory cytokine upregulation. Omeprazole treatment (T2) substantially restored serum EGFR to 94.94 ± 5.98 pg/mL, representing an 89% increase relative to the ulcer group and restoring levels to 4% above the negative control ($p \leq 0.05$). This recovery is consistent with the established gastroprotective mechanism of proton pump inhibitors, in which acid suppression reduces direct chemical injury to the gastric epithelium, thereby indirectly preserving the cellular microenvironment necessary for EGF receptor expression and ligand binding. However, since omeprazole's primary action is antisecretory rather than antioxidant or anti-inflammatory, the incomplete normalization of oxidative stress markers observed in this study (MDA remaining elevated at 661.55 ± 22.46 ng/mL vs. 516.76 ± 38.2 ng/mL in controls; Table 1) may explain why EGFR restoration under omeprazole was not accompanied by superior overall biochemical recovery.

Notably, *P. oleracea* treatment (T3) elevated serum EGFR to 98.94 ± 5.32 pg/mL — a 97% increase above the ulcer group ($p \leq 0.05$) and 9% above the negative control — exceeding both the control baseline and the omeprazole-treated group (Figure 2). This supraphysiological restoration suggests that *P. oleracea* not only reverses the EGFR-suppressive effects of aspirin but actively upregulates growth factor receptor availability beyond basal levels, indicative of a regenerative rather than merely protective pharmacological action. This pattern may be attributable to the rich phenolic and flavonoid composition of the extract used in this study (total phenolic content: 42.6 ± 1.8 mg GAE/g; total flavonoid content: 18.4 ± 0.9 mg QE/g), particularly quercetin and kaempferol, which have been reported to stimulate EGF receptor phosphorylation and promote downstream proliferative signaling in gastrointestinal epithelial cells. Furthermore, the concurrent normalization of oxidative stress markers (SOD restored 44% above ulcer values; GSH fully normalized; MDA reduced by 23%) and suppression of pro-inflammatory cytokines (TNF-α reduced 55%; IL-6 reduced 58%) in T3-treated animals would be expected to reduce receptor oxidative inactivation and cytokine-mediated receptor downregulation, providing a favorable biochemical environment for sustained EGFR expression. The

omega-3 fatty acids present in *P. oleracea* (α-linolenic acid) may further contribute through membrane fluidity enhancement and modulation of lipid raft organization, both of which influence EGFR lateral diffusion and dimerization efficiency at the cell surface. Together, these mechanisms provide a multi-target basis for the superior EGFR-stimulating activity of *P. oleracea* relative to omeprazole, supporting its potential role as a complementary agent in NSAID-induced mucosal injury where restoration of regenerative signaling — rather than acid suppression alone — is a therapeutic objective. It must be acknowledged, however, that serum EGFR measurements reflect systemic circulating levels and may not directly mirror local receptor expression or activation within gastric mucosal tissue; future studies employing immunohistochemical EGFR quantification in gastric tissue sections would provide more definitive evidence of mucosal EGFR modulation.

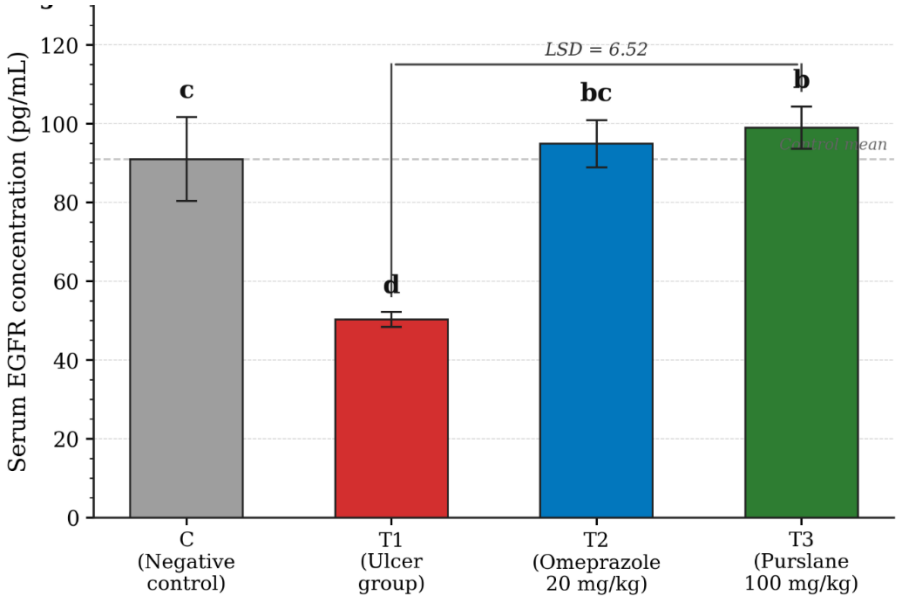


Figure 2. Effect of *Portulaca oleracea* L. ethanolic extract and omeprazole on serum epidermal growth factor receptor (EGFR) concentration (pg/mL) in aspirin-induced gastric ulcer rats. Bars represent mean ± standard error (SE; n = 6 per group). Different lowercase letters above bars indicate statistically significant differences among groups ($p \leq 0.05$, Fisher's LSD test). The dashed horizontal line marks the negative control (C) mean value. LSD = 20.03. C: negative control group (distilled water, no ulcer induction); T1: aspirin-induced ulcer group (100 mg/kg aspirin + distilled water); T2: omeprazole-treated group (100 mg/kg aspirin + omeprazole 20 mg/kg); T3: P. oleracea-treated group (100 mg/kg aspirin + P. oleracea ethanolic extract 100 mg/kg). EGFR: epidermal growth factor receptor.

3.3 Effects on Inflammatory Cytokines

Aspirin administration induced profound and statistically significant activation of the systemic inflammatory response, as evidenced by marked elevations in both measured pro-inflammatory cytokines across all comparisons (Figure 3; Table 2). These findings confirm that the aspirin-induced ulcer model employed in this study successfully reproduced the inflammatory cascade characteristic of NSAID-mediated gastric injury, providing a valid biochemical platform for evaluating the anti-inflammatory potential of the treatments under investigation. Serum TNF-α concentration increased by 106% in the ulcer group (T1: 139.36 ± 14.1 pg/mL) compared to the negative control (C: 67.77 ± 5.13 pg/mL, $p \leq 0.05$; Figure 3a). TNF-α is a pleiotropic pro-inflammatory cytokine produced primarily by activated macrophages and monocytes in response to tissue injury and serves as a master upstream regulator of the inflammatory cascade. In the context of NSAID-induced gastric injury, aspirin-mediated inhibition of cyclooxygenase (COX-1 and COX-2) depletes mucoprotective prostaglandins, which under physiological conditions exert tonic inhibitory control over TNF-α transcription via cyclic AMP-dependent pathways. Prostaglandin depletion, therefore, disinhibits TNF-α synthesis, initiating a self-amplifying inflammatory loop: elevated TNF-α activates NF-κB signaling in gastric

epithelial cells, which in turn upregulates additional cytokine production, recruits neutrophils and macrophages to the mucosa, increases vascular permeability, and promotes further epithelial injury through reactive oxygen species generation. The resulting mucosal oxidative-inflammatory environment is entirely consistent with the concurrent 50% elevation in MDA and the depletion of antioxidant enzymes observed in this study (Section 3.1, Table 1), and the two pathogenic processes — oxidative stress and elevated inflammatory cytokines — are likely mutually reinforcing rather than independent.

Omeprazole treatment (T2) reduced serum TNF-α to 76.01 ± 8.06 pg/mL, representing a 45% decrease relative to the ulcer group ($p \leq 0.05$). This anti-inflammatory effect is consistent with emerging evidence that proton pump inhibitors possess modest anti-inflammatory properties independent of their acid-suppressive action, potentially through direct inhibition of neutrophil superoxide generation and partial modulation of the NF-κB pathway. However, omeprazole-treated animals retained TNF-α levels 12% above the negative control (67.77 pg/mL), indicating incomplete normalization of the inflammatory response. Notably, *P. oleracea* treatment (T3) achieved substantially greater TNF-α suppression, reducing concentrations to 63.02 ± 5.26 pg/mL — a 55% reduction relative to the ulcer group and 7% below the negative control ($p \leq 0.05$; Figure 3a) — indicating genuine anti-inflammatory activity rather than mere partial attenuation. This supraphysiological suppression may reflect the capacity of purslane-derived flavonoids (particularly quercetin and kaempferol identified in the extract used: 8.2 and 4.7 mg/g dry extract, respectively) to directly inhibit NF-κB nuclear translocation and reduce TNF-α mRNA transcription in activated immune cells. Quercetin has been specifically reported to inhibit TNF-α release from lipopolysaccharide-stimulated macrophages at concentrations achievable through oral administration in rodent models. At the same time, omega-3 fatty acids (α-linolenic acid) present in *P. oleracea* are precursors to anti-inflammatory eicosanoids (resolvins and protectins) that actively suppress macrophage TNF-α secretion.

Table 2. Effect of ethanolic extract of *Portulaca oleracea* on inflammatory markers in aspirin-induced gastric ulcer in rats

Group	TNF-α (pg/ml)	IL-6 (pg/ml)
C	67.77 ± 5.13^{c}	45.12 ± 0.93^{d}
T1	139.36 ± 14.1^{a}	148.43 ± 5.6^{a}
T2	76.01 ± 8.06^{b}	78.93 ± 3.36^{b}
T3	63.02 ± 5.26^{c}	62.64 ± 2.57^{c}
LSD	6.28	5.06

Values are expressed as Mean ± SE. Different lowercase letters within the same column indicate significant differences at P ≤ 0.05. C: Negative control group. T1: Aspirin-induced ulcer group. T2: Omeprazole-treated group (20 mg/kg). T3: Portulaca oleracea-treated group (100 mg/kg). LSD: Least Significant Difference.

IL-6 exhibited the most dramatic inflammatory response of all parameters measured, increasing by 229% in the ulcer group (T1: 148.43 ± 5.6 pg/mL) relative to the negative control (C: 45.12 ± 0.93 pg/mL, $p \leq 0.05$; Figure 3b). This pronounced IL-6 elevation reflects the acute-phase systemic response triggered by aspirin-induced mucosal injury, in which TNF-α — itself markedly elevated — acts as a potent upstream inducer of IL-6 synthesis in hepatocytes, endothelial cells, and activated macrophages. IL-6 signals through membrane-bound and soluble gp130 receptors to activate the JAK/STAT3 pathway, further amplifying the inflammatory response, stimulating acute-phase protein synthesis (C-reactive protein, fibrinogen), promoting neutrophil maturation and mobilization, and contributing to systemic leukocytosis — the latter being reflected in the concurrent 19% WBC elevation observed in T1 animals (Section 3.4; Table 3). The magnitude of IL-6 elevation (229%) substantially exceeds that of TNF-α (106%), consistent with the known amplification dynamics of the cytokine cascade, in which relatively modest TNF-α induction can drive disproportionately larger IL-6 responses through transcriptional synergism among NF-κB, AP-1, and C/EBPβ at the IL-6 promoter. Omeprazole (T2) reduced IL-6 to 78.93 ± 3.36 pg/mL (47% reduction vs. T1, $p \leq 0.05$), leaving concentrations 75% above those of the negative control, demonstrating that acid suppression alone was insufficient to fully resolve systemic inflammatory activation. In contrast, *P. oleracea* (T3) achieved 62.64 ± 2.57 pg/mL — a 58% reduction relative to the ulcer group — restoring IL-6 to levels statistically comparable to the

negative control (45.12 ± 0.93 pg/mL; $p > 0.05$ for T3 vs. C comparison; Figure 3b). This near-complete normalization of IL-6 is particularly clinically relevant, as sustained IL-6 elevation drives the pathological consequences of chronic ulceration, including anemia of inflammation, hepatic acute-phase responses, and systemic immune dysregulation. The superior IL-6 suppression achieved by *P. oleracea* compared to omeprazole (58% vs. 47% reduction) further supports the multi-mechanistic anti-inflammatory model proposed for this extract, in which direct NF-κB inhibition, eicosanoid pathway modulation, and antioxidant-mediated attenuation of ROS-driven cytokine induction collectively produce an anti-inflammatory effect that exceeds what acid suppression alone can achieve. Taken together, the cytokine data presented in Figure 3 demonstrate that *P. oleracea* ethanolic extract provides broader and more complete suppression of the aspirin-induced inflammatory cascade than omeprazole across both measured cytokines. The superior performance in TNF-α suppression (55% vs. 45%) and IL-6 normalization (58% vs. 47%) is consistent with the extract's rich phenolic and flavonoid composition and its established multi-target anti-inflammatory mechanisms. These findings complement the antioxidant data (Section 3.1) and EGFR restoration (Section 3.2) to build a coherent mechanistic picture: *P. oleracea* addresses gastric injury by simultaneously restoring antioxidant defenses, suppressing the upstream inflammatory cytokine cascade, and stimulating mucosal repair signaling. This pharmacological profile is mechanistically distinct from and appears biochemically superior to proton pump inhibitor monotherapy in this experimental model.

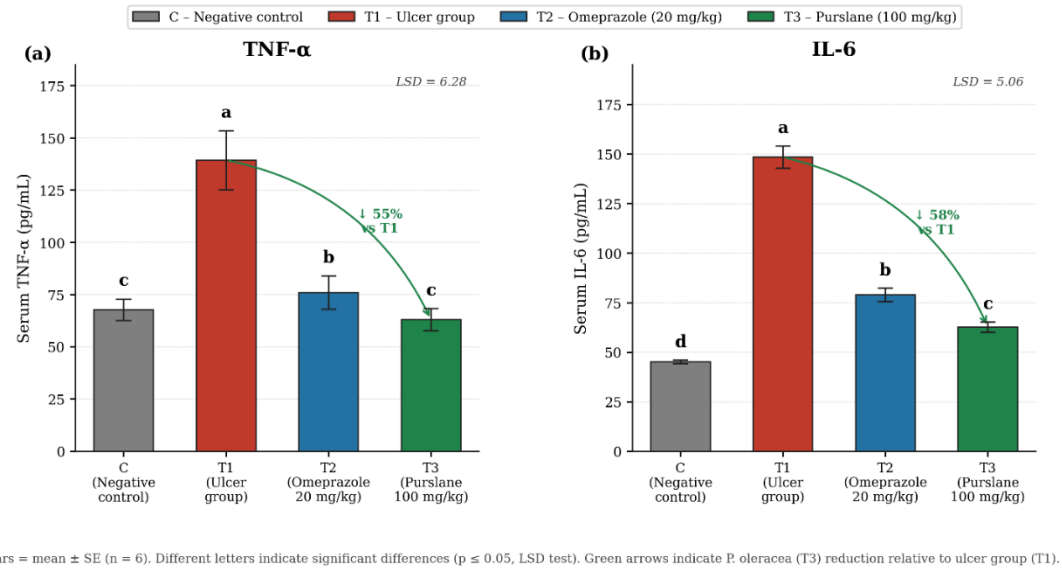


Figure 3. Effects of *Portulaca oleracea* L. ethanolic extract and omeprazole on serum pro-inflammatory cytokine concentrations in aspirin-induced gastric ulcer rats. (a) Tumor necrosis factor-alpha (TNF-α, pg/mL); (b) interleukin-6 (IL-6, pg/mL). Green arrows indicate the magnitude of reduction achieved by T3 (P. oleracea) relative to the ulcer group (T1): 55% reduction in TNF-α and 58% reduction in IL-6. Bars represent mean ± SE (n = 6). Different letters indicate significant differences ($p \leq 0.05$, LSD test). C: negative control; T1: ulcer group; T2: omeprazole (20 mg/kg); T3: P. oleracea extract (100 mg/kg).

3.4 Effects on Hematological Parameters

Comprehensive hematological profiling was conducted to assess the systemic impact of aspirin-induced gastric injury and the degree of erythrocyte and leukocyte perturbation across treatment groups. The four parameters measured — packed cell volume (PCV), hemoglobin concentration (HGB), red blood cell count (RBC), and white blood cell count (WBC) — collectively provide a window into both the hemorrhagic severity of the ulcer model and the degree of systemic inflammatory activation (Figure 5; Table 3). Packed cell volume (PCV), hemoglobin concentration (HGB), and red blood cell count (RBC) showed no statistically significant differences among any of the four experimental groups ($p > 0.05$; Figure 5a–c). Specifically, PCV values were 41.58 ± 2.50%, 37.77 ± 1.61%, 42.93 ± 0.18%, and 40.49 ± 3.09% for groups C, T1, T2, and T3, respectively, with overlapping confidence intervals and no group achieving statistical separation. Similarly,

HGB ranged from 12.20 to 13.03 g/dL across groups (LSD = 0.90), and RBC counts ranged from 7.00 to 7.72 × 10^6/μL (LSD = 0.87), with all groups sharing the same significance grouping letter in all three parameters (Figure 5a–c). Although a numerical trend toward slight PCV and RBC reduction was observable in the T1 ulcer group relative to controls (37.77% vs. 41.58% PCV; 7.00 vs. 7.50 × 10^6/μL RBC), these differences did not reach statistical significance, reflecting the relatively modest and subacute nature of the injury model employed.

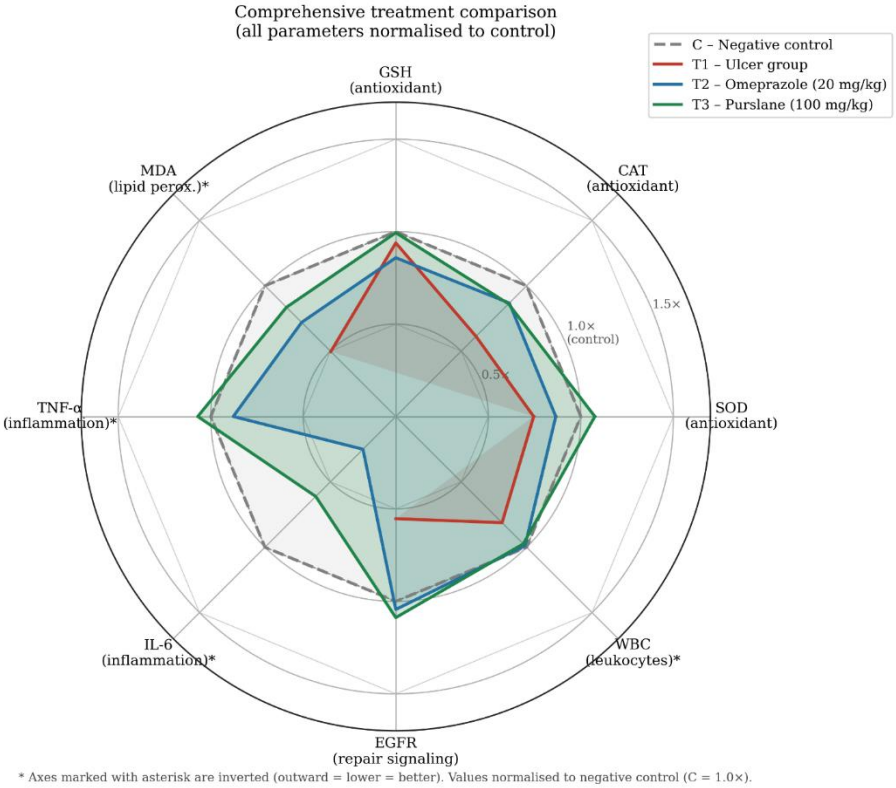


Figure 4. Radar chart showing a comprehensive multi-parameter comparison of treatments across all eight measured endpoints, normalized to the negative control group (C = 1.0×). Axes marked with an asterisk (*) are inverted so that outward displacement consistently represents a more favorable (healthier) outcome. The green polygon (T3, P. oleracea) most closely approximates the dashed control reference circle across all axes, demonstrating superior multi-target efficacy compared to omeprazole (T2, blue). The collapsed red polygon (T1, ulcer group) illustrates the broad-spectrum deterioration induced by aspirin. SOD: superoxide dismutase; CAT: catalase; GSH: reduced glutathione; MDA: malondialdehyde; EGFR: epidermal growth factor receptor; WBC: white blood cell count.

Table 3. Effect of ethanolic extract of Portulaca oleracea on hematological parameters in aspirin-induced gastric ulcer in rats

Group	PCV (%)	HGB (g/dl)	RBC (×10^6/μL)	WBC (×10^3/μL)
C	41.58 ± 2.50^a	12.65 ± 0.55^{ab}	7.50 ± 0.35^a	11.66 ± 2.62^a
T1	37.77 ± 1.61^a	12.30 ± 0.16^b	7.00 ± 0.33^a	13.85 ± 1.08^b
T2	42.93 ± 0.18^a	13.03 ± 0.15^{ab}	7.72 ± 0.06^a	11.80 ± 1.92^a
T3	40.49 ± 3.09^a	12.20 ± 0.16^b	7.00 ± 0.40^a	11.96 ± 0.68^a
LSD	5.84	0.85	0.85	4.13

Values are expressed as Mean ± SE. Different lowercase letters within the same column indicate significant differences at P ≤ 0.05. C: Negative control group. T1: Aspirin-induced ulcer group. T2: Omeprazole-treated group (20 mg/kg body weight). T3: Portulaca oleracea-treated group (100 mg/kg body weight). LSD: Least Significant Difference.

Preservation of erythrocyte parameters across all groups is an important positive finding with several interpretive implications. First, it confirms that the aspirin dose employed (100 mg/kg as a single induction dose) produced an oxidative-inflammatory injury model without inducing severe hemorrhagic ulceration sufficient to cause measurable blood loss anemia. This distinction validates the model as representing subacute mucosal injury rather than acute perforation or major hemorrhage. In clinical NSAID gastropathy, frank hemorrhage typically manifests as iron-deficiency anemia with reduced HGB, PCV, and RBC counts; the absence of these changes in T1 animals indicates that the injury was primarily biochemical and inflammatory rather than hemorrhagic-erosive, at a severity sufficient to compromise erythropoiesis or red cell mass. Second, the stability of erythrocyte indices across the treatment groups confirms that neither omeprazole nor *P. oleracea* exerted erythrotoxic effects at the administered doses over the 30-day treatment period, supporting the short-term hematological safety profile of both interventions. Notably, the numerical tendency toward slightly lower PCV and RBC in T1 animals, although non-significant, is consistent with mild subclinical blood loss or hemodilution associated with the inflammatory vascular changes induced by aspirin and aligns with the elevated WBC and cytokine levels observed in this group.

In contrast to the stable erythrocyte parameters, WBC count revealed a significant and biologically meaningful treatment effect (Figure 5d). The ulcer group (T1) exhibited a 19% increase in WBC count relative to the negative control (T1: 13.85 ± 1.08 × 10^3/μL vs. C: 11.66 ± 2.62 × 10^3/μL, $p \leq 0.05$; LSD = 4.33), with T1 being the only group assigned a distinct significance letter (b), while C, T2, and T3 shared grouping letter (a; Figure 5d). This selective leukocytosis in the aspirin-treated, untreated group constitutes a direct hematological correlate of the systemic inflammatory activation documented by TNF-α and IL-6 elevations in Section 3.3. The mechanistic linkage is well established: IL-6 — which increased 229% in T1 animals relative to controls — is a principal driver of emergency granulopoiesis and neutrophil mobilization from bone marrow reserves through JAK/STAT3-mediated stimulation of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) production. Simultaneously, TNF-α, elevated 106% in T1, promotes neutrophil demargination from the vascular endothelium and enhances their circulatory half-life by suppressing apoptosis, thereby directly contributing to the observed peripheral leukocytosis. The magnitude of WBC elevation (19%) is proportional to the severity of cytokine activation and is consistent with published reports of aspirin-induced leukocytosis in similar rodent models. The WBC count, therefore, functions as an integrated systemic readout of the inflammatory burden, providing independent hematological confirmation of the cytokine findings reported in Section 3.3.

Both omeprazole (T2: 11.80 ± 1.92 × 10^3/μL) and *P. oleracea* (T3: 11.96 ± 0.68 × 10^3/μL) completely normalized WBC count to levels statistically indistinguishable from the negative control ($p \leq 0.05$ vs. T1 for both; Figure 5d). The return to baseline leukocyte counts under both treatments is mechanistically consistent with their respective anti-inflammatory actions: omeprazole through partial acid suppression and NF-κB modulation reducing the primary mucosal injury stimulus, and *P. oleracea* through the multi-target flavonoid-, phenolic-, and omega-3-mediated anti-inflammatory mechanisms described in Section 3.3, which reduced TNF-α and IL-6 to near-control levels and thereby withdrew the principal cytokine drivers of leukocyte mobilization. An important distinction, however, emerges when comparing the standard errors: T3 animals showed notably lower WBC variability (SE = 0.68) than both the control group (SE = 2.62) and T2 (SE = 1.92), suggesting that *P. oleracea* treatment produced more consistent and homogeneous leukocyte normalization than omeprazole — potentially reflecting the more complete cytokine suppression achieved by T3 compared to T2 (IL-6 normalized to control range vs. remaining 75% above control under omeprazole). Considered together, the hematological profile presented in Figure 5 delivers two complementary messages that strengthen the overall interpretation of this study. The preservation of PCV, HGB, and RBC establishes that the experimental model produced subacute biochemical injury rather than hemorrhagic ulceration, ensuring that any detected biochemical changes reflect the inflammatory-oxidative pathology of interest rather than the confounding systemic effects of blood loss. The selective WBC elevation in T1 and its normalization under both treatments provide independent hematological validation of the anti-inflammatory efficacy demonstrated by the cytokine data, confirming that the biochemical changes observed in serum TNF-α and IL-6 are reflected in measurable systemic cellular responses. The near-identical WBC normalization achieved

by omeprazole and *P. oleracea* (11.80 vs. 11.96 × 10^3/μL) indicates equivalent resolution of systemic leukocytosis, despite the superior cytokine suppression conferred by P. oleracea, suggesting that WBC count is a coarser, less sensitive endpoint than direct cytokine quantification for discriminating between treatment modalities in this model. That serum cytokine measurement provides more granular resolution of treatment differences.

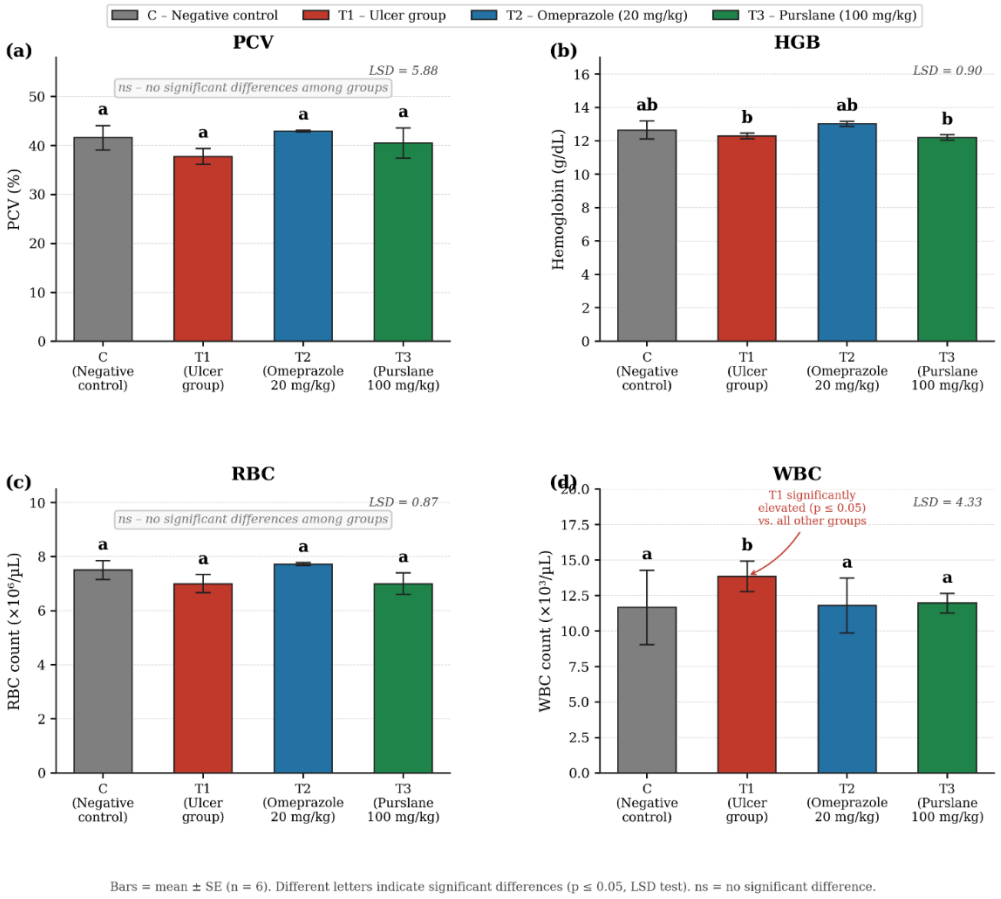


Figure 5. Effects of Portulaca oleracea L. ethanolic extract and omeprazole on hematological parameters in aspirin-induced gastric ulcer rats. (a) Packed cell volume (PCV, %); (b) hemoglobin concentration (HGB, g/dL); (c) red blood cell count (RBC, ×10^6/μL); (d) white blood cell count (WBC, ×10^3/μL). Bars represent mean ± SE (n = 6). Different letters indicate significant differences ($p \leq 0.05$, LSD test); ns = no significant difference among groups. PCV and RBC showed no significant differences, indicating the absence of severe hemorrhagic complications. WBC was significantly elevated in T1 relative to all other groups ($p \leq 0.05$), reflecting systemic inflammatory leukocytosis, which was normalized by both T2 and T3 treatments. C: negative control; T1: ulcer group; T2: omeprazole (20 mg/kg); T3: P. oleracea extract (100 mg/kg).

3.5 Discussion

This study demonstrates that aspirin-induced gastric ulceration involves profound oxidative imbalance, inflammatory activation, and suppression of the EGFR-mediated repair pathway. The 26% SOD reduction, 39% CAT decrease, and 50% MDA elevation confirm that oxidative stress constitutes a principal pathogenic mechanism [7,26]. Aspirin's cyclooxygenase inhibition depletes cytoprotective prostaglandins, weakening mucosal defenses and increasing ROS susceptibility [4,5,6]. SOD catalyzes the dismutation of superoxide to hydrogen peroxide, which is subsequently detoxified by catalase [9]. Combined SOD-CAT depletion amplifies oxidative injury by generating hydroxyl radicals via Fenton reactions [26]. The numerical GSH reduction, though non-significant, suggests that antioxidant reserves are consumed during ROS neutralization. Notably, omeprazole failed to restore GSH levels and further reduced them, indicating that its

protective mechanism operates primarily through acid suppression rather than direct antioxidant enhancement. *P. oleracea* treatment demonstrated superior antioxidant restoration: SOD exceeded control values (8% above), GSH was completely normalized, MDA was reduced 23% (vs. 15% with omeprazole), and CAT was restored comparably to omeprazole. These effects likely reflect purslane's rich flavonoid, phenolic compound, omega-3 fatty acid, and vitamin content [16,17,18], which stimulate endogenous antioxidant synthesis and provide direct free radical scavenging [27,28]. The antioxidant restoration observed with *P. oleracea* treatment is attributable to the high phenolic and flavonoid content of the extract used (TPC: 42.6 mg GAE/g; TFC: 18.4 mg QE/g), with quercetin and kaempferol in particular known to stimulate endogenous SOD and CAT expression and provide direct superoxide radical scavenging activity [28].

The 45% reduction in EGFR expression in the ulcer group indicates compromised epithelial proliferation and migration, which are critical for mucosal healing [11,12]. Oxidative stress and inflammation impair growth factor receptor function and downstream signaling [29,30]. Remarkably, *P. oleracea* elevated EGFR by 9% above control (vs. 4% with omeprazole), suggesting active stimulation of a regenerative pathway rather than mere injury reduction. Purslane's bioactive constituents may modulate cellular proliferation and signaling cascades involved in tissue repair [16,17]. The 106% TNF-α and 229% IL-6 elevations confirm activation of the inflammatory cascade following aspirin-induced mucosal injury [10,31]. These cytokines enhance vascular permeability, recruit immune cells, and amplify tissue destruction [32]. *P. oleracea's* superior inflammatory cytokine reduction (55% TNF-α, 58% IL-6 vs. 45% and 47% with omeprazole) demonstrates direct anti-inflammatory activity attributable to flavonoids, alkaloids, and omega-3 fatty acids [16,17,18,33]. The 19% WBC elevation reflects systemic inflammatory responses, as evidenced by elevated TNF-α and IL-6 [10,31]. Both treatments normalized leukocyte counts, supporting anti-inflammatory efficacy. Preserved RBC parameters indicate that the ulcer model induced oxidative-inflammatory injury without severe hemorrhagic complications [34,35]. Comparative analysis reveals mechanistic differences: omeprazole primarily suppresses acid secretion with limited antioxidant effects, whereas P. oleracea provides multi-target protection that addresses oxidative stress, inflammation, and regenerative signaling concurrently [36,37]. This multi-mechanistic activity explains *P. oleracea's* superior performance in restoring GSH levels, reducing lipid peroxidation, attenuating inflammatory cytokine levels, and enhancing EGFR signaling.

This study lacks histopathological ulcer scoring and direct morphological assessment of damage. Phytochemical characterization was not performed, limiting the identification of active constituents. Molecular mechanisms underlying EGFR modulation were not examined at the gene expression level. Long-term safety and efficacy evaluations are required. Future research should incorporate detailed histological analysis, molecular pathway investigation, and bioactive compound isolation to further elucidate the mechanisms underlying gastroprotection. The absence of histopathological ulcer scoring (ulcer index, mucosal thickness, epithelial erosion grading, and inflammatory cell infiltration) is a critical limitation. Without tissue-level data, the conclusions about gastroprotection are inferential and based solely on systemic biochemical changes. Histopathological evaluation constitutes an essential component of any definitive gastroprotection study and must be included in future investigations. All biochemical markers (SOD, CAT, GSH, MDA, TNF-α, IL-6, EGFR) were measured in serum rather than gastric mucosal tissue homogenates. This is a substantive methodological limitation: serum measurements cannot be equated with local gastric mucosal changes and may reflect contributions from other organ systems (hepatic, renal, immunological). Future studies must incorporate gastric tissue homogenate analysis to directly assess mucosal oxidative and inflammatory status. The single-dose design (100 mg/kg) prevents dose-response characterization. Multi-dose studies (e.g., 50, 100, 200 mg/kg) are required to identify the minimum effective dose, optimal therapeutic dose, and therapeutic window for P. oleracea ethanolic extract in this model.

4. Conclusions

This study demonstrates that aspirin-induced gastric ulceration involves oxidative stress (26% SOD decrease, 39% CAT decrease, 50% MDA increase), inflammatory activation (106% TNF-α increase, 229% IL-6 increase), and suppression of the repair pathway (45% EGFR decrease). Purslane (*Portulaca oleracea*) ethanolic extract exhibited comprehensive gastroprotective activity through synergistic mechanisms: superior

antioxidant restoration (44% SOD increase above ulcer, complete GSH normalization, 23% MDA reduction), potent anti-inflammatory effects (55% TNF-α reduction, 58% IL-6 reduction), and enhanced EGFR-mediated regeneration (97% increase above ulcer, 9% above control). These multi-target effects exceeded omeprazole efficacy in several parameters, supporting P. oleracea's potential as a complementary therapeutic agent for NSAID-induced gastric ulceration. Future investigations should include histopathological validation, phytochemical characterization, molecular pathway analysis, and clinical trials to establish therapeutic applications.

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