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MicroRNA Dysregulation in NSAID/Stress-Induced Gastric Ulcers: Restoration of Mucosal Integrity via RNA-Mediated Healing by Phytochemicals (A narrative review)

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) and physiological stress remain leading causes of gastric ulceration worldwide, yet current therapies incompletely address upstream injury pathways. Mounting evidence suggests that microRNAs (miRNAs) play a crucial role in coordinating mucosal vulnerability and repair.
Objectives: This narrative review synthesizes empirical studies that interrogate miRNA dynamics across established models of indomethacin/aspirin injury and restraint-stress paradigms, with ethanol/HCl comparators which were mechanistically informative.
Methods: A narrative review was NSAIDs or sympathoadrenal ischemia with mucus failure (stress) are models of ulcerogenesis that causes cyclooxygenase-1 inhibition and atropine-sensitive gastric hypermotility, driving oxidative stress, inflammatory signaling, mitochondrial dysfunction, and apoptosis.
Results and Discussion: Recurrent miRNA signatures include up-regulation of pro-inflammatory/apoptotic miRNAs—particularly matured microRNAs (miR) such as miR-21, miR-155, miR-181, and miR-34a—and stress-responsive miR-143/miR-152 that suppress the cystine transporter xCT/SLC7A11, thereby weakening glutathione-based antioxidant defenses. In parallel, cytoprotective miRNAs such as miR-223 and angiogenesis-supporting miRNAs (e.g., miR-126) tend to decline, collectively repressing targets involved in barrier integrity, redox homeostasis (xCT), survival signaling (BCL2/BAX balance), and restitution/angiogenesis. Interventional data, spanning pharmacologic comparators and plant-derived agents such as ginger and curcumin extracts, suggest that effective gastroprotection correlates with normalization of ulcer-associated miRNAs alongside restoration of redox tone and dampening of NF-κB/iNOS/COX-2 axes.
Conclusion: Overall, miRNA dysregulation provides a unifying mechanistic layer in peptic ulcer pathogenesis and a promising therapeutic entry point. Priorities include standardized miRNA panels across models, causal perturbation with mimics/antagomirs, pharmacokinetic optimization of miRNA-active phytochemicals, and translational studies leveraging circulating miRNAs as biomarkers of injury and healing.

INTRODUCTION

Gastric ulcers remain a prevalent gastrointestinal disorder, imposing a significant health burden. It is estimated that up to 10% of the world's population will suffer a gastric ulcer in their lifetime (roughly 4 million new cases annually).[1] In Western countries, the lifetime risk is around 5–10%, whereas developing regions report even higher prevalence.[2] Ulcers result from an imbalance between aggressive factors (acid, pepsin, reactive oxygen species, pro-inflammatory mediators) and the mucosal defences (mucus-bicarbonate barrier, prostaglandins, adequate blood flow, and rapid epithelial restitution).[3] Two major ulcerogenic triggers aside from *H. pylori* infection are NSAIDs and severe physiological stress. NSAIDs such as aspirin, indomethacin and others are widely used analgesics that cause gastric mucosal injury primarily by inhibiting cyclooxygenase (COX) and depleting prostaglandins, leading to reduced mucus and bicarbonate secretion, impaired blood flow, and weakened epithelial resistance.[1] NSAID injury is exacerbated by topical irritation, oxidative stress, and microvascular dysfunction, culminating in bleeding erosions or ulcers of the stomach lining.[4] Meanwhile, "stress ulcers" can develop in critically ill patients (incidence 15–50% in intensive care unit (ICU) settings) due to splanchnic ischemia, neuroendocrine dysregulation, and excessive sympathetic output in the context of trauma, shock, burns, or sepsis.[5] Both NSAID-related and stress-related ulcers contribute to significant morbidity (pain, bleeding, perforation) and healthcare costs, underscoring the need for deeper insight into their pathogenesis and improved therapies.

Recent research has expanded our understanding of gastric ulceration beyond the classical acid-centric paradigm, revealing complex regulatory roles for non-coding RNAs (ncRNAs) in mucosal injury and repair. NcRNAs, including microRNAs (miRNAs) are critical post-transcriptional and epigenetic regulators that fine-tune gene expression networks involved in inflammation, cell death, angiogenesis, and tissue regeneration.[6] Dysregulated microRNA expression has been implicated in the gastric mucosal damage caused by NSAIDs and stress, as well as in the subsequent healing processes.[5] Importantly, a growing body of evidence indicates that certain dietary and herbal phytochemical constituents can mitigate ulcer injury and promote mucosal healing by modulating these same RNA signaling pathways.[7] This review provides a comprehensive overview of microRNA alterations in NSAID- and stress-induced gastric ulcer models and discusses how plant-derived compounds exert gastroprotective and pro-healing effects via RNA-mediated mechanisms.

Experimental Models of NSAID and Stress-Induced Gastric Ulcers

Gastric ulcers induced by NSAIDs and psychological or physiological stress remain among the most experimentally tractable and clinically relevant forms of mucosal injury in gastrointestinal research (Table 1). Indomethacin, diclofenac, and aspirin provide the most reproducible NSAID models. Across rat studies, indomethacin depletes prostaglandins and undermines mucosal defenses (mucus/bicarbonate secretion and perfusion) while provoking atropine-sensitive gastric hypermotility; permeability increases, neutrophils accumulate, oxyradicals rise, and corpus-predominant hemorrhagic erosions emerge within hours [8]. The ulcerogenic phenotype scales with both dose and age: when indomethacin (10–40 mg/kg), diclofenac (40–80 mg/kg), or aspirin (100 mg/kg) are delivered by gavage, older rats develop larger lesion areas, higher myeloperoxidase (MPO) and/or cytosolic phospholipase A2 ($cPLA_2$), and worse histology than young adults, underscoring the translational relevance of host factors in NSAID injury [9]. Within this framework, interventional readouts have been carved out along inflammatory, redox, and epithelial restitution axes. For example, a single indomethacin injection (30 mg/kg i.p.) increased ulcer index, acid and pepsin output, and mucosal malondialdehyde (MDA), while depleting mucus and endogenous antioxidants; pretreatment with curcumin restored mucus and nitric oxide (NO), raised Superoxide dismutase (SOD)/catalase (CAT), and suppressed Inducible nitric oxide synthase (iNOS), nuclear factor kappa B cells (NF-κB), and caspase-3 with parallel histologic rescue [10]. A complementary two-hit indomethacin protocol (150 mg/kg at 0 and 4 h) revealed microcirculatory pathology—marked leukocyte–endothelium adhesion and elevated intercellular adhesion molecule (ICAM)-1/ tumor necrosis factor (TNF)-α—that was halved or normalized by curcumin, linking inflammatory adhesion biology to macroscopic erosions.[11] More recently, the same NSAID milieu has been validated against phytochemicals with canonical anti-oxidant/anti-inflammatory signatures: carnosic acid pretreatment attenuated gross and microscopic damage induced by 100 mg/kg indomethacin while lowering MDA/ Total Oxidant Status(TOS) and cytokines (IL-1β, IL-6, TNF-α) and up-regulating Nrf2/HO-1 [12]. Traditional extracts (*Spondias mombin* and *Ficus exasperata*) likewise reduced ulcer index, gastric volume, pepsin activity, and MDA while increasing pH, mucin, and SOD in a 30 mg/kg oral indomethacin model, indicating convergent protection via cytoprotection and antioxidant mechanisms [13]. The mechanistic sequence is schematized in Figure 1.

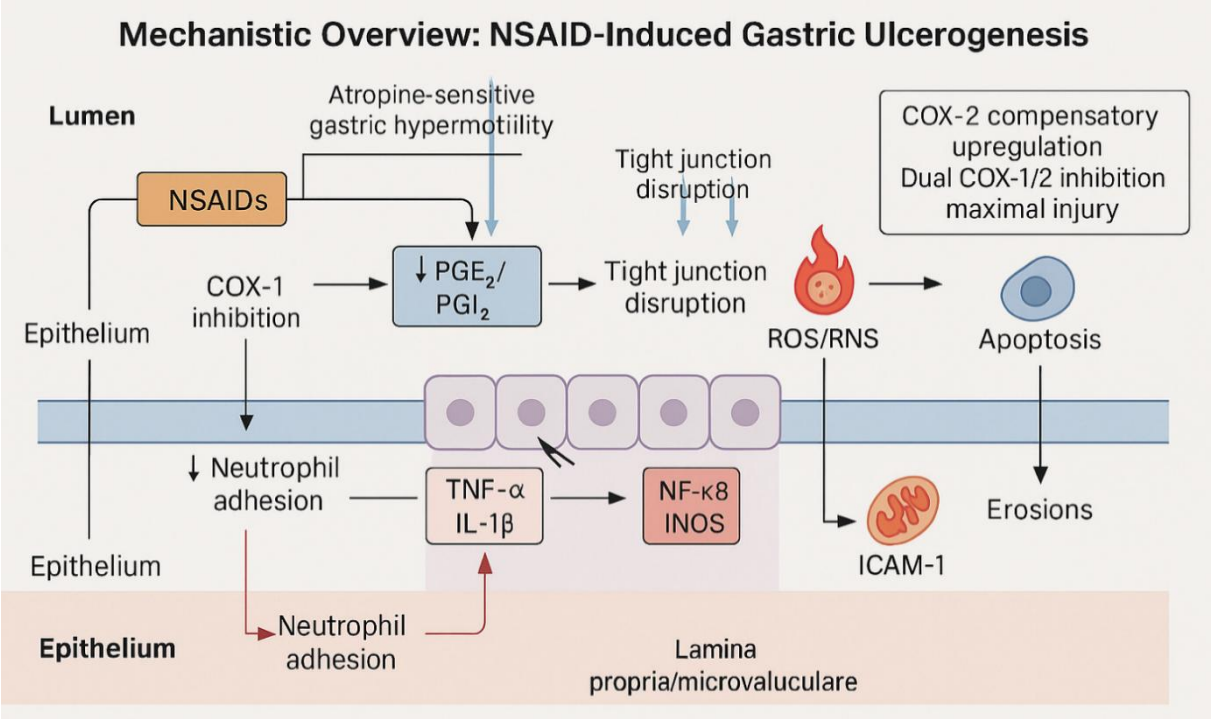

Figure 1: Mechanistic Schema of NSAID-induced Gastric Mucosal Injury. COX-1 inhibition lowers mucosal prostaglandins (PGE_2/PGI_2), triggering atropine-sensitive gastric hypermotility and weakening epithelial defenses (mucus/bicarbonate and tight-junction integrity). These upstream events promote paracellular acid back-diffusion, neutrophil–endothelium interactions (ICAM-1–mediated), and activation of inflammatory and oxidative pathways (TNF-α/IL-1β, NF-κB, iNOS; ROS/RNS), culminating in microvascular stasis, epithelial apoptosis, and surface erosions. (created in BioRender)

Abbreviations: COX, cyclooxygenase; PGE_2, prostaglandin E_2; PGI_2, prostacyclin; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; NF-κB, nuclear factor kappa-B; iNOS, inducible nitric oxide synthase; ICAM-1, intercellular adhesion molecule-1; ROS, reactive oxygen species; RNS, reactive nitrogen species.

Stress-type models recapitulate catecholamine surge, vagal activation, ischemia–reperfusion, and mucus failure seen in clinical stress ulcers and are particularly effective for testing cytoprotectants and antioxidants. In cold-restraint stress (CRS), adult Wistar rats subjected to 3.5 h at 4 °C develop shallow erosions and mucus depletion; seven-day oral N-acetyl-cysteine [NAC] (500 mg/kg) confers a preventive index of ~66.7% compared with ulcer controls, with overall protection attributed to NAC's antioxidant actions [14]. These outcomes dovetail with the COX–hypermotility view of NSAID injury [8], pointing to a shared downstream node—oxidative stress, leukocyte recruitment, and impaired restitution—despite distinct triggers (drug-induced PG loss versus neurohumoral ischemia and barrier failure), as shown in Figure 2.

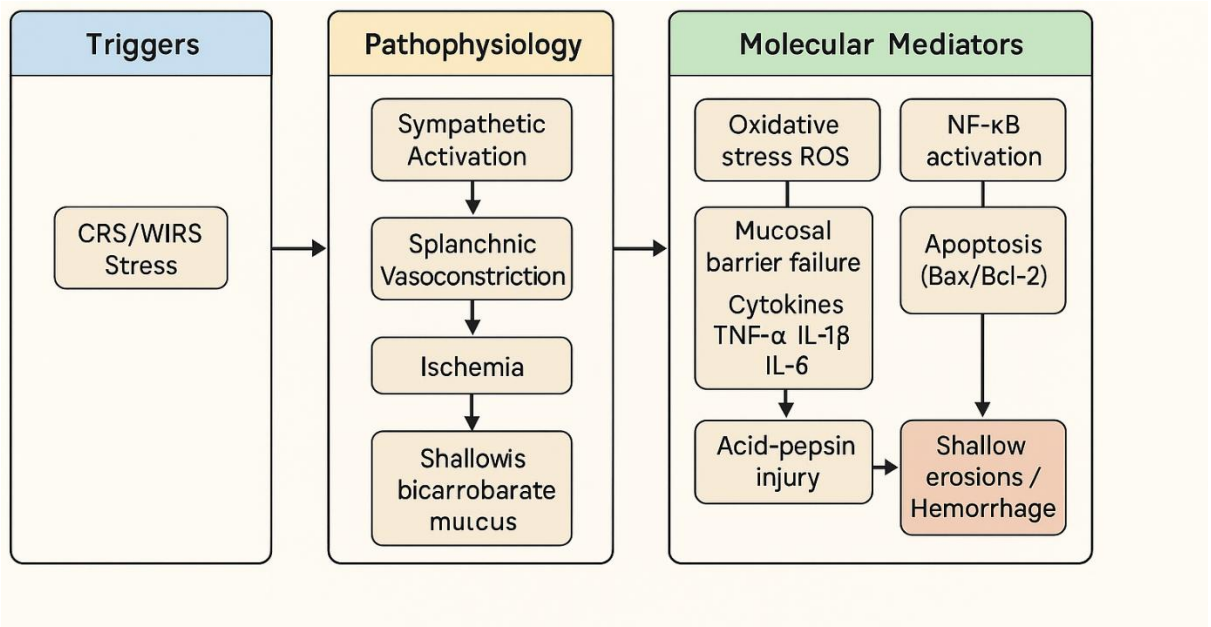

Figure 2. Pathophysiology of Stress-related (CRS/WIRS) Gastric Mucosal Injury. Acute stressors—CRS or WIRS—activate central autonomic pathways, driving sympathetic-mediated splanchnic vasoconstriction, mucosal ischemia, and loss of protective bicarbonate/mucus. Concomitant histamine-dependent acid output and motility changes predispose to acid–pepsin injury, while oxidative stress (reactive oxygen species), NF-κB activation, and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) promote apoptosis (Bax/Bcl-2 shift) and culminate in shallow erosions or hemorrhage.

Abbreviations: CRS, cold restraint stress; WIRS, water-immersion restraint stress; ROS, reactive oxygen species; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6.

Chemical "stress" models using ethanol or HCl/ethanol overlap with CRS/WIRS in oxidative and apoptotic signatures but are prized for speed and readout richness. In rats, the Nrf2 activator tert-butylhydroquinone (25–50 mg/kg, 10 days) reduced ethanol-induced ulcer index, apoptotic cells, and MDA, increased pH, GSH, and mucus, up-regulated Nrf2/HO-1/CAT and suppressed NF-κB/COX-2 [15]. Ethanolic leaf extract of *Jasminum sambac* given 1 h before acidified ethanol sharply decreased ulcer area and edema/leukocyte infiltration, raised pH, mucus, PGE_2 and SOD, lowered MDA, and shifted IHC markers toward protection (HSP70 up, Bax down) [16]. The monoterpene p-cymene (30–60 mg/kg) showed a similar protective spectrum—increased mucus/pH/SOD/CAT/PGE_2 and PAS intensity, reduced MDA, HSP70 up/Bax down, and favorable cytokine modulation (TNF-α, IL-6 down; IL-10 up) [17]. In a curative schedule, quercetin (50 mg/kg for 7 days post-ethanol) reduced gastric volume (−86%) and lesion count (−3.5-fold), up-regulated Nrf2/HO-1, and suppressed HMGB1/TLR4/NF-κB with a Bax→Bcl-2 shift, aligning antioxidant and anti-inflammatory repair with apoptosis control [18]. Extending generalizability, a composite mouse model that pairs repeated indomethacin with luminal acid (INDO/HCl) recapitulates lesion biology (↑NF-κB/p65, iNOS, COX-2, TNF-α; ↑MDA/ROS; ↓GSH/CAT), and a standardized 12-herb formula (SR-5) suppresses these signals while cutting lesion area and ulcer index by up to ~77% [19].

Table 1: Summary of included studies on NSAID- and stress-ulcer models

Model	Species	Ulcerogen / Stressor	Dose / Regimen	Intervention(s) / Comparator(s)	Key outcomes (selected)	References
NSAID (age–dose)	Rat (7 wk; 25 wk; 1 yr)	Indomethacin; diclofenac; aspirin	Indo 10–40; diclo 40–80; aspirin 100 mg/kg (gavage)	—	Lesion indices and damage area ↑ with age; MPO and cPLA₂ higher in older rats	[9]
NSAID acute (secretory/barrier)	Rat	Indomethacin (i.p.)	30 mg/kg, single	Curcumin 50 mg/kg (−30 min); (method comparator)	↓ Ulcer index, acid, pepsin, MDA; ↑ mucin, NO, SOD/CAT; ↓ iNOS, NF-κB, caspase-3	[10]
NSAID microcirculation	Rat	Indomethacin	150 mg/kg at 0 & 4 h (p.o.)	Curcumin 200 mg/kg (−30 min); vehicle	↓ Leukocyte adhesion; ↓ ICAM-1/TNF-α; histology improved	[11]
NSAID	Rat	Indomethacin	100 mg/kg (p.o.)	Carnosic acid 100 mg/kg (14-day pretreatment); esomeprazole 20 mg/kg	↓ Gross/histologic injury; ↓ MDA/TOS and cytokines; ↑ Nrf2/HO-1	[12]
Mixed (INDO/HCl; HCl/EtOH)	Mouse	Indomethacin/ HCl; HCl/EtOH	Acute	SR-5, 100–200 mg/kg	Lesion inhibition; ↑ GSH/CAT; ↓ MDA/ROS; ↓ NF-κB, iNOS, COX-2, TNF-α	[19]
Stress (CRS)	Rat	Cold restraint stress	3.5 h after 7-day pretreatment	NAC 500 mg/kg; ranitidine 50 mg/kg	Preventive index 66.7%; milder necrosis; iNOS increased with NAC+CRS and RAN+CRS	[14]
Ethanol ulcer + Nrf2 activation	Rat	Absolute ethanol (5 mL/kg)	Single	tBHQ 25–50 mg/kg ×10 days; omeprazole 20 mg/kg	↓ Lesions, ulcer index, apoptosis, MDA; ↑ pH, GSH, mucus; ↑ Nrf2/HO-1/CAT; ↓ NF-κB/COX-2	[15]
Ethanol ulcer + flavonoid	Rat	Ethanol	Acute (post-induction treatment)	Quercetin 50 mg/kg; Antodine® 20 mg/kg	↓ Gastric volume 86%; ↓ lesion count 3.5-fold; ↑ Nrf2/HO-1; ↓ HMGB1/TLR4/	[18]

					NF-κB/TNF-α; favorable Bax/Bcl-2	
HCl/EtOH ulcer + plant extract	Rat	Acidified ethanol	Acute	*Jasminum sambac* (62.5–500 mg/kg); omeprazole 20 mg/kg	↑ pH, mucus, PGE_2, SOD; ↓ MDA; ↑ HSP70; ↓ Bax; histologic protection	[16]
Ethanol ulcer + monoterpene	Rat	Absolute ethanol	Acute	*p*-Cymene 30–60 mg/kg; omeprazole 20 mg/kg	↓ Lesion area/edema/infilt rate; ↑ mucus, pH, SOD/CAT/PGE_2; ↓ MDA; ↑ HSP70; ↓ Bax; cytokine modulation	[17]
NSAID ulcer	Rat	Indomethacin	30 mg/kg, single	*Spondias mombin*/*Ficus exasperata* 100–200 mg/kg ×21 days; esomeprazole 20 mg/kg	↓ Ulcer index, gastric volume, pepsin, MDA; ↑ pH, mucin, SOD; % inhibition reported	[13]
Ethanol ± irradiation	Rat	Ethanol ± γ-irradiation	Acute	*Ipomoea carnea* (dose-graded); omeprazole arm	↑ Nrf2/HO-1; ↓ lipid peroxidation; improved histology; 39 phenolics annotated (LC-HRMS/MS)	[20]

Note: Bax: Bcl-2–associated X protein; Bcl-2: B-cell lymphoma 2; CAT: catalase; COX-1: cyclooxygenase-1; COX-2: cyclooxygenase-2; CRS: cold restraint stress; $cPLA_2$: cytosolic phospholipase A_2; EtOH: ethanol; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: reduced glutathione; HCl: hydrochloric acid; HMGB1: high-mobility group box 1; HO-1: heme oxygenase-1; HSP70: heat shock protein 70; ICAM-1: intercellular adhesion molecule-1; IL-6: interleukin-6; IL-10: interleukin-10; INDO: indomethacin; iNOS: inducible nitric oxide synthase; LC-HRMS/MS: liquid chromatography–high-resolution mass spectrometry/tandem mass spectrometry; MDA: malondialdehyde; MPO: myeloperoxidase; NAC: N-acetylcysteine; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: nitric oxide; Nrf2: nuclear factor erythroid 2-related factor 2; PAS: periodic acid–Schiff; PGE_2: prostaglandin E_2; ROS: reactive oxygen species; SOD: superoxide dismutase; SR-5: specific-ratio Korean multi-herbal formula; tBHQ: tert-butylhydroquinone; TLR4: Toll-like receptor 4; TNF-α: tumor necrosis factor-alpha; TAS: total antioxidant status; TOS: total oxidant status.

MicroRNA Dysregulation in Gastric Mucosal Injury

An increasing number of studies indicate that gastric mucosal injury is accompanied by dysregulation of specific miRNAs, which can exacerbate or ameliorate damage by modulating key target genes. miRNAs are ~22 nucleotide RNAs that typically bind to the 3'UTR of mRNAs to repress translation or promote messenger RNA (mRNA) degradation, thus acting as fine-tuners of gene expression. In the context of gastric ulcers, several miRNAs (miR-16, miR-21, miR-151, miR-425, miR-98, miR-328a, and miR-210) have been identified as crucial regulators of apoptosis, inflammation, and mucosal defense. Yin *et al.* [21] found that acute cold stress (4 °C immersion) significantly upregulated miR-143, miR-152, and miR-181a in gastric tissues. Using bioinformatics and *in situ* hybridization, these three miRNAs were pinpointed as the intersection of cold stress-responsive, pro-apoptotic, and cystine/glutamate transporter (xCT)-related miRNA networks. The cystine/glutamate antiporter (xCT, encoded by *SLC7A11*) is critical for importing cystine needed for glutathione synthesis and for exporting glutamate. In the stressed gastric mucosa, xCT activity and glutamate release were markedly reduced, correlating with the rise in miR-143/152/181. Each of these miRNAs was shown to directly or indirectly target xCT. Functionally, transfecting miR-143/152/181 mimics into gastric epithelial cells significantly suppressed xCT expression, lowered extracellular glutamate, and triggered apoptosis (increased BAX/Bcl-2 ratio, caspase-3 activity, and LDH release). In essence, stress-elevated miR-143, miR-152, and miR-181 contribute to mucosal injury by inhibiting xCT-mediated cystine uptake/glutamate efflux, thereby depleting glutathione and impairing the antioxidant defenses of the epithelium[21].

Beyond the cold-stress model, other acute ulcer models also demonstrate miRNA perturbations. In ethanol-induced gastric injury model (an acute chemical stress), studies have observed changes in apoptosis-related miRNAs. Luo *et al.*[22] reported altered expression of certain miRNAs (including pro-apoptotic and anti-apoptotic miR) in rat stomachs following ethanol exposure, suggesting miRNA involvement in ethanol-triggered epithelial cell death (via pathways like JNK signaling). Although specific miRNA identities from that study need further elucidation, a related cell culture experiment provides insight: gastric epithelial cells (GES-1 line) exposed to 8% ethanol show significant apoptosis, which can be mitigated by the hormone ghrelin through a microRNA-mediated mechanism[23]. Ghrelin pretreatment of ethanol-stressed GES-1 cells upregulated miR-21 ~3-fold (which ethanol alone had suppressed), and this rise in miR-21 was required for ghrelin's anti-apoptotic effect. miR- 21 is known to target the tumor suppressor programmed cell death 4 (PDCD4) and to activate pro-survival signaling (e.g. PI3K/Akt) in cells[23]. In the ethanol-injury scenario, restoring miR-21 levels with ghrelin increased Akt and Bcl-2 and reduced Bax and caspase-3, thereby protecting cells from apoptosis. These findings suggest that miR-21 plays a context-dependent role in gastric mucosa: it is generally pro-survival and anti-apoptotic in acute injury (hence its upregulation promotes epithelial cell survival), yet in other contexts (chronic inflammation or neoplasia) miR-21 can act as a pro-inflammatory oncomiR. Indeed, in *H. pylori*-associated chronic gastritis, miR-21 is often elevated and contributes to the inflammatory cascade by downregulating PDCD4 and augmenting cytokine release [24]. Thus, miR-21 exemplifies how the same ncRNA can have dualistic roles: in acute stress ulcers its presence is beneficial (preventing excessive apoptosis), whereas in chronic injury its overabundance may drive pathological inflammation. Furthermore, miR-155 is a prototypical pro-inflammatory miRNA induced by NF-κB that amplifies cytokine production (partly by suppressing negative regulators like suppressor of cytokine signaling-1 (SOCS1). While one clinical study found that short-term aspirin/NSAID use did not appreciably change gastric mucosal miR-155 levels in healthy individuals, miR-155 is heavily upregulated in *H. pylori* gastritis and peptic ulcer disease associated with chronic active inflammation [25]. Its role in acute NSAID injury per se remains to be clarified, but extrapolating from other systems, one can speculate that NSAID-induced mucosal inflammation might trigger miR-155 in infiltrating macrophages and monocytes, thereby enhancing TNF-α/IL-6 production and tissue damage. In support, *in vitro* experiments demonstrate that curcumin can suppress LPS-induced macrophage activation by downregulating miR-155, leading to reduced TNF-α and IL-6 levels [26]. This indicates miR-155 is a key driver of inflammatory injury that can be pharmacologically modulated.

Overall, current evidence identifies a set of miRNAs frequently dysregulated during gastric ulcerative injury: injury-promoting miRNAs (like miR-143, -152, -181, -155) tend to be upregulated by NSAIDs/stress and further pathogenic processes (reducing cytoprotective factors or amplifying inflammation), whereas injury-limiting miRNAs (like miR-21 and miR-223 which are induced during resolution phases) may be inactivated or insufficiently upregulated in acute ulcers, thereby removing brakes on inflammation and cell death. Table 2 summarizes key ncRNAs implicated in gastric ulcer pathology, their known targets, and functional effects.

Table 2. Key ncRNAs Implicated in NSAID-/Stress-Induced Gastric Ulcer Pathology

ncRNA	Expression Change in Ulcer Models	Experimental Model	Target(s)	Functional Role in Gastric Pathology	Reference
miR-143	**Upregulated** (acute stress ulcer)	Cold-restraint stress in rats	xCT (cystine/glutamate antiporter)	**Pro-injury:** suppresses xCT, reducing glutamate & GSH, leading to oxidative damage and epithelial apoptosis.	[21]
miR-152	**Upregulated** (acute stress ulcer)	Cold-restraint stress in rats	xCT (SLC7A11)	**Pro-injury:** similar mechanism as miR-143 – inhibits cystine uptake/glutathione, promotes cell apoptosis under stress.	[21]
miR-181a	**Upregulated** (acute stress ulcer)	Cold-restraint stress in rats	xCT (SLC7A11)	**Pro-injury:** part of the miR-143/152/181 cluster targeting xCT; exacerbates glutamate depletion and mucosal injury during stress.	[21]
miR-21	**Downregulated** (in acute ethanol injury)	Ethanol-induced injury in GES-1 cells	PDCD4 (programmed cell death 4); PTEN, others	**Protective in acute injury:** loss of miR-21 during ethanol or stress leads to excess apoptosis; restoration of miR-21 (e.g. by ghrelin) activates PI3K/Akt and increases Bcl-2, aiding cell survival	[23]
miR-155	**Upregulated** (in inflammatory conditions; effect of acute NSAIDs is minimal)	LPS-stimulated macrophages	SOCS1, SHIP1 (negative regulators of cytokine signaling); NF-κB pathway components	**Pro-injury/pro-inflammatory:** MiR-155 is induced by NF-κB in immune cells and amplifies inflammation by repressing SOCS1 (relieving inhibition on cytokine signaling) and enhancing TNF-α, IL-1/6 production. In gastric mucosa, high miR-155 correlates with active inflammation; curcumin and PPIs can reduce miR-155, thereby dampening inflammatory damage.	[26]

Note: "Upregulated" or "downregulated" refers to expression changes relative to normal gastric mucosa. miR-143/152/181 are highlighted as injury-promoting miRNAs induced by stress, whereas miR-21 and miR-146a function in mucosal protection or repair. miR-155 is a driver of inflammation.

MicroRNAs in Mucosal Healing: Reparative RNA Networks in Regeneration, Angiogenesis, and Inflammation Resolution

Healing of a gastric ulcer is a complex, well-orchestrated process involving epithelial regeneration, revascularization of the mucosa (angiogenesis), extracellular matrix remodelling, and resolution of inflammation.[33] Emerging evidence suggests that microRNAs are intimately involved at each stage of this mucosal healing process, often by coordinating the switch from a pro-inflammatory, injury state to a pro-resolution, regenerative state (see Table 3).

MicroRNAs promoting epithelial regeneration: During the early healing phase, surviving epithelial cells at the ulcer margin migrate and proliferate to re-epithelialize the denuded area. Certain microRNAs can enhance (or impede) these processes. For instance, miR-21, aside from its anti-apoptotic role, is known to promote cell proliferation by targeting phosphatase and tensin homolog (PTEN) and phosphatase regulators – thereby activating the Akt/mTOR pathway which drives cell growth [23]. In cutaneous wound healing models, miR-21 is upregulated and has been shown to accelerate re-epithelialization, in part by modulating MMPs and growth factor signaling; a similar upregulation likely occurs in gastric ulcer granulation tissue to aid coverage of the ulcer crater [23]. Another microRNA, miR-200a/200b, which are negative regulators of epithelial-to-mesenchymal transition (EMT), could influence the phenotypic plasticity of gastric epithelial cells during healing – although primarily studied in cancer, their downregulation in a healing ulcer might permit a transient, more migratory phenotype for cells to crawl over the wound bed [27]

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Table 3: MicroRNAs (and lncRNA) implicated in gastric-ulcer healing: regeneration, angiogenesis, and inflammation resolution

Healing phase	ncRNA	Direction in healing phase	Principal target(s)/pathway	Mechanistic effect on healing	Reference(s)
Epithelial regeneration	miR-21	↑	PTEN → Akt/mTOR; MMP/EGF signaling	Promotes cell survival and proliferation; accelerates re-epithelialization	[23]
Epithelial regeneration (phenotypic plasticity)	miR-200a/200b	↓ (transient)	EMT regulators (ZEB1/2)	Permits a temporary migratory phenotype to cover the ulcer bed	[27]
Hypoxia-adaptation/NO	miR-210	↑	HIF-responsive cassette; NOS induction	Supports hypoxic survival and nitric-oxide–mediated cytoprotection	[28]
Matrix remodeling	miR-29; miR-133	↓ (putative)	MMP-2 regulation	Facilitates matrix turnover and granulation tissue maturation	[28]
Angiogenesis (pro-angiogenic)	miR-126	↑	VEGF pathway (targets negative regulators)	Favors endothelial sprouting and capillary formation	[29]
Angiogenesis (anti-angiogenic brake)	miR-15b/16	↓	VEGF-A mRNA	Relieves repression of VEGF to permit vessel growth	[30]
Angiogenesis (lncRNA axis)	lncRNA MEG3 → miR-421 → TSP-1	MEG3 ↓ / miR-421 ↑ (net)	TSP-1 (angiogenesis inhibitor)	Lowers TSP-1 to allow neovascularization	[31,32]
Inflammation resolution (macrophage switch)	miR-146a/miR-146b	↑	IRAK1, TRAF6 → NF-κB	Dampens TLR signaling; shifts M1→pro-resolving state	[33]
Neutrophil restraint / IL-6 control	miR-223	↑	STAT3/IL-6–related nodes; neutrophil activation	Limits neutrophil-driven injury; promotes quieting of cytokine flux	[25,34]
Pro-inflammatory driver (should fall)	miR-155	↓	SOCS1/SHIP1 (negative regulators) → NF-κB	Reduces cytokine amplification when down-regulated	[35,36]

Notes: Arrows (↑/↓) indicate the direction desirable for healing based on the text. Rows labelled "putative/proposed" denote biologically grounded hypotheses requiring direct gastric-ulcer validation. A**bbreviations:** EMT, epithelial–mesenchymal transition; EGF, epidermal growth factor; HIF, hypoxia-inducible factor; IRAK1, interleukin-1 receptor-associated kinase 1; MMP-2, matrix metalloproteinase-2; NF-κB, nuclear factor kappa-B; NOS, nitric oxide synthase; PTEN, phosphatase and tensin homolog; STAT3, signal transducer and activator of transcription 3; TLR, Toll-like receptor; TRAF6, TNF receptor–associated factor 6; TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor.

MicroRNAs in angiogenesis: Angiogenesis is important in providing nutrients and oxygen to enhance ulcer healing. Vascular endothelial growth factor (VEGF) is a master regulator of angiogenesis in ulcers; interestingly, multiple ncRNAs interface with the VEGF pathway [37]. miR-126, one of the most pro-angiogenic miRNAs (highly expressed in endothelial cells), promotes angiogenesis by targeting inhibitors of the VEGF signaling cascade. In ischemic injuries, miR-126 enhances capillary formation and could similarly assist in gastric ulcer neovascularization [29]. On the flip side, miR-15b/16 family members are known to directly target VEGF-A mRNA – these are often upregulated by stress or injury and can impair angiogenesis by blunting VEGF. Thus, downregulation of miR-15/16 in the ulcer microenvironment would be favourable for new vessel growth [30].

ncRNAs beyond miRNAs also partake: lncRNA MEG3 can sponge miR-421 to upregulate thrombospondin-1(TSP-1) an angiogenesis inhibitor; hence, if MEG3 is suppressed during healing, the result is freer miR-421 to possibly reduce thrombospondin-1 (TSP-1) and allow angiogenesis [31,32]. There is evidence that successful gastric ulcer healing is accompanied by a burst of pro-angiogenic gene expression (VEGF, FGF2, angiopoietins) [38], and ncRNAs are likely upstream modulators of this burst. For example, curcumin treatment in a rat chronic ulcer model upregulated VEGF and TGF-β expression, correlating with enhanced angiogenic response [38]. Since curcumin also modulates miRNAs, one hypothesis is that it may downregulate an anti-angiogenic miRNA (like miR-15b or miR-206) to achieve this effect, though direct data are pending.

Inflammation resolution and microRNA switching: A critical aspect of healing is the resolution of inflammation – turning off the neutrophil influx and inflammatory cytokine production and activating macrophages toward a pro-resolving phenotype [35,36]. miRNAs are key in this transition. miR-146a and miR-146b are induced in macrophages as they shift from a classically activated (M1, pro-inflammatory) state to a healing (M2) state. These miRNAs target IL-1 receptor-associated kinase (IRAK1) and TNF receptor-associated factor 6 (TRAF6), dampening NF-κB activity [33]. Thus, high miR-146a in ulcer-associated macrophages would help silence the production of IL-1β, TNF-α, and other damaging cytokines, fostering a milieu conducive to tissue repair. Indeed, administration of anti-inflammatory agents like curcumin and certain flavonoids is associated with upregulation of miR-146a in inflamed tissues [33]. Similarly, miR-223 is a myeloid-derived miRNA that acts to restrain neutrophil hyperactivity and IL-6 production; it often increases as inflammation proceeds to resolution. In *H. pylori* gastritis, miR-223 is elevated in neutrophil-rich inflammation [39], possibly as a counter-regulatory mechanism. It is plausible that in NSAID or stress ulcers, a delayed or insufficient rise in miR-223 could prolong neutrophil-mediated injury [34]. miR-155 versus miR-125b/miR-10a levels in macrophages also distinguish inflammatory vs. anti-inflammatory states – with miR-155 dropping and miR-125b rising as inflammation resolves. Thus, a coordinated switch in the microRNA profile is part of the normal healing trajectory: injury-phase microRNAs (e.g. miR-155, miR-21 in inflammatory mode, etc.) give way to healing-phase microRNAs (miR-146a, miR-223, miR-21 in pro-survival mode, etc.). Understanding this temporal regulation could open avenues to therapeutically "push" an ulcer from a non-healing inflammatory state into a healing state by mimicking the ncRNA switches.

Phytochemicals Modulating microRNAs to Restore Gastric Mucosal Integrity

A remarkable insight from pharmacological research is that many plant-derived compounds (phytochemicals) like cardiac glycoside, saponin, phenolic and flavonoid exert gastroprotective and ulcer-healing effects by impacting the same molecular pathways that microRNAs regulate. In some cases, these compounds directly modulate the expression of specific microRNAs, thus normalizing the aberrant RNA signals driving injury. Below is a review of key phytochemicals including ginger constituents, and curcumin and their influence on microRNA-mediated pathways in gastric ulcer models.

Ginger (*Zingiber officinale*)

Ginger rhizome is a well-known gastroprotective agent, rich in phenolics (gingerols, shogaols) with antioxidant and anti-inflammatory properties. It has been shown to prevent experimental ulcers (e.g. ASA-induced ulcers) and alleviate gastritis by inhibiting MAPK/NF-κB signaling and reducing oxidative stress [40,41]. A particularly fascinating aspect of ginger is its content of edible plant microRNAs and exosome-like nanoparticles that can communicate with mammalian cells. Zhu and He, (2024)[42] discovered that ginger-derived exosome-like nanoparticles (GELNs) contain an abundance of stable plant miRNAs (over 125 distinct miRNAs identified) and can survive digestion to be taken up by intestinal cells. When administered orally or added to cell cultures, these ginger nanoparticles are specifically internalized (via endocytosis) by gut epithelial and immune cells and exert measurable regulatory effects. Notably, Yin *et al.* [21] characterized the miRNA profile of GELNs and found 27 miRNAs

highly enriched relative to ginger tissue. Bioinformatics indicated these miRNAs target pathways involved in inflammation (e.g. NF-κB, cytokine signaling) and even cancer-related pathways. Functionally, GELNs added to human intestinal Caco-2 cells counteracted LPS-induced inflammation, reducing NF-κB nuclear translocation and lowering IL-6, IL-8, and TNF-α levels. The anti-inflammatory effect was attributed in part to the plant miRNAs delivered by the nanoparticles, as these miRNAs could potentially target human transcripts in the NF-κB pathway (this is an example of cross-kingdom gene regulation)[41].

Applying this to gastric ulcers, ginger consumption may supply bioactive plant miRNAs to the gastric mucosa that help quell inflammation and oxidative injury. Indeed, ginger has long been observed to protect the stomach – for example, it significantly reduced aspirin-induced gastric ulcer severity and histological damage in rats [43]. Some of this benefit likely comes from ginger's direct antioxidant action (scavenging free radicals and boosting host antioxidant enzymes), and inhibition of acid secretion to some extent.[43] But the discovery of ginger miRNAs raises the intriguing possibility that part of ginger's efficacy is through "RNA therapy": delivering cross-kingdom miRNAs that supplement the host's own regulatory RNAs. Additionally, ginger contains 6-gingerol, which has been shown to influence gene expression and could upregulate certain host miRNAs [44,45]. The notion of cross-kingdom RNA uptake means that a simple dietary agent could introduce new regulatory molecules into the ulcer milieu. The safety profile of ginger is excellent, making it a tantalizing candidate for adjunct therapy [46,47]. More research is needed to identify which specific ginger miRNAs are most relevant and whether they directly target human COX-2 or IL-1β transcripts. Nonetheless, the current evidence indicates that ginger's gastroprotective effects extend beyond classical antioxidant/anti-secretory mechanisms to include miRNA-mediated modulation of inflammation [41]. Embracing this mechanism could lead to innovative therapies, such as plant exosome-derived nanocarriers delivering healing miRNAs to the gut.

***Curcumin longa* (Turmeric)**

Curcumin, the principal polyphenol in turmeric (*Curcuma longa*), is one of the most studied nutraceuticals for its gastroprotective properties. It has demonstrated potent protection against both NSAID-induced gastric injury and ethanol/stress ulcers in numerous studies [10,11,28]. Curcumin's actions are famously pleiotropic – it is anti-inflammatory (inhibiting NF-κB, COX-2, iNOS), antioxidant (boosting glutathione, SOD, etc.), anti-apoptotic (maintaining Bcl-2, inhibiting caspases), and it even promotes angiogenesis and tissue remodelling required for ulcer healing [38]. A remarkable aspect is that many of these effects are mediated through changes in gene expression that mirror the effects of modulating certain ncRNAs. For example, curcumin consistently downregulates miR-155 in activated macrophages and monocytes, which leads to reduced pro-inflammatory cytokine production (TNF-α, IL-6) and a tilt toward an anti-inflammatory state [26]. In the same study, curcumin prevented LPS-induced sepsis mortality in mice in part by suppressing miR-155 and thereby allowing increased expression of SOCS1, a negative regulator of cytokine signalling [26]. This likely translates to the gastric setting: by lowering miR-155, curcumin would dampen the NSAID- or stress-induced cytokine surge that damages mucosal cells. Curcumin and its analogs also upregulate miR-146a, reinforcing the shutdown of NF-κB inflammatory loops [33]. Furthermore, in cancer cell research, curcumin was found to restore expression of certain suppressed miRNAs (e.g. miR-34a tumor suppressor in gastric cancer cells, and miR-33b which impacts Wnt signaling)[48]. Translating that to ulcers: curcumin might reinstate miR-34 or others that help control excessive cell proliferation in the healing layer, ensuring an ordered regeneration instead of dysplastic changes. It has been reported that curcumin can induce miR-99a/100 which target mTOR, a pathway also involved in mucosal repair and fibrosis control [49,50]. The interplay is complex, but curcumin's ability to influence a broad network of ncRNAs is part of why it can simultaneously reduce inflammation, oxidative stress, and promote regeneration.

Experimentally, curcumin has been shown to markedly improve ulcer healing indicators (Figure 3). In indomethacin-ulcerated rats, a single dose of curcumin significantly reduced ulcer index, increased gastric mucus and nitric oxide levels, and elevated endogenous antioxidant enzymes (catalase, SOD)[10]. It also lowered mucosal MDA, iNOS and NF-κB expression, and even reduced gastric acid output[28]. These effects align with what one would expect if curcumin were activating an "anti-stress" microRNA program: for instance, downregulating miR-34a can increase mucus secretion via growth factor pathways, and upregulating miR-210 (a hypoxia-responsive miR) could induce protective NO synthase. In a chronic ulcer model, a zinc–curcumin complex was even more effective, and curcumin-treated ulcers showed upregulation of genes like VEGF, TGF-β, and Matrix Metalloproteinase-2 (MMP-2), indicating enhanced angiogenesis and matrix remodeling [28]. We know that MMP-2 is often regulated by miR-29 and miR-133; curcumin's effect on those miRNAs in wounds is an area to explore. In summary, curcumin

acts as a "master regulator" that tilts the molecular milieu from ulcer-promoting to ulcer-healing. It accomplishes this by simultaneously targeting multiple pathways, likely including ncRNA circuits. Its ability to normalize dysregulated miRNAs (like lowering miR-155, raising miR-146a) and possibly lncRNAs (though less studied, curcumin has been seen to modulate lncRNA expression in cancer cells too) makes it exceptionally well-suited as a therapeutic adjuvant for gastric ulcers[33].

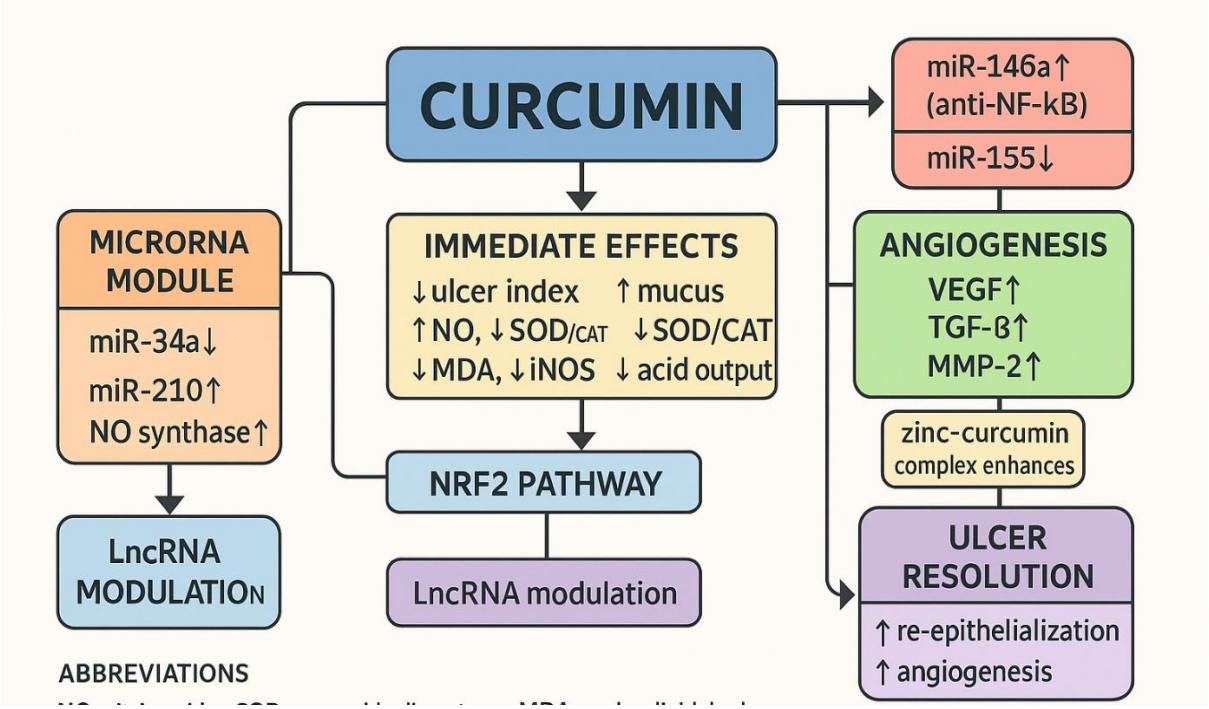

Figure 3: Curcumin-driven protection and healing in NSAID ulcer models via antioxidant, anti-inflammatory, secretory, angiogenic, and ncRNA nodes. In indomethacin-ulcerated rats, curcumin lowers ulcer index and gastric acid output while increasing mucus and nitric oxide and raising endogenous antioxidants (SOD, CAT); mucosal MDA, iNOS, and NF-κB fall in parallel, with histological rescue (10,47). The diagram also depicts a proposed ncRNA "anti-stress" program: miR-34a↓ (favoring mucus/growth-factor signalling) and miR-210↑ (supporting hypoxia-responsive NO synthase), together with miR-155↓ and miR-146a↑ that restrain NF-κB-dependent cytokines. In chronic settings, a zinc–curcumin complex drives gene programs for tissue repair—VEGF, TGF-β, and MMP-2↑—supporting angiogenesis and matrix remodeling; putative links to miR-29/miR-133 regulation of MMP-2. (adopted from google image)

Cross-Kingdom RNA Uptake: Dietary Plant miRNAs in Gastric Healing

An exciting frontier in RNA research is the concept of cross-kingdom regulation – that is, small RNAs from our diet or microbiome can enter our circulation and affect our gene expression. As highlighted with ginger, plants contain many miRNAs; other edible plants (fruits, rice, herbs) do as well. The bioavailability of dietary miRNAs is still debated, but some studies have detected plant miRNA sequences in the plasma and tissues of animals after feeding. One famous example is a rice miRNA (miR-168a) reported to bind to the LDL receptor adapter in mice and slow its clearance, although follow-up studies have given mixed results on reproducibility. Nonetheless, the robust data from ginger and from other edible exosome studies (e.g. grape exosome-like nanoparticles delivering anti-inflammatory miR to mice with colitis) support that cross-kingdom transfer is feasible under certain conditions[21]. If plant miRNAs can reach the gastric mucosa, they could directly influence ulcer healing. For instance, many plant miRNAs have sequence complementarity to mammalian inflammatory genes. A miRNA from turmeric might target human CXCL. While our focus here is on empirical evidence, it is worth noting that one study in mice showed oral ginger exosomes not only reduced intestinal inflammation but also altered the gut microbiota and gene expression in intestinal cells via delivered miRNAs[21]. Given the anatomical proximity, ginger miRNAs likely also bathe the stomach lining. Similarly, any consumed plant used as herbal medicine (chamomile, liquorice, etc.) comes with its cargo of RNAs. Cross-kingdom uptake could help explain some folklore remedies: perhaps cabbage juice (a classic ulcer folk remedy)

contains miRNAs that promote mucous cell growth or suppress acid secretion genes.

However, challenges remain: the stomach's low pH and RNases presumably degrade most dietary RNAs. Exosome encapsulation (as with ginger) seems to protect them. Milk is another rich source of dietary exosomal miRNAs, but those are animal-derived. In the context of herbal therapies, leveraging cross-kingdom miRNAs may become a novel therapeutic angle – for example, engineering edible probiotics or plants to express specific miRNAs beneficial for ulcer healing, packaging them in nanoparticles, and delivering orally. Currently, cross-kingdom miRNA effects in gastric tissue remain suggestive but not conclusively proven, so they should be seen as complementary to the well-documented host ncRNA changes. Going forward, it will be fascinating to identify if any plant miRNA sequences are found enriched in gastric ulcer tissue of patients who consume certain diets or herbal medicines, as this could open a new class of "xenomiR" therapeutics. The principle has been demonstrated in a lab setting: exogenous plant miRNAs can regulate mammalian transcripts in vitro[21]. So, while one should be cautious, the potential is that we might one day treat ulcers with, say, a corn-derived miRNA mimic that boosts VEGF, delivered in an edible nanoparticle.

Future Directions and Translational Opportunities

The burgeoning understanding of ncRNA dysregulation in gastric ulcers presents several promising avenues for clinical translation and further research:

1. **MicroRNA-based Therapeutics:** The pathogenic microRNAs identified (such as miR-143/152/181 in stress ulcers, and miR-155 in inflammatory injury) are attractive targets for therapeutic inhibition. Oligonucleotide inhibitors (antagomiRs) or sponges could be designed to locally silence these miRNAs in the gastric mucosa during an ulcer episode. For example, an antagomir-143/152/181 cocktail delivered via a stomach-retentive gel or nanoparticle could potentially mitigate stress ulcer damage by restoring xCT and glutathione levels. Similarly, delivering miR-155 antagomir to ulcer beds might accelerate resolution of inflammation. Indeed, in preclinical models of colitis, silencing miR-155 or boosting miR-146a has shown anti-inflammatory benefits [33,51]. The challenge will be targeted delivery: one solution is using endoscopy to spray ncRNA therapeutics onto ulcer sites, another is encapsulating them in polymer beads that release in the stomach.
2. **Phytochemicals as Adjunct Treatments:** The evidence reviewed here strongly suggests that diets or supplements rich in certain phytochemicals can favourably modulate gastric ncRNA profiles and hasten mucosal recovery. A foreseeable future direction is the integration of nutraceuticals into ulcer management protocols. For instance, curcumin or turmeric supplements could be given alongside proton pump inhibitors (PPIs) for NSAID-ulcer patients, potentially reducing the needed PPI dose or preventing relapse by addressing inflammatory and regenerative pathways that PPIs do not. Similarly, a standardized ginger extract or ginger nanoparticle formulation could be used prophylactically in patients on long-term NSAIDs to bolster mucosal defences via cross-kingdom miRNAs and antioxidant effects.
3. **Biomarkers for Ulcer Risk and Healing:** ncRNAs could also serve as minimally invasive biomarkers to predict ulcer risk (or diagnose silent ulcers) and to monitor healing. For example, patients on NSAIDs who develop ulcers might exhibit a specific serum microRNA signature – perhaps elevated miR-155 and reduced miR-21 or miR-223 in circulating exosomes. A study found that serum miR-200c and miR-139 were dysregulated in patients with peptic ulcer disease and might predict progression to gastric cancer if *H. pylori* is present[52,53]. Expanding this concept, one could develop a "gastric ulcer panel" of miRNAs (and maybe lncRNAs) measurable in blood or gastric juice that indicates active mucosal injury or conversely, successful healing.
4. **Personalized Therapy via ncRNA Profiling:** In the future, clinicians might biopsy an ulcer edge and profile its ncRNA expression to tailor therapy. An ulcer with high inflammation-driving miRNAs might benefit from an RNA-based drug or a specific phytochemical known to counter that miRNA. This personalized approach aligns with the precision medicine trend. Moreover, certain patient populations (e.g. those with polymorphisms affecting miRNA binding sites in COX-2 or TNF genes) might be more ulcer-prone – genomic screening could identify them, and prophylactic dietary recommendations (like regular celery seed or curcumin intake) could be given.
5. **Combinatorial Approaches:** Future therapy for a difficult ulcer might involve a multi-pronged approach: a PPI or acid-suppressant to reduce ongoing damage, a curcumin/ginger-based nutraceutical to modulate inflammation and miRNAs, and a targeted ncRNA drug to kickstart healing (for example, a synthetic lncRNA mimic delivered in a hydrogel that promotes angiogenesis and epithelial closure). The safety

of such approaches will have to be established, but since many phytochemicals are diet-derived, the bar for safety is lower than synthetic drugs.

CONCLUSION

The convergence of RNA biology and ulcer pharmacology is opening new horizons. MicroRNAs act as pivotal regulators in gastric ulcer pathogenesis and recovery, and harnessing their power – either by directly targeting them or by using phytochemicals as natural "RNA modulators" – holds great promise for improving outcomes in gastric ulcer disease. The next few years should see translational studies moving these concepts from bench to bedside. Patients with NSAID or stress ulcers, especially those with chronic or refractory ulcers, could greatly benefit from such innovative therapies that not only suppress acid (the traditional focus) but also actually correct the underlying molecular derangements (inflammation, impaired defence, poor angiogenesis) via ncRNA pathways. As we embrace this ncRNA-centric view, we get closer to the goal: rapid, scar-free healing of ulcers and prevention of complications, achieved with safe, mechanism-based treatments possibly derived from nature's own pharmacy.

Declaration of Competing Interest

The authors declared to have no known competing interests that could influence this article.

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