



Sudarshan
Publications

Available online at <https://s-epub.in/index.php/trp/index>

Pharma Research

An International Peer Reviewed, Indexed Journal

[10.62655/s-epub.2025.v17.i02.pp105-114](https://s-epub.in/index.php/trp/index)

GASTROPROTECTIVE EFFECT OF ZINC CARNOSINE AGAINST INDOMETHACIN-INDUCED GASTRIC ULCERS

DEREK DELGADO^{1*}, KONSTANTINOS PAPADAKIS², PHILIPPA
ROWNTREE³

Affiliation

¹Department of Pharmacology, Shenandoah Valley College of Pharmacy, Harrisonburg, USA

²Department of Experimental Pharmacology, Macedonia Plain Institute of Pharmacy, Serres, Greece

³Department of Experimental Pharmacology, Exmoor Institute of Pharmaceutical Sciences,
Taunton, United Kingdom

*Corresponding author: Derek Delgado, d.delgado@svcp.edu

ORCID iD: Derek Delgado 0000-0001-2807-9097; Konstantinos Papadakis 0000-0001-3897-3826; Philippa Rowntree
0000-0001-4781-1941

Article info

Received date:31-05-2025

Accepted date:16-08-2025

Published date:13-12-2025

ISSN;0975-8216

Keywords:

Zinc carnosine, Indomethacin, Gastric
ulcer, Gastroprotection, Oxidative stress

1. INTRODUCTION

Indomethacin is one of the oldest and most potent non-selective inhibitors of cyclooxygenase, and it remains in clinical use for gout, ankylosing spondylitis, patent ductus arteriosus and some forms of acute pain. It is also among the most reliable ways to damage a stomach. Within hours of a high oral or subcutaneous dose in a fasted rat, the glandular mucosa develops haemorrhagic linear lesions that look much like the erosions seen in people who take non-steroidal anti-inflammatory drugs (NSAIDs) for long periods [1, 2]. That reproducibility is the

Abstract

Indomethacin-induced gastric injury in the rat is a standard model of non-steroidal anti-inflammatory drug toxicity, and zinc carnosine (polaprezinc) is a mucosal protective compound used clinically for gastric ulcer. This narrative review summarises what published experimental and clinical work reports about zinc carnosine in this setting. It outlines how indomethacin damages the stomach, the antioxidant, anti-inflammatory and reparative properties of the chelate, the way the model is run and scored, and the strength of the evidence. The review reports no new data. Findings are consistent with protection through antioxidant and mucosal pathways, but direct human evidence is limited and preclinical reporting often lacks randomisation and blinding.

reason the indomethacin model sits in so many pharmacology laboratories, and it explains why a large number of candidate gastroprotective agents have been tested

against it. Its potency also makes it a stringent test: an agent that protects against indomethacin has met a demanding challenge, while one that fails may still have value against milder insults. Interpreting any single result therefore depends on the dose of the challenge as much as on the dose of the protectant.

Zinc carnosine, known in Japan as polaprezinc, is a chelate in which zinc is bound to L-carnosine, the dipeptide beta-alanyl-L-histidine. It was developed as an anti-ulcer drug and has been used clinically for gastric ulcer for many years, usually at doses in the tens of milligrams twice daily [3, 4]. Its attraction is that it does not suppress acid. Instead, it appears to act at the mucosa, where it combines antioxidant, anti-inflammatory and reparative properties. Because NSAID injury is driven by loss of mucosal defence and by oxidative stress rather than by acid alone, an agent with that profile is an obvious candidate for protection. Japanese clinical practice has accumulated decades of experience with it, which is unusual for a mucosal protectant, though most of that experience was gathered before modern trial standards and reporting conventions.

This review brings together what published experimental and clinical work says about the gastroprotective effect of zinc carnosine against indomethacin-induced gastric ulcers. It describes how indomethacin damages the stomach, what is known of the pharmacology of zinc carnosine, how the model is set up and interpreted, and what the evidence does and does not establish. The review reports no new experimental data. Where findings come from related injury models, such as aspirin, ethanol or acetic acid, this is stated, because extrapolation between models is itself a source of uncertainty [5, 6]. The aim is to give pharmacists, formulation scientists and early-career researchers an honest picture of the strength of the case, along with practical pointers on how future studies might be designed more rigorously.

2. HOW INDOMETHACIN DAMAGES THE STOMACH

The starting point is inhibition of cyclooxygenase-1, the constitutive enzyme that supplies the gastric mucosa with prostaglandins. The recognition that aspirin-like drugs act by blocking prostaglandin synthesis explained both their benefit and their toxicity [1]. Prostaglandin E_2 and prostacyclin maintain mucosal blood flow, stimulate mucus and bicarbonate secretion, limit acid output and help the epithelium to reconstitute after injury [2, 7]. When they fall, the mucus gel thins, microcirculatory flow becomes unstable and the surface cells are left more exposed to acid, pepsin and bile. Early cytoprotection work with exogenous prostaglandins showed that the stomach could be protected without lowering acid at all, which established the idea of mucosal defence as a target in its own right [8]. It is worth remembering that the stomach is not defenceless without prostaglandins; rather, the margin of safety narrows, and additional stressors such as acid, bile or ethanol then tip the balance towards injury.

Loss of prostaglandins is necessary but not sufficient. Studies in rats found that indomethacin lesions are accompanied by increased lipid peroxidation, depletion of reduced glutathione and a fall in antioxidant enzyme activity, and that lesions were attenuated by free radical scavengers [9, 10]. Neutrophils are drawn into the microvasculature, adhere to the endothelium and release proteases and reactive oxygen species. Work on small intestinal damage further suggested that blocking COX-1 triggers compensatory COX-2 up-regulation and a rise in inflammatory mediators, which adds to injury [11]. The result is a layered process in which reduced defence, vascular compromise and oxidative inflammation reinforce each other. Experimental evidence also shows that damage to the microvasculature precedes the visible lesion, with stasis and ischaemia in the superficial capillaries, so the haemorrhagic bands seen at autopsy are the late expression of events that began earlier [9, 10].

Indomethacin has additional features that help to explain why it is such a potent damaging agent. It undergoes enterohepatic circulation,

so the intestine is re-exposed to the drug after it has left the stomach, and it can interfere with mitochondrial oxidative phosphorylation in epithelial cells [12]. Different mechanisms have been proposed for formation and for prevention of indomethacin ulcers, and studies using agents with different pharmacology show that more than one pathway can be interrupted with benefit [10, 13]. This matters when interpreting protection by zinc carnosine, because a positive result does not by itself identify which pathway is responsible. None of these features is unique to the model, but together they make it a particularly harsh and sensitive one.

The clinical counterpart is well documented. NSAID-related upper gastrointestinal events range from dyspepsia and superficial erosions to bleeding and perforation, and risk climbs with age, prior ulcer, concomitant corticosteroids or anticoagulants, and higher doses [6, 14]. Reviews of NSAID effects on the whole gut also stress the damage lower down, which proton pump inhibitors do not prevent [15]. Selective COX-2 inhibitors were designed to spare the stomach, and large trials showed a reduced rate of upper gastrointestinal events relative to non-selective drugs, though the cardiovascular questions that followed limited their use [16, 17]. These data underline why a mucosal protective strategy that is independent of acid might still have a place in practice.

A practical point concerns timing. In the classic model the stomach is examined only a few hours after the dose, long before any chronic ulcer could form, so the lesions are acute erosions and haemorrhagic bands more than true ulcers. The word ulcer is used loosely in the literature, and clinical readers should keep in mind that protection against acute mucosal injury in a fasted rat is a different thing from healing of an established chronic ulcer in a patient [5, 18]. Other models, such as the acetic acid ulcer, address chronic healing more directly and are covered later in this review. The distinction also affects how outcomes are worded: acute erosion scores and ulcer healing rates answer separate questions, and mixing them blurs the message [5, 18].

3. ZINC CARNOSINE: CHEMISTRY AND PHARMACOLOGY

Zinc carnosine is a polymeric chelate with a one-to-one ratio of zinc to carnosine, poorly soluble in water, and it dissolves slowly in the gastric contents. This slow release is thought to explain a distinctive property: it adheres to the ulcerated mucosa and delivers zinc and carnosine locally rather than being absorbed as a single bolus [3]. In experimental models it appeared to bind preferentially to damaged tissue. That behaviour gives the drug a degree of targeting that a simple zinc salt does not offer, and it may help to explain why the intact chelate has been preferred to either of its components given separately. Formulation matters for that reason: particle size, crystallinity and the vehicle used for suspension all alter how the chelate disperses in the stomach and how long it remains in contact with the surface [3, 4].

The antioxidant profile of the compound has been studied directly. The chelate scavenged hydroxyl radicals in cell-free systems and reduced lipid peroxidation, behaviour attributed to both the imidazole ring of histidine and the zinc ion [4, 19]. Zinc itself stabilises membranes, induces metallothionein, which can bind free radicals, and competes with redox-active iron and copper. Carnosine has been described as a scavenger of reactive aldehydes. Neither component alone reproduces the whole effect, which is why most authors treat the intact chelate as the active unit, even though the exact balance between zinc and carnosine in vivo is not fully settled [3, 19]. Experiments using cell-free assays have an obvious limitation, which is that a compound that scavenges radicals in a tube need not do so at the concentrations reached in the gastric wall, and tissue studies are needed to confirm relevance [4].

Beyond direct antioxidant action, studies reported several effects on cellular defence. Polaprezinc induced the 72 kDa heat shock protein in cultured rat gastric mucosal cells and in rat gastric mucosa, and this protein is known to protect cells from oxidative and thermal stress [20]. In rats with aspirin-induced injury, polaprezinc reduced mucosal lipid peroxidation, neutrophil

accumulation and tumour necrosis factor- α expression [21]. These findings suggest that the compound can intervene at points that are directly relevant to the NSAID injury cascade, including the oxidative and inflammatory steps described in the previous section [9, 10]. Whether heat shock protein induction is a cause of protection or simply a marker of cellular stress response is an open question, and the experiments described do not fully separate the two.

Zinc status is relevant to repair in general. Zinc is a cofactor for many enzymes involved in cell proliferation and protein synthesis, and deficiency impairs immune responses and wound healing [22, 23, 24]. In rats, zinc deficiency delayed the healing of experimental gastric ulcers [25]. Reviews of zinc in wound healing support a role in re-epithelialisation, collagen synthesis and control of inflammation, though they stress that supplementation helps mainly where deficiency exists [24]. These observations place zinc carnosine in a plausible framework, but they do not prove that extra zinc is needed in a well-nourished animal given a single dose of indomethacin. Careful interpretation is needed, because in a well-nourished adult human the stomach is unlikely to be limited by zinc supply in the way that a deficient laboratory animal might be.

Absorption and safety are comparatively unremarkable. Only a fraction of an oral dose of zinc carnosine is absorbed, and the clinical experience in Japan describes few adverse effects at the usual doses [3]. A study of healthy volunteers also tested zinc carnosine as a gut-stabilising supplement and found that it attenuated the increase in small bowel permeability caused by indomethacin, which links the compound to the same drug used in the animal model [26]. Dose conversion from animal studies to human exposure should follow body surface area rules, not simple weight scaling, to avoid overstating equivalence [27]. The absence of an acid-suppressing action is also a safety point, because it avoids the drug interactions and altered gut flora considerations linked with long-term acid suppression.

Compared with the major drug classes used to prevent NSAID ulcers, the mechanism of zinc carnosine is clearly distinctive. Proton pump inhibitors lower acid and reduce ulcer incidence in at-risk NSAID users, and misoprostol replaces prostaglandins directly [28, 29]. Neither addresses oxidative injury as such. Zinc carnosine addresses it but has no strong head-to-head clinical data against these agents in NSAID prophylaxis, and a fair reading is that it is a mucosal protective option with mechanistic appeal and incomplete comparative evidence [6, 28]. In practical terms, a clinician looking for prevention in a patient who must continue an NSAID would reach for the established agents first, and consider zinc carnosine only as an addition within a research protocol or where local practice already uses it.

4. EXPERIMENTAL EVIDENCE FOR GASTROPROTECTION

The published evidence is gathered in table 1, arranged by the type of finding, and the distribution of entries across the four groups is shown in fig. 1. The table includes work on indomethacin and also closely related injury models, because direct studies of zinc carnosine against indomethacin ulcers are fewer than the general literature on its gastric effects. Readers should treat the entries as pointers to mechanisms with reasonable support, not as a tally of positive trials [3, 4, 20]. The group labels are simplifications, since several compounds act through more than one mechanism, and a finding is placed under the group that its authors emphasised.

Table 1: Published findings relevant to zinc carnosine and indomethacin-type gastric injury

Evidence item	Reported finding	Ref.
Radical scavenging cell-free systems	The chelate scavenged hydroxyl radicals and limited lipid peroxidation	[4, 19]
Indomethacin injury glutathione and lipid peroxides	Oxidative stress marks the lesions, and radical scavengers reduced them	[9, 10]
Aspirin injury polaprezinc in rats	Lower lipid peroxidation, neutrophil accumulation and TNF- α expression	[21]

Evidence item	Reported finding	Ref.
Neutrophil infiltration NSAID models	Adherence of neutrophils to vessels is a step in lesion formation	[9, 11]
Heat shock protein 70	Induced in cultured gastric cells and rat mucosa	[20]
Adherence to damaged mucosa	Slow dissolution delivers zinc and carnosine at the lesion	[3]
Small bowel permeability healthy volunteers	Indomethacin-induced rise in permeability was reduced	[26]
Zinc deficiency rats	Delayed healing of experimental gastric ulcers	[25]
Acetic acid ulcer model	Reported to accelerate healing of chronic ulcers	[3, 18]
Epithelial migration cell culture	Stimulated migration, consistent with an effect on restitution	[26, 30]

Several lines of evidence agree. In antioxidant assays and injury models, the chelate lowered markers of lipid peroxidation and protected against radical-mediated damage [4, 19]. In aspirin-induced injury, which shares the COX-1 and neutrophil components of the indomethacin model, polaprezinc reduced inflammatory cell accumulation and cytokine expression [21]. Induction of heat shock protein 70 offers a plausible link between these effects, because the protein limits apoptosis and stabilises damaged proteins in the face of oxidative stress [20]. Together these observations make a coherent case for protection of the mucosa against NSAID-type injury. Equally, the aspirin findings should be interpreted with the caveat that aspirin and indomethacin differ in potency, pharmacokinetics and the extent of intestinal involvement [21].

Healing models add a second strand. The acetic acid ulcer model, introduced as a way of producing chronic, slowly healing lesions, has been used extensively to show that zinc carnosine accelerates ulcer repair, and reviews of the compound summarise this as a consistent finding [3, 31]. Healing of such ulcers involves epithelial migration, angiogenesis and the formation of granulation tissue, all processes in which zinc takes part [24, 30, 31]. In cultured cell systems, zinc carnosine stimulated migration of gut

epithelial cells, which supports an action on restitution [26]. Dependence of repair on adequate zinc is supported by the delayed healing seen in zinc-deficient rats [25]. Taken at face value, these findings suggest that zinc carnosine could act both before and after injury, but the experiments supporting each role used different models, and no single study demonstrates both in the same animals.

It would be wrong to give the impression that every question has been answered. Many reports come from a small number of research groups, particularly in Japan, and the dose range and route used in indomethacin experiments differ between papers. Some entries in the evidence base used prevention schedules, in which the compound is given before indomethacin, and others used treatment after injury. The two designs ask different questions. Prevention tests whether the mucosa can be shielded, while treatment tests whether recovery can be accelerated, and conclusions from one should not be applied automatically to the other [5, 18]. A further complication is that zinc carnosine is sold in several formulations of unequal quality in some markets, so published results cannot be assumed to apply to every product.

Comparisons with reference agents are informative where they exist. In rat NSAID models, antisecretory drugs may protect to some extent, but their protection is often partial, because indomethacin damage is not acid-dependent alone [10, 13]. Prostaglandin analogues protect more completely because they replace the missing mediator [8, 29]. A gastroprotectant that works through antioxidant and reparative routes may therefore be best viewed as complementary. Studies that combine zinc carnosine with an acid suppressant or a prostaglandin analogue in the same model would test that idea directly, and they appear to be rare [28, 29]. Combination studies are sensible from the clinician's point of view, since patients at high risk are rarely given a single protective drug.

The clinical translation is modest. Zinc carnosine is used in some countries as a gastric mucosal protectant and as a supplement for gut comfort, yet no large randomised trials show that it prevents NSAID ulcers in routine practice, and

guideline recommendations for ulcer prevention rest on proton pump inhibitors, misoprostol and use of COX-2 selective drugs in selected patients [6, 28, 29]. The small human study of intestinal permeability is encouraging, but permeability is a surrogate marker and not a clinical outcome [26]. Honest reporting of this gap is part of reading the preclinical literature fairly. Until such trials exist, claims of NSAID ulcer prevention in patients should be treated cautiously.

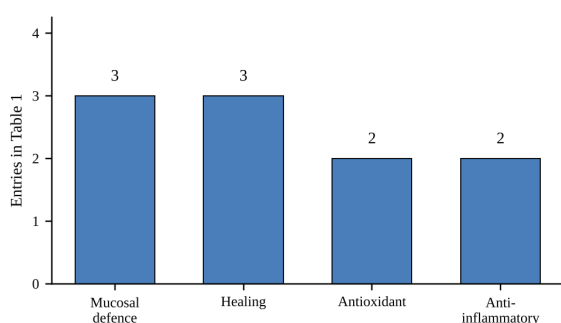


Fig. 1: Number of entries in table 1 by type of finding

From a methodological perspective, many ulcer studies have weaknesses that are common across preclinical pharmacology. Allocation to groups is often not described as randomised, assessors are not always blinded to treatment, and group sizes are chosen without a stated power calculation. Systematic reviews of guidelines for animal experiments have catalogued the threats to validity that should be flagged, and reporting guidelines now ask for the details needed to judge each one [32, 33, 34]. Applying those standards to the indomethacin literature would likely downgrade the certainty of some positive findings. Several of these gaps are easy to fix, and journals could help by requiring an explicit statement on randomisation, blinding and sample size for every animal study they publish. Sensible sample sizes and pre-specified primary endpoints are further features of a convincing study in this area [33].

5. MODEL DESIGN AND INTERPRETATION

The typical indomethacin model uses adult rats, deprived of food for around a day with free access to water to empty the stomach, and given a single dose of indomethacin by oral gavage or subcutaneous injection, often

in the region of 20 to 50 mg/kg. The animals are killed some hours later, the stomachs are opened along the greater curvature, and lesions are scored. Tests of a protective agent normally administer it for one or more days before indomethacin. Housing and procedures should follow recognised guidance on laboratory animal care [35]. Lesion scoring after sacrifice is then carried out under a dissecting microscope or with calibrated images.

Lesion scoring is the weakest step. Common methods include summing the length of haemorrhagic bands in millimetres, counting lesions, or applying an ordinal ulcer index. Each is subjective, and the scorers' choices affect the result. Blinded scoring and image analysis help, and histology adds information about depth of injury, mucus layer thickness and inflammatory infiltrate. Biochemical readouts, including malondialdehyde as a marker of lipid peroxidation, reduced glutathione, myeloperoxidase for neutrophil infiltration and prostaglandin E_2 content, tell the reader which mechanism was engaged, and several of these were used in the antioxidant studies described above [9, 10, 21]. Stating how scoring was done, and by whom, adds little effort and adds a great deal to credibility [32].

Statistical treatment deserves the same attention. Ulcer indices on an ordinal scale call for non-parametric tests, whereas lesion lengths and biochemical readouts may suit analysis of variance after checking the distribution. Multiple dose groups require correction for multiple comparisons, and reporting exact values with measures of spread is more useful than a bare statement of significance. Small groups of five or six animals, common in this literature, give little protection against chance findings, and a power calculation based on the expected effect size would make results far easier to trust [32, 33]. Many papers also fail to say how many animals were excluded and why, even though exclusions can quietly shift the result in either direction [34].

A prostaglandin measurement matters here. If zinc carnosine acted by restoring prostaglandin synthesis, mucosal prostaglandin content would rise; if it acted

downstream, prostaglandin levels would stay low despite protection. Indomethacin by design suppresses prostaglandins, so a protective effect that persists in this setting points to a mechanism independent of the cyclooxygenase pathway, which fits the antioxidant and heat shock protein hypotheses [10, 20]. Reports that include such measurements are the most informative for mechanism, whereas those that report only ulcer scores cannot discriminate between possibilities. Mucosal blood flow and mucus content can be measured as well, giving a more complete mechanistic picture at modest additional cost [7, 8]. In the same spirit, intermediate readouts must be matched to the question being asked, and a mechanistic claim without the relevant measurement is a hypothesis rather than a result.

Dose selection and vehicle are further details that deserve attention. Zinc carnosine is poorly soluble and is generally given as a suspension, for instance in carboxymethylcellulose, and the particle size and suspension stability may affect the contact time with the mucosa [3]. Dose-response designs with at least three dose levels, a vehicle control, a positive control and a drug-only control are the minimum needed to interpret protection with confidence. Extrapolating the rat dose to humans through body surface area gives a rough check on whether the tested exposure lies near what is used clinically [27]. Reporting the batch and purity of the compound, and the exact preparation of the vehicle, helps other groups reproduce the work [34]. Studies of the intact chelate, compared with zinc sulphate and carnosine given alone at equivalent doses, are the cleanest way to show that the complex is the active entity [3, 4].

Sex, strain and diet influence the outcome. Male rats are used most often, which limits what can be said about females, and different strains vary in sensitivity to indomethacin. The zinc content of the diet is rarely reported, even though the baseline zinc status of the animals may alter the response to a zinc compound [22, 25]. Zinc-replete animals would be expected to show a smaller benefit than animals on marginal intake. Stating diet

composition and, ideally, plasma zinc is therefore a low-cost way to make results more interpretable and reproducible across laboratories [32, 33]. Because zinc status is rarely measured, the apparent variability between laboratories may be partly nutritional in origin.

Finally, the translational relevance of a single high-dose challenge deserves comment. Human NSAID injury develops over weeks of exposure at therapeutic doses, often in older people with comorbidity and *Helicobacter pylori* infection, whereas the rat model delivers an acute chemical challenge to a healthy young stomach [6, 14]. The model is a good screen for mechanisms of mucosal protection, but it is a weak predictor of clinical benefit. Studies with repeated lower dosing, chronic ulcer models, and combined risk factors would bring the laboratory closer to the clinic [5, 18]. Even so, the combination of antioxidant and reparative effects reported for zinc carnosine suggests that it would be worth testing in such more demanding models. It is also worth separating the question of gastric protection from that of small intestinal protection, since the two sites respond differently to the same drugs [12, 26].

6. LIMITATIONS AND FUTURE DIRECTIONS

The strongest limitation is the gap between mechanism and outcome. Zinc carnosine has a plausible and well-described set of actions, and several experimental models show protection or accelerated healing, but direct controlled evidence in humans taking indomethacin or other NSAIDs is minimal [6, 26]. Many animal studies are small, and publication bias towards positive results is likely in a field where negative experiments are seldom written up. The literature should therefore be read as supportive and hypothesis-generating rather than conclusive [32, 33]. Heterogeneity of dose, schedule and endpoint also prevents a meaningful pooled estimate, and no formal meta-analysis of zinc carnosine in NSAID injury seems to exist.

Several research priorities follow. Head-to-head experiments against a proton pump inhibitor and a prostaglandin analogue,

and in combination with them, would show where zinc carnosine fits. Chronic or repeated-dose NSAID models, with histology and markers of oxidative stress, would be more relevant than single-dose challenge. Pharmacokinetic work on local mucosal zinc delivery could clarify whether the adherence of the chelate to damaged tissue is as important as it seems [3]. Transparent reporting, with a clearly described design and analysis, would help all of these studies to be compared [34]. Studies in older animals, in animals with comorbid conditions and in both sexes would improve relevance. Dose-ranging studies in the chronic models, with pharmacokinetic sampling of mucosal zinc, would link exposure to effect in a way that current work does not [27].

In clinical research, trials in patients who must continue NSAIDs, with endoscopic ulcer rates as the primary endpoint, are the obvious next step, with attention to the lower gut as well as the stomach, since the permeability data suggest possible small bowel effects [15, 26]. Safety monitoring should include serum zinc and copper, because prolonged high zinc intake can cause copper deficiency, a risk that is well known from zinc supplementation generally [36]. Until such data appear, zinc carnosine should be regarded as an adjunct of promising but unproven value. Patient-reported outcomes such as dyspepsia scores could be collected alongside endoscopy, since symptoms are what lead patients to stop treatment.

One more consideration is the broader pattern of drug development. A compound approved in one country on the basis of local trials often has a long tail of experimental literature that was never designed to meet current regulatory expectations. Reviewing that literature critically, and repeating key experiments under modern reporting rules, is a cheaper way to settle uncertain questions than starting afresh with a new molecule [32, 34]. Regulators and journal editors both have a part to play in encouraging this kind of re-examination, which is rarely glamorous but often decisive. Where the original data survive, re-analysis with modern statistics could also be informative.

7. CONCLUSION

The published work gives a consistent, if incomplete, picture of zinc carnosine as a gastroprotective compound. Indomethacin injures the stomach by removing prostaglandin-dependent defence and by provoking oxidative and neutrophil-driven damage, and zinc carnosine acts at several of the downstream points: it scavenges radicals, limits lipid peroxidation and inflammatory cell accumulation, induces heat shock protein 70 and supports epithelial repair [3, 4, 9, 10, 20, 21]. Its adherence to damaged mucosa gives it a degree of local targeting that distinguishes it from conventional zinc salts. Taken as a whole, the evidence supports a mechanistic rationale more strongly than it supports a clinical claim. Given the clinical role the compound already holds in some countries, this evidence base deserves the same scrutiny that newer agents receive.

What is lacking is high-quality evidence that these effects translate into fewer ulcers in people who take NSAIDs. Animal studies rarely describe randomisation or blinding, doses and designs vary widely, and the strongest human data concern intestinal permeability [26, 32, 33]. Zinc carnosine is best seen as a promising mucosal protective adjunct, not a replacement for acid suppression or prostaglandin replacement, until head-to-head and clinical outcome studies are available [6, 28, 29]. Better-designed animal studies and, above all, a controlled trial in NSAID users with endoscopic endpoints would settle most of the open questions. Researchers designing future experiments should report the compound, vehicle, dose schedule and scoring method in enough detail for others to repeat them.

8. ABBREVIATIONS

COX-Cyclooxygenase, HSP70-72 kDa heat shock protein, MDA-Malondialdehyde, NSAID-Non-steroidal anti-inflammatory drug, PGE₂-Prostaglandin E₂, TNF-Tumour necrosis factor, ARRIVE-Animal Research: Reporting of In Vivo Experiments, PPI-Proton pump inhibitor

9. FUNDING

Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

1. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;340:1888–99.
2. Wallace JL. Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. *Gastroenterology* 1997;112:1000–16.
3. Matsukura T, Tanaka H. Applicability of zinc complex of L-carnosine for medical use. *Biochemistry (Mosc)* 2000;65:817–23.
4. Yoshikawa T, Naito Y, Tanigawa T, Yoneta T, Kondo M. The antioxidant properties of a novel zinc-carnosine chelate compound, N-(3-aminopropionyl)-L-histidinato zinc. *Biochim Biophys Acta* 1991;1115:15–22.
5. Okabe S, Amagase K. An overview of acetic acid ulcer models: the history and state of the art of peptic ulcer research. *Biol Pharm Bull* 2005;28:1321–41.
6. Lanás A, Chan FKL. Peptic ulcer disease. *Lancet* 2017;390:613–24.
7. Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? *Physiol Rev* 2008;88:1547–65.
8. Robert A, Nezamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats: prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl, and thermal injury. *Gastroenterology* 1979;77:433–43.
9. Takeuchi K, Ueshima K, Hironaka Y, Fujioka Y, Matsumoto J, Okabe S. Oxygen free radicals and lipid peroxidation in the pathogenesis of gastric mucosal lesions induced by indomethacin in rats. *Digestion* 1991;49:175–84.
10. Yoshikawa T, Naito Y, Kishi A, Tomii T, Kaneko T, Iinuma S, *et al.* Role of active oxygen, lipid peroxidation, and antioxidants in the pathogenesis of gastric mucosal injury induced by indomethacin in rats. *Gut* 1993;34:732–7.
11. Tanaka A, Hase S, Miyazawa T, Takeuchi K. Up-regulation of cyclooxygenase-2 by inhibition of cyclooxygenase-1: a key to nonsteroidal anti-inflammatory drug-induced intestinal damage. *J Pharmacol Exp Ther* 2002;300:754–61.
12. Bjarnason I, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. *Gastroenterology* 1993;104:1832–47.
13. Suleyman H, Albayrak A, Bilici M, Cadirci E, Halici Z. Different mechanisms in formation and prevention of indomethacin-induced gastric ulcers. *Inflammation* 2010;33:224–34.
14. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009;104:728–38.
15. Sostres C, Gargallo CJ, Lanás A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther* 2013;15(Suppl 3):S3.
16. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study. *JAMA* 2000;284:1247–55.
17. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520–8.
18. Takagi K, Okabe S, Saziki R. A new method for the production of chronic gastric ulcer in rats and the effect of several drugs on its healing. *Jpn J Pharmacol* 1969;19:418–26.
19. Boldyrev AA, Aldini G, Derave W. Physiology and pathophysiology of carnosine. *Physiol Rev* 2013;93:1803–45.
20. Odashima M, Otaka M, Jin M, Wada I, Horikawa Y, Matsushashi T, *et al.* Induction of a 72-kDa heat-shock protein in cultured rat gastric mucosal cells and rat gastric mucosa by zinc L-carnosine. *Dig Dis Sci* 2002;47:2799–804.
21. Naito Y, Yoshikawa T, Yagi N, Matsuyama K, Yoshida N, Seto K, *et al.* Effects of polaprezinc on lipid peroxidation, neutrophil accumulation, and TNF-alpha expression in rats with aspirin-induced gastric mucosal injury. *Dig Dis Sci* 2001;46:845–51.
22. Prasad AS. Zinc in human health: effect of zinc on immune cells. *Mol Med* 2008;14:353–7.

23. Rink L, Haase H. Zinc homeostasis and immunity. *Trends Immunol* 2007;28:1–4.
24. Lansdown AB, Mirastschijski U, Stubbs N, Scanlon E, Ågren MS. Zinc in wound healing: theoretical, experimental, and clinical aspects. *Wound Repair Regen* 2007;15:2–16.
25. Watanabe T, Arakawa T, Fukuda T, Higuchi K, Kobayashi K. Zinc deficiency delays gastric ulcer healing in rats. *Dig Dis Sci* 1995;40:1340–4.
26. Mahmood A, FitzGerald AJ, Marchbank T, Ntatsaki E, Murray D, Ghosh S, *et al.* Zinc carnosine, a health food supplement that stabilises small bowel integrity and stimulates gut repair processes. *Gut* 2007;56:168–75.
27. Boxenbaum H. Interspecies scaling, allometry, physiological time, and the ground plan of pharmacokinetics. *J Pharmacokinet Biopharm* 1982;10:201–27.
28. Scheiman JM, Yeomans ND, Talley NJ, Vakil N, Chan FK, Tulassay Z, *et al.* Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. *Am J Gastroenterol* 2006;101:701–10.
29. Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, *et al.* Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev* 2002;(4):CD002296.
30. Tarnawski AS. Cellular and molecular mechanisms of gastrointestinal ulcer healing. *Dig Dis Sci* 2005;50(Suppl 1):S24–33.
31. Tarnawski AS, Ahluwalia A. Molecular mechanisms of epithelial regeneration and neovascularization during healing of gastric and esophageal ulcers. *Curr Med Chem* 2012;19:16–27.
32. Henderson VC, Kimmelman J, Fergusson D, Grimshaw JM, Hackam DG. Threats to validity in the design and conduct of preclinical efficacy studies: a systematic review of guidelines for in vivo animal experiments. *PLoS Med* 2013;10:e1001489.
33. Sena E, van der Worp HB, Howells D, Macleod M. How can we improve the pre-clinical development of drugs for stroke? *Trends Neurosci* 2007;30:433–9.
34. Vesterinen HM, Sena ES, Egan KJ, Hirst TC, Churolov L, Currie GL, *et al.* Meta-analysis of data from animal studies: a practical guide. *J Neurosci Methods* 2014;221:92–102.
35. European Parliament and Council of the European Union. Directive 2010/63/EU on the protection of animals used for scientific purposes. *Off J Eur Union* 2010;L276:33–79.
36. Fosmire GJ. Zinc toxicity. *Am J Clin Nutr* 1990;51:225–7.