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Tumor Necrosis Factor-Alpha in NSAID-Induced Gastropathy and the Immunomodulatory Potential of Propolis: A Literature Review

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) remain widely used analgesic and anti-inflammatory agents, yet their gastric toxicity is a persistent clinical problem. Cyclooxygenase (COX) inhibition and prostaglandin depletion explain only part of NSAID-induced gastropathy. Epithelial injury, oxidative stress, and altered mucosal permeability release damage-associated molecular patterns that engage pattern recognition receptors, activate NF-κB and MAPK signaling, and drive pro-inflammatory cytokine production. Tumor necrosis factor-alpha (TNF-α) is a central cytokine in this response. It is produced by macrophages, T-cells, and, under inflammatory conditions, epithelial cells, and it signals through TNFR1 and TNFR2 to promote inflammation, apoptosis, or survival depending on the signaling complexes formed. This review summarizes the immunological mechanisms linking NSAID exposure to TNF-α expression and examines propolis, including nano-formulated propolis, as a candidate immunomodulatory agent. Experimental and in vitro studies suggest that propolis constituents, particularly flavonoids, suppress pro-inflammatory cytokines in activated macrophages and modulate NF-κB and Nrf2 pathways, and a systematic review reports gastroprotective effects in NSAID-induced gastric injury. Nano-formulation may improve solubility and bioavailability. However, evidence that propolis lowers TNF-α specifically in NSAID gastropathy is limited; much of the mechanistic reasoning is inferred, and propolis composition varies with origin. Controlled in vivo studies using standardized preparations, with TNF-α measured alongside histopathology, are needed.

Keywords: healthy lifestyle; NSAID-induced gastropathy; TNF-α; nano propolis; aspirin

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used agents for pain and inflammation, but their use carries a recognized risk of injury to the gastrointestinal tract [1]. Gastritis is defined as an abnormal change in the gastric mucosa resulting from infection or an immunologically mediated inflammatory reaction, and NSAIDs are one of its most frequent causes [2]. In the literature, NSAID-related damage is described as NSAID-induced gastritis [3]. Gastroprotection with proton pump inhibitors is widely practiced, yet its co-prescription involves a balance of risks and benefits [4]. These considerations sustain interest in complementary strategies that address the biology of mucosal injury.

The classical explanation of NSAID gastropathy centers on inhibition of cyclooxygenase (COX) enzymes and the resulting loss of mucosal prostaglandins. However, mucosal injury is not explained by prostaglandin depletion alone [5]. Epithelial cells damaged by NSAIDs release danger signals that are recognized by innate immune receptors, and the downstream cytokine response is now regarded as an integral part of the lesion [6]. Among the cytokines produced, tumor necrosis factor-alpha (TNF-α) is a prominent candidate biomarker and mediator of NSAID-induced gastric damage [3]. However, TNF-α is a pleiotropic molecule whose effects depend on the receptor engaged and the intracellular complexes formed [7], so understanding its regulation requires an immunological rather than a purely pharmacological perspective.

Propolis, a resinous product made by bees, has attracted attention as a source of anti-inflammatory and antioxidant compounds [8,9], and nano-formulated versions are being explored to overcome

limited solubility and bioavailability [10]. Whether propolis can modulate the TNF-α axis in NSAID-induced gastric injury is still a question of biological plausibility more than of proven effect.

This review synthesizes the immunological mechanisms that link NSAID-induced mucosal injury to TNF-α expression and appraises the evidence for propolis, including nano propolis, as an immunomodulatory approach. It proceeds from the initiating events in the gastric mucosa, through innate and adaptive immune activation, and the regulation of TNF-α to the properties of propolis and its reported effects on inflammatory pathways. The literature was selected for topical relevance without systematic screening, and the implications of this are considered in the limitations.

INITIATING EVENTS IN NSAID-INDUCED GASTROPATHY

Overview

Gastric mucosal homeostasis can be disrupted by several factors, and the resulting imbalance underlies gastritis [11]. NSAID-related injury is generally attributed to two overlapping processes: a topical, cytotoxic effect on epithelial cells that involves apoptotic biomarkers, and a systemic effect arising from COX inhibition [3]. Non-selective COX inhibitors are particularly prone to damage the gastrointestinal tract, because contact irritation by the carboxylic acid group adds to prostaglandin depletion [12]. NSAIDs increase intestinal permeability, and inhibition of both COX-1 and COX-2 aggravates the resulting damage [5].

COX-Dependent Mechanisms

COX-1 supplies prostaglandins constitutively and maintains homeostasis, whereas COX-2-derived prostaglandins, mainly prostaglandin E2 (PGE2), appear during inflammation [13]. Prostaglandins protect the mucosa by increasing mucus and bicarbonate secretion and blood flow, and by inhibiting acid secretion [5]. NSAIDs such as indomethacin and diclofenac reduce prostaglandin synthesis through COX-dependent routes [13].

Blocking COX also changes the fate of arachidonic acid. After phospholipase A2 liberates arachidonic acid, it can be converted through either the COX or the lipoxygenase (LOX) pathway [14]. Inhibition of COX can activate the 5-LOX route and increase leukotriene production, which helps to maintain inflammation [14]. Aspirin, however, irreversibly acetylates COX-1 and inhibits its cyclooxygenase activity [15], which may contribute to decreased mucosal protection.

COX-Independent Mechanisms

Mucosal damage is not due solely to reduced prostaglandin synthesis [5]. NSAIDs cause oxidative stress and mitochondrial damage, including increased production of reactive oxygen species (ROS) [16]. NSAIDs also disturb the tight junctions that connect epithelial cells, thus increasing mucosal permeability [17]. Through such COX-independent routes, including ROS, NSAIDs can injure the mucosa [5].

FROM EPITHELIAL INJURY TO INNATE IMMUNE ACTIVATION

Damaged epithelial cells, especially those undergoing necrosis, release damage-associated molecular patterns (DAMPs) [6]. DAMPs are recognized by pattern recognition receptors (PRRs) on innate immune cells, of which the Toll-like receptors (TLRs) are among the best characterized [6]. TLR activation recruits adaptor signaling that activates the NF-κB and mitogen-activated protein kinase (MAPK) pathways and induces the main pro-inflammatory cytokines, namely TNF-α, IL-1β, and IL-6 [18]. In this way, cell injury initiated by NSAIDs is converted into an immune signal, and TNF-α amplifies the injury by recruiting neutrophils and macrophages to the gastric mucosa [3].

The gastric mucosa differs from other mucosal sites in its immune architecture. The gastric mucosa is generally considered to lack organized mucosa-associated lymphoid tissue (MALT) under normal conditions, although its defense relies on innate and adaptive components, including T-cells [19]. Disturbed gastric immune homeostasis contributes to mucosal disease [11], and damaged epithelium is characterized by excessive production of pro-inflammatory cytokines [11].

TNF-α: CELLULAR SOURCES, FORMS AND RECEPTORS

Cytokines are small proteins that take part in cell signaling and modulate the immune system by inhibiting or amplifying cellular responses [20]. TNF-α is a pro-inflammatory cytokine produced by both innate and adaptive immune cells [20]. It is made mainly by macrophages and T-cells, but epithelial cells can also express it under inflammatory conditions [21]. It exists in a soluble form (sTNF-α) and a transmembrane form (tmTNF-α) [22]. Both forms can bind TNFR1 and TNFR2 [23], although the transmembrane form tends to act through TNFR2 [22].

The two receptors differ in expression and in the pathways they activate. TNFR1 is expressed on nearly all cell types, whereas TNFR2 is inducible on endothelial and immune cells [24]. TNFR1 tends to initiate pro-inflammatory responses and apoptosis, and it can activate death receptor signaling [24]. TNFR2 lacks a death domain, so its signaling cascade is directed more towards cell proliferation and survival [24,25]. It is also inferred that TNFR2 is involved in the function of regulatory T-cells [25]. TNFR2 signaling in T-cells has also been shown to be crucial for TNF-driven inflammation in vivo [26]. TNF-α therefore acts both as an initiator and as an effector of inflammation [26], which is why it is regarded as a potential inflammatory biomarker [27].

REGULATION OF TNF-α EXPRESSION IN NSAID-INDUCED GASTRIC INJURY

Oxidative Stress and NF-κB Activation

ROS are reactive molecules, such as superoxide anion, hydrogen peroxide, and the hydroxyl radical,

that can damage cellular macromolecules [28]. When ROS production is not balanced by antioxidants, oxidative stress occurs [28]. NSAIDs can trigger cytotoxic effects by damaging mitochondria and inducing mitochondrial oxidative stress [16]. Released ROS can in turn activate NF-κB signal transduction, which allows NF-κB to enter the nucleus and transcribe pro-inflammatory cytokine genes, including IL-8, IL-1, and TNF-α [29]. NF-κB is a key regulator of cytokine expression during inflammation [29], so oxidative injury and TLR signaling converge on this transcription factor.

Downstream Signaling and Cell Fate

TNF-α is a pleiotropic cytokine and acts through several pathways, including NF-κB, MAPK, and caspases [30]. Binding of TNF-α to TNFR1 activates NF-κB, which can induce transcription of either apoptotic or anti-apoptotic genes, and TNF-α stimulation can lead to apoptosis and necroptosis through the formation of signaling complexes I and II [31]. The direction of the NF-κB response is determined by the complexes formed downstream of TNFR. When signaling is dominated by IKK activation and transcription of cIAP genes leading to TAK1 activation, NF-κB is protective, whereas a bias towards TRADD and caspases allows NF-κB to facilitate expression of pro-apoptotic genes [32].

T-Cell Involvement and Self-Amplification

TNF-α enhances the activation of $CD4^+$and $CD8^+$ T-cells, and it also increases the expression of IL-2 receptors [33].

TNF-α is produced largely by T-cells and innate immune cells, and it drives both inflammatory Th1 and Th17 differentiation [26]. NF-κB also regulates inflammatory T-cells [29]. Because the normal gastric mucosa lacks organized lymphoid tissue, the contribution of T-cells depends on their infiltration during inflammation, and one example of this is the α4β7-integrin-dependent homing of $CD4^+$ T-cells, which has been proposed as one of the pathways T-cells use to reach the stomach and increase pro-inflammatory cytokine expression [11]. Finally, TNF itself can regulate its own expression through upregulation [34], which provides a positive feedback loop that can sustain inflammation after the initiating stimulus has passed.

TNF-α AS AN INFLAMMATORY MARKER

TNF-α is a cytokine produced by activated macrophages and is considered a marker for the degree of gastric mucosal damage [35]. TNF has also been proposed as a promising therapeutic target in NSAID enteropathy [34]. NSAIDs differ in toxicity, so that the degree of gastric damage varies with the agent and the dose chosen [36].

Aspirin is one of the many drugs that are used to induce gastric lesions in rats [37]. Table 1 summarises three rat studies from the literature. The regimens differ markedly in dose and duration, and only one of them reported cytokine endpoints. In one rat study, aspirin-induced gastric damage coincided with raised TNF-α, IL-6, and IL-1β [38].

TABLE 1: Representative aspirin-induced gastritis models in rats.

Study	Model and Regimen	Reported Findings
Sari et al. [39]	27 male rats (*Rattus norvegicus*); aspirin 600 mg/kg body weight for 9 days	Increased inflammatory cell infiltration above the basement membrane of the gastric mucosa (microscopic examination)
Ahmed et al. [38]	24 male rats (*Rattus norvegicus*); aspirin 200 mg/kg body weight for 4 days	Hemorrhage, edema, epithelial degeneration, necrosis, and inflammatory cell infiltration (microscopic examination); elevated TNF-α, IL-6, and IL-1β after aspirin administration
Silitonga et al. [40]	35 male rats (*Rattus norvegicus*); aspirin 200 mg/kg body weight for 3 days	Atrophy of acinar glands in the gastric mucosa (microscopic examination)

PROPOLIS: NANO-FORMULATION, COMPOSITION, AND SAFETY CONSIDERATIONS

Propolis is a natural resin produced by bees of the family Apidae [9]. It contains polyphenols and other bioactive components, but its composition varies with the time of extraction and the geographical origin [41]. Cycloartane-type triterpenes such as cycloartenol, ambonic acid, mangiferonic acid, and ambolic acid were first reported in propolis from Indonesia, produced by both Apidae and Meliponini bees [42]. Stingless bees of the genus *Tetragonula* produce propolis in large amounts, and *Tetragonula sapiens* is one of the productive species in Indonesia [42,43]. Propolis has been proposed as a promising material for pharmaceutical use [9]. Its flavonoids have also shown a considerable amount of antioxidant activity [8].

Nanotechnology deals with materials at the scale of 1–100 nm [44], which is relevant to drug absorption in the gastrointestinal environment. Luminal factors, such as pH, affect drug solubility, and poor solubility can limit absorption from the gut and thereby reduce bioavailability [45]. Nano propolis is propolis whose particle size has been reduced to improve solubility and biological performance, including controlled release of active compounds [10]. As for dosing, nano propolis from East Java administered at 200 mg/kg body weight was reported to significantly reduce interstitial fibrosis compared with the control group in a rat model of adenine-induced chronic kidney disease, whereas the 100 mg/kg group did not differ significantly from control [46]. These data come from different organ and disease models and cannot be transferred directly to gastric injury.

IMMUNOMODULATORY ACTIONS OF PROPOLIS RELEVANT TO THE TNF-α AXIS

Through immunomodulatory mechanisms, propolis constituents have been reported to inhibit or reduce the activity of pro-inflammatory cytokines, such as IL-1β, IL-6, IFN-γ, and TNF-α [47]. In activated macrophages, temperate propolis suppressed pro-inflammatory output and was a potent inhibitor of nitric oxide formation [48]. Propolis from the Indonesian stingless bee *T. sapiens* showed anti-inflammatory potential in RAW 264.7 macrophage cells [43]. At the signaling level, flavonoids from propolis have been linked to activation of the Nrf2 pathway and inhibition of the NF-κB pathway [49], which would be expected to dampen ROS-driven NF-κB activation and the transcription of TNF-α described above. Caffeic acid phenethyl ester (CAPE) has also been highlighted as an active component with pleiotropic activities [50].

In the gastric setting, a systematic review concluded that propolis has gastroprotective effects in NSAID-induced gastric ulcer, attributed in part to suppression of acid production and of pro-inflammatory cytokines [51]. Effects on inflammation and oxidative stress markers have also been examined in a GRADE-assessed meta-analysis of clinical trials [52].

CONCLUSION

NSAID-induced gastropathy goes beyond prostaglandin depletion. It involves an immune cascade in which epithelial injury, DAMP release, TLR signaling, oxidative stress, and NF-κB activation converge on TNF-α, which is amplified by T-cells and by its own positive feedback, and signals through TNFR1 and TNFR2 with divergent consequences for cell fate. Propolis, and potentially its nano-formulations, is a plausible immunomodulatory candidate because its constituents act on several nodes of this pathway, but direct evidence in NSAID gastropathy is limited. Standardized, well-characterized preparations tested in controlled studies that combine TNF-α measurement with histopathology and pathway markers are needed before conclusions about efficacy can be drawn. As this review was not systematic, selection bias is possible, and several mechanistic links are inferred from cell-based or non-gastric models.

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