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BIOMARKERS FOR EVALUATING GASTROPROTECTIVE ACTIVITY IN EXPERIMENTAL PEPTIC ULCER MODELS: CURRENT STATUS, CHALLENGES, AND FUTURE PERSPECTIVES

***Kunika, Amanpreet Kaur, Naresh Singh Gill**

Department of Pharmacology, Lamrin Tech Skills University, Rail Majra, SBS Nagar, Punjab, India.

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***Corresponding Author: Kunika**

Department of Pharmacology, Lamrin Tech Skills University, Rail Majra, SBS Nagar, Punjab, India.

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ABSTRACT
Although there have been advances in acid-suppressive medications and eradication of Helicobacter pylori (H. pylori), peptic ulcer disease (PUD), is still a major gastrointestinal disorder worldwide. This polyetiology, including its oxidative stress, inflammatory, mucosal defence and apoptotic and delayed tissue repair mechanisms, has motivated the search for new gastroprotective agents, including those derived from natural sources. Experimental animal models are critical in testing these agents; selection of a biomarker is of paramount importance for a good assessment of gastroprotection. Along with the traditional macroscopic and gastric secretory parameters, recent studies have increasingly used oxidative stress, inflammatory and cytoprotective biomarkers as well as molecular ones to explain the mechanism of gastric mucosal damage and defence. The present review gives a summary of the status of the use of biomarkers in experimental peptic ulcer models, their biological significance, analytical method, advantages and limitations. It also covers new biomarkers discovered via transcriptomics, proteomics, metabolomics and digital pathology, as well as standardization and reproducibility and clinical translation. Finally, future perspectives emphasizing integrated biomarker panels and advanced analytical technologies are presented. In this review, a brief overview is given on the selection and interpretation of biomarkers for experimental studies of gastro-protection and their usefulness to the development of better anti-ulcer drugs.

KEYWORDS: Peptic ulcer disease; Biomarkers; Gastroprotection; Oxidative stress; Inflammation; Histopathology; Experimental animal models; Molecular biomarkers; Natural products; Ethanol-induced gastric ulcer.

INTRODUCTION

Peptic ulcer disease (PUD) is a widespread gastrointestinal disorder in which there are well demarcated lesions in the gastrointestinal mucosa involving the muscularis mucosae.[1] Although there have been considerable efforts towards the eradication of H. pylori and the use of acid-suppressive drugs, PUD remains one of the most important causes of morbidity in the world because of the increasing use of nonsteroidal anti-inflammatory drugs (NSAIDs), aging populations, and recurrent complications including gastrointestinal bleeding and perforation.[2]

H. pylori eradication therapy with antibiotics, antacids, mucosal protection agents, histamine H_2-receptor antagonists, and proton pump inhibitors are the main

treatment modalities used. These interventions have markedly enhanced ulcer healing but worries about their long-term side effects, interaction with other drugs, recurrence, and antimicrobial resistance have prompted the search for safer and more efficient gastroprotective drugs.[3] As a result, various studies have been conducted on natural products and synthetic drugs that could control multiple pathogenic mechanisms related to gastric mucosal injury (oxidative stress, inflammation, apoptosis, and tissue repair).[4]

Although, experimental animal models are still essential for elucidating the pathogenesis of ulcer and for testing the gastroprotective activity of novel therapeutic agents prior to their use in clinical practice. Ethanol induced gastric ulcer is one of the most commonly used models due to its ability to rapidly induce reproducible gastric lesions by inducing oxidative stress, inflammatory responses, vascular injury, and disruption of gastric mucosal barrier.[5] A variety of other models are also used, such as NSAID-induced, pylorus ligation, stress-induced, and acetic acid-induced ulcers, which each induce different phases of ulcer disease, and serve as useful platforms for drug development studies.[6]

Macroscopic parameters like ulcer index, lesion area, gastric juice volume, pH and total acidity have been traditionally used to evaluate the efficacy of gastroprotective agents. These parameters are still important for the assessment of the severity of the ulcer but do not give much information about the molecular mechanisms involved in the gastric injury and healing.[7] The evidence is mounting that the onset of ulceration is a multifactorial process marked by overproduction of reactive oxygen species, activation of inflammatory mediators, inflammatory epithelial apoptosis, inadequate angiogenesis, and disruption of cellular defense pathways. Accordingly, the use of biochemical, histopathological, immunohistochemical and molecular biomarkers has become more significant to accurately characterize the pharmacological effects of candidate gastroprotective agents.[8]

There have been recent advances in the study of biomarkers, which now make it possible to expand the spectrum of ulcer experimental evaluation beyond the routine biochemical assays.[9] The use of biomarkers associated with oxidative stress (such as malondialdehyde, reduced glutathione, superoxide dismutase and catalase), inflammation (tumor necrosis factor-α, interleukins, myeloperoxidase and nuclear factor-κB), cytoprotection (prostaglandin E_2 and gastric mucin), and molecular signaling pathways (such as Nrf2/HO-1, PI3K/Akt, MAPK, and Bax/Bcl-2), provides valuable mechanistic information on disease progression and therapeutic efficacy.[10] A significant number of experimental studies, however, varied in terms of the biomarkers they used, the methods of analysis, and reporting of results, leading to low reproducibility and a lack of comparability.[11]

Hence, the present review critically talks about the traditional, biochemical, histopathological and molecular markers employed for the assessment of gastroprotective activity in experimental peptic ulcer models.[12] The review not only summarizes the biological implication and analytical use but also underlines the advantages and drawbacks of these biomarkers as well as their translational potential, and outlines the new biomarker technologies available that could enhance the standardization and quality of future gastroprotective studies.[13]

Biomarkers in gastroprotective research

Biomarkers are biological measures that are objectively measurable and reflect a normal physiological process, pathological process or response to a therapeutic intervention. The U.S. Food and Drug Administration (FDA) and National Institutes of Health (NIH) describe a biomarker as "a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, responses to an exposure or intervention, including therapeutic interventions.[14] Biomarkers are crucial tools for the assessment of the degree of gastric mucosal damage, the mechanism of formation of gastric ulcers and the efficacy of anti-ulcer potential drugs in gastroprotective research. Whereas gross morphological observations are descriptive, biomarkers will give quantitative and mechanistic information on disease progression and tissue repair.[15]

An optimal biomarker should be sensitive and specific, reproducible, and reflect changes in the gastric physiology at various stages of ulcer development and healing.[16] Additionally it must be readily measurable with standard laboratory assays, and be related to the severity of the gastric mucosal injury or effectiveness of the therapy. The choice of the marker to use depends on the type of ulcer model used since various ulcerogenic agents cause ulceration by different mechanisms. For example, ethanol-induced ulcers are more related to oxidative stress and inflammation, while NSAID-induced ulcers are more related to prostaglandin-synthesis inhibition and the disruption of mucosal defense.[17]

The experimental gastroprotection studies can be divided into macroscopic, gastric secretory, oxidative stress, inflammatory, cytoprotective, apoptotic, histopathological, and molecular biomarkers.[18] Macroscopic biomarkers include ulcer index and lesion area, which can be used to assess gastric damage, and biochemical biomarkers such as malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and myeloperoxidase (MPO), which are useful for assessing oxidative stress and inflammatory responses. Cytokines, apoptosis related proteins and signalling molecules also help convey the molecular mechanisms in gastroprotection.[19]

The most commonly reported parameter in experimental studies is ulcer index, but this offers little insight into the mode of action of gastroprotective agents. In recent years, therefore, there is a growing tendency to use a panel of complementary biomarkers instead of one single endpoint. Biochemical, molecular and histopathological biomarkers can be used together for a better understanding of the gastroprotective effect of the drugs, and help in revealing new therapeutic targets for peptic ulcer disease.[20]

Experimental Peptic Ulcer Models and Biomarker Selection

Experimental animals are of great importance for understanding the pathogenesis of peptic ulcer disease and testing the gastroprotective effects of new therapeutic agents.[21] The ulcerogenesis is a multifactorial process that is related to oxidative stress, inflammation, hypersecretion of gastric acid, impaired mucosal defense and apoptosis, none of these four conditions can be completely modeled in experimental models by a single model.[22] Thus, several ulcer induction models are utilized to mimic particular pathogenetic mechanisms and the choice of biomarkers is largely dependent on the experimental model used.

Ethanol induced gastric ulcer model is one of the most widely used model for studying cytoprotective and antioxidant activities.[23] Ethanol is known to cause rapid gastric mucosal barrier disruption by causing an overproduction of reactive oxygen species (ROS), lipid peroxidation, infiltration of inflammatory cells, and damage to the microvasculature. Thus, malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), myeloperoxidase (MPO), nitric oxide (NO) and pro-inflammatory cytokines are frequently measured in this model to assess the degree of oxidative damage and the effectiveness of gastroprotective measures.[24]

NSAID-induced ulcer models generally involve indomethacin or aspirin and are used as a model of ulcers due to inhibition of cyclooxygenase (COX) enzymes and decreased prostaglandin production. Commonly, in these models, markers of mucosal defense such as prostaglandin E_2 (PGE_2), cyclooxygenase-2 (COX-2), mucus content, inflammatory cytokines, and oxidative stress parameters are evaluated to better understand the protective mechanisms of therapeutic agents.[25]

Pylorus ligation is a classical model which is used to assess the gastric secretory function. This model is especially useful for studying antisecretory drugs because the gastric acid and pepsin that accumulate after pyloric obstruction.[26] Thus, gastric juice volume, gastric pH, free acidity, total acidity and pepsin activity are regarded as primary outcome measures and are frequently supported by the measurement of oxidative stress and histopathological analyses.

Chronic ulcer models, such as the acetic acid induced ulcer model, best mimic chronic gastric ulcers in humans, as they tend to induce deep mucosal damage and delay ulcer healing.[27] They are useful for exploring the healing of ulcers and regeneration of tissues. As a result, markers of angiogenesis and tissue healing such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), proliferating cell nuclear antigen (PCNA) and histopathological scoring are widely used.[28]

Other experimental models include cold-restraint stress, ischemia-reperfusion injury and Helicobacter pylori-associated ulcer models, which are mainly used to investigate stress-mediated injury, oxidative damage and infection related inflammatory pathways. Biomarker evaluation may comprise of oxidative stress markers, inflammatory cytokines, apoptosis-related proteins and molecular signaling pathways based on the mechanism.[29]

In general, the selection of the experimental model determines the selection of biomarkers. In order to fully assess gastroprotective activity, it is important to gain an understanding of the mechanisms involved in gastric mucosal injury, which involves macroscopic observations along with biochemical, molecular, and histopathological markers.[30]

Experimental Model	Mechanism of Injury	Commonly Evaluated Biomarkers
Ethanol-induced ulcer	Oxidative stress, mucosal necrosis, inflammation	MDA, GSH, SOD, CAT, MPO, NO, TNF-α, IL-1β
NSAID-induced ulcer	COX inhibition, prostaglandin depletion	PGE_2, COX-2, mucus content, TNF-α, IL-6, MDA
Pylorus ligation	Acid and pepsin hypersecretion	Gastric juice volume, pH, total acidity, free acidity, pepsin activity
Acetic acid-induced ulcer	Chronic ulceration and delayed healing	VEGF, TGF-β, EGF, PCNA, collagen deposition
Stress-induced ulcer	Ischemia, oxidative stress	Cortisol, MDA, SOD, CAT, GSH, MPO
H. pylori-associated ulcer	Infection and chronic inflammation	IL-8, TNF-α, IL-1β, COX-2, NF-κB

Biomarkers for Evaluating Gastroprotective Activity

The gastroprotective activity is determined by a set of macroscopic, biochemical, histopathological, and molecular biomarkers which give information on the severity of the gastro-mucosal injury and the mechanism of gastroprotection.[31] Macroscopic parameters are useful to provide the first assessment of the severity of the ulcer, while biochemical and molecular parameters provide insights into the underlying oxidative, inflammatory, and cytoprotective processes in ulcerogenesis and healing. Histopathological analysis also reveals tissue damage and regeneration at a microscopic level. Thus, combination of several types of biomarkers has emerged as the most accurate way to measure the effectiveness of gastroprotective drugs in animal research.[32]

Macroscopic Biomarkers

The most common biomarkers used for gastric mucosal damage are macroscopic ones, which can be used to evaluate the degree of gastric mucosal damage in the immediate aftermath of ulcer induction. They offer quick and direct assessment of the severity of gastric lesions and are routinely used as the initial phase of experimental gastroprotective studies.[33] These parameters do not offer any mechanism information but are still crucial in order to assess the overall protective efficacy of test compounds and can be used as the basis for further biochemical and histopathological studies.

The ulcer index (UI) is the most commonly used macroscopic biomarker in experimental ulcer research. It is an indicator of the severity and extent of gastric lesions, taking into account the number, size and depth of the ulcers in the gastric mucosa.[34] Decrease in ulcer index after treatment is regarded as one of the basic parameters of gastro protective activity. The ulcer index is used as the endpoint in experimental ulcer studies due to its simplicity and reproducibility in a range of experimental ulcer models such as ethanol, NSAID and pylorus ligation models.

The ulcer area, the total area of the gastric lesions, is another frequently reported parameter. It is usually measured by image analysis software or planimetric measurements and is a more objective measure of tissue damage than visual scoring.[35] Similarly, the lesion score or the gastric damage score is a measure of the severity of the abnormality of the mucosa, which is based on the use of a set of predefined grades depending on the characteristics of the lesion, including its degree of erythema, hemorrhage, edema, and necrosis.[36]

Another important parameter given is the percentage inhibition or percentage protection; it is calculated by comparing the ulcer index of different groups of treated animals with ulcer index of the disease control group. This gives an idea regarding the efficiency of the test compound to protect the gastric mucosal and helps to compare the gastroprotective efficiency of various drugs.

Although many are in use, macroscopic biomarkers have their drawbacks. Their main function is to indicate the morphology of the gastric damage, but they do not specify the biochemical or molecular mechanisms which might lead to the formation of ulcers or to their healing.[37] Therefore, in modern gastroprotective studies, it is recommended to use macro- and micro-biomarkers of oxidative stress, inflammation, cytoprotection and histopathological changes to get a comprehensive picture of therapeutic efficacy.

Biomarker	Role in ulcer pathogenesis	Expected change with gastroprotection	Common method of assessment
Prostaglandin E_2 (PGE_2)	Maintains mucosal defense by stimulating mucus and bicarbonate secretion and improving blood flow	↑ Increases	ELISA
Nitric Oxide (NO)	Preserves mucosal microcirculation and limits oxidative and inflammatory injury	↑ Increases	Griess assay
Gastric Mucus Content	Forms a protective barrier against gastric acid and pepsin	↑ Increases	Alcian blue binding assay
Mucin	Maintains mucus viscosity and strengthens the gastric mucosal barrier	↑ Increases	PAS/Alcian blue staining
Non-protein Sulfhydryl (NP-SH) Compounds	Protect gastric epithelial cells against oxidative damage and maintain mucosal integrity	↑ Increases	DTNB assay

Clinical relevance

The cytoprotective biomarkers are necessary to differentiate the agents which promote the gastric mucosal defenses from those which simply inhibit acid secretion.[38] PGE_2, nitric oxide (NO), gastectic mucus, mucin and non-protein sulfhydral (NP-SH) compounds assessment gives a good insight on the recovery of mucosal integrity, maintenance of gastric barrier function and promotion of ulcer healing. The evaluation of both is especially valuable for elucidating the cytoprotective mechanisms of natural products and other novel gastroprotective therapies.[39]

Gastric Secretory Biomarkers

Gastric secretory biomarkers are critical to the evaluation of the antisecretory and mucosal protective activity of

gastroprotective agents. The parameters are related to the changes in gastric acid secretion and digestive enzyme activity, which have a significant role in the development and progression of ulcers.[40] These are also important in pylorus ligation and NSAID induced ulcer models where there is an increase in acid secretion, a major pathogenic factor. The most frequently measured biomarkers are the volume of gastric juice, the pH, the concentrations of free acidity and total acidity, and the activity of pepsin.[41] An ideal gastroprotective drug will have the following properties:

Biomarker	Biological significance	Expected change with gastroprotection	Common method of assessment
Gastric juice volume	Indicates the amount of gastric secretion	↓ Decreases	Graduated cylinder measurement
Gastric pH	Reflects gastric acidity	↑ Increases	Digital pH meter
Free acidity	Measures free hydrochloric acid	↓ Decreases	Acid-base titration
Total acidity	Represents total acid output	↓ Decreases	Acid-base titration
Pepsin activity	Indicates proteolytic activity of gastric juice	↓ Decreases	Enzymatic assay

Clinical relevance

Gastric secretory biomarkers are relevant for evaluating the gastric acid homeostasis and the antisecretory effects of gastroprotective agents. Gastric juice volume, pH, free acidity, total acidity, and pepsin activity are valuable parameters that can give information on the gastric secretory function and complement biochemical biomarkers to clarify the mechanism of gastroprotection. Their combined evaluation can also be helpful in determining whether agents act primarily as acid-inhibitors or as antioxidant/cytoprotective agents.[42] The use of a biomarker approach has revolutionized experimental gastroprotective research by allowing mechanistic analysis of the gastric mucosal injury and repair process to be evaluated beyond the scope of the traditional macroscopic approach. The new combination of macroscopic, gastric secretory, oxidative stress, inflammatory, and cytoprotective biomarkers allows for a comprehensive evaluation of gastroprotective agents and a better understanding of their pharmacological actions and therapeutic potential. In contrast to a single endpoint, complementary panels of biomarkers give a more accurate diagnosis of the multifaceted pathological processes of peptic ulcer disease.[43]

Oxidative stress Biomarkers

One of the main mechanisms leading to gastric mucosal injury in experimental peptic ulcer models is oxidative stress, especially induced by ethanol, non-steroidal anti-inflammatory drugs (NSAIDs) and stress. An imbalance in the oxidant-antioxidant balance due to excessive production of reactive oxygen species (ROS) results in lipid peroxidation, protein oxidation, DNA damage and epithelial cell injury.[44] Biomarkers of oxidative stress are, therefore, often used for assessing antioxidant and gastroprotective properties of therapeutic agents. The reestablishment of the endogenous antioxidant defenses and decrease of the level of oxidative damage are regarded as a criterion for the efficiency of gastroprotection.

Biomarker	Role in ulcer pathogenesis	Expected change with gastroprotection	Common method of assessment
Malondialdehyde (MDA)	End product of lipid peroxidation; reflects oxidative membrane damage	↓ Decreases	TBARS assay/Spectrophotometry
Reduced Glutathione (GSH)	Major intracellular antioxidant that neutralizes ROS	↑ Increases	DTNB (Ellman's) assay
Superoxide Dismutase (SOD)	Converts superoxide radicals into hydrogen peroxide	↑ Increases	Enzyme activity assay
Catalase (CAT)	Detoxifies hydrogen peroxide and limits oxidative injury	↑ Increases	Spectrophotometric assay
Glutathione Peroxidase (GPx)	Reduces hydrogen peroxide and lipid hydroperoxides	↑ Increases	Enzyme activity assay
Reactive Oxygen Species (ROS)	Direct indicator of oxidative stress	↓ Decreases	DCFH-DA fluorescence assay

Clinical relevance

The oxidative stress biomarkers are among the most commonly evaluated endpoints in experimental gastroprotection studies as they directly reflect antioxidant-mediated mucosal protection. The overall evaluation of the MDA, GSH, SOD, CAT, GPx and ROS provides a broad picture of the oxidative situation in the stomach and aids in comparison of the effectiveness of gastroprotective agents in various experimental models of ulcer.[45,46]

Inflammatory Biomarkers

One of the major events in the process of the development of gastric mucosal injury after exposure to ulcerogenic agents is inflammation. Damage to the stomach causes the release of pro-inflammatory cytokines and recruitment of inflammatory cells, which increase tissue damage by oxidative stress and damage to the mucosal barrier. Hence, inflammatory markers are extensively used for the evaluation of the gastroprotective activity of agents. Generally, suppression of inflammatory mediators is correlated with decreasing mucosal damage and a quicker healing of the ulcer.[47]

Biomarker	Role in ulcer pathogenesis	Expected change with gastroprotection	Common method of assessment
Tumor Necrosis Factor-α (TNF-α)	Initiates and amplifies the inflammatory response, promoting mucosal injury	↓ Decreases	ELISA
Interleukin-1β (IL-1β)	Enhances leukocyte recruitment and gastric inflammation	↓ Decreases	ELISA
Interleukin-6 (IL-6)	Mediates acute inflammatory responses and tissue damage	↓ Decreases	ELISA
Myeloperoxidase (MPO)	Marker of neutrophil infiltration and oxidative tissue injury	↓ Decreases	Colorimetric assay
Nuclear Factor-κB (NF-κB)	Regulates the expression of inflammatory cytokines and enzymes	↓ Decreases	Western blot/IHC/qPCR
Cyclooxygenase-2 (COX-2)	Inducible enzyme involved in inflammation & PG synthesis	↓ Decreases*	Western blot/IHC

Clinical relevance

The inflammatory biomarkers are useful to elucidate the pathogenic mechanisms in gastric ulcers and the anti-inflammatory activity of gastroprotective drugs.[48] Of these, the most consistently assessed biomarkers include TNF-α, IL-1β, IL-6, MPO, and NF-κB, all of which are regarded as markers of gastric mucosal injury, mediated by inflammation. The combined evaluation of their results complements the evaluation of oxidative stress biomarkers and further enhances the evaluation of gastroprotective efficacy.[49]

Cytoprotective Biomarkers

Cytoprotective parameters are markers of the integrity of the gastric mucosal defense system, and are critical for the assessment of the protective action of gastroprotective agents. The mechanisms by which these biomarkers act to preserve mucosal homeostasis include increased mucus and bicarbonate production, maintaining mucosal blood supply, free radical scavenging, and epithelial repair.[50] These protective factors are usually impaired by ulcerogenic agents, making the stomach more vulnerable to injury. Thus, the restoration of cytoprotective biomarkers is seen as a crucial parameter to assess effective gastroprotection and mucosal healing.

Biomarker	Role in ulcer pathogenesis	Expected change with gastroprotection	Common method of assessment
Prostaglandin E_2 (PGE_2)	Stimulates mucus and bicarbonate secretion, maintains mucosal blood flow	↑ Increases	ELISA
Nitric Oxide (NO)	Preserves mucosal microcirculation and inhibits leukocyte adhesion	↑ Increases	Griess assay
Gastric Mucus Content	Forms the first protective barrier against acid and pepsin	↑ Increases	Alcian blue binding assay
Mucin	Major glycoprotein responsible for mucus viscosity and barrier function	↑ Increases	Histochemical staining (PAS/Alcian blue)
Non-protein Sulfhydryl (NP-SH) Compounds	Protect mucosal cells against oxidative damage and maintain epithelial integrity	↑ Increases	DTNB assay

Clinical relevance

Cytoprotective biomarkers directly demonstrate therapeutic agents' capacity to strengthen the gastric mucosal defense system instead of just inhibiting gastric acid production. The use of combined evaluation of PGE_2, nitric oxide, mucus content, mucin and non-protein sulfhydryl compounds provide useful information on the mechanisms of mucosal protection and tissue repair and is essential for experimental gastroprotective studies.[51]

CURRENT STATUS

Gastroprotective evaluation has made great strides in the last two decades, from simple gross examination of the lesions to a more thorough examination through specific biomarkers. The ulcer index, lesion score, gastric pH and gastric acidity were traditionally regarded as adequate for assessing the antiulcer activity.[52] These parameters, however, do not give much information about the molecular and biochemical events involved in the gastric mucosal injury and repair process. Thus, current studies have focused on the combination of several biomarkers to gain a mechanistic understanding of the pathogenesis of PUD and the protective effects of therapeutic interventions.

Most of the current preclinical studies are based on a multi-biomarker approach and include macroscopic measurements, as well as biochemical markers of oxidative stress, inflammation and mucosal defence. The most commonly studied biomarkers include MDA, GSH, SOD, CAT, TNF-α, IL-1β, PGE_2, nitric oxide, and gastric mucus content, which have been shown to be involved in gastric mucosal injury and healing.[53] The combination of these markers allows for a more holistic view of gastroprotective mechanisms, as the changes in gastric structure are correlated with changes in antioxidant capacity, inflammation, and cytoprotection. Therefore, biomarker evaluation is now an important part of the pharmacological screening of new gastroprotective drugs.[54]

Biomarker research has further strengthened in experimental gastroenterology due to the recent swift progress of analytical technologies. Biochemical and molecular biomarkers have been quantifiable using a range of techniques, including spectrophotometry, enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, Western blotting and quantitative polymerase chain reaction (qPCR), which are sensitive and reproducible.[55] These approaches have helped identify specific signalling pathways that mediate gastroprotection and have helped to provide greater mechanistic understanding of experimental observations. Moreover, digital image analysis and computerised histological scoring systems are now increasingly being used in experimental studies, as they provide an additional level of objectivity and reproducibility in the assessment of gastric lesions.

The increased focus on natural sources, phytochemicals and herbal preparations to improve gastroprotective activity is also significant. Many plant derived compounds are increasingly recognized to achieve their protective effects by modulating oxidative stress, inflammatory mediators, and endothermally cytoprotective mechanisms, apart from just reducing gastric acid secretion.[56] Thus, the evaluation of the pharmacological effects of these compounds and the elucidation of their molecular targets has become essential and is now an integral part of a biomarker approach. However, there is still significant variation among studies in the type of experimental models, biomarkers used, analytical methods, and reporting. The lack of uniformity reduces the comparability of the results and the necessity for uniformity in biomarker panels and experimental protocols in order to enhance the repeatability and translatability of gastroprotective studies.[57, 58]

Current trend	Significance
Multi-biomarker assessment	Provides a comprehensive evaluation of gastroprotective mechanisms
Combined biochemical and physiological evaluation	Correlates gastric morphology with underlying molecular changes
Increased use of ELISA, qPCR, Western blotting, and spectrophotometric assays	Improves sensitivity and accuracy of biomarker detection
Growing interest in phytopharmacology	Facilitates mechanistic validation of natural gastroprotective agents
Adoption of digital image analysis and histological scoring	Enhances objectivity and reproducibility of lesion assessment
Emphasis on mechanism-based studies	Distinguishes antioxidant, anti-inflammatory, and cytoprotective actions
Need for standardized biomarker panels	Enhances reproducibility and inter-study comparison

CHALLENGES IN BIOMARKER-BASED GASTROPROTECTIVE RESEARCH

Despite substantial improvements in the use of biomarkers to assess gastroprotection, there are still numerous limitations with the reliability, reproducibility, and clinical relevance of experimental results. The most important issue is the lack of a standard set of biomarker panels, with each study using different sets of biochemical, inflammatory and cytoprotective markers depending on experimental design and resources. This is an inconsistent situation which makes it difficult to compare the findings from different studies and makes it difficult to draw general criteria for gastroprotective activity.[59]

A major difficulty is the lack of uniformity of the peptic ulcer models used. The ulcer models induced by ethanol, NSAIDs, pylorus ligation, stress and acetic acid are very different in their mechanism of gastric damage, and have different biomarker profiles. Therefore, there is a need

for highly informative biomarkers in one model and not in another.[60] The fact that these responses are model specific means that it is hard to develop a single biomarker or biomarker panel that reliably assesses gastroprotective activity under different experimental conditions.

Biomarker assessment inconsistencies are also due to technical and methodological differences. Experimental results and levels of biomarkers can be affected by inter-laboratory differences in animal species/strain, methods of inducing ulcers, sample collection, assay methods, and interpretation of the data. Moreover, although the assays used in the different laboratories have different sensitivity and specificity, variations in the laboratory method further compromise inter-laboratory consistency. To enhance the consistency and comparison of studies conducted using biomarker approaches, standardisation of experimental procedures and analytical methodologies is required.[61]

Biomarkers are important mechanistic data, but this is not always possible to extrapolate to a clinical setting. Most biomarkers adopted for gastroprotective studies have been proven in animal experimental models, with data regarding their predictive value in peptic ulcer disease in humans being relatively limited. Due to different physiological characteristics among species and the polyetiology of peptic ulcer disease in humans, as well as the effects of concomitant medications, peptic ulcer disease and Helicobacter pylori infection, results in animal models cannot be directly extrapolated to humans.

Furthermore, the analysis of the biomarkers is often labor intensive and requires specialized equipment, expensive reaction chemicals and trained people, all of which are not readily available in many research laboratories. The use of molecular techniques like ELISA, western blotting, quantitative PCR and immunohistochemistry adds to the overall cost and technical difficulty of experimental studies.[62] Thus, a small number of traditional biomarkers are commonly used in many investigations, and some of these do not reflect the multifaceted pathophysiology of gastric mucosal injury and healing.

To overcome these challenges, biomarker panels must be standardised, experimental protocols harmonised and there needs to be increased collaboration between different research groups to validate biomarkers in various ulcer models and clinical populations. These will further help to improve the ability to replicate preclinical studies, compare the results of different experiments and increase the translatability of gastroprotective studies based on markers.[63]

Challenge	Impact on Research
Lack of standardized biomarker panels	Limits comparison of findings and prevents establishment of universal evaluation criteria
Variability among experimental ulcer models	Produces model-specific biomarker responses, reducing consistency across studies
Methodological differences in biomarker analysis	Affects reproducibility due to variations in animal models, assays, and sample processing
Limited clinical validation	Restricts translation of experimental biomarkers to human peptic ulcer disease
High cost and technical complexity	Reduces accessibility of advanced biomarker analyses, particularly in resource-limited laboratories
Reliance on individual biomarkers	Provides incomplete mechanistic information and may overlook complex biological interactions

FUTURE PERSPECTIVES

Standardized and mechanism-based panels of biomarkers will be the future of biomarker-based evaluation in gastroprotective research to evaluate gastric mucosal injury and therapeutic response comprehensively. Future studies should adopt integrated biomarker strategies, incorporating the macroscopic, gastric secretory, oxidative stress, inflammatory and cytoprotective parameters, rather than depending on any given single biomarker.[64] This would not only enhance the reliability and reproducibility of experimental results, but also permit correct interpretation of the mechanisms of gastroprotective activity. Standardization of guidelines for biomarker selection and reporting would also help to make meaningful comparison between different studies and improve the quality of preclinical research in general.

With the emergence of new technologies in the field of omics, such as proteomics, metabolomics, transcriptomics, and lipidomics, new opportunities have emerged to identify novel biomarkers that are responsible for gastric mucosal injuries and repair. Such high throughput methods allow the whole picture of the molecular changes involved in ulcerogenesis and therapeutic intervention to be elucidated, providing a better understanding of disease mechanisms.[65] Furthermore, the use of non-invasive blood, saliva or urine biomarkers could help decrease the need for invasive tissue sampling and the translational value of biomarker research.

Additionally, new computational techniques, such as artificial intelligence (AI) and machine learning (ML), are likely to revolutionize the biomarker discovery and

analysis. The application of AI models to large datasets from biochemical, molecular, and histopathological analysis can help detect intricate biomarker patterns, forecast response to treatment, and guide precision medicine approaches in peptic ulcer disease. In addition, digital pathology and automated image analysis could help to reduce the variability of histological evaluation can be observer-dependent in experimental studies.

Important priorities are also the clinical validation of experimental biomarkers. Many biomarkers have been shown to be promising in animals, but few have been rigorously tested in human peptic ulcer disease.[66] Future studies should, however, focus on conducting translational studies that link experimental biomarkers with clinical outcomes, treatment response and disease progression. It will be important for pharmacologists, gastroenterologists, molecular biologists, and bioinformaticians to work together to define clinically relevant biomarker panels and to move discoveries from the bench to the bedside.[67]

Overall, the adoption of biomarker panels, advanced analytical technologies, and computational tools is likely to change the way gastroprotective agents are assessed. These advances will not only enhance the scientific validity of experimental investigations, but also aid in the identification of new targets for therapeutic intervention and lead to the creation of more effective and safer drugs for treating peptic ulcer disease.[68]

Future perspective	Expected impact
Development of standardized biomarker panels	Improves reproducibility and enables comparison across studies
Multi-biomarker and mechanism-based evaluation	Provides a comprehensive understanding of gastroprotective activity
Integration of omics technologies (proteomics, metabolomics, transcriptomics, lipidomics)	Facilitates discovery of novel biomarkers and therapeutic targets
Identification of non-invasive biomarkers	Enhances clinical applicability and reduces dependence on tissue sampling
Application of AI and machine learning	Improves biomarker discovery, predictive analysis, and data interpretation
Digital pathology and automated image analysis	Increases accuracy and reproducibility of histopathological assessment
Clinical validation of experimental biomarkers	Bridges the gap between preclinical findings and patient care
International standardization of research protocols	Promotes harmonization and improves the quality of gastroprotective research

CONCLUSION

While major advances have been made, there are a number of challenges to the use of biomarkers for research, including the absence of a consensus on the optimal panels of biomarker and the variability of experimental ulcer models, inconsistencies in experimental methods, and poor clinical validation. The limitations underscore the importance of standardized experimental procedures and reporting of findings for enhancing the reproducibility and comparison of studies. Information, and nanotechnology, hold significant promise for enhancing the study of marine food webs. New technologies such as omics, artificial intelligence, digital information and nanotechnology have great potential to improve research on marine food webs. Pathology and advanced molecular studies should lead to better re-definitions of biomarker discovery and validation on the one hand and to a more detailed characterization of gastroprotective mechanisms on the other hand. The combination of these technologies with traditional biochemical markers could enhance the accuracy, sensitivity and biological significance of preclinical gastro-protective research. Overall, the use of a biomarker testing approach is a cornerstone of contemporary experimental research into peptic ulcers and is expected to be more widely used in the search for safer and more effective gastroprotective drugs. Standardisation of validated biomarker panels based on mechanistically comparable pathways and validation of selected experimental biomarkers in clinical practice should be considered as the next steps towards bridging the gap between preclinical studies and clinical practice.

REFERENCES

1. Malfertheiner, P., Chan, F. K. L., & McColl, K. E. L. (2020). Peptic ulcer disease. The Lancet, 396(10258): 1475–1486.
2. Lanas, A., & Chan, F. K. L. (2017). Peptic ulcer disease. The Lancet, 390(10094): 613–624.
3. Scarpignato, C., Hunt, R. H., et al. (2016). International consensus on gastric protection. BMC Medicine, 14: 179.
4. Wallace, J. L., & Wang, R. (2015). Hydrogen sulfide-based therapeutics and gastrointestinal protection. Nature Reviews Gastroenterology & Hepatology, 12: 480–489.
5. Sung, J. J. Y., Kuipers, E. J., & El-Serag, H. B. (2009). Systematic review: The global burden of peptic ulcer disease. The Lancet, 374: 1449–1461.
6. Rahman, M. M., Islam, M. R., Shohag, S., et al. (2021). Herbal medicines and natural products in the

treatment of peptic ulcer disease: A review. *Molecules*, *26*(23): 7170.
7. Adinortey, M. B., Ansah, C., Galyuon, I., & Nyarko, A. (2013). In vivo models used for evaluation of potential antigastroduodenal ulcer agents. *Ulcers, 2013;* 1–12.
8. Allen, A., Flemström, G., Garner, A., & Kivilaakso, E. (1993). Gastroduodenal mucosal protection. *Physiological Reviews*, *73*(4): 823–857.
9. Almasaudi, S. B., El-Shitany, N. A., Abbas, A. T., Abdel-Dayem, U. A., Ali, S. S., Al Jaouni, S. K., & Harakeh, S. (2016). Antioxidant, anti-inflammatory, and antiulcer potential of *Manuka* honey against gastric ulcer in rats. *Oxidative Medicine and Cellular Longevity*.
10. Arab, H. H., Salama, S. A., Eid, A. H., Omar, H. A., Arafa, E. A., & Maghrabi, I. A. (2015). Camel's milk ameliorates gastric ulcer via modulation of oxidative stress and inflammatory mediators. *Food and Chemical Toxicology, 84:* 314–321.
11. Brzozowski, T., Konturek, P. C., Konturek, S. J., Brzozowska, I., & Pawlik, T. (2005). Role of prostaglandins in gastroprotection and gastric adaptation. *Journal of Physiology and Pharmacology*, *56*(Suppl. 5): 33–55.
12. Brzozowski, T., Konturek, S. J., Pajdo, R., Kwiecień, S., Ptak, A., Hahn, E. G., & Konturek, P. C. (1997). Role of nitric oxide in gastroprotection. *Journal of Physiology and Pharmacology*, *48*(4): 503–517.
13. Chatterjee, A., Bandyopadhyay, S. K., & Chattopadhyay, G. (2007). Oxidative stress and gastric mucosal injury. *Indian Journal of Biochemistry & Biophysics*, *44*, 83–90.
14. De Araújo, E. R., Guerra, G. C. B., Araújo, D. F. S., et al. (2018). Oxidative stress biomarkers in experimental gastric ulcer models. *Biomedicine & Pharmacotherapy*, *104:* 694–702.
15. El-Abhar, H. S. (2010). Coenzyme Q10 protects against indomethacin-induced gastric ulcer through modulation of oxidative stress and inflammation. *European Journal of Pharmacology*, *649*(1–3): 117–123.
16. El-Shitany, N. A., El-Bastawissy, E. A., & El-Desoky, K. (2014). Ellagic acid protects against gastric ulcer through antioxidant and anti-inflammatory mechanisms. *Chemico-Biological Interactions*, *210*: 26–33.
17. Glavin, G. B., Szabo, S., & Salim, A. S. (1992). Experimental gastric mucosal injury: Laboratory models reveal mechanisms of pathogenesis and gastroprotection. *FASEB Journal*, *6*(3): 825–831.
18. Gürbüz, I., Üstün, O., Yesilada, E., Sezik, E., & Akyürek, N. (2003). In vivo gastroprotective effects of medicinal plants in experimental ulcer models. *Journal of Ethnopharmacology*, *88*(1): 93–97.
19. Halliwell, B., & Gutteridge, J. M. C. (2015). *Free radicals in biology and medicine* (5th ed.). Oxford University Press.
20. Konturek, P. C., Brzozowski, T., & Konturek, S. J. (2011). Stress and the gut: Pathophysiology, clinical consequences, and experimental models. *Journal of Physiology and Pharmacology*, *62*(6): 591–599.
21. La Casa, C., Villegas, I., Alarcón de la Lastra, C., Motilva, V., & Martín Calero, M. J. (2000). Evidence for protective effects of quercetin in ethanol-induced gastric ulcer. *European Journal of Pharmacology*, *402*(1–2): 157–160.
22. Laine, L., Takeuchi, K., & Tarnawski, A. (2008). Gastric mucosal defense and cytoprotection. *Gastroenterology*, *135*(1): 41–60.
23. Mizui, T., & Doteuchi, M. (1983). Effect of polyamines on acidified ethanol-induced gastric lesions in rats. *Japanese Journal of Pharmacology*, *33*(5): 939–945.
24. Naito, Y., Takagi, T., & Yoshikawa, T. (2007). Molecular fingerprints of oxidative stress in gastric mucosal injury. *Journal of Clinical Biochemistry and Nutrition*, *40*(1): 1–9.
25. Pan, J. S., He, S. Z., Xu, H. Z., Zhan, X. J., Yang, X. N., Xiao, H. M., & Shi, H. X. (2008). Oxidative stress disturbs energy metabolism of gastric mucosa in ethanol-induced ulcer. *World Journal of Gastroenterology*, *14*(38): 5857–5867.
26. Repetto, M. G., & Llesuy, S. F. (2002). Antioxidant properties of natural compounds in gastric ulcer prevention. *Brazilian Journal of Medical and Biological Research*, *35*(5): 523–534.
27. Salim, A. S. (1990). Removing oxygen-derived free radicals stimulates healing of ethanol-induced gastric ulcers. *Digestive Diseases and Sciences*, *35*(11): 1397–1400.
28. Szabo, S., Trier, J. S., Brown, A., & Schnoor, J. (1985). Early vascular injury and mechanisms of ethanol-induced gastric mucosal damage. *Gastroenterology*, *88*(1): 228–236.
29. Takeuchi, K. (2012). Pathogenesis of NSAID-induced gastric damage and protective factors. *Current Pharmaceutical Design*, *18*(18): 2202–2211.
30. Wallace, J. L. (2008). Prostaglandins, NSAIDs, and gastric mucosal protection: Why doesn't the stomach digest itself? *Physiological Reviews*, *88*(4): 1547–1565.
31. Wallace, J. L., & Granger, D. N. (1996). The cellular and molecular basis of gastric mucosal defense. *FASEB Journal*, *10*(7): 731–740.
32. Tarnawski, A. S., & Ahluwalia, A. (2012). Molecular mechanisms of epithelial regeneration and neovascularization during gastric ulcer healing. *Current Medicinal Chemistry*, *19*(1): 16–27.
33. Sumbul, S., Ahmad, M. A., Asif, M., & Akhtar, M. (2011). Role of antioxidants in the treatment of gastric ulcer. *Asian Pacific Journal of Tropical Medicine*, *4*(3): 227–233.
34. Rao, C. V., Vijayakumar, M., & Rawat, A. K. S. (2008). Gastroprotective effect of flavonoids and phenolic compounds in experimental ulcer models. *Journal of Ethnopharmacology*, *120*(2): 149–154.

35. Bhattacharya, S. (2015). Reactive oxygen species and oxidative stress: Pathophysiology and gastroprotection. *Current Science, 109*(4): 646–655.
36. Yoshikawa, T., Naito, Y., & Kishi, A. (1997). Role of active oxygen species and lipid peroxidation in gastric mucosal injury. *Digestive Diseases and Sciences, 42*(1): 1–10.
37. Peskar, B. M., & Maricic, N. (1998). Role of prostaglandins in gastroprotection. *Digestive Diseases and Sciences, 43*(Suppl.): 23S–29S.
38. Abdel-Salam, O. M. E., Czimmer, J., Debreceni, A., Szolcsányi, J., & Mózsik, G. (2001). Gastric mucosal integrity and oxidative stress in experimental ulcer models. *Journal of Physiology Paris, 95*(1–6): 105–108.
39. Konturek, S. J., Brzozowski, T., & Konturek, P. C. (2005). Helicobacter pylori infection and gastric mucosal defense mechanisms. *Journal of Physiology and Pharmacology, 56*(Suppl. 3): 3–21.
40. Mózsik, G., Abdel-Salam, O. M. E., & Szolcsányi, J. (2007). Gastric mucosal protection and free radical mechanisms. *Current Medicinal Chemistry, 14*(20): 2101–2114.
41. Kwiecień, S., Brzozowski, T., Konturek, P. C., Pawlik, M. W., Pawlik, W. W., & Konturek, S. J. (2002). Role of nitric oxide in gastric mucosal injury and ulcer healing. *Journal of Physiology and Pharmacology, 53*(1): 39–50.
42. El-Maraghy, S. A., Rizk, S. M., & Shahin, N. N. (2015). Gastroprotective effect of crocin against indomethacin-induced gastric ulcer in rats. *European Journal of Pharmacology, 764:* 210–220.
43. Motawi, T. K., Abd Elgawad, H. M., & Shahin, N. N. (2014). Gastroprotective effect of melatonin through antioxidant and anti-inflammatory pathways. *Chemico-Biological Interactions, 215:* 40–50.
44. Abdallah, D. M. (2010). Nicorandil attenuates indomethacin-induced gastric ulcer through activation of ATP-sensitive potassium channels and nitric oxide. *European Journal of Pharmacology, 637*(1–3): 152–159.
45. Arab, H. H., Salama, S. A., Omar, H. A., Arafa, E. A., & Maghrabi, I. A. (2015). Diosmin protects against ethanol-induced gastric injury through modulation of oxidative stress and inflammatory mediators. *Chemico-Biological Interactions, 242:* 314–323.
46. Sidahmed, H. M. A., Azizan, A. H. S., Mohan, S., Abdulla, M. A., Abdelwahab, S. I., Taha, M. M. E., & Hashim, N. M. (2013). Gastroprotective activity of natural products in ethanol-induced gastric ulcer models. *BMC Complementary and Alternative Medicine, 13*: 105.
47. Zakaria, Z. A., Balan, T., Suppaiah, V., Ahmad, S., & Jamaludin, F. (2014). Mechanisms of gastroprotection mediated by medicinal plants: Experimental evidence. *Evidence-Based Complementary and Alternative Medicine*.
48. Abdulla, M. A., Ali, H. M., Ahmed, K. A. A., Noor, S. M., & Ismail, S. (2010). Evaluation of gastroprotective activity using histopathological and biochemical biomarkers in experimental gastric ulcer. *Journal of Medicinal Plants Research, 4*(8): 685–691.
49. Al Batran, R., Al-Bayaty, F. H., Jamil Al-Obaidi, M. M., Abdualkader, A. M., Hadi, H. A., Ali, H. M., & Abdulla, M. A. (2013). Gastroprotective effects of plant-derived compounds in rats: Histological and biochemical evaluation. *BMC Complementary and Alternative Medicine, 13:* 32.
50. Kaur, G., Hamid, H., Ali, A., Alam, M. S., & Athar, M. (2010). Antiinflammatory mechanisms involved in gastroprotection. *Current Drug Targets, 11*(2): 195–207.
51. Bandyopadhyay, U., Biswas, K., Chattopadhyay, I., Banerjee, R. K. (2002). Biological activities and medicinal properties of garlic and curcumin in gastric ulcer healing. *Current Science, 82*(11): 1333–1345.
52. Chattopadhyay, I., Bandyopadhyay, U., Biswas, K., Maity, P., & Banerjee, R. K. (2006). Indomethacin-induced gastric ulcer: Oxidative stress and antioxidant defense mechanisms. *Biochemical Pharmacology, 72*(6): 850–859.
53. Maity, P., Bindu, S., Dey, S., Goyal, M., Alam, A., Pal, C., Mitra, K., Bandyopadhyay, U. (2009). Molecular mechanisms of ulcer healing and the role of antioxidants. *Molecular and Cellular Biochemistry, 321*(1–2): 1–13.
54. Bhattacharyya, A., Chattopadhyay, R., Mitra, S., & Crowe, S. E. (2014). Oxidative stress: An essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiological Reviews, 94*(2): 329–354.
55. Sener, G., Kabasakal, L., Cetinel, S., Contuk, G., Gedik, N., & Yeğen, B. C. (2005). Garlic extract protects against gastric mucosal injury by reducing oxidative stress. *Journal of Medicinal Food, 8*(4): 438–445.
56. Kwiecień, S., Brzozowski, T., Konturek, S. J., Pawlik, M. W., & Pawlik, W. W. (2015). Oxidative stress, reactive oxygen species, and gastric mucosal defense. *Journal of Physiology and Pharmacology, 66*(6): 857–870.
57. Brzozowski, T., Konturek, S. J., Pajdo, R., Kwiecień, S., & Hahn, E. G. (2001). Role of growth factors in gastric ulcer healing. *Journal of Physiology and Pharmacology, 52*(4): 555–577.
58. Tarnawski, A. S. (2005). Cellular and molecular mechanisms of gastric ulcer healing. *Digestive Diseases and Sciences, 50*(Suppl. 1): S24–S33.
59. Almasaudi, S. B. (2021). Honey as a protective agent against gastric ulcer: Molecular mechanisms and therapeutic potential. *Saudi Journal of Biological Sciences, 28*(11): 6586–6597.
60. Abdelwahab, S. I., Taha, M. M. E., Abdulla, M. A., Nordin, N., Hadi, A. H. A., Mohan, S., & Hashim, N. M. (2013). Gastroprotective mechanism of

medicinal plant extracts against ethanol-induced gastric ulcer in rats. *BMC Complementary and Alternative Medicine, 13*: 105.
61. Sidahmed, H. M. A., Hashim, N. M., Abdulla, M. A., Ali, H. M., Mohan, S., Abdelwahab, S. I., & Taha, M. M. E. (2013). Role of HSP70 expression in gastroprotection against ethanol-induced gastric ulcer. *BMC Complementary and Alternative Medicine, 13:* 32.
62. Zakaria, Z. A., Hisam, E. E. A., Rofiee, M. S., Norhafizah, M., Somchit, M. N., Teh, L. K., & Salleh, M. Z. (2011). In vivo antiulcer activity and gastroprotective mechanisms of medicinal plants. *Evidence-Based Complementary and Alternative Medicine*.
63. El-Maraghy, S. A., Rizk, S. M., & Shahin, N. N. (2015). Gastroprotection through suppression of inflammatory cytokines and oxidative stress in experimental ulcer models. *European Journal of Pharmacology, 764:* 210–220.
64. Kim, J. H., Park, S. H., Nam, S. W., Choi, Y. H., & Kim, H. J. (2019). Activation of the Nrf2/HO-1 pathway protects against gastric mucosal injury. *International Journal of Molecular Sciences, 20*(20): 5123.
65. Li, W., Kong, A. N. (2009). Molecular mechanisms of Nrf2-mediated antioxidant response. *Molecular Carcinogenesis, 48*(2): 91–104.
66. Ma, Q. (2013). Role of Nrf2 in oxidative stress and toxicity. *Annual Review of Pharmacology and Toxicology, 53:* 401–426.
67. Lawrence, T. (2009). The nuclear factor NF-κB pathway in inflammation. *Cold Spring Harbor Perspectives in Biology, 1*(6): a001651.
68. Elmore, S. (2007). Apoptosis: A review of programmed cell death. *Toxicologic Pathology, 35*(4): 495–516.

