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REVIEW

Cyanidin and Cyanidin-3-Glucoside Alleviate Peptic Ulcer Disease: Insights from in vitro, and in vivo Studies

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Abstract: Peptic ulcer disease (PUD) remains a significant global health issue, affecting millions despite a decrease in overall prevalence. However, complications continue to persist, with substantial mortality rates in regions like India and China. Current treatments, though effective, have limitations, driving interest in plant-derived therapy. Anthocyanins, including cyanidin and cyanidin-3-glucoside (C3G), are known for their antioxidant and anti-inflammatory properties. This study aims to explore the potential of cyanidin and C3G in alleviating PUD, focusing on their mechanisms of action and therapeutic efficacy in preclinical studies. Articles were searched in Scopus and PubMed databases and filtered for publication from 2014 to 2024, resulting in 89 articles from Scopus and 11 articles from PubMed. The articles were further screened by title, abstract, and full text, resulting in 6 articles. Cyanidin and C3G were described to be able to alleviate PUD by inhibiting the cytokine pro-inflammatory, reducing inflammation in gastric mucosa, and reducing lipid peroxidation in the gastric mucosa. These compounds have proven effective in managing other health problems, including peptic ulcers, but more in-depth exploration in clinical settings is required to confirm therapeutic potential in humans. It is necessary to validate the therapeutic efficacy and safety in human populations. This review provides an overview of preclinical studies of cyanidin and C3G, such as in vitro and in vivo, focusing on mechanism of action or their effectiveness in alleviating peptic ulcers.

Keywords: anthocyanins, anti-inflammatory, antioxidant, gastroprotective, preclinical studies

Introduction

Peptic ulcer disease (PUD) affects millions globally, with an estimated lifetime prevalence of 5–10% in the general population.[1–3] Although the overall prevalence of PUD has decreased over recent decades, the incidence of complications remains steady.[4,5] In 2019, there were approximately 8.09 million cases worldwide, marking a 25.82% increase since 1990. However, despite this rise in case numbers, the age-standardized prevalence rate dropped from 143.47 per 100,000 population in 1990 to 99.50 per 100.000 population in 2019.[6,7] Based on world life expectancy data (www.worldlifeexpectancy.com) and the World Health Organization's Mortality Database (www.platfrom.who.int/mortality), India (68,108 deaths) and China (37,723 deaths) report the highest number of ulcer-related deaths, followed by several other countries with significant mortality rates. Regions like Australia, Canada, and Europe show a moderate impact, while some countries, including New Zealand and certain African nations, report fewer than 100 deaths, indicating a lower effect (Figure 1).

The geographical variation in ulcer-related mortality is influenced by factors such as *Helicobacter pylori* infections, prolonged non-steroidal anti-inflammatory drugs (NSAIDs) use, and lifestyle choices that may weaken the stomach's protective barrier,[8] leading to ulcers and severe complications like perforation or obstruction and disrupting physiological

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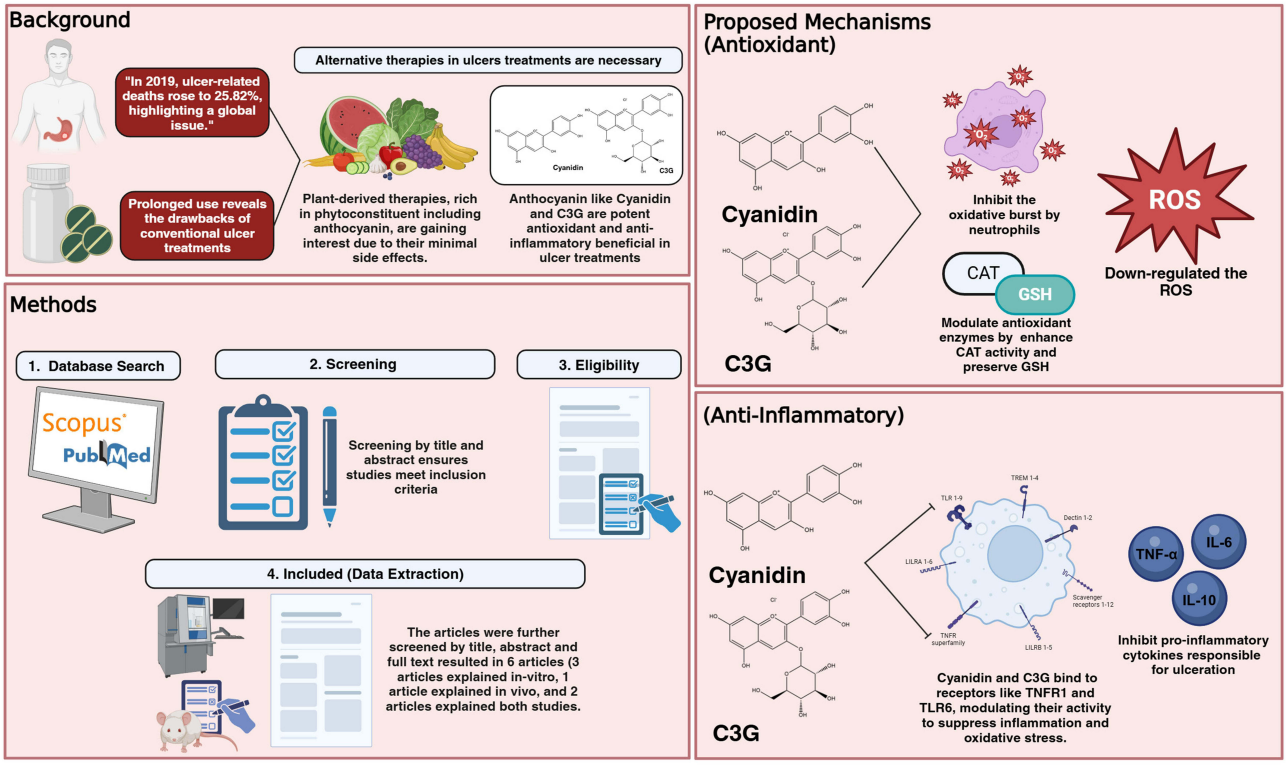
Graphical Abstract



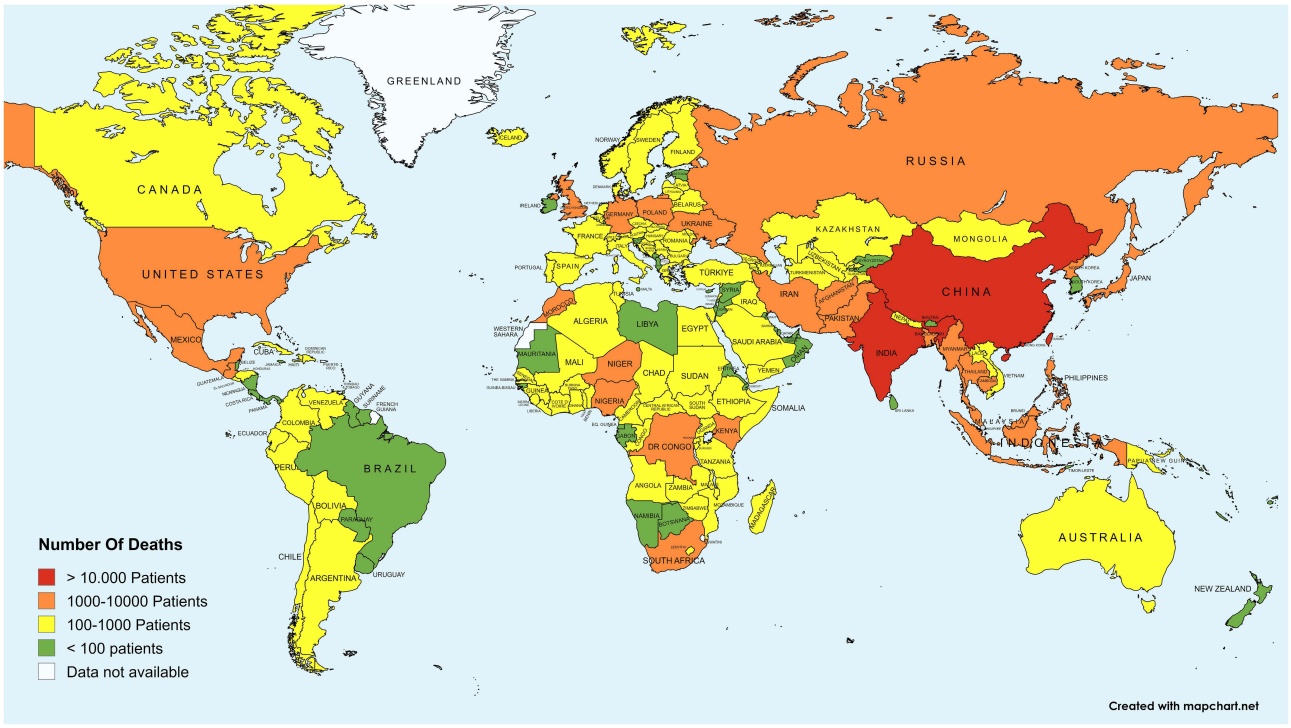


Figure 1 The global number of deaths due to PUD, reported by countries to WHO, covers the period from 2010 to 2022 and is compiled by World Life Expectancy (This figure was created using mapchart.net).

functions.[9–11] Peptic ulcers can also result from excessive alcohol consumption, elevated stress, and bile salt reflux.[12] Current treatments for PUD, including proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), antacids, and sucralfate, operate by suppressing gastric acid secretion, neutralizing stomach acid, and protecting the gastric mucosa. Additionally, the development and refinement of synthetic medications have significantly decreased the incidence of complications related to PUD, including bleeding and perforations.[13,14] Notably, PPIs are exceptionally effective in controlling acid production and fostering an environment conducive to ulcer healing, and their usage has increased substantially over the past decade.[15] However, prolonged use of these drugs raises side effects and financial costs. Sudden discontinuation of PPI may cause recurrence, thus secure discontinuation strategy is by tapering the dose.[16–18]

Ulcers pose a significant clinical challenge, often leading to weak mucosal regeneration and increased vulnerability to further damage. As the first line, PPIs were thought to have a low incidence of side effects. Still, evidence has cumulated to indicate that long-term use might not be as harmless as first considered, with concerns about possible adverse side effects, such as hypomagnesemia and drug interactions, raised.[15] Nonetheless, the discontinuation of PPIs can trigger a withdrawal, such as rebound acid hypersecretion (RAHS), where the stomach produces excessive acid levels beyond pre-treatment amounts.[19,20] Due to these challenges, there is increasing interest in alternative treatments from natural sources, as reported by the WHO, that 80–85% of the global population relies on natural products for disease management.[21,22]

Anthocyanins, eg, cyanidin and cyanidin-3-glucoside (C3G), are plant-derived secondary metabolites belonging to the monomeric anthocyanin class within the flavonoid family.[23–25] These water-soluble compounds are widely found in fruits, vegetables, and various plant parts, including leaves, petals, flowers, and red-colored fruits.[26] They are traditionally used as medicinal treatments in many countries and have been extensively reported to offer therapeutic potential against various diseases.[27] Notably, cyanidin is recognized for its significant anti-inflammatory and antioxidant properties, suggesting potential therapeutic applications for conditions like asthma,[28,29] cancer,[30–32] diabetes,[33–35] and inflammatory bowel disease.[36,37] Additionally, cyanidins exhibit antiproliferative effects and promote apoptosis, contributing to their role in cancer prevention. Recent studies have highlighted the potential of anthocyanins in modulating key receptors such as tumor necrosis factor receptor 1 (TNFR1) and toll-like receptor 1–9 (TLR1-9), which can reduce inflammation and oxidative stress.[38,39.] Furthermore, these compounds enhance mucosal defense by neutralizing reactive oxygen species (ROS) and strengthening endogenous antioxidant systems, including catalase (CAT) and glutathione (GSH).[40] This presents a promising avenue for developing safer and more effective treatment strategies for PUD.

Considering all, this review aims to provide a comprehensive overview of the role of cyanidin and C3G in alleviating PUD. The review synthesizes from in vitro studies, animal models, and human clinical trials to present an understanding of the mechanisms through which these plant-derived metabolites exert gastroprotective effects. This review thoroughly analyzes preclinical studies investigating the critical areas of cyanidin and C3G potential in alleviating PUD, focusing on their efficacy and safety across various study models. Special emphasis is placed on elucidating the underlying mechanisms of action, including their role in enhancing gastric mucosal protection, modulating oxidative stress, and reducing inflammation. This review will provide a nuanced understanding and may contribute to improved therapeutic outcomes in PUD management.

Methods

Search Strategy

Briefly, a literature search using the (1) PubMed database using the keywords cyanidin OR cyanidin-3-glucoside AND gastroprotective searched within Abstract, free full text, in the last 10 years, and resulted in n = 11; (2) in the Scopus database using the keywords cyanidin OR cyanidin-3-glucoside AND gastroprotective searched within All fields, resulted in n = 89, with a total of all publications found through these searches were reviewed. The authors retrieved and evaluated all documents that met the inclusion criteria, such as using cyanidin and cyanidin-3-glucoside in treating peptic ulcers. Finally, 6 articles were selected for review, as depicted in Figure 2. However, an additional search was conducted to support the discussion during the process.

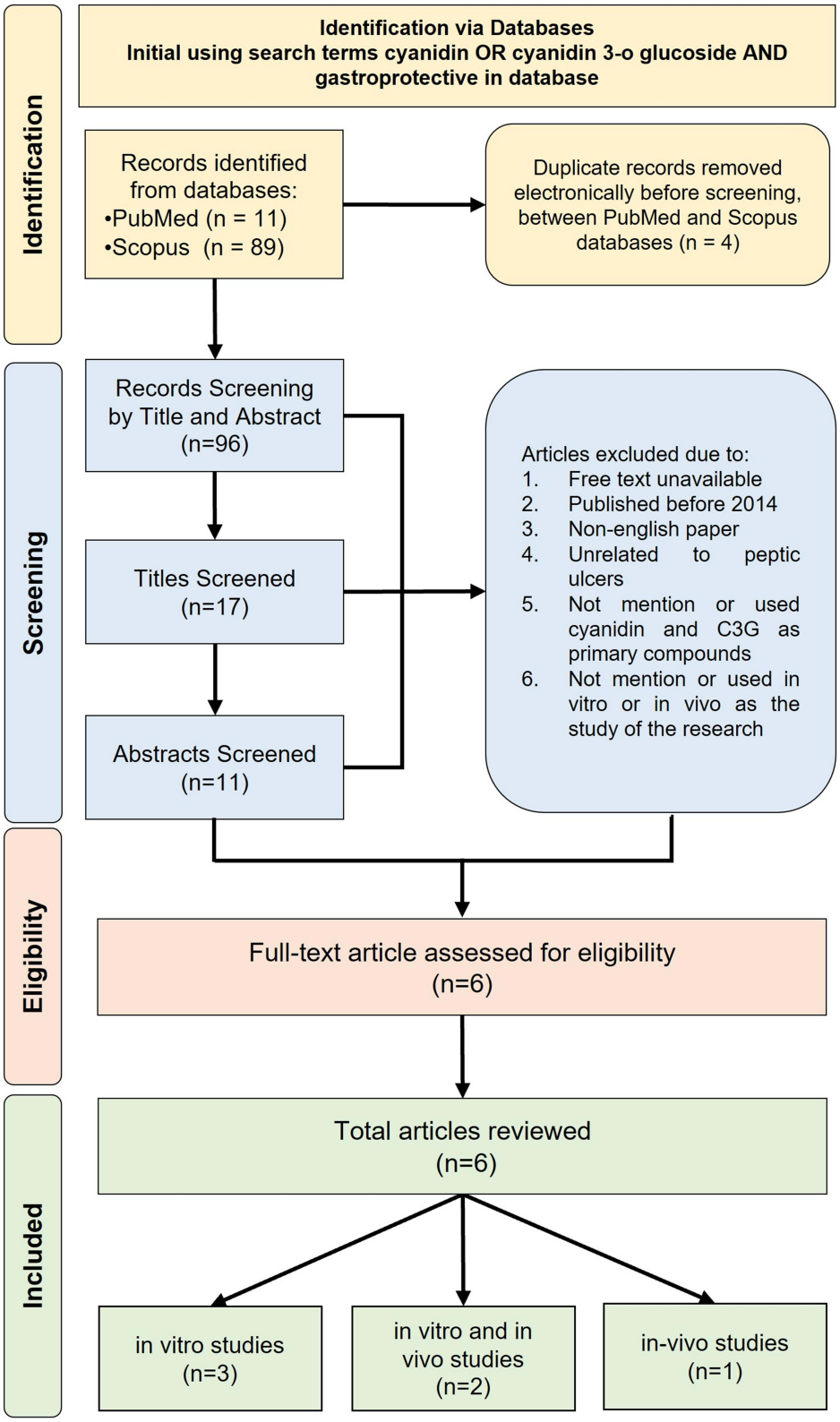


Figure 2 The study design of the article review.

Data Extraction

Each investigator independently evaluated and selected articles that were reasonable or relevant to the topic. Key data extracted from each article includes the medicinal plant isolated, collection location and year, plant part used, extraction method and solvents, other metabolites aside from cyanidin and cyanidin-3-glucoside, animal models employed, study controls, inducement method dosage and duration, reported findings, and interpretations of the results.

Results

Cyanidin and C3G may have an essential role in human health. Studies considered these metabolites to work synergistically as a gastroprotective by inhibiting pro-inflammatory cytokines, reducing inflammation, and antioxidants. Of the 6 articles, 3 discussed in vitro studies, 1 discussed in vivo studies, and 2 discussed both in vitro and in vivo studies. For example, 3 articles described the mechanism for alleviating PUD as an antioxidant that decreases or inhibits ROS productions; 2 articles described the mechanism for alleviating PUD as an anti-inflammatory that inhibits the production of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, IL-10, IL-12, IL-18, and TNF-α,[41–43] These are the key cytokines that contribute to the development and progression of the inflammatory pathways within the gastric mucosa.[44] Of these studies, three articles confirmed the effects of gastroprotective using in vivo studies.

Chemical Structure and Properties of Cyanidin and Cyanidin 3- Glucoside

Cyanidins are natural, organic pigments that belong to the anthocyanins group.[27] They are the most represented pigments in plants,[45,46] including leaves, stems, and flowers, and in fruits and vegetables such as cranberry, blackberry, cherry, grapes, raspberry, apples, plums, peaches, beans, and onions.[26,47–50] Anthocyanins have been categorized to belong to the flavonoid family and possess a C6-C3-C6 molecular structure, 15 carbons constituted by a common skeleton of phenyl benzo-γ-pyran, composed of two phenyl rings (A and B) and a heterocyclic ring (pyran, C).[51] Cyanidin or cyanidol (3,5,7,3′,4′-pentahydroxy flavylium) is a relatively unstable molecule. It is present rarely in free form in plant tissues.[52] Cyanidin predominantly exists as glycosides, where monosaccharides or disaccharides are linked to anthocyanidin analogs through glycosidic bonds.[53] A secondary sugar residue is often attached to the aglycone structure.[54] Its glycosylation gives it better stability and water solubility.[52] Cyanidin is characterized by its high hydrophilicity, with a solubility of 0.049 mg/mL, a Log P of 3.05, a molecular surface area of 114.3 $Å^2$, and molecular weight by mass spectroscopy in tandem with mass spectroscopy (MS/MS) at an m/z of 287.[55] It has a distinctive red-orange color, although this can change with pH, indeed, its solutions are red at acidic pH of < 3, purple/blue/violet at pH 3–10, and green to yellow at basic pH of > 10.[52] However, at very high pH, this compound loses its color due to its molecular degeneration.[27] Moreover, very stable salt formation with heavy metal cations may lead to different colors in plant tissues, in particular when the 3′ and 4′ positions contain free phenolic hydroxyls.[56]

Cyanidin-3-glucoside (C3G) and cyanidin-3-galactoside (C3Gal) were identified as the most widespread cyanidin glycosides in the plant kingdom.[55] Additionally, other glycosides, such as cyanidin-3-arabinoside, cyanidin-3-xyloside, cyanidin-3-sambubioside, cyanidin-3-sophoroside, cyanidin-3-rutinoside, were also found. These derivatives, belonging to the anthocyanin family, provide a basis for detailed exploration of the anthocyanin composition across various plant species.[25]

It has long been assumed that anthocyanidins only, ie, the aglycones of anthocyanins, were absorbed by intestinal cells and entered the bloodstream due to the absence of a bound sugar residue. Previously, it was presumed that anthocyanins were poorly absorbed because specific enzymes to hydrolyze glycosidic bonds were unknown.[25] However, recent research has demonstrated the absorption of glycosidic flavonoids, particularly C3G, an anthocyanin derived from the aglycone cyanidin. C3G is a standard red pigment found naturally in various vegetables and fruits.[57] C3G is a water-soluble secondary metabolite of the monomeric anthocyanin class within the flavonoid family, widely utilized in food products such as yogurt and porridge attributed to their dual role as natural pigments,[58–60] and their potential health benefits from regular consumption.[57] C3G is characterized by its high hydrophilicity, with a solubility of 0.6 mg/mL, a Log P of 0.39, a molecular surface area of 193.4 $Å^2$, and molecular weight by mass spectroscopy in tandem with mass spectroscopy (MS/MS) at an m/z of 449.[61] Furthermore, the UV-visible spectrum analysis of C3G across different pH levels (pH 3–8) revealed that C3G exhibits pH-dependent behavior.[62] Specifically, the results indicate that at pH 3, the absorbance is dominated by the flavylium cation, but this intensity diminishes at pH 4–5. At pH 5, the quinoidal species becomes predominant, and at pH 6–8, C3G transitions into quinoidal and chalcone forms.[62]

Metabolism and Absorption of Cyanidin and Cyanidin 3-Glucoside

In the gastrointestinal tract, most anthocyanins, including C3G, remain stable, particularly in the stomach and upper intestine, where they are primarily absorbed.[57,63,64] As the pH increases in the intestine, anthocyanins lose their color and change form.[53] Although a significant amount (85%) is found in the distal intestine,[65] the stomach is still considered a key site for anthocyanin absorption. The absorption process is accompanied by extensive first-pass metabolism, allowing these compounds to enter the systemic circulation as metabolites.[66] C3G catabolism predominantly occurs in the distal small intestine (the ileum) and the upper large intestine (the colon), where the gut microbiota plays a crucial role in breaking it down.[67–69] Enzymes in the small intestine hydrolyze C3G into aglycones, which are further degraded into phenolic compounds. The gut microbiota cleaves the heterocyclic flavylium ring of C3G, leading to dehydroxylation or decarboxylation. Following these processes, Phase II and multistage metabolites, including bacterial metabolites, enter the liver and kidneys, where they undergo further modifications such as methylation, glucuronidation, and sulfation through enterohepatic and blood circulations.[57,70]

At the oral pH of approximately 6.8, C3G predominantly exists in its quinoidal form, with the glucose moiety enhancing solubility,[71] and nearly 50% of C3G undergoes biotransformation into metabolites like protocatechuic acid (PCA), facilitated by microbial B-glycosidase, which may contribute to its preventive effects against oral diseases.,[68,69,72–75] and in the stomach it is rapidly absorbed by gastric epithelial cells (0.25 to 2 h),[76–78] after intake through active transport mechanisms,[79] including bili translocase, SGLT1 (sodium-glucose transporter 1), GLUT1 (glucose-transporter 1), GLUT3 (glucose-transporter 3), and mono-carboxylated transporter 1 (MCT1).[77,80–82] Despite efficient absorption, extensive first-pass metabolism significantly reduces the bioavailability of intact C3G, although both the intact compound and its metabolites are detectable in plasma shortly after ingestion.[83–86] Upon reaching the small intestine, C3G bioavailability is further diminished by 40–50% due to the intestinal environment and has been confirmed by studies conducted in humans,[87] mice,[88] and rats,[89] where factors such as pH, enzymatic activity, and the food matrix play crucial roles.[90] Although cleavage of the glucose moiety is not required for C3G metabolism, it does facilitate trans-epithelial transport.[76,91] Subsequent metabolism in the small intestine produces Phase I enzymes that metabolize anthocyanins into hippuric acid (HA), vanillic acid (VA), or isovanillic acid (IVA). Subsequently, C3G, cyanidin, PCA, VA, and IVA undergo further metabolism by phase II enzymes, forming their respective glucuronide or sulfate conjugates.[61,67] In the large intestine, C3G and its remaining metabolites are released from fibrous food matrices and undergo further transformation by the gut microbiome.[67] These metabolites are predominantly excreted after additional phase II conjugation, with less than 0.005% C3G remaining intact.[87] The slightly basic pH of the large intestine supports these transformations, leading to the production of various phenolic acids and other metabolites.[71,92,93]

In general, C3G is considered non-toxic within the range of regular dietary consumption. Safe intake levels (LD50) have been established in mice and rats at 25,000 mg/kg and 20,000 mg/kg, respectively, with no observed adverse effects; studies in rabbits administered anthocyanins orally (6 g/kg BW) revealed no changes in blood pressure.[94] C3G is considered safe and anti-mutagenic.[95] Despite C3G's chemical instability and low bioavailability, foods rich in anthocyanin (Figure 3) have shown biological value in treating many acute and chronic human disorders.[96–99] Multiple studies have also confirmed that cyanidin and C3G are essential in human health.

In vitro Studies

The protective effect of these compounds in alleviating PUD is primarily based on their antioxidant ability in vitro studies (Table 1). However, cyanidin, C3G, and their bioactive phenolic metabolites, such as PCA, VA, and FA, can enhance the antioxidant enzyme system by increasing the activities of manganese-dependent superoxide dismutase (MnSOD) and glutathione (GSH).[100,101] Additionally, these compounds down-regulate pro-oxidant system by reducing cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS),[37,101] as well as lowering levels of free radicals, including reactive oxygen species (ROS) such as superoxide anion ($O.^{2\bullet-}$), superoxide hydroxy radicals ($HO^{\bullet}$), alkyl peroxyl radicals ($ROO^{\bullet}$),[102,103] and reactive nitrogen species (RNS).[37] Cyanidin and its derivatives exhibit antioxidant effects primarily through their ability to donate hydrogen atoms or electrons, thereby neutralizing free radicals. The diphenyl structure in the B ring plays a key role in this activity. Additionally, the hydroxyl groups at specific positions (eg, 3' and 4') enhance the antioxidant capacity by stabilizing free radicals.[104–108]

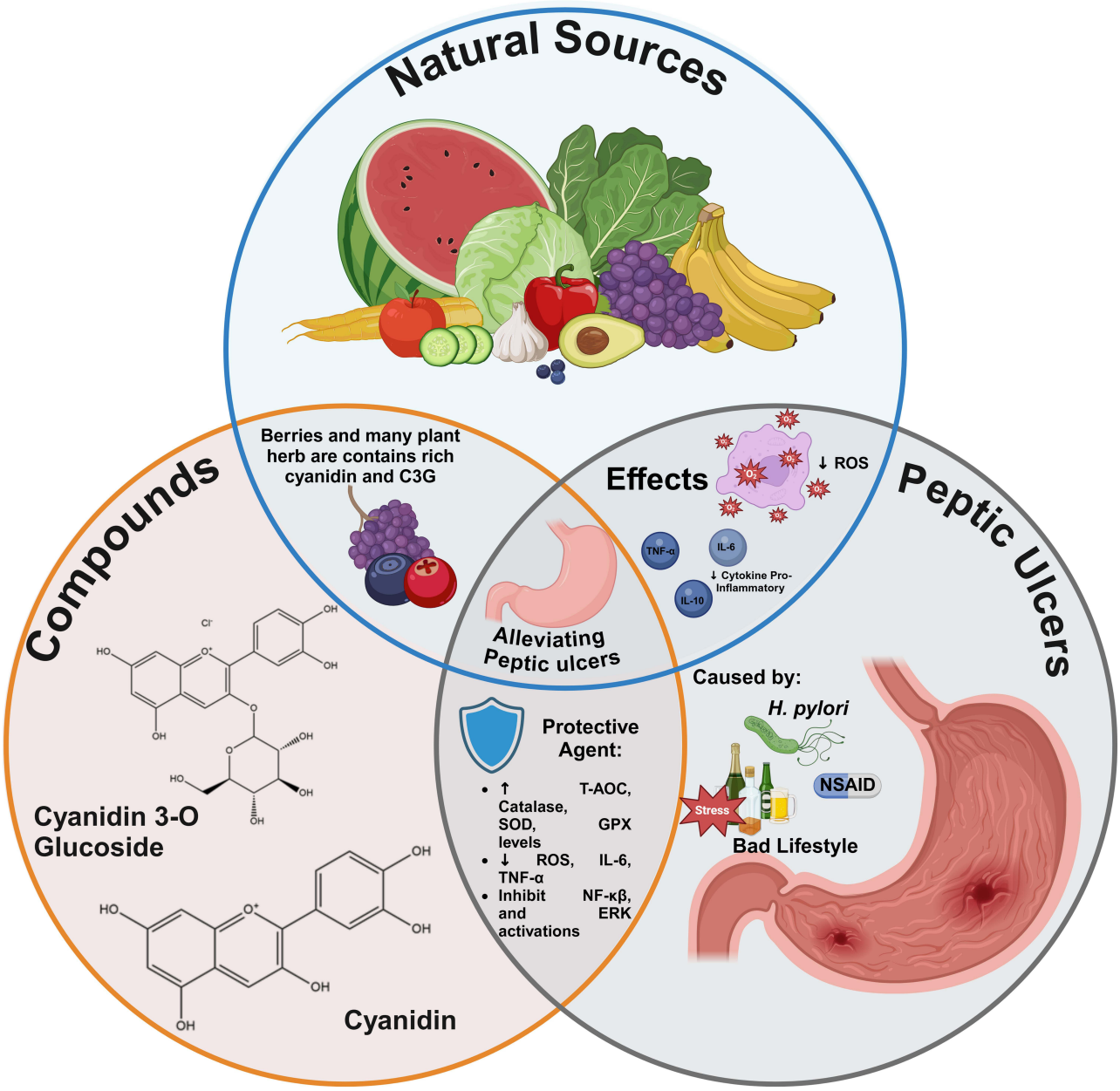


Figure 3 The role of cyanidin and C3G in alleviating PUD.

The in vitro studies also demonstrate that cyanidin and C3G exhibit significant anti-inflammatory effects in addition to their antioxidant activity (Table 1). These compounds inhibit the production of key pro-inflammatory cytokines such as IL-6, IL-10, and TNF-α, which are crucial in the development and progression of gastric ulcers.[41–43]Cyanidin and its derivatives' anti-inflammatory properties extend to gastric ulcers, where they effectively inhibit cytokines secreted by macrophages.[113] Specifically, C3G has been shown to inhibit TNF-α production by 50% and IL-6 production by 30% in human neutrophils,[112] Thus highlighting its potential therapeutic role in managing gastric inflammation.

In vivo Studies

In vivo studies further confirm the anti-inflammatory potential of cyanidin and C3G (Table 2). These compounds significantly reduce the inflammation induced by ethanol and hydrochloric acid, which mimics gastric ulcers.[111] Results from various studies indicate that alcohol consumption is strongly linked to the development of gastric mucosal

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Table 1 In vitro Studies Approach in Cyanidin and Cyanidin 3-O-Glucoside

Medicinal Plant (Family), Collected In, Year	Plant Part Used/ Compound Used	Solvent	Class of Metabolites	Type of Study		%Inhibition or Effective Concentration		Interpretation	Ref.
				Chemical Reaction (Redox) Scavenging Activity Using	Determination of pro-Inflammatory Cytokines in Response to				
Quercus crassifolia Humb. and Bonpl. (Beech). Michoacan. 2018.	Barks	Ethanol	**Cyanidin chloride**, Gallic Acid	NBT Sodium nitroprusside ORAC HClO Fenton Reaction	N/A	EC_{50}	40.9 µg/mL 653 µg/mL 873 µg/mL 1747 µg/mL 2024 µg/mL	Moderate Activity	[103]
Callistemon citrinus (Myrtaceae), Messina, 2020	Flowers	Acetic acid: methanol: water	**Cyanidin 3-Glucoside**, Cyanidin 3-5-diglucoside, Cyanidin-coumaroylglucoside-pyruvic acid, Peonidin-3,5-diglucoside	DPPH TEAC ORAC	N/A	$IC_{50:}$	2.20 µg/mL 1.64 µg/mL 5.66 µg/mL	Strong Activity	[109]
Euterpe oleracea Mart. (Arecaceae), Sao Paulo, 2020	Fruits	Methanol, HCl	**Cyanidin-3-Glucoside**, Cyanidin-3,5-hexoside-pentoside, Pelargonin-3-rutinoside, Pelargonidin-3-glucoside, Peonidin-3-glucoside, Peonidin-3-rutinoside	DPPH	N/A	IC_{50}	90%	Strong Activity	[110]
Prunus cerasus (Rosaceae). N/a	Fruits	Ethyl Acetate	**Cyanidin-3-Glucoside**	N/A	TNF-α IL-6 IL-10	IC_{50}	1.75 µg/mL 1.04 µg/mL 1.99 µg/mL	Strong Activity	[111]
Prunus spinosa L. (Rosaceae). Krasnobród, 2018	Fruits	Methanol: water	**Cyanidin-3-Glucoside**, Cyanidin-3-rutinoside, Peonidin-3-glucoside	Luminol-dependent chemiluminescence	 IL-8 TNF-α	IC_{50}	90% 50% 30%	Strong Activity	[112]

Abbreviations: DPPH, 2,2-diphenyl-1-picrylhydrazyl; EC, Effective Concentration; HClO, Hypochlorous Acid; IC, Inhibition Concentration; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-10, Interleukin-10; NBT, Nitroblue Tetrazolium; ORAC, Oxygen Radical Absorbance Capacity; TEAC, Trolox Equivalent Antioxidant Capacity; TNF-α, Tumor Necrosis Factor-alpha.

Table 2 In vivo Studies Approach in Cyanidin and Cyanidin-3-Glucoside

Isolated Medicinal Plants Authority (Family), Collected In, Year	Plant part, and Extraction Method (Solvent Used)	Class of Metabolites	Animal used in the Preclinical Study (n)	Control (Negative and Positive)	Inducement Method and Dose	Duration (Days)	Results	Interpretation	Ref.
Euterpe oleracea Mart. (Arecaeceae), Sao Paulo, 2020	Fruits, Fractionation (Methanol, HCl)	**Cyanidin-3-Glucoside**, Cyanidin-3,5-hexoside-pentoside, Pelargonin-3-rutinoside, Pelargonidin-3-glucoside, Peonidin-3-glucoside, Peonidin-3-rutinoside	Female Wistar rats (*Rattus norvegicus*) (**200–250 g**) (n= 6)	Vehicle (Water) as control, and Omeprazole (30 mg/kg) as positive control	Ethanol (98% ethanol)	1	The plants that contained anthocyanidin including C3G showed doses 30 and 100 mg/kg were effective as gastroprotective which were reduced by 83% and 67% ulcer area	Strong as Gastroprotective	[110]
N/a	N/a	Purified **Cyanidin Chloride**	Male and female Swiss mice (*Mus musculus*) (n=20)	Vehicle (0.9% saline) as negative control and Lansoprazole (30 mg/kg) as Positive Control	Ethanol (Absolute Ethanol	56	The purified cyanidin showed all doses (5; 10; 20 mg/kg) were effective and indicated a high level of gastroprotection. Male mice at doses 20 mg/kg achieved a 93.4% reduction in lesions ($p<0.01$) and female mice at the same doses achieved an 80.7% reduction in lesions;	Strong as Gastroprotective	[116]
Prunus cerasus (Rosaceae). N/a	Fruits, Sonicated (Ethyl acetate)	Purified **Cyanidin-3-Glucoside**	Male mice *Swiss-albino (Mus musculus)* (**20–35 g**) (n=28)	Vehicle (Saline) as negative control and Ranitidine HCl (50 mg/kg) as Positive Control	Ethanol (60% ethanol) and hydrochloride Acid (60%)	1	The purified C3G showed all doses (10; 15; 20 mg/kg) were effective as gastroprotective indicated 68.5% gastro-lesion reduction in 20 mg/kg doses, respectively	Strong as Gastroprotective	[111]
		Isolated **Cyanidin-3-Glucoside**					The isolated C3G from plants showed all doses (100; 150; 200 mg/kg) were effective as gastroprotection indicated 74.9% gastro-lesion reduction in 200 mg/kg doses, respectively		

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lesions. Chronic ethanol intake has been shown to promote gastric ulceration by decreasing mucus production and reducing blood flow, leading to microvascular injury and triggering inflammatory processes.[114] The damage induced by ethanol is primarily attributed to tissue lipid peroxidation caused by the accumulation of ROS and inflammation.[115] Upon induction of inflammation, both cyanidin and C3G have shown considerable promise in counteracting these ethanol-induced effects by enhancing the integrity of the gastric mucosal barrier.

Based on in vivo studies, cyanidin has demonstrated efficiency as gastroprotection varied between males and females, with males showing reduced myeloperoxidase (MPO) activity. In contrast, females, both supplemented and non-supplemented hormones, exhibited reduced MPO activity alongside increased glutathione (GSH) levels, thus suggesting that the antioxidant systems play a more significant role in females treated with cyanidin compared to males and indicating that MPO and GSH are crucial in reducing inflammation caused by ethanol. MPO, an enzyme found in neutrophils, is closely associated with the body's inflammatory response. Elevated MPO levels typically correlate with increased oxidative stress and inflammation. However, Cyanidin and its derivatives have shown that a reduction in MPO activity leads to decreased oxidative stress and inflammation, thereby contributing to the protective effects against ethanol-induced gastric damage.[116]

Discussion

This study unveils the remarkable potential of cyanidin and C3G as powerful agents in alleviating PUD, combining insights from preclinical studies such as in vitro and in vivo studies. The findings reveal that these compounds offer a dual-action approach to ulcer management, effectively targeting the underlying inflammation and the oxidative damage that exacerbates gastric Injuries. C3G, a glycosylated form of cyanidin, enhances water solubility, stability, and bioactivity. C3G is hydrolyzed by β-glucosidase in the gastrointestinal tract upon ingestion, releasing cyanidin. Both cyanidin and its metabolites are then absorbed and undergo first-pass metabolism in the liver, which involves phase I oxidation followed by phase II conjugation.[36] Hence, these compounds isolated from plants are paving the way for developing targeted and efficacious treatments for PUD. Cyanidin and C3G are metabolized into active phenolic compounds, including PA, VA, and FA, through pathways involving gut microbiota. These stable metabolites enhance antioxidant activity by neutralizing reactive oxygen species (ROS) and modulating pro-inflammatory cytokines such as TNF-α and IL-6. Additionally, the gut microbiota's role in producing low-molecular-weight phenolics further improves their absorption and protective effects on the gastric mucosa.[49,65] Assessing the anti-ulcer potential of cyanidin and C3G is crucial for validating their therapeutic effectiveness and understanding the broader role that plant-based therapies can play in managing complex gastrointestinal conditions (Figure 3).

Oxidative stress plays a pivotal role in the inflammation of the digestive tract, primarily driven by the excessive production of ROS during the oxidative burst by neutrophils.[117] This overproduction leads to progressive intestinal mucosa damage and exacerbates tissue inflammation, prolonged neutrophil activation further accelerates the recruitment of monocytes, which differentiate into macrophages at the site of injury, thereby perpetuating the inflammatory response.[118] The antioxidant properties of polyphenols may counteract this process either by directly scavenging ROS or through indirect pathways, including the modulation of transcription factors like NF-kappaB and the secretion of regulatory cytokines, such as TNF-*α*, which primes neutrophils for oxidative burst.[119] Cyanidin and C3G, with their potent antioxidant properties, have been shown to effectively scavenge ROS, thereby mitigating oxidative stress and its associated inflammatory pathways.[120] This is particularly important as regulating transcription factors, such as the secretion of pro-inflammatory cytokines like TNF-α, is crucial in controlling the oxidative burst that drives the severity of gastric ulcers.[111,121]

The anti-inflammatory effects of these compounds are further highlighted by their ability to inhibit key pro-inflammatory cytokines, such as TNF-α and IL-6, which play a role in the development of gastric ulcers. TNF-α, secreted progressively by macrophages during ulcer formation,[113] and IL-6, a cytokine involved in acute inflammation and immune regulation,[122] Both significantly amplify the oxidative pathways that lead to local tissue damage. Elevated IL-6 levels stimulate the activation of lymphocytes, neutrophils, and macrophages at the site of inflammation, thereby intensifying oxidative stress driven by mitochondrial ROS generation.[123] The regulation of these pro-inflammatory cytokines is essential in determining the severity of gastric ulcers as they contribute to oxidative stress-induced tissue

damage.[124] Furthermore, the anti-inflammatory cytokine IL-10 counteracts this inflammatory response by inhibiting TNF-α production, thereby reducing the overall impact of oxidative stress on gastric tissue.[113] These cytokines exacerbate local tissue damage by activating oxidative pathways and contribute to the overall severity of gastric ulcers.

Furthermore, the study demonstrated that ethanol-induced neutrophil infiltration in the gastric mucosa significantly contributes to lesion formation.[125] This process, characterized by elevated MPO activity (a key marker of neutrophil infiltration), is closely linked to acute gastric injury.[126] The increased presence of neutrophils not only intensifies mucosal damage but also initiates the release of additional pro-inflammatory mediators, thereby escalating the inflammatory response and worsening gastric tissue damage.[127] In the context of antioxidant defense, catalase (CAT) is vital for neutralizing ROS by catalyzing the decomposition of hydrogen peroxide into water and oxygen.[128] GSH, an endogenous antioxidant with a thiol group in its structure, also plays a crucial role in scavenging free radicals or acting as a cofactor for antioxidant enzymes.[129,130]

Ethanol administration can increase ROS levels while depleting GSH levels in the gastric mucosa.[131] However, treatment with cyanidin demonstrated a beneficial effect, with a dose of 5 mg/kg enhancing catalase activity in male rats and a dose of 20 mg/kg elevating GSH levels in ovariectomized female rats, compared to the control group. Cyanidin and C3G exhibited gastroprotective effects through different mechanisms in this model. Additionally, estrogen appears to be directly linked to the antioxidant defense, as it activates antioxidant enzymes and reduces ROS levels.[132] Based on a study, men over 70 years old and postmenopausal women had a higher incidence of peptic ulcers, likely due to decreased serum estrogen levels leading to reduced mucus production in the stomach.[133] Estrogen is also known for its anti-inflammatory properties and ability to delay gastroesophageal reflux development.[134] Furthermore, research has shown that estrogen possesses anti-ulcer activity by maintaining the gastric mucus layer and providing protection through its antioxidant properties.[135]

These findings highlight the gastroprotective effects of cyanidin and C3G against ethanol-induced damage, mediated through their influence on antioxidant and anti-inflammatory pathways (Figure 3). These compounds significantly suggested mechanisms of action, including cytoprotective effects, such as increasing gastric mucus production, and antioxidant activities that prevent and reduce lipid peroxidation and myeloperoxidase activity in the gastric mucosa. Additionally, their anti-inflammatory properties are evident in their ability to inhibit pro-inflammatory cytokines responsible for ulceration. Furthermore, the small size of these metabolites allows them to efficiently pass through the mucus layer, facilitating interactions with colonic cells and initiating an immune response.

Conclusion

This review elaborates on an overview of the complex and multifaceted processes involved in the absorption, metabolism, and safety of anthocyanins, particularly cyanidin and C3G, as promising agents for mitigating PUD from preclinical studies. Cyanidin and C3G, derived from various plants, exhibit a dual-action approach, addressing inflammation and oxidative stress (key contributors to the progression of gastric injuries). Both anthocyanins are effective in scavenging ROS, thereby reducing oxidative stress and inflammation, which are critical in the development and severity of gastric ulcers. Cyanidin and C3G inhibit key pro-inflammatory cytokines like TNF-α and IL-6, and thus can be developed as novel therapies for alleviating PUD. While the study provides valuable insights into the potential therapeutic effects of cyanidin and C3G, we encountered some limitations, such as the fact that all the articles are primarily based on preclinical studies, which may not fully translate to human physiology. Moreover, there are varying effects observed between genders, as well as the influence of hormonal factors like estrogen, and the mechanisms by which these compounds exert their protective effects require more in-depth exploration in clinical settings to confirm their therapeutic effects in humans. From a future perspective, clinical trials are necessary to validate the therapeutic efficacy and safety of cyanidin and C3G in humans, these studies should focus on different demographic groups, considering ethnicity, age, gender, BMI, and hormonal status, to understand better how these variables influence the outcomes. However, this review provides scientific evidence supporting the utilization of anthocyanins as a potential approach for treating PUD.

Abbreviations

C3G, cyanidin-3-glucoside; CAT, catalase; COX-2, cyclooxygenase-2; FA, ferulic acid; GLUT1, glucose-transporter 1; GLUT3, glucose-transporter 3; GSH, glutathione; H2RA, histamine-2 receptor antagonist; HA, hippuric acid; HO, superoxide hydroxy radicals; IL-10, interleukin-10; IL-12, interleukin-12; IL-18, interleukin-18; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8,

interleukin-8; iNOS, inducible nitric oxide synthase; IVA, iso-vanillic acid; MnSOD, manganese-dependent superoxide dismutase; MPO, myeloperoxidase; NSAID, non-steroidal anti-inflammatory drugs; O2−, Superoxide anion; PCA, protocatechuic acid; PPI, Proton Pump Inhibitor; PUD, peptic ulcer disease; RAHS, rebound acid hypersecretion; RNS, reactive nitrogen species; ROO, alkyl peroxyl radicals; ROS, reactive oxygen species; SGLT1, sodium-glucose transporter 1; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor 1; VA, vanillic acid.

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Disclosure

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