Therapeutic Potential of *Croton Blanchetianus* for the Treatment of Gastric Ulcers: A Brief Review

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Abstract: Natural products are considered one of the main sources that contribute to advances in research in medical science, in such a way that the elucidation of the mechanism of action enables the industry to design new drugs, providing new applications, inputs, and alternatives for the treatment of various pathologies. Studies show the importance of secondary metabolites, presenting pharmacological, microbiological, and food functions. Given the above, this review aims to describe the importance of studies with natural products, emphasizing the gastroprotective activity of the *Croton* genus. The genus *Croton* (Euphorbiaceae) is characteristic of the Brazilian biome, especially in the semiarid climate. The species of the genus have anti-inflammatory and curative properties, correlating their gastroprotective effect. Among the plurality of species, one that has therapeutic and economic potential is *Croton blanchetianus*. The population widely uses the species as it has medicinal properties, used to prepare teas and compresses, helping with inflammatory processes and pain. Thus, it was observed that *Croton* species have great potential in anti-inflammatory activity and gastroprotection. Therefore, studies with the *Croton blanchetianus* species should be deepened regarding this activity, providing greater knowledge about this plant.

Keywords: natural products; gastric ulcer; *Croton*.

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1. Introduction

Brazil has one of the greatest biological diversities in the world, and currently, all this biodiversity has a high economic value for several purposes, since natural products are used in the food industry, as well as for the development of new therapeutic approaches [1]. Natural products are considered one of the main sources that contribute to the research advances in medical science, in such a way that the elucidation of the action mechanism of the active principle enables the industry to design new drugs, providing new applications, inputs, and alternatives for the treatment of various pathologies [2].

In recent times, great advances have been observed in studying chemical compounds present in plant species, an essential premise for producing new therapeutic products [3]. One of the main products of plant origin is the plant extracts, composed of a mixture of several
molecules with the therapeutic value obtained from medicinal plants by means of specific processes [4].

Among the plurality of species, one that holds therapeutic and economic potential is *Croton blanchetianus*. It is a species of the Euphorbiaceae family, characteristic of the Brazilian biome, especially the semiarid climate. It is characterized as a shrub that can reach up to a small tree, adapted to arid conditions [5]. For the species, there are reports of the presence of several secondary metabolites, such as flavonoids, alkaloids, and terpenes, which are responsible for the biological activities already described for the species [6].

The literature provides several studies on the therapeutic activities of *Croton blanchetianus*, among which are the gastroprotective, anti-inflammatory, antinoceptive, and antimicrobial activities, among others [5-7]. Thus, this review describes the importance of studies with natural products regarding their pharmacological activities, emphasizing the gastroprotective activity of species of the genus *Croton*.

2. Materials and Methods

This study is a literature review carried out in several databases (SciELO, PubMed, and Science Direct) and included original articles, books, dissertations, and theses. The main aspects related to anti-inflammatory, antimicrobial, and gastroprotective activities and the chemical composition of the species, published between 2006 and 2021, were considered. The keywords used were: secondary metabolites, plant extract, *Croton*, gastroprotection, and gastroprotective mechanism.

3. Results and Discussion

3.1. Secondary Metabolites.

Plants have a variability of secondary metabolites synthesized by several metabolic pathways, which can protect the species and can be considered active principles, many of which are still unknown. Several studies show the importance of these compounds, from the performance of pharmacological or toxicological functions to their use in the food and cosmetics industries [8-11].

Such bioactive compounds can be extracted from different parts of plants, such as leaves, fruits, flowers, seeds, bark, and roots [12]. In this sense, products obtained from natural sources, such as plant species, have been the object of study. Considering the above and the importance of secondary metabolites, in this review, we will emphasize the three major groups of secondary metabolism, polyphenols, terpenes, and alkaloids, exploring the general view of the application of these molecules in gastric ulcers [9, 13].

3.1.1. Polyphenols.

The largest group of secondary metabolites is polyphenols, consisting of compounds with an aromatic ring and can be found in both simple and complex forms. Among the compound classes that are part of this group are flavonoids and tannins, which will be discussed here [14].

Flavonoids constitute one of the largest and most important groups of phenolic compounds distributed in most plant species. Structurally, they are composed of a chain of the C6-C3-C6 type, which comprises 3 rings (A-B-C) [15]. The group is subdivided into classes
of flavanones, flavones, flavonol, flavonols, flavanol, and flavandiol, in addition to isoflavones and anthocyanidins (Figure 1), which are present in different concentrations in plant species and are recognized for having good antioxidant activity [3, 16, 17]. In addition to antioxidant activity, they have anti-inflammatory, antimicrobial, and antiviral properties, and some reviews report the benefits of flavonoids in reducing cardiovascular disease and obesity [16], eye diseases [11], anticancer [18], among others [1].

![Flavonoids groups](https://doi.org/10.33263/BRIAC126.82198230)

Figure 1. Flavonoids groups.

Tannins are also part of the polyphenols and are present everywhere in the plant. Most tannins have a high molecular weight (between 1,000 and 5,000) and are recognized for their ability to form strong complexes with carbohydrates and proteins. In addition, they protect the plant against microbial agents, herbivores, and insects [19-21]. Tannins are divided into two classes: hydrolyzable tannins, whose main representatives are gallic acid and ellagic acid, and condensed tannins, consisting of oligomers and polymers formed by several flavon-3-ol units, whose main representative is catechin [22, 23] (Figure 2).

![Tannins groups](https://doi.org/10.33263/BRIAC126.82198230)

Figure 2. Tannins groups.
For gastroprotection activities, these chemical compounds have an important role. The evaluation of the methanolic extract of *Mouriri pusa* leaves, rich in polyphenols, showed the important role of these compounds in the protection of gastric mucosa [24]. de Cândida dos Santos, Bonamin, Périco [25] studied the leaves of *Byrsonima intermedia* and obtained fractions rich in polyphenols, such as flavonoids and tannins, and obtained a good gastroprotective effect on ulcers induced by ethanol, indomethacin, and cysteamine. In another study performed with hydroalcoholic extract of *Urera baccifera* leaves [26], which presented flavonoids as the main metabolites, evidenced the role of the class as an anti-inflammatory and healing agent in ethanol-induced ulcers.

3.1.2. Terpenes.

Terpenes are natural compounds built from isoprene units, also known as terpenoids or isoprenoids, occurring in nature as hydrocarbons, alcohols, glycosides, and ethers, aldehydes, ketones, carboxylic acids, and esters. Some terpenes are part of the composition of volatile oils (or essential oils) and have fat-soluble characteristics. These compounds can be found in leaves, roots, stems, flowers, barks [27-29]. Some activities of terpenes present in plant species are well described in the literature, such as anticancer [30], antifungal [31], and antioxidant activity [32].

Research describes the use of essential oils in gastroprotective mechanisms, decreasing the areas of ulcer lesions. For example, a study involving essential oil obtained from the bark of *Vanillosmopsis arborea* [33] contained α-bisabolol as the compound that acted most in the gastroprotective effect in ethanol-induced ulcers. In another study with terpenes, nerolidol was used to obtain an inclusion complex with β-cyclodextrin, performing gastroprotective action in ulcers induced by ethanol and indomethacin and anti-inflammatory activity in symptoms of rheumatoid arthritis, demonstrating the healing potential of this compound [34].

3.1.3 Alkaloids.

Alkaloids constitute another large group of substances that are part of secondary metabolism. The species containing alkaloids constitute a varied group, both with respect to taxonomy and chemical composition. The presence of basic nitrogen (whether in the heterocyclic ring or not) becomes a common factor [21, 35]. In addition to plants, they can be found in algae, fungi, and animals [36]. Alkaloids have several biological properties already reported, including anti-inflammatory and antioxidant activity[37], antitumor, antimycotic activity [38], and antifungal [39].

Studies conducted for the healing of gastric ulcers show the alkaloids as compounds that act with this property, as reported in Ugwah, Ugwah-Oguejiofor, Etuk [40], which used the aqueous extract of *Balanites aegyptiaca* bark to study the antiulcer activity. The phytochemical profile showed the presence of alkaloids, terpenes, saponins, and flavonoids, being the main responsible for the healing action of the injured area. In another study, the 2-phenylquinoline compound derived from *Galipea longiflora* bark was extracted. Its use in gastric lesions decreased the area of ulcers and increased the levels of mucosal antioxidant factors, corroborating the gastroprotective activity [41].

Given the described works, it is possible to infer that the chemical compounds in plant species promote a healing and protective effect on gastric lesions. In Figure 3, some compounds that act in the gastroprotective activity are described.
3.2. Gastroprotection and natural products.

3.2.1. Gastric ulcer.

The stomach is responsible for storing, mixing food with gastric secretions, and progressively emptying the small intestine. The gastric mucosa consists of mucus-secreting cells and two types of tubular glands, the oxyntic glands, acid-forming, where the hydrogen pump has the main role in the secretion of hydrochloric acid; and the pyloric glands, which in addition to the production of mucus, participates in the control of gastric secretion [42].

Mucus has very important characteristics, with lubricating and protective function of the gastrointestinal tract wall. When the mucosa is not protected, gastric lesions occur, which can progress to ulcers and cancer [25]. Regarding ulcers, this is the term used to indicate the existence of a mucosal lesion, which is caused by an imbalance that occurs between factors that protect the mucosa and factors that attack the mucosa (Figure 4). Therefore, the lesions result from the association between gastric hypersecretion and the physiological imbalance between gastric hormones. Such lesions can lead to loss of local mucosal tissue, promoting the appearance of wounds in deeper areas of the mucosa [43].

Several factors may be related to the development of gastric ulcers, ranging from physiological changes to infections by microorganisms, especially *Helicobacter pylori* infection and indiscriminate use of nonsteroidal anti-inflammatory drugs. In addition, other factors can cause the emergence of ulcers, such as smoking, use of corticosteroids, excessive use of alcohol, and dietary habits [44].
3.2.2. Treatment.

The treatment and control of gastric ulcers are primarily aimed at raising the gastric pH and allowing the gastric mucosa to heal, and such results are achieved with the use of antacid drugs, anticholinergics, H₂ histamine receptor antagonists, and proton pump inhibitors. However, the occurrence of side effects is widely observed [45].

Antacids interact with hydrochloric acid because they are weak bases, thus neutralizing gastric acid and reducing the formation of pepsin. This treatment promotes immediate relief of symptoms, but it is temporary and is not considered a definitive therapy. Among the class representatives are aluminum hydroxide, magnesium hydroxide, sodium carbonate, and calcium carbonate [46, 47].

H₂ receptor antagonists act by reversibly and competitively blocking the binding of histamine to their respective receptors in the membrane (CYP450), thus achieving suppression of gastric acid secretion. Among the main representatives of the class are cimetidine, ranitidine, nizatidine, and famotidine. These drugs act by partially inhibiting acid secretion stimulated by gastrin, and their efficiency occurs mainly at night [46].

Proton pump inhibitors are considered the most effective therapeutic agents in treating ulcers; their main mechanism of action is to irreversibly inhibit the final step of acid secretion through the H⁺/K⁺-ATPase pump. Among the main representative drugs of the class are omeprazole, lanzoprazole, pantoprazole, and esomeprazole. The therapeutic efficacy of the class is superior to H₂ receptor antagonists and antacids [46].

Despite the diversity of synthetic drugs used in gastroprotection, there are numerous side effects caused by constant use; some of these effects are related to certain classes of drugs and are described in table 1.

| Treatments                      | Side Effect                  | Reference |
|--------------------------------|------------------------------|-----------|
| Antacids                       | Diarrhea                     | [46]      |
|                                | Constipation                 |           |
|                                | Hypokalemia                  |           |
| Proton Pump Inhibitors (agents) | Acute coronary syndrome      | [48]      |
|                                | Major cardiovascular events  |           |
|                                | Risk of stroke               |           |
3.2.3. Use of medicinal plants as an alternative.

In addition to the above-mentioned allopathic medicine, the use of phytotherapeutic drugs to treat this pathology is also worthy of note. In the list of herbal medicines available in the Brazilian market, two medicines are used for the treatment of gastric ulcers: Maytenus ilicifolia (Schrad.), popularly known as “espinheira-santa”, which has a well-described gastroprotective activity [56]; and, Cynara scolymus L., known as “alcachofra”, which, in addition to gastroprotective activity, has the antioxidant and anti-inflammatory potential [57].

Therefore, one of the alternatives for treatment with fewer side effects, good results, and low cost are the products obtained from medicinal plants [58]. Studies proving the effectiveness of medicinal species in gastroprotection are described by Freitas, Fernandes, Piauilino [59], who reported the gastroprotective effect of the ethanolic extract of Zanthoxylum rhoifolium, increasing mucus and stimulating endogenous prostaglandins, besides presenting an antioxidant mechanism. Studies by de da Silva, Martins, de Oliveira [60] showed that allantoin, isolated from the species M. nodosa, exhibited a gastroprotective role, being associated with reducing the inflammatory process.

The gastroprotective activity can be mediated by several pathways, some of which are related to the involvement of nitric oxide (NO), prostaglandins, described in the research of which, based on a tea produced by infusion of Sedum dendroideum, promoted gastroprotection of ulcers induced by ethanol and indomethacin through the mediation of NO. Opioid receptors, α2-adrenergic receptors, and NO synthesis and stimulation of mucus secretion mediated by prostaglandins were responsible for the gastroprotective effect of the hydroalcoholic extract of Caryocar coriaceum leaves in the study by de Lacerda Neto, Ramos, Santos Sales [61].

Corroborating such evidence, species of the genus Croton have anti-inflammatory and healing properties, besides studies correlating their effect on gastroprotection. The essential oil of Croton rhunnifoliioides showed proven gastroprotective effects, decreasing the amount of gastric acid present in the stomach and showing potential antiulcerogenic effect (Vidal, Oliveira Brito Pereira Bezerra Martins, de Alencar Silva [58]. In the study of de Nascimento, Maria-Ferreira, Dal Lin [62], with the species C. cajucara, the extract showed a decrease in ulcers and preservation of gastric mucus due to the secondary metabolites present in the genus of this plant that help in this action.

Júnior et al., obtained a hydroalcoholic extract of C. campestres roots and observed the inhibition of lesions in the stomach, helping to protect the tissue [63]. In the studies of Wolff Cordeiro, Aparecida Pinto, Nazari Formagio [64], the gastroprotective activity was also proven using the methanolic extract of C. urucurana bark, promoting increased mucus production and decreased gastric acid production.

3.4. Gênero Croton.

It is a genus of the Euphorbiaceae family, characteristic of the Brazilian biome,
especially the semiarid climate. It is characterized as a shrub that can reach up to a small tree, adapted to arid conditions [65]. The genus *Croton* has approximately 1300 species spread in tropical regions, and about 350 species are in Brazil, most of them located in the Northeast. The plants of this genus have chemical compounds that exert biological activities, but many are still unknown [66].

The *Croton* genus is rich in phenolic compounds and terpenes and is usually found in the leaves, roots, and fruits of the plants, with flavonoids, diterpenes, and alkaloids being the most found secondary metabolites [67, 68]. These metabolites have several properties already described, such as anti-inflammatory, antioxidant, antimicrobial, analgesic, anticancer, diabetes, and hypertension prevention [65, 69].

Several studies are being conducted with plants of the genus of *Croton*. da Silva Brito, Silva, Malheiro [66] conducted a study characterizing an essential oil of *Croton argyrophyllus*, in which it observed antioxidant and antimicrobial action, inhibiting the growth of gram-positive and gram-negative bacteria. An ethanolic fraction of *Alcalypha indica* and *Croton bonplandianus* [70] showed dual antibacterial and anticancer activity by decreasing the growth of multidrug-resistant gram-negative bacteria and blood cancer cells. According to the work of [68], *Croton velutinus* species has phenylpropanoid derivatives, which were able to inhibit the growth of cancer cell lines, trypanocidal and anti-inflammatory activity.

3.4.1 Croton blanchetianus.

*Croton blanchetianus* is a species found in the Caatinga, popularly known as the quince tree. It has simple leaves containing phenolic compounds that help heal disorders in the body [5]. It is a species widely used by the population because it is reported to have medicinal properties, being used in the preparation of teas, compresses, baths, helping in inflammatory processes and pain [7].

Studies of Pereira et al. (2020) correlated the composition of the ethanolic extract of *C. blanchetianus* with potential leishmanicidal action, presenting activity against promastigotes and amastigotes forms of *L. amazonenses* and *L. infantum*. Another research with the species [6], showed antibiofilm action against strains of *S. mutans* and *S. parasanguinis* from diterpenes present in the plant root, exerting therapeutic potential in oral streptococcal infections. Moreover, its action in inflammatory processes is also described in the literature, as in [7], who studied the ethanolic extract of *C. blanchetianus* leaves and observed a decrease in pain and inflammation in mice, presenting analgesic activity. Recently, studies [71] demonstrated the absence of toxicity of a polyphenol-rich fraction obtained from the species leaves' ethanolic extract and increased antioxidant activity.

Considering the above, the studies with the species *Croton blanchetianus* have demonstrated good results against inflammation and antimicrobial action. However, studies on gastroprotection are not described for this species, even though the activity is proven for some species of the genus, thus contributing to good results with *C. blanchetianus*.

4. Conclusions

Plants have a variety of pharmacological activities, being used in several ways to treat diseases. The secondary metabolites in plants play a fundamental role in these activities, providing greater knowledge about these natural products. Among the therapeutic potentials, the gastroprotective activity is being widely studied, where the compounds present in the plants
improve the production of gastric mucus and tissue healing. Thus, we have seen that the plants of the genus *Croton* have great potential in anti-inflammatory activity and gastroprotection. Therefore, studies with the species *Croton blanchetianus* should be deepened regarding this activity, providing greater knowledge about this plant.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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