Abstract: Peptic ulcer disease is a deep gastrointestinal erosion disorder that involves the entire mucosal thickness and can even penetrate the muscular mucosa. Numerous natural products have been evaluated as therapeutics for the treatment of a variety of diseases, including this one. These products usually derive from plant and animal sources that contain active constituents such as alkaloids, flavonoids, terpenoids, tannins and others. The alkaloids are natural nitrogen-containing secondary metabolites mostly derived from amino acids and found in about 20% of plants. There has been considerable pharmacological research into the antiulcer activity of these compounds. In this work we review the literature on alkaloids with antiulcer activity, which covers about sixty-one alkaloids, fifty-five of which have activity against this disease when induced in animals.

Keywords: Alkaloids; Antiulcer activity; Peptic ulcer; Review.
Introduction

For over a century, peptic ulcer disease has been one of the leading causes of gastrointestinal surgery, with high morbidity and mortality rates. The prevalence of gastrointestinal ulcers differs around the world: duodenal ulcers are dominant in the Western populations and gastric ulcers are more frequent in Asia, especially in Japan. As the prevalence of this disease increases over time, one would expect peptic ulcers to continue to have a significant global impact in the basic health and economic systems and in patients’ life quality [1].

Peptic ulcers are a deep gastrointestinal erosion disorder that involves the entire mucosal thickness, penetrating the muscular mucosa [2]. For decades it was believed that gastrointestinal ulcerations were caused by the excessive secretion of gastric acid, but many patients presenting such ulcerations had normal acid secretion rates [3]. Then, researchers reported that peptic ulcers were caused by an imbalance between the aggressive factors and a number of known defense mechanisms. Exogenous aggressive factors such as smoke, anti-inflammatory drugs, alcohol, stress, fatty foods and *Helicobacter pylori* infections triggered tissue necrosis through mucosal ischemia, free radical generation and cessation of nutrient delivery, hydrochloric acid together with pepsin, pancreatic enzymes and bile decreased the defense mechanisms of gastrointestinal mucosa such as the intercellular junctions, local blood flow, mucus/bicarbonate secretion and cellular growth [2, 4, 5].

In recent years, a large advance in chemical and pharmacological studies has contributed to the knowledge about new therapeutically active compounds obtained from the natural products [6]. These compounds can be used directly as leads for the development of new medicines or as pharmacological tools to discover new active compounds, so they can be life-saving or determine the quality of life in long-lasting diseases [7, 8]. However, the incorrect use of the natural products offers dangers to society, so it is important to identify the active compounds, linking its structure with the biological activity and report the correct manner to use them with regards to dose, route of administration and frequency of use [9].

The natural active compounds classes or secondary metabolites as alkaloids, flavonoids, terpenoids, tannins and others have attracted researchers to investigate their chemical, toxicological and pharmacological features. The alkaloids represent a group of natural products that has had a major impact throughout history on the economic, medical, political and social affairs of humans. They are a diverse group of low molecular weight nitrogen-containing compounds derived mostly from amino acids [10]. These secondary metabolites are found in about 20 % of plant species and they classified as true alkaloids, which have nitrogen atoms in heterocyclic rings, protoalkaloids, which do not have the nitrogen atom(s) in heterocyclic rings and pseudoalkaloids, which don’t derive from amino acids but may have nitrogen atoms in heterocyclic rings [11].

Several alkaloids are being used in therapeutics and as pharmacological tools. A wide range of biological activities of alkaloids have been reported: emetic, anti-cholinergic, antitumor, diuretic, sympathomimetic, antiviral, antihypertensive, hypnoanalgesic, antidepressant, miorelaxant, antitussigen, antimicrobial and anti-inflammatory [11]. However, the alkaloids and other natural compounds have complex activities and it is necessary to analyze pharmacological activities in the
general tissues, linking the structure with the activity presented. It is common to find pharmacological results where a single experimental model generalizes a biological answer, but these can’t be accepted because all the pathologies in question are also complex and it is necessary to investigate specific experimental models.

In the course of our continuing search for bioactive natural products from plants, we have recently published reviews on crude plant extracts and plant-derived compounds with the following potential activities and uses: as inhibitors of mammary, uterine cervical and ovarian neoplasia [12-14]; as inhibitors of HMG CoA reductase [15]; with central analgesic activity [16]; employed in prevention of osteoporosis [17]; for the treatment of Parkinson’s disease [18]; antileishmanial, hypoglycemic and anti-inflammatory activities [19-22]; as inhibitors of the acetylcholinesterase enzyme [23], inhibitors of the angiotensin-converting enzymes [24], with giardicidal and antileprotic activities [25, 26] and plant extracts with antiulcer activity [27].

In this article, we have reviewed some reports about alkaloids with antiulcer activity in the specialized literature published up to December 2007. The search was carried out on data banks such as SciFinder Scholar, Periódicos CAPES, Pubmed and NAPRALERT (acronym for Natural Products ALERT - University of Illinois in Chicago, U.S.A.). The references were consulted for details of the experimental models used for testing the alkaloids against peptic ulcer, activities, route of administration, organism tested and subtypes of alkaloids studied.

Alkaloids studied in models that investigate the antiulcer activity

For this review we identified sixty-one alkaloids studied in models that evaluate the antiulcer activity and distributed among thirteen subtypes: imidazole, indole, isoquinoline, non-nitrogen heterocycle alkaloid, phenylalkylamide, piperidine, pyrazine, pyridine, pyrrolidine, pyrrolizidine, quinolizidine, steroid and tropane alkaloids. Fifty-five of these alkaloids have reported antiulcer activity (see Table 1).

Among the different alkaloids showing potent pharmacological properties are the narcotic analgesic morphine, the antimicrobial berberine and the sympathomimetic ephedrine. These isoquinoline alkaloids occur mainly in the Papaveraceae, Berberidaceae and Ephedraceae families [10]. The compounds morphine and ephedrine also have confirmed antiulcer activity, inhibiting gastric lesions induced by reserpine, aspirin or indomethacin [28, 29]. Berberine didn’t display this activity towards ethanol-induced ulcers [30-32], but 7,8-dihydro-8-hydroxypalmatine, a new type of protoberberine alkaloid obtained from the bark of Enantia chlorantha, accelerated ulcer-healing and increased the gastric mucus production after the lesions have been caused by acetic acid, HCl/ethanol or absolute ethanol and it also has been investigated in the pylorus ligature model [33, 34]. Other isoquinoline alkaloids isolated from Coptidis rhizome, coptisine and 8-oxocoptisine, showed protection of gastric mucosa similar to that offered by gastroprotective medicines such as cimetidine and sucralfate [30, 35, 36].

Tropane alkaloids are dicyclic compounds formed by condensation of a pyrrolidine precursor amino acid (ornithine) with three acetate-derived carbon atoms. Some of these alkaloids such as atropine and scopolamine constitute an important class of anticholinergic compounds derived from plants that occur in several Atropa and Datura species [10]. Clinically, they are used to block the muscarinic activity of
acetylcholine showing antispasmodic and antisecretory effects in the treatment of spastic colitis, gastroenteritis and peptic ulcer. They also are useful pharmacological tools to discover new active principles with gastrointestinal tract actions [37-40]. Anisodamine and anisodine are analogs of atropine and they were evaluated as protectors of gastric mucosa against the damaging effects induced in rats by indomethacin, reserpine, stress, pylorus ligature, acetic acid or absolute ethanol. In this research, these compounds inhibited the lesions caused by aggressor agents and altered the gastric acid secretion through increase of luminal gastric output of basal bicarbonate and pH [39, 41-43]. Another well known tropane alkaloid, cocaine, showed antiulcer activity against ulcers induced by reserpine in rats when it was used in the dose of 10 mg/kg by oral route of administration [29]. This substance is obtained of the *Erythroxylum coca* leaves and has multiple actions in the central and peripheral nervous system. It is a psychomotor stimulant with a strong abuse potential and has ability to dominate or decreasing behaviors such as eating and sleeping.

A pyridine alkaloid well known in society is nicotine, which is found in the Solanaceae family, mainly in the dried leaves of the tobacco plant *Nicotiana tabacum* Linné. This substance acts on the nicotinic receptors of acetylcholine in autonomic ganglia, adrenal medulla, neuromuscular junction and brain of mammals. The chronic use of nicotine may result in psychologic and physical dependence. However, this alkaloid protected the stomach from damage induced by aspirin by decreasing hemorrhages and increasing the pH gradient/gastric fluid volume [44].

Quinolizidine alkaloids such as matrine, 13-alpha-hydroxymatrine and oxy-matrine were isolated from *Sophora flavescens* (Fabaceae) and they were experimentally tested for inhibition of gastric ulcers induced by pylorus ligature, water immersion stress and indomethacin. These alkaloids decreased the acid secretion and inhibited the gastric motility [45-49].

A piperidine alkaloid is piperine, which has a pungent taste and was studied in connection with the gastric mucosa damage caused by stress, indomethacin, ethanol or pylorus ligature in rats or mice. This substance protected the stomach against ulceration by decreasing the volume of gastric juice, gastric acidity and pepsin-A activity in doses of 1.5 mg/kg and 25 mg/kg after intravenous and oral administrations, respectively [50, 51]. Capsaicin is a phenylakylamide alkaloid and it also has a pungent taste. This substance provides a selective probe for mechanisms involving slowly conducting primary afferent neurons. In the stomach, capsaicin (0.3 nanomol/kg - 10 mg/kg) stimulates these neurons and signalizes for protection inhibiting the acid secretion, stimulating the alkali/mucus secretions and mainly increasing the gastric mucosal blood flow which help in prevention and healing of ulcers against injury caused by aggressive agents. However, neurotoxic doses of capsaicin have augmented the susceptibility of gastric mucosa to injury caused by strong irritants [52, 53].

Steroidal alkaloids have been found in the Apocynaceae, Buxaceae, Liliaceae and Solanaceae families. In this review, pachystermine A, pachysamine A, epipachysamine A, pachysandrine A and spiropachysine obtained from *Pachysandra terminalis* (Buxaceae), used in Ainu folk medicine for gastrointestinal diseases, were investigated for their preventive effects on gastric lesions induced by water-immersion stress in mice and the results this evaluation suggested that these alkaloids may contribute partly to the traditional use of the plants for the gastrointestinal complaints [54].

An important class of alkaloid is the indole constituted by melatonin, cantinone, hirsuteine, reserpine, lysergic acid (LSD), yohimbine and nigakinone. Melatonin has been found in algae and humans. This human hormone is secreted by pineal gland and gastrointestinal cells. Moreover, it has...
antiulcer activity because showed to protect the gastric mucosa from the damage caused by ischemia-reperfusion and absolute ethanol through of the attenuation of the gastric blood flow failed and scavenging of free radicals [55]. Reserpine was isolated of *Rauwolfia serpentina* (Apocynaceae) and didn’t show antiulcer effect in the dose of 2.5 mg/kg when the gastric ulcers were induced by stress in mice [46], while yohimbine, obtained of *Pausinystalia yohimbe* (Rubiaceae), was active in the reduction of gastrointestinal ulceration [56]. Other alkaloids such as hirsutine, hirsuteine, and rhynchophylline isolated from the domestic plant *Uncaria rhynchophylla* Miq. showed mild central depressive, anti-spasmodic and hypotensive effects in mice or rats. These substances also were effective in the dose of 60 mg/kg against gastric lesions, while isorhynchophylline didn’t have a preventive effect on the development of gastric erosions in mice [56]. Nigakinone and methylnigakinone are also indole alkaloids and they can be found in *Picrosma quassioides*, *P. ailanthoides* or *Ailanthus altissima*. These substances had antiulcer effects associated with decreases in gastric acid/pepsin secretions and protection of the mucous membrane [57, 58]. Cantin-6-one and 4-methoxycantinone are alkaloids extracted from Simaroubaceae plants. These substances were found in *Quassia amara*, *Simaba multiflora*, *S. polyphylla*, *S. feruginea* and *Eurycoma longifolia* which are popularly indicated for gastrointestinal disorders, obesity, anti-inflammatory, stimulant of the intestinal motility and central nervous system activities. These compounds were effective against gastric lesions induced by ethanol and indomethacin [59].

The pyrrolizidine alkaloids integerrimine, retrorsine, senecionine, usaramine and seneciphylline were extracted from *Senecio brasiliensis*. These alkaloids demonstrate significant activity in acute and chronic gastric ulcers in the dose of 12.5 mg/kg. These alkaloids increased free mucus and prostaglandin in the mucosal gastric. Moreover, they showed a reduction of exfoliation of superficial cells, hemorrhages and blood cell infiltration that can be mediated by increase in gastrin secretion and mRNA expression of epidermal growth factors [60].

**Table 1. Alkaloids with gastrointestinal antiulcer activity**

| Substance                                           | Experimental models/dose – Route of administration | Organism tested | Effect          |
|-----------------------------------------------------|-----------------------------------------------------|-----------------|-----------------|
| **Imidazole alkaloids**                              |                                                     |                 |                 |
| Allantoin                                           | Phenylbutazone induced ulcer/6 g/kg – gastric intubation */oral | Rat             | Active [61]     |
|                                                     |                                                     | Human adult     | * [62]         |
| Histamine, *para*-coumaroyl                         | */ 100 mg/kg – intragastric                          | Mouse           | Equivocal [63]  |
| Substance | Experimental models/dose | Organism tested | Effect |
|-----------|-------------------------|----------------|--------|
| 4-Methoxycantin-6-one | 50% ethanol induced gastric ulcer/2.5; 10 and 20 mg/kg – oral and intraperitoneal | Mouse | Active [59] |
| Hirsuteine | */60 mg/kg – intraperitoneal | Mouse | Active [56] |
| Hirsutine | */60 mg/kg – intraperitoneal | Mouse | Active [56] |
| LSD-25 | 5-HT induced gastric ulcers/30mg/kg – intramuscular | Guinea pig | Active [64] |
| Melatonin | */intragastric Ischemia-reperfusion induced ulcer/intragastric | Rat | Active [55] |
Table 1. Cont.

| Substance                | Experimental models/Route of administration | Organism tested | Effect       |
|--------------------------|---------------------------------------------|-----------------|--------------|
| Nigakinone               | */* Pylorus-ligated induced ulcer/31.3 mg/kg - * | Rat             | Active [57]  |
|                          |                                             |                 |              |
| Nigakinone, methyl       | Pylorus-ligated induced ulcer/62.5 mg/kg - * | Rat             | Active [58]  |
|                          |                                             |                 |              |
| Reserpine                | Stress induced ulcer/2.5 mg/kg – subcutaneous | Mouse           | Inactive [46]|
|                          |                                             |                 |              |
| Rhynchophylline          | */60 mg/kg – intraperitoneal                | Mouse           | Active [56]  |
|                          |                                             |                 |              |
| Rhynchophylline, iso     | */60 mg/kg – intraperitoneal                | Mouse           | Inactive [56]|
|                          |                                             |                 |              |
Table 1. Cont.

| Substance                | Experimental models/Route of administration | Organism tested | Effect       |
|--------------------------|---------------------------------------------|-----------------|--------------|
| Tabersonine              | */50 mg/kg – intragastric                    | Rat             | Active [34]  |
|                          | ![Tabersonine structure](tabersonine_structure.png) |                 |              |
| Vinpocetine              | */10 mg/kg – oral                           | Human adult     | Active [65]  |
|                          | ![Vinpocetine structure](vinpocetine_structure.png) |                 |              |
| Yohimbine, beta          | */20 mg/kg – intraperitoneal                 | Mouse           | Active [56]  |
|Isoquinoline alkaloids    |                                             |                 |              |
| Berberine                | Ethanol induced gastric ulcer/              | Rat             | Inactive [30]|
|                          | 25 mg/kg – intragastric                     |                 |              |
|                          | */15 mg/kg – gastric intubation              | Rat             | Weak activity [31] |
|                          | Pylorus-ligated induced ulcer/              |                 | Inactive [32]|
|                          | 10 mg/kg – oral                            |                 |              |
| Berberine, oxy           | Ethanol induced gastric ulcer/              | Rat             | Inactive [30]|
|                          | 50 mg/day - intragastric                    |                 |              |
| Substance          | Experimental models/ Route of administration | Organism tested | Effect   |
|-------------------|---------------------------------------------|-----------------|----------|
| Cathinone         | */intragastric                              | Rat             | Active [66] |
| Cathinone, (-)    | Aspirin induced gastric ulcer/              | Rat             | Active [28] |
|                   | 10 mg/kg - intragastric                    |                 |          |
|                   | Indomethacin induced gastric ulcer/         | Rat             | Active [28] |
|                   | 10 mg/kg - intragastric                    |                 |          |
|                   | Phenylbutazone induced gastric ulcer/       | Rat             | Active [28] |
|                   | 10 mg/kg - intragastric                    |                 |          |
| Cathinone, (+)    | Aspirin induced gastric ulcer/              | Rat             | Active [28] |
|                   | 10 mg/kg - intragastric                    |                 |          |
|                   | Indomethacin induced gastric ulcer/         | Rat             | Active [28] |
|                   | 10 mg/kg - intragastric                    |                 |          |
|                   | Phenylbutazone induced gastric ulcer/       | Rat             | Active [28] |
|                   | 10 mg/kg - intragastric                    |                 |          |
| Coptisine         | Ethanol induced gastric ulcer/              | Rat             | Active [30] |
|                   | 0.1 mg/kg - intragastric                   |                 |          |
|                   | 80% ethanol induced ulcer/                 | Rat             | Active [35] |
|                   | 0.1 mg/kg - intragastric                   |                 |          |
|                   | 80% ethanol induced ulcer/                 | Rat             | Active [36] |
|                   | 0.1 mg/kg - intragastric                   |                 |          |
| Coptisine, 8-oxo  | Ethanol induced gastric ulcer/              | Rat             | Active [30] |
|                   | 0.1 mg/kg - intragastric                   |                 |          |
|                   | 80% ethanol induced ulcers/                | Rat             | Active [35] |
|                   | 0.1 mg/kg - intragastric                   |                 |          |
| Corydaline        | */15 mg/kg - oral                          | Human adult     | Active [67] |
| Substance                      | Experimental models/Route of administration | Organism tested | Effect     |
|--------------------------------|---------------------------------------------|-----------------|------------|
| Corydaline, dehydro           | */40 mg/kg - oral                           | Mouse           | Active [68]|
|                                | */*                                         | Bullfrog        | Active [68]|
| Pylorus-ligated induced gastric ulcer/oral | Rat                                          | Active [69]     |
| Stress induced gastric ulcer/oral | Rat                                          | Active [69]     |
| Pylorus-ligated induced gastric ulcer/subcutaneous | Rat                                          | Active [69]     |
| Stress induced gastric ulcer/subcutaneous | Rat                                          | Active [69]     |
| Histamine induced ulcers of duodenum/oral | Guinea pig                                   | Active [69]     |
| Histamine induced ulcers of duodenum/subcutaneous | Guinea pig                                   | Inactive [69]   |
| Reserpine induced gastric ulcer/oral | Rat                                          | Active [69]     |
| Reserpine induced gastric ulcer/subcutaneous | Rat                                          | Inactive [69]   |
| Corydamine                    | /*/*                                        | *               | Active [70]|

| Substance                      | Experimental models/Route of administration | Organism tested | Effect     |
|--------------------------------|---------------------------------------------|-----------------|------------|
| Corydamine, tetrahydro         | */*                                         | *               | Active [71]|

| Substance                      | Experimental models/Route of administration | Organism tested | Effect     |
|--------------------------------|---------------------------------------------|-----------------|------------|
| Ephedrine, nor-n-formyl (-)    | Aspirin induced ulcers/5 mg/kg - intragastric | Rat             | Active [28]|
|                                | Indomethacin induced ulcers/10 mg/kg - intragastric | Rat             | Active [28]|
| Substance | Experimental models/Route of administration | Organism tested | Effect |
|-----------|--------------------------------------------|----------------|--------|
| Ephedrine, nor-n-formyl (+) | Aspirin induced ulcers/5 mg/kg - intragastric | Rat | Active [28] |
| Glaziovine | Histamine induced ulcers/5 mg/kg - intraperitoneal | Guinea pig | Active [72] |
| | Reserpin induced ulcers/5 mg/kg - intraperitoneal | Rat | Active [72] |
| | Serotonin induced ulcers/5 mg/kg - intraperitoneal | Rat | Active [72] |
| | Restraint stress induced ulcers/5 mg/kg - intraperitoneal | Rat | Active [72] |
| | Pylorus-ligated induced ulcers/5 mg/kg - intraperitoneal | Rat | Active [72] |
| | */10 mg/person - oral | Human adult | Active [73] |
| | Reserpin induced ulcers/10 mg/kg - oral | Rat | Active [29] |
| Palmatine, 7-8-dihydro: 8-hydroxy | Ethanol induced gastric ulcers/50 mg/kg - intragastric | Rat | Active [33] |
| | Pylorus-ligated induced ulcers/50 mg/kg - intragastric | Rat | Active [33] |
| | Acetic acid induced ulcers/80 mg/kg - intragastric | Rat | Active [33] |
| | */100 mg/kg - intragastric | Rat | Active [34] |
| Non- nitrogen heterocycle alkaloid | Pylorus-ligated induced ulcers/1 g/kg - intravenous | Rat | Active [74] |
| Substance                        | Experimental models/Route of administration | Organism tested | Effect       |
|---------------------------------|---------------------------------------------|-----------------|--------------|
| Phenylalkylamide alkaloid       |                                             |                 |              |
| Capsaicin                       | Ethanol induced gastric ulcer/0.3 nanomol/kg - intragastric | Rat             | Active [52]  |
|                                 | 80% ethanol induced ulcer/2 mg/kg - intragastric | Rat             | Active [75]  |
|                                 | 80% ethanol induced ulcer/2 mg/kg - subcutaneous | Rat             | Active [75]  |
|                                 | Pylorus-ligated induced ulcer/1 μg/kg - intragastric | Rat             | Active [76]  |
|                                 | Aspirin induced ulcer/0.6 μg/kg - intragastric | Rat             | Active [77]  |
|                                 | Ethanol induced ulcer/0.105 μg/kg - intragastric | Rat             | Active [77]  |
|                                 | HCl induced ulcer/0.1 μg/kg - intragastric | Rat             | Active [77]  |
|                                 | Acetic acid induced ulcer/10 mg/kg - intragastric | Rat             | Active [78]  |
|                                 | */0.5 mg/kg - intragastric                   | Rat             | Active [53]  |
| Piperidine alkaloid             |                                             |                 |              |
| Piperine                        | Aspirin induced ulcer/1,5 mg/kg - intravenous | Rabbit          | Active [50]  |
|                                 | Restraint stress induced ulcer/25 mg/kg - intragastric | Rat             | Active [51]  |
|                                 | Indomethacin induced ulcer/25 mg/kg - intragastric | Rat             | Active [51]  |
|                                 | HCl/ethanol induced gastric ulcer/25 mg/kg - intragastric | Rat             | Active [51]  |
|                                 | Pylorus-ligated induced ulcer/25 mg/kg - intragastric | Rat             | Active [51]  |
|                                 | Restraint stress induced ulcer/25 mg/kg - intragastric | Mouse           | Active [51]  |
|                                 | Indomethacin induced ulcer/25 mg/kg - intragastric | Mouse           | Active [51]  |
|                                 | HCl/ethanol induced gastric ulcer/25 mg/kg - intragastric | Mouse           | Active [51]  |
|                                 | Pylorus-ligated induced ulcer/25 mg/kg - intragastric | Mouse           | Active [51]  |
|                                 | 25 mg/kg - intragastric                     |                 |              |
| Substance                        | Experimental models/Route of administration | Organism tested | Effect     |
|---------------------------------|--------------------------------------------|-----------------|------------|
| **Pyrazine alkaloid**           |                                            |                 |            |
| Ligustrazine                    | Water-immersion stress induced ulcer/intragastric | Rat             | Active [79]|
|                                 | Restraint stress induced ulcer/intragastric | Rat             | Active [79]|
| **Pyridine alkaloids**          |                                            |                 |            |
| Gentianine                      | Pylorus-ligated induced ulcers/100 mg/kg - oral | Rat             | Weak activity [80] |
|                                 | Water-immersion stress-induced ulcers/100 mg/kg - oral | Rat             | Active [80] |
| Mallorepine                     | Stress induced gastric ulcer/300 mg/kg - subcutaneous | Mouse           | Inactive [81] |
| Nicotine                        | Aspirin induced ulcer/1 mg/animal - intragastric | Rat             | Active [44] |
| **Pyrrolidine alkaloid**        |                                            |                 |            |
| Cuscohygrine                    | */*                                        | Rat             | Active [82] |

*/*: Not specified
| Substance                  | Experimental models/Route of administration                                                                 | Organism tested | Effect     |
|----------------------------|----------------------------------------------------------------------------------------------------------------|-----------------|------------|
| Pyrrolizidine alkaloids    |                                                                                                               |                 |            |
| Interregimine             | Hypothermic restraint stress induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                  | Mouse           | Active [60]|
|                            | Ethanol induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                                        | Rat             | Active [60]|
|                            | Cysteamine induced duodenal ulcer/12.5 mg/kg of crude alkaloid extract - oral                                    | Rat             | Active [60]|
|                            | Indomethacin induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                                   | Mouse           | Active [60]|
| Retrorsine                 | Hypothermic restraint stress induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                  | Mouse           | Active [60]|
|                            | Ethanol induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                                        | Rat             | Active [60]|
|                            | Cysteamine induced duodenal ulcer/12.5 mg/kg of crude alkaloid extract - oral                                    | Rat             | Active [60]|
|                            | Indomethacin induced gastric ulcer/12.5 mg/kg of crude alkaloid extract – oral                                  | Mouse           | Active [60]|
| Senecionine               | Hypothermic restraint stress induced gastric ulcer/12.5 mg/kg of crude alkaloid extract – oral                  | Mouse           | Active [60]|
|                            | Ethanol induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                                        | Rat             | Active [60]|
|                            | Cysteamine induced duodenal ulcer/12.5 mg/kg of crude alkaloid extract - oral                                    | Rat             | Active [60]|
|                            | Indomethacin induced gastric ulcer/12.5 mg/kg of crude alkaloid extract – oral                                  | Mouse           | Active [60]|
Table 1. Cont.

| Substance       | Experimental models/Route of administration                                                                 | Organism tested | Effect            |
|-----------------|---------------------------------------------------------------------------------------------------------------|-----------------|-------------------|
| Seneciphylline  | Hypothermic restraint stress induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                | Mouse           | Active [60]       |
|                 | Ethanol induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                                       | Rat             | Active [60]       |
|                 | Cysteamine induced duodenal ulcer/12.5 mg/kg of crude alkaloid extract - oral                                  | Rat             | Active [60]       |
|                 | Indomethacin induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                                 | Mouse           | Active [60]       |

Usaramine

| Substance       | Experimental models/Route of administration                                                                 | Organism tested | Effect            |
|-----------------|---------------------------------------------------------------------------------------------------------------|-----------------|-------------------|
|                 | Hypothermic restraint stress induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                | Mouse           | Active [60]       |
|                 | Ethanol induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                                       | Rat             | Active [60]       |
|                 | Cysteamine induced duodenal ulcer/12.5 mg/kg of crude alkaloid extract - oral                                  | Rat             | Active [60]       |
|                 | Indomethacin induced gastric ulcer/12.5 mg/kg of crude alkaloid extract - oral                                 | Mouse           | Active [60]       |

Quinolizidine alkaloids

Matrine

| Substance       | Experimental models/Route of administration                                                                 | Organism tested | Effect            |
|-----------------|---------------------------------------------------------------------------------------------------------------|-----------------|-------------------|
|                 | Water-immersion stress induced ulcers/25 mg/kg - gastric intubation                                          | Mouse           | Active [45]       |
|                 | Restriction stress induced ulcers/25 mg/kg - gastric intubation                                              | Mouse           | Active [45]       |
|                 | Water-immersion stress induced ulcers/10 mg/kg - intraperitoneal                                              | Mouse           | Weak activity [45]|
|                 | Restriction stress induced ulcers/10 mg/kg - intraperitoneal                                                  | Mouse           | Weak activity [45]|
|                 | Water-immersion stress induced ulcers/10 mg/kg - intravenous                                                | Mouse           | Active [45]       |

Water-immersion stress induced ulcers/10 mg/kg - intravenous

Restriction stress induced ulcers/10 mg/kg – intravenous
| Substance                        | Experimental models/Route of administration | Organism tested | Effect              |
|---------------------------------|--------------------------------------------|----------------|---------------------|
|                                | Stress induced ulcer/50 mg/kg - gastric intubation | Mouse          | Active [46]         |
| Matrine, 13-alpha-hydroxy       |                                            |                |                     |
| Matrine, oxy                    | Pylorus-ligated induced ulcers/* - intraduodenal | *              | Active [49]         |
|                                 | Indomethacin induced ulcers/* - intraduodenal | *              | Active [49]         |
|                                 | Restraint stress induced ulcers/ * - intraduodenal | Rat            | Active [49]         |
|                                 | Water-immersion stress induced ulcers/* - intragastric | Rat            | Active [48]         |
|                                 | Indomethacin plus alcohol induced gastric ulcers/* -intragastric | Rat            | Active [48]         |
|                                 |                                            |                |                     |
|                                 | Water-immersion stress induced ulcers/25mg/kg - intraperitoneal | Rat            | Active [45]         |
|                                 | Restraint stress induced ulcers/ 25 mg/kg - gastric intubation | Mouse          | Active [45]         |
|                                 | 25 mg/kg - gastric intubation               |                |                     |
|                                 | Water-immersion stress induced ulcers/10 mg/kg - intraperitoneal | Mouse          | Active [45]         |
|                                 | Restraint stress induced ulcers/ 10 mg/kg – intraperitoneal | Mouse          | Active [45]         |
| Substance                          | Experimental models/Route of administration | Organism tested | Effect            |
|-----------------------------------|---------------------------------------------|----------------|------------------|
| Water-immersion stress induced ulcers/10 mg/kg - intravenous | Mouse | Weak activity [45] |
| Restraint stress induced ulcers/10 mg/kg - intravenous | Mouse | Weak activity [45] |
| Stress induced ulcer/50 mg/kg - gastric intubation | Mouse | Active [46] |
| Stress induced ulcer/50 mg/kg - intraperitoneal | Mouse | Active [46] |
| Restraint stress induced ulcers/50 mg/kg - gastric intubation | Mouse | Active [47] |
| Restraint stress induced ulcers/50 mg/kg - intraperitoneal | Mouse | Active [47] |
| Restraint stress induced ulcers/50 mg/kg - intravenous | Mouse | Weak activity [47] |
| Indomethacin induced ulcers/100 mg/kg - gastric intubation | Mouse | Active [45] |
| Reserpine induced ulcers/50 mg/kg - gastric intubation | Mouse | Active [45] |
| Reserpine induced ulcers/50 mg/kg - intravenous | Mouse | Inactive [45] |
| Pylorus-ligated induced ulcers/* - gastric intubation | Rat | Active [84] |

**Steroid alkaloids**

Pachysamine A, epi

Water-immersion stress induced ulcers/50 mg/kg - intraperitoneal | Mouse | Active [54] |

Restrained stress induced ulcers/50 mg/kg – intraperitoneal | Mouse | Active [54] |

Pachysandrine A

Water-immersion stress induced ulcers/50 mg/kg - intraperitoneal | Mouse | Active [54] |
Table 1. Cont.

| Substance       | Experimental models/Route of administration | Organism tested | Effect       |
|-----------------|---------------------------------------------|-----------------|--------------|
| Pachystermine A | Restraint stress induced ulcers/50 mg/kg - intraperitoneal | Mouse           | Active [54]  |
|                 | Water-immersion stress induced ulcers/50 mg/kg - intraperitoneal | Mouse           | Active [54]  |
| Spiropachysine  | Water-immersion stress induced ulcers/50 mg/kg - intraperitoneal | Mouse           | Active [54]  |
|                 | Restraint stress induced ulcers/50 mg/kg - intraperitoneal | Mouse           | Active [54]  |
| Tropane alkaloids | Water-immersion stress induced ulcers/10 mg/kg – intraperitoneal | Rat             | Active [41]  |
| Anisodamine     | Reserpine induced ulcers/1.5 mg/kg - intraperitoneal | Rat             | Active [42]  |
|                 | Cold stress induced ulcers/2.5 mg/kg - intraperitoneal | Rat             | Active [39]  |
|                 | Indomethacin induced ulcers/0.5 mg/kg - intraperitoneal | Rat             | Active [39]  |
|                 | Acetic acid induced ulcers/10 mg/kg - intraperitoneal | Rat             | Active [39]  |
|                 | Ethanol induced ulcers/25 mg/kg - intragastric | Rat             | Active [43]  |
|                 | Indomethacin induced ulcers/25 mg/kg - intragastric | Rat             | Active [43]  |
### Table 1. Cont.

| Substance             | Experimental models/Route of administration | Organism tested | Effect     |
|------------------------|----------------------------------------------|-----------------|------------|
| Anisodine              | Cold stress induced ulcers/2 mg/kg - intraperitoneal | Rat             | Active [39]|
|                        | Indomethacin induced ulcers/8 mg/kg - intraperitoneal | Rat             | Active [39]|
|                        | Acetic acid induced ulcers/32 mg/kg - intraperitoneal | Rat             | Active [39]|
| Atropine               | Pylorus-ligated induced ulcers/10 mg/kg - intragastric | Rat             | Active [37]|
|                        | Pylorus-ligated induced ulcers/10 mg/kg - gastric intubation | Rat             | Active [38]|
|                        | Aspirin induced ulcers/10 mg/kg - gastric intubation | Rat             | Active [38]|
| Cocaine                | Reserpine induced ulcers/10 mg/kg - oral | Rat             | Active [29]|
| Scopolamine            | Cold stress induced ulcers/0.5 mg/kg - intraperitoneal | Rat             | Active [39]|
|                        | Indomethacin induced ulcers/1 mg/kg - intraperitoneal | Rat             | Active [39]|
|                        | Acetic acid induced ulcers/8 mg/kg - intraperitoneal | Rat             | Active [39]|
| Scopolamine, methyl    | Propionitrile-induced duodenal ulcers/2.5 mg/kg - subcutaneous | Rat             | Active [40]|
Table 1. Cont.

| Substance                                                                 | Experimental models/Route of administration | Organism tested | Effect          |
|--------------------------------------------------------------------------|----------------------------------------------|-----------------|----------------|
| Tropine, n-(4'-ethoxy-carbonyl-phenyl-amine-n'-acetyl)                   | */10 mg/kg - intragastric                     | Rat             | Active [83]    |

* = Data not provided

Conclusions

The studied alkaloids have shown gastroprotective and antiulcer activities, nevertheless many of them as senecionine, cocaine, nicotine and LSD have several toxic effects on the body such as hepatotoxic, neurotoxic and carcinogenic properties, although some compounds such as morphine (hypnoanalgesic) and ephedrine (nasal decongestant) are more effective in other afflictions. Consequently many alkaloids are not viable for development as gastroprotective drugs or they would need modification of functional groups in their chemical structures for this propose. Nevertheless, they can be used as pharmacological tools in pathophysiological understanding of gastrointestinal diseases, particularly peptic ulcers, and in the viability of new active compounds for synthesis of new medicines. In this context, it is necessary to support financially the multidisciplinary and
interdisciplinary research, mostly those related to natural products enabling the discovery of new antulcer or gastroprotective pharmaceuticals.

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