Abstract: Many natural substances with proven anti-inflammatory activity have been isolated throughout the years. The aim of this review is to review naturally sourced alkaloids with anti-inflammatory effects reported from 2000 to 2010. The assays were conducted mostly in vivo, and carrageenan-induced pedal edema was the most used experimental model. Of the 49 alkaloids evaluated, 40 demonstrated anti-inflammatory activity. Of these the most studied type were the isoquinolines. This review was based on NAPRALERT data bank, Web of Science and Chemical Abstracts. In this review, 95 references are cited.

Keywords: alkaloids; anti-inflammatory activity; inflammation; experimental models; review
1. Introduction

Inflammation has been studied for thousands of years. Celsius (in 30 A.D.) described the four classical signs of inflammation (redness, heat, pain, and swelling), and used willow leaf extracts to relieve them [1].

The inflammatory process is a reaction of the body to the penetration of an infectious agent, an antigen, or cell damage. Inflammation is the most frequent sign of disease, and is also a fundamental biological process involving complex pathways that are often induced by the products of bacterial degradation from various microorganisms; lipopeptides, lipopolysaccharides, peptidoglycans, formylmethionyl peptides, flagellin, microbial DNA), fungi (zymosans), viruses (double-stranded RNA), or even the body’s own cells upon damage and death [2].

The inflammatory response starts with signal recognition that may have an infectious or inflammatory origin, and the release of chemicals from tissues and migrating cells called mediators [3]. The list of these mediators includes amines like histamine and 5-hydroxytryptamine, bradykinin, (representing short peptides), long peptides such as interleukin-1 (IL-1), lipids such as prostaglandins (PGs) and leukotrienes (LTs), and enzymes [1]. During the immune response, these mediators recruit adjacent cells through the paracrineal process. When these mediators exceed local borders, they disseminate, and distribute through the blood, producing endocrinial generalized cellular activation, or systematic inflammatory response syndrome (SIRS). SIRS is a host defense mechanism, and part of the tissue repair process. To effectively initiate this defense mechanism, cytokines with pro-inflammatory function are required, such as TNF-α, IL-1β, interleukin-12 (IL-12), interferon-γ (IFN-γ) and possibly IL-6 [4-7]. The initial inflammatory response is controlled by immune-regulating molecules through specific inhibitors, and soluble cytokine receptors. The main anti-inflammatory cytokines are transforming beta growth factor (TGF-β) and interleukins 4 and 10. Specific receptors for IL-1, TNF-α and interleukin-18 (IL-18) act as inhibitors of their own pro-inflammatory cytokines. Under physiological conditions immune-modulator molecules act to limit the potentially harmful effects of the inflammatory response [3]. The importance of each of these mediators can be seen when it is removed (either by preventing its generation with enzyme inhibitors or by preventing its pharmacological effects with selective antagonists) [1].

In inflammation research, several experimental models have been used to evaluate inflammation. The usual method of determining whether compounds have anti-inflammatory activity is to test them in animal, and biochemical inflammation models. However there is no single experimental model that covers all aspects of inflammation.

Natural products have long been recognized as an important source of therapeutically effective medicines. It is recognized that natural-product structures have great chemical diversity, biochemical specificity, and other molecular properties that make them favorable lead structures [8-13].

Among the 877 small-molecules New Chemical Entities (NCEs) introduced between 1981 and 2002, roughly 49% (~429 molecules) were natural products, semi-synthetic natural product analogues, or synthetic compounds based on natural-products [9], moreover, between 2005 and 2007, 13 natural, product-derived drugs were approved in the United States, with five of them being the first members of new classes [14]. In recent years advances in chemical and pharmacological techniques have contributed to the knowledge of new therapeutically active compounds obtained from natural products [15].
The alkaloids represent the largest single class of plant secondary metabolites. They have a remarkable range of often dramatic pharmacological activity, and are also often toxic to man [16]. Many alkaloids are used in therapeutics and as pharmacological tools. A wide range of biological effects has been reported for alkaloids, including emetic, anti-cholinergic, antitumor, diuretic, sympatho-mimetic, antiviral, antihypertensive, hypno-analgesic, antidepressant, mio-relaxant, anti-tussigen, antimicrobial and anti-inflammatory activities [17-19]. However, alkaloids and other natural compounds are generally complex, making it necessary to analyze their pharmacological activities using several experimental methods and demonstrate their structure/activity correlation. It is common to find pharmacological data where a single experimental model was used to demonstrate a biological activity. However pathological responses are extremely complex involving many biological events, so it is necessary to use different experimental models to define the exactly mechanism of action of the analyzed molecule [20].

In the course of our continuing search for bioactive natural plant products, we have published reviews on crude plant extracts and plant-derived compounds with potential uses [21-37]. Moreover, our group has also reviewed the medicinal and poisonous plants of Northeast Brazil [38,39], among others [40-52]. Recently we published a review on the anti-inflammatory activity of alkaloids reported in the twentieth century, more precisely covering the period from 1907 to 2000 [53]. Now we present an update of the literature on alkaloids with anti-inflammatory activity from 2000 to 2010. The search was carried out on data banks such as Web of Science, Chemical Abstracts, and NAPRALERT (acronym for the University of Illinois Natural Products ALERT service). The references found in the searches were later consulted. For details on the mechanism-based bioassays utilized for anti-inflammatory activity, the original references should be consulted.

2. Results and Discussion

Isoquinoline, quinoline and indole alkaloids were the most studied classes for anti-inflammatory activity. Among the isoquinolines, berberine was the most studied compound, being active in almost all the experimental models described in Table 1. This compound is present in numerous plants of the Berberis and Coptis genera [54]. It is one of the major components of Coptis chinesis, which is frequently utilized in Chinese herbal drugs to treat inflammatory reactions. Berberine has a variety of pharmacologic effects, including inhibition of TPA-induced mouse ear edema, indicating that this alkaloid may have activity against chronic inflammation [55].

Investigations demonstrated that warifteine, a bisbenzylisoquinoline alkaloid isolated from Cissampelos sympodialis, inhibits eosinophil recruitment, CXC chemokines and cyclooxygenase production in the pleural cavities, and lungs of allergic mice, as well as inhibiting in the production of nitric oxide mediators. These data highlight the role of warifteine as a potential anti-allergic and anti-inflammatory molecule [56,57]. Other isoquinoline alkaloids like berbamine, palmatine and columbamine were also examined demonstrating significant dose-dependent inhibitory activity in serotonin-induced hind paw edema assays for both oral and topical applications, and in oral administration, on acetic acid-induced vascular permeability [58].

The quinolizidine alkaloids matrine and oxymatrine, isolated from Sophora subprostrata (a Chinese plant used as an antipyretic, antidote, and analgesic) exhibited in vitro cyclooxygenase inhibition and antioxidant activity, providing scientific support for their existing medicinal use in traditional Chinese medicine [59].
Indole alkaloids such as brucine and brucine-N-oxide were also reported in this review. They demonstrated significant analgesic and anti-inflammatory properties. Both compounds demonstrated a substantial protective effect in experimental models such as hot-plate test and writhing test. Although, in formalin test, they exhibited their analgesic activity in different phases. In carrageenan-induced rat paw edema experiment, brucine N-oxide showed stronger inhibitory effect than brucine. In addition, these two substances have diminished acetic-acid induced vascular permeability and inhibited the release of PGE2 in inflammatory tissue. These results suggest that brucine and brucine-N-oxide have different biochemical mechanisms, in spite of having similar chemical structure [60].

Marine natural products have been the focus for discovery of new chemical and pharmacological products. A bisindolic alkaloid named caulerpin isolated from the lipoid extract of the algae Caulerpa racemosa exhibited anti-inflammatory activity in mice when given orally at a concentration of 100 μmol/kg [63]. The bisindolic pharmacophoric nucleus of caulerpin is most likely responsible for the wide variety of biological properties tested; anti-inflammatory, antinociceptive [61] insecticidal [62], tumor inhibition [63], and inhibition of hypoxia transcription factor [64], all for this one alkaloid.

Amide alkaloids such as riparin I (N-benzoyl tyramine) and II (N-(2-hydroxybenzoyl) tyramine), isolated from the unripe fruit of Aniba riparia decreased carrageenan-induced paw edema at 4 h and 2 h respectively, when compared to a control [65,66]. It appears that the degree of hydroxylation of the benzoyl moiety increases the anti-inflammatory activity.

Most of the alkaloids reported in this review offer considerable promise as anti-inflammatory compounds or drug candidates and some of them appear to be remarkably active. The results of this search are presented in Table 1 in alphabetical order of their chemical names, followed by the plant species of origin. The references were consulted for details of the experimental models used while testing the alkaloid’s anti-inflammation activities (assay, organism tested, dose or concentration, activity, and references).

| Substance and (Source) | Assay | Organism tested | Dose | Activity | Ref. |
|------------------------|-------|-----------------|------|----------|------|
| Acanthine, oxy (Berberis crataegina) | In vivo, 5-HT-Induced pedal edema | Mouse | 200 mg/Kg | Inactive | [58] |
| | | Mouse | 200 mg/Kg | Active | [58] |
| Ailanthamide (Zanthoxylum ailanthoides) | In vivo, inhibitory activity on superoxide generation by human neutrophils | Human | IC50 ≤ 5.34 μg/mL | Active | [67] |
| | | Human | IC50 ≤ 5.53 μg/mL | Active | [67] |
| Substance (Source) | Assay | Organism tested | Dose | Activity | Ref. |
|--------------------|-------|-----------------|------|----------|------|
| Akuammigine, pseudo (Picralima nitida) | *In vivo*, carrageenan-induced pedal edema | Rat | 1 mg/Kg | Active | [68] |
| Amide, (2*E*,4*E*)-N-isobutyl-6-oxohepta-2,4-dien (Zanthoxylum ailanthoides) | *In vivo*, inhibitory activity on superoxide generation by human neutrophils | Human | IC₅₀ ≤ 5.34 µg/mL | Active | [67] |
| Berbamine (Berberis crataegina) | *In vivo*, 5-HT-induced pedal edema | Mouse | 200 mg/Kg | Active | [58] |
| Berberine (Hydrastis canadensis, Coptidis rhizoma, Phellodendri cortex and Berberis crataegina) | *In vivo*, TNB-induced colitis | Rat | 15 mg/Kg | Active | [69] |
| | *In vivo*, LPS-induced hepatotoxicity | Mouse | 100 mg/Kg | Inactive | [70] |
| | *In vivo*, carrageenan-induced pedal edema | Mouse | 2 mg/Kg | Active | [70] |
| | *In vivo*, LPS-induced hepatotoxicity | Mouse | 209 mg/Kg | Active | [70] |
| | *In vivo*, 5-HT induced-pedal edema | Mouse | 200 mg/Kg | Active | [58] |
| | *In vivo*, Carrageenan-induced pedal edema | Rat | 5 mg/Kg | Active | [55] |
| | *In vivo*, acute inflammation induced by *E. coli* LPS | Chicken | 15 mg/Kg | Active | [71] |
| Substance          | Assay                                      | Organism tested | Dose      | Activity | Ref. |
|-------------------|--------------------------------------------|-----------------|-----------|----------|------|
| Brucine           | *In vivo*, carrageenan-induced pedal edema | Rat             | 15 mg/Kg  | Active   | [60] |
| (Strychnos nux-vomica) |                                            |                 |           |          |      |
| MeO               |                                            |                 |           |          |      |
| MeO               |                                            |                 |           |          |      |
| Brucine-NO-oxyde  | *In vivo*, carrageenan-induced pedal edema | Rat             | 100 mg/Kg | Active   | [60] |
| (Strychnos nux-vomica) |                                            |                 |           |          |      |
| MeO               |                                            |                 |           |          |      |
| MeO               |                                            |                 |           |          |      |
| Caulerpin         | *In vivo*, capsaicin-induced ear edema     | Mouse           | 100 µmol/Kg | Active   | [61] |
| (Caulerpa racemosa) |                                            |                 |           |          |      |
| Colchicine        | *In humans*, oral                         | Human adult     | 0.5 mg/ person | Active | [72] |
| (Colchicum autumnale) |                                            |                 |           |          |      |
| MeO               |                                            |                 |           |          |      |
| MeO               |                                            |                 |           |          |      |
| Columbamine       | *In vivo*, External, 5-HT-induced pedal edema | Mouse           | 200 mg/Kg | Inactive | [58] |
| (Berberis crataegina) |                                            |                 |           |          |      |
| MeO               |                                            |                 |           |          |      |
| MeO               |                                            |                 |           |          |      |

Table 1. Cont.
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| Substance (Source) | Assay                                                                 | Organism tested | Dose            | Activity | Ref. |
|--------------------|----------------------------------------------------------------------|-----------------|-----------------|----------|------|
| Decarine (Zanthoxylum ailanthoides) | *In vivo*, inhibitory activity on superoxide generation by human neutrophils | Human            | IC<sub>50</sub> ≤ 5.34 µg/mL | Active   | [67] |
|                     | *In vivo*, inhibitory activity on elastase release by human neutrophils | Human            | IC<sub>50</sub> ≤ 5.53 µg/mL | Active   | [67] |
| Eleagnine (Chrysophyllum albidum) | *In vivo*, carrageenan-induced paw edema                              | Rat             | 10 mg/Kg        | Active   | [73] |
| Evolitrine (Evodia lunu-ankeda)    | *In vivo*, carrageenan-induced rat paw edema                           | Rat             | 20 mg/Kg        | Active   | [74] |
| Fangchinoline (Stephania tetrandrae) | *In vivo*, croton oil-induced edema                                    | Mouse           | 20 mg/Kg        | Active   | [75] |
|                     | *In vivo*, croton oil-induced edema                                    | Mouse           | 0.1 mg/Kg       | Active   | [75] |
|                     | *In vitro*, fMLP-induced neutrophil adhesion and transmigration       | Human           | 10 µg/mL        | Active   | [76] |
| Guanidine, N1,N2-diisopentenyl (Alchornea cordifolia) | *In vivo*, croton oil-induced ear edema                               | Mouse           | 4.2 ± 0.5 mg/Kg | Active   | [77] |
| Guanidine, N1,N2,N3-triisopentenyl (Alchornea cordifolia) | *In vivo*, croton oil-induced ear edema                               | Mouse           | 3.7 ± 0.8 mg/Kg | Active   | [77] |
Table 1. Cont.

| Substance (Source) | Assay | Organism tested | Dose | Activity | Ref. |
|--------------------|-------|-----------------|------|----------|------|
| Henningsamine, 11-methoxy (*Strychnos cathayensis*) | *In vitro*, inhibitory activity on superoxide anion generation | Human | IC₅₀ < 5.5<br>5.43 ± 1.52 µg/mL | Active | [78] |
| | *In vitro*, inhibitory activity on elastase release by human neutrophils | Human | IC₅₀ < 5.5<br>3.25 ± 0.31 µg/mL | Active | [78] |
| Indigo (*Indigofera tinctoria*) | *In vivo*, carrageenan-induced pedal edema | Mouse | 1 mg/Kg | Active | [79] |
| Indirubin (*Indigofera tinctoria*) | *In vivo*, carrageenan-induced pedal edema | Mouse | 1 mg/Kg | Active | [79] |
| Ircinal A, 31-keto-12,34-oxa-32,33-dihydro (*Acanthostrongylophora sp*) | * | * | * | Inactive | [80] |
| Ligustrazine (*Ligusticum chuanxiong*) | *In vitro*, macrophages | Human adult | 400 mg/L | Active | [81] |
| | *In vivo*, carrageenan-induced pedal edema | Rat | 50 mg/Kg | Active | [82] |
| | *In vivo*, Cotton pellet granuloma | Mouse | 50 mg/Kg | Active | [82] |
| Substance (Source) | Assay | Organism tested | Dose | Activity | Ref. |
|-------------------|-------|-----------------|------|----------|------|
| Magnoflorine (Berberis crataegina) | * | * | * | Inactive | [58] |
| Manzamine A, 12,28-Oxa (Acanthostrongylophora sp) | * | * | * | Inactive | [80] |
| Manzamine A, 12,28-oxa-8-hydroxy (Acanthostrongylophora sp) | * | * | * | Inactive | [80] |
| Matrine (Sophora subprostrata) | * | * | * | Inactive | [58] |
| Matrine, oxy (Sophora subprostrata) | * | * | * | Inactive | [58] |
| Substance (Source) | Assay | Organism tested | Dose   | Activity | Ref.  |
|-------------------|-------|-----------------|--------|----------|-------|
| Norisoboldine (Radix linderae) | * | Mouse | 10 mg/Kg | Active | [83] |
| Palmatine (Berberis crataegina) | * | Mouse | 200 mg/Kg | Inactive | [58] |
| Persicaside (Prunus persica) | * | Rat | 40 µg/mL | Active | [84] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Inactive | [85] |
| Piperine (Piper spp) | * | * | 100 µM | Weak activity | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
| Picrinine (Alstonia scholaris) | * | * | 100 µM | Active | [85] |
### Table 1. Cont.

| Substance (Source)                          | Assay                                      | Organism tested | Dose    | Activity | Ref. |
|--------------------------------------------|--------------------------------------------|-----------------|---------|----------|------|
| Quinine (Cinchona spp)                     | In humans, oral                            | Human adult     | 200 mg/day | Inactive | [87] |
| Riparin I (Aniba riparia)                  | In vivo, formalin test                     | Mice            | 25 mg/Kg | Active   | [88] |
| Schlaricine (Alstonia scholaris)           | In vitro, inhibitory activity on COX-1     | Mice            | 100 µM   | Active   | [85] |
|                                           | In vitro, inhibitory activity on COX-2     | Mice            | 100 µM   | Active   | [85] |
|                                           | In vitro, inhibitory activity on 5-LOX     | Mice            | 100 µM   | Active   | [85] |
|                                           | In vivo, carrageenan-induced air pouch formation | Mouse         | 5 mg/Kg  | Active   | [85] |
|                                           | In vivo, xylene-induced ear edema          | Mouse           | 5 mg/Kg  | Active   | [85] |
| Scytonemin (Extracellular sheath of cyanobacteria) | In vitro, phorbol-induced edema of the mouse ear | Mouse       | 5–100 µg/ear | Active | [89] |
| Sinomenine (Sinomenium acutum)             | In vivo, collagen II induced arthritis      | Rat             | 3.036 mg/Kg | Active | [90] |
Table 1. Cont.

| Substance (Source) | Assay | Organism tested | Dose | Activity | Ref. |
|--------------------|-------|-----------------|------|----------|------|
| Skimmianine (Decatropis bicolor) | *In vivo*, TPA-induced inflammation | Mouse | 0.75 mg/ear | Active | [91] |
| Strychnine (Strychnos nuxvomica) | *In vivo*, carrageenan-induced pedal edema | Rat | * | Inactive | [92] |
| | *In vivo*, cotton pellet granuloma | Rat | * | Inactive | [92] |
| Swatinine (Aconitum laeve) | *In vitro*, colorimetric assay with tetrazolium salt | Blood drawn from healthy volunteers | 100 µg/mL | Weak Activity | [93] |
| Tetrandrine (Stephania tetrandrae) | *In vivo*, croton oil-induced edema | Mouse | 20 mg/Kg | Active | [75] |
| | *In vivo*, croton oil-induced edema | Mouse | 0.1 mg/Kg | Active | [75] |
| | *In vitro*, FMLP-induced neutrophil adhesion and transmigration | Human | 10 µg/mL | Active | [76] |
| Theacrine (Camellia kucha) | *In vivo*, xylene-induced ear edema | Mouse | 8 mg/Kg | Active | [94] |
| | *In vivo*, acetic acid-induced vascular permeability | Mouse | 16 mg/Kg | Active | [94] |
| | *In vivo*, carrageenan-induced paw edema | Mouse | 8 mg/Kg | Active | [94] |
| Toddaliopsin A (Toddaliopsis bremekampii) | *In vitro*, zymosan activated human polymorphonuclear leucocytes in a chemoluminescence assay system | Human | IC$_{50}$ = 27.3 µg/mL | Weak activity | [95] |
**Table 1. Cont.**

| Substance (Source)       | Assay                                                                 | Organism tested | Dose          | Activity     | Ref. |
|--------------------------|-----------------------------------------------------------------------|-----------------|---------------|--------------|------|
| Toddaliopsin B (Toddaliopsis bremekampii) | *In vitro*, zymosan activated human polymorphonuclear leucocytes in a chemoluminescence assay system | Human           | IC$_{50}$ = 48.3 µg/mL | Weak activity | [95] |
| Toddaliopsin C (Toddaliopsis bremekampii) | *In vitro*, zymosan activated human polymorphonuclear leucocytes in a chemoluminescence assay system | Human           | IC$_{50}$ = 4.21 µg/mL | Active | [95] |
| Toddaliopsin D (Toddaliopsis bremekampii) | *In vitro*, zymosan activated human polymorphonuclear leucocytes in a chemoluminescence assay system | Human           | IC$_{50}$ = 79.1 µg/mL | Weak activity | [95] |
| Vallesamine (Alstonia scholaris) | *In vitro*, inhibitory activity on COX-1 | Mice            | 100 µM        | Active | [85] |
|                           | *In vitro*, inhibitory activity on COX-2 | Mice            | 100 µM        | Active | [85] |
|                           | *In vitro*, inhibitory activity on 5-LOX | Mice            | 100 µM        | Active | [85] |
|                           | *In vivo*, carrageenan-induced air pouch formation | Mouse           | 8 mg/Kg       | Active | [85] |
|                           | *In vivo*, xylene-induced ear edema | Mouse           | 8 mg/Kg       | Active | [85] |
| Warifteine (Cissampelos sympodialis) | *In vivo*, allergic eosinophilia and cysteinyl leukotrienes production | Mice            | 50 µg/animal  | Active | [56] |
|                           | *In vitro*. OVA-sensitized animals were evaluated. The response was related with the increase of NO production | Mice            | 0.4–10 mg/Kg | Active | [57] |

* Data incomplete, derived from an abstract.
3. Conclusions

Of the 49 alkaloids evaluated, 40, among which the isoquinolines figured most prominently, demonstrated anti-inflammatory activity. Carrageenan-induced pedal edema was the most utilized experimental model for evaluating anti-inflammatory activity. In this review, 95 references were cited.

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