Plants as anti-inflammatory drugs

Subjects: Pharmacology & Pharmacy

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Plants represent the main source of molecules for the development of new drugs, which intensifies the interest of transnational industries in searching for substances obtained from plant sources, especially since the vast majority of species have not yet been studied chemically or biologically, particularly concerning anti-inflammatory action. Anti-inflammatory drugs can interfere in the pathophysiological process of inflammation, to minimize tissue damage and provide greater comfort to the patient. Therefore, it is important to note that due to the existence of a large number of species available for research, the successful development of new naturally occurring anti-inflammatory drugs depends mainly on a multidisciplinary effort to find new molecules. Although many review articles have been published in this regard, the majority presented the subject from a limited regional perspective.

Keywords: : drugs ; inflammation ; bioactive compounds

1. Introduction

The magnitude of global plant diversity is estimated at more than 500,000 species [1][2], and the variety and complexity of plant metabolites represent a challenge when considering exploration of the chemical repertoire offered. From this point of view, the Plant Kingdom has been pragmatic, especially when these molecules are reported as substances with the high medicinal potential to treat diseases that affect living beings [3].

Medicinal plants continue to be an interesting source of natural products for treating various health conditions. It is estimated that more than 150,000 plant species have been studied, many of which contain valuable therapeutic agents, and the applications of novel compounds from plants for pharmaceutical purposes have been gradually increasing in recent years [4][5].

Plants have played an important role in human health care since ancient times. In an adaptation against attacking pathogen and environmental stress, plants produce several substances that exert biological activities. These small organic molecules come from secondary metabolism and have several biological activities. Among the diverse functions, anti-inflammatory actions are highlighted [6][7].

It is known that inflammation is an evolutionarily conserved process of protection and a critical survival mechanism [8]. It is composed of complex sequential changes in the tissue to eliminate the initial cause of the cell injury, which may have been caused by infectious agents or substances from their metabolism (microorganisms and toxins), as well as by physical agents (radiation, burn, and trauma), or chemicals (caustic substances) [9][10]. The signs of inflammation are local redness, swelling, pain, heat, and loss of function [7].

In general, this complex biological response leads to the restoration of homeostasis. However, in cases of prolonged release of inflammatory mediators and the activation of harmful signal-transduction pathways, the inflammatory process persists, and a mild but chronic proinflammatory state may arise [8]. A low-grade inflammatory state is correlated with various disorders and chronic health conditions, such as obesity, diabetes, cancer, and cardiovascular diseases, among others [11][12][13][14][15][16][17][18].

Therefore, the discovery of a new generation of therapeutic agents to use in the resolution of inflammation is desirable. The treatment of inflammation involves some mechanisms that can be used as therapeutic targets [8]. Due to the production of secondary metabolites with clinically curative effects, medicinal plants play an important role in the development of new and potent drugs [19][20].

Another motivating scientific investigation related to drugs and medicines made from plants is their interaction with gut microbiota. Certain gut bacteria intensively metabolize drugs rich in the low-molecular-mass products of secondary metabolisms, such as tannins and anthocyanins. Metabolites derived from bacterial metabolization are small, bioavailable,

and potentially bioactive metabolites. They also have potential modulatory effects on the gut microbiome, which is interesting to prevent metabolic disorders [21].

2. Anti-Inflammatory Drugs

Anti-inflammatory drugs can interfere in the pathophysiology of inflammation, seeking to minimize tissue damage and provide greater patient comfort. The major classes of anti-inflammatory agents are the glucocorticoids and non steroidal anti-inflammatory drugs (NSAIDs). Fundamentally these differ in their mode of action. In short, glucocorticoids act by inhibiting prostaglandins and proteins involved in inflammatory processes, such as corticosteroids, which among other indications are used in treatment for asthma and autoimmune inflammatory response. Non-steroidal drugs, on the other hand, have an inhibitory action through the enzyme cyclooxygenase and are indicated for moderate and mild pain and body temperature control. An example of a non-steroidal drug is acetylsalicylic acid [22].

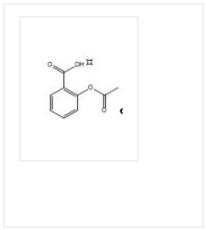
NSAIDs are the most commonly used drugs worldwide , utilized to treat acute and chronic pain resulting from an inflammatory process [22]. NSAIDs encompass a range of agents and, in general, all their effects are related to the inhibition of COX action in the production of prostaglandins and thromboxanes [23][24][25][26].

The main mechanism of action of NSAIDs is the inhibition of COX, both central and peripheral, interfering in the conversion of arachidonic acid to prostaglandins E2, prostacyclins, and thromboxanes. Enzymes related to the action of NSAIDs can be divided into COX-1 and COX-2, acting in different regions. COX-1 appears in most cells, even fetal and amniotic fluid, and participates in physiological effects, such as regulatory and protective effects. On the other hand, COX-2 is activated by inflammation and proinflammatory cytokines [27][28].

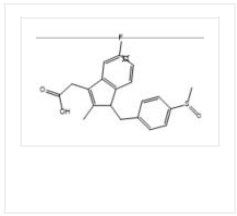
There are several ways to classify NSAIDs; according to COX-2 inhibitory potency over COX-1, concentration to achieve clinical effects, among others. NSAIDs can be classified into non-selective NSAIDs (ketoprofen, aspirin, naproxen, flunixin, meglumine, and others), preferential COX-2 inhibitors (meloxican, etodolac, nimesulide), and highly selective COX-2 inhibitors (coxib). Most of the side effects are related to the inhibition of COX-1 due to its performance in several systems related to cell cleansing. Besides, NSAIDs can also be classified according to their chemical structure (Table 1).

Table 1. Classification of NSAIDs [29]

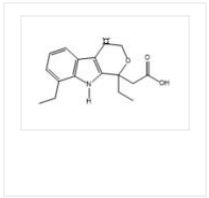
Salicylates	**Indoleacetic acid Derivatives**	**Aryl Acetic Derivatives**	**Enolic Acids**	
				Pyrazolones:
Acetylsalicylic acid	Acemethacin	Aceclofenac		Phenylbutazone
Lysine clonixinate	Glucamethacin	Diclofenac		Mofebutazone
Benorilate	Indomethacin	Etodolac	**Oxicans**:	Oxyphenbutazone
Diflunisal	Proglumethacin	Fentiazac	Droxicam	Kebuzone
Salicylamide	Oxamethacin	Ketorolac	Meloxicam	Metamizole (Dipyrone)
Etersalate	Sulindac	Bufexamac	Piroxicam	Feprazone
Salsalate or	Tolmetin	Lonazolac	Tenoxicam	Nifenazone
salicylic acid	Difenpiramide	Alclofenac	Oxaprozin	Suxibuzone
		Zomepirac	Lornoxicam	
				Aminophenazone



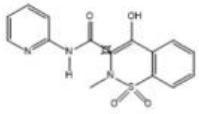
Aspirin



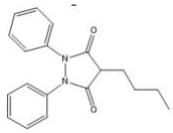
Sulindac



Etodolac



Piroxicam



Phenylbutazone

Arylpropionic Derivatives

Butibufen

Phenoprofen

Phenobufen

Flurbiprofen

Benoxaprofen

Suprofen

Ibuprofen

Ibuproxam

Ketoprofen

Dexetoprofen

Pyprophene

Indoprofen

Naproxen

Oxaprozin

Tiaprofen

Dexibuprofen

Phenoprofen

Flunoxaprofen

Alminoprofen

Phenemates

Meclofenamic acid

Mefenamic acid

Flufenamic acid

Tolipanic acid

Niflumic acid

Etofenamate

Others

Nabumetone

Glucosamine

Diacerhein

Nimesulide

Proquazone

Azapropazone

Benzidamine

Orgotein

Feprazone

Morniflumato

Tenidap

Glucosaminoglycan

Coxibs:

Celecoxib

Rofecoxib

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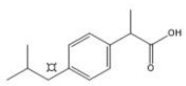
Valdecoxib

Etoricoxib

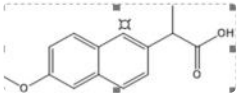
4-Aminophenol

Paracetamol

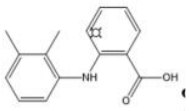
(Acetaminophen)



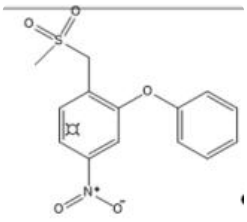
(*S*)-Ibuprofen



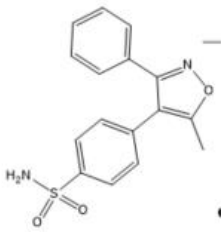
Naproxen



Mefenamic acid



Nimesulide



Valdecoxib

Structurally, COX-2 selective drugs contain sulfonamide groups or sulfones, responsible for the selectivity of the enzyme and do not have a carboxylic group and, therefore, they can selectively target the COX-2 enzyme. They have little water solubility, which hinders parenteral administration [30].

Acetylsalicylic acid (ASA) is one of the most widely used drugs in the world. It is used as an analgesic, antipyretic, and anti-inflammatory [31][32]. This drug also has antiplatelet or anticoagulant effects and is used to prevent heart attacks, strokes, and blood clots [33]. However, its use can also lead to exacerbated respiratory tract disease and cancer [34].

Historically, non-steroidal anti-inflammatory drugs, such as acetylsalicylic acid (Aspirin®), indomethacin, ibuprofen, and piroxicam have been used clinically for the treatment of inflammation due to their suppression of the effects of COX activity .

However, these traditional NSAIDs act in a non-selective manner inhibiting both forms of COX and have also demonstrated side effects. Specific modalities of anti-inflammatory effects and side effects are associated with the existence of two COX isoforms [35].

Inhibitory actions of aspirin or other non-steroidal anti-inflammatory drugs against COX-1 may present crucial problems in pharmacotherapy. Some anti-inflammatory drugs that act only to inhibit COX-1 are ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, and oxaprozin (derivatives of propionic acid); indomethacin, sulindac, and etodolac (indoleacetic acids); piroxicam (derived from oxyanas); mefenamic acid and meclofenamate (phanamates); and diclofenac .

Thus, the scientific community has focused its efforts on the search for selective COX-2 inhibitors, with lower adverse side effects, since highly selective COX-2 inhibitors are required for the treatment of inflammatory diseases [35]. The first selective COX-2 inhibitor was celecoxib (Celebrex®), followed by rofecoxib (Vioxx®). In a short time, the coxibs (celecoxib and rofecoxib) have achieved wide dissemination [36]. Other drugs are also more selective for COX-2 than for COX-1, such as nimesulide and etodolac [37].

Despite initial success, shortly after the launch of selective COX-2 inhibitors, adverse cardiovascular and renal effects have been reported and, in high-doses, gastrointestinal effects. These adverse effects occur due to inhibition of the constitutive production of COX-2 in some tissues. Thus, in recent years, the safety of the use of NSAIDs in clinical practice has been questioned, due to the emergence of evidence that suggests a high risk of acute myocardial infarction, stroke, heart failure, renal failure, and arterial hypertension [38].

There is no absolute selectivity in COXs. Even a selective COX-2 inhibitor will also inhibit COX-1 when in high concentrations. Therefore, in all NSAIDs selective for COX-1 or COX-2, to different degrees, there is a risk of adverse cardiovascular side effects .

In September 2004, Merck removed Vioxx® from the world market and in April 2005, the coxib study led the American Committee to conclude about the Cardiovascular Risk and suspension of Pfizer's Bextra® (valdecoxib). Celecoxib is marketed only with a black stripe indication and the adverse cardiovascular effects are explained in the package leaflet .

A derivative of celecoxib based a benzo[b]furan moiety was reported to demonstrate selective activity against COX-2. Besides, new molecules containing rhodanine and benzofuran scaffolds were designed, synthesized, and reported to exhibit dual COX-2, and 5-LOX inhibitory potential [39][40]. A recent patent survey reported a review focused on benzofuran inhibitors [41][42].

Since a large proportion of NSAIDs available on the market have significant undesirable effects, the need for new anti-inflammatory drugs contributes to the advancement of research for newer, safer, effective molecules with fewer side effects and from vegetal sources. Therefore, it can be observed that a significant number of substances of vegetal origin form part of the therapeutic arsenal of modern medicine. It is important to emphasize that due to the existence of a large number of species available for research, the success of the development of new naturally occurring anti-inflammatory drugs depends fundamentally on a multidisciplinary effort in the discovery of new leading molecules.

3. Plant Use and the Development of Drugs

The World Health Organization (WHO) estimates that approximately 65% of the world's population incorporates traditional medicine (ethnobotanical uses) into medical care. Ethnobotanical studies over the years have allowed the association of highly diversified plants with biological activities, from observation, description, and experimental research, which has greatly contributed to the discovery of natural products with biological action. The use of medicinal plant-based natural compounds to treat many illnesses has become a great trend in clinical research. Polyphenolic compounds have drawn significant attention due to their modulation effects on inflammasomes [43]. These multi-protein complexes are associated with the initiation and progression of metabolic disorders and chronic diseases, such as cancer and neurodegenerative diseases [44].

Thus, plants have become the first source of substances for the development of new drugs, and a considerable part of the drugs prescribed in the world are derived from them[45][46][47]. Plants contain reservoirs of potential secondary metabolites that are the major sources of drugs, which intensifies the interest of transnational industries in the search for substances obtained from plant sources, particularly since the great majority of species have not been studied chemically or biologically [48].

The use of plants or plant products for medicinal purposes is mostly documented in books and, lately, on an enormous number of websites (the reliability of some of which must be examined carefully). In recent decades, hundreds of research and review articles have been published regarding the anti-inflammatory activities of plants (Table 2) [49][50][51][52].

Table 2. Anti-inflammatory activity of some medicinal plants.

Number	Botanical Name	Plant/Family	Parts Used	Constituent Compounds
01	*Acacia catechu*	Mimosaceae	Bark, wood, flowering tops, gum.	Tannin, gum, catechuic acid
02	*Azadirachta indica*	Meliaceae	Leaf, root, oil, seed, gum, fruit, flower.	Margosine, bitter oil, azadirachtin.
03	*Caesalpinia crista*	Caesalpiniaceae	Seeds, root, leaf, root bark.	Oleic, linoleic, palmitic, stearic acid, phytosterols.
04	*Cassia angustifolia*	Caeasalpinaceae	Pods, dried leaves.	Emodin, eatharitin, mucilage, senna-picrin, opleanic acid.
05	*Coriandrum sativum*	Umbelliferae apiaceae	Leaf, bark, flower	Tannin, cathartin, malic acid, cathartin, albuminoids.
06	*Cuscuta reflexa*	Convolvulaceae	Plant, seed, fruit, stem.	Cuscutine, flavonoid, glucoside, bergenin, coumarin.
07	*Enicostema littorale*	Gentianaceae	Whole plant.	Alkaloids, gentiocrucine
08	*Erythrina variegate*	Papilionaceae	Leaves, bark, roots, flower.	2-Hydroxygenistein, genistein.
09	*Euphorbia hirta*	Euphorbiaceae	Plant, roots, leaves	Ascorbic acid, β-amyrin, choline, inositol, linoleic acid, β-sitosterol.
10	*Euphorbia tirucalli*	Euphorbiaceae	Root, plant (milk, juice).	β-sitosterol, ellagic acid, citric acid, malic acid, eupholglucose.
11	*Fagonia cretica*	Zygophyllaceae	Leaves, twigs, bark.	Betulin

12	*Ficus benghalensis*	Moraceae	Aerial roots, bark, seeds, leaves, buds, fruits, latex.	Skin, fruits contain 10% tannin.
13	*Ficus carica*	Moraceae	Fruit, root.	Alkaloids, ascorbic acid, caffeic acid, niacin, linoleic acid, lutein, b-carotene, pantothenic acid, b-amyrin.
14	*Ficus religiosa*	Moraceae	Bark, leaves, fruits, tender shoots, seeds.	The bark contains tannins, rubber, wax.
15	*Foeniculum vulgare*	Apiaceae	Fruit, root, seeds, leaves.	Ascorbic acid, estragole, coumaric acid, caffeic acid, α-terpinene, scoparone, scopoletin, cynarin, D-limonene, α-phellandrene.
16	*Gentiana kuroo*	Gentianaceae	Rhizomes (roots)	Gentiopicrine, gentianic acid
17	*Gloriosa superba*	Liliaceae	Rhizome, tuber, leaves, flower	Choline, colchicine, stigmasterol, salicylic acid, 2-methylcolchicine.
18	*Glycyrrhiza glabra*	Papilionaceae	Roots, leaves.	Genistein, eugenol, bergapten, glycyrrhizin, acetophenone, estragole, camphor, ascorbic acid, apigenin, anethole.
19	*Gmelina arbórea* Roxb	Verbenaceae	Whole plant.	Betulin
20	*Grewia asiatica*	Tiliaceae	Leaves, roots,fruits, bark.	Betulin
21	*Hibiscus rosa-Sinensis*	Malvaceae	Buds, roots, leaves, flower	Quercetin, ascorbic acid.
22	*Hygrophila auriculata*	Acanthaceae	Roots, leaves, seeds.	Oleic and linoleic acids in seed oil, palmitic acid, stearic acid.
23	*Manihot esculenta*	Euphorbiaceae	Tuberous roots.	Ascorbic acid, palmitic acid, lauric acid, stearic acid, oleic acid.
24	*Martynia annua*	Pedaliaceae	Fruits, leaves.	Pelargonidin-3,5-diglucoside, cyanidin-3-galactoside, semi-drying oil.
25	*Momordica charantia*	Cucurbitaceae	Whole plant	5-Hydroxytryptamine, alkaloids, ascorbic acid, b-carotene, cholesterol, lutein, diosgenin, lanosterol, lycopene, momordicin, charantin niacin, momordicoside.

26	*Moringa oleifera*	Moringaceae	Roots, bark, leaves, seeds.	Choline, moringinine, myristic, ascorbic acid, β-carotene, niacin, oleic acid, spirochin, stearic acid, tocopherol, vanillin.
27	*Nelumbo nucifera*	Nymphaeaceae	Whole plant.	Anonaine, ascorbic acid, β-carotene, copper, erucic acid, glutathione, hyperoside, myristic acid, nuciferine, oxoushinsunine, rutin, stearic acid, trigonelline, kaempferol, D-catechin.
28	*Nicotiana tobacum*	Solanaceae	Leaves.	1,8-Cineole, 4-vinylguaiacol, acetaldehyde, acetophenone, alkaloids, anabasine, nicotinic acid, nicotine, scopoletin, quercitrin, sorbitol, tocopherol stigmasterol, trigonelline.
29	*Nigella sativa*	Ranunculaceae	Seeds.	α-spinasterol, ascorbic acid, β-sitosterol, carvone, D-limonene, linoleic acid, myristic acid, methionine, nigellone, stearic acid, stigmasterol, tannin, thymoquinone, hederagenin.
30	*Ocimum basilicum*	Laminaceae	Whole plant	Acetic acid, ascorbic acid, aspartic acid, apigenin, arginine.
31	*Plumbago zeylanica*	Plumbaginaceae	Root, leaves, root, bark.	Plumbagin, droserone, 3-chloroplumbagin, chitranone, zeylinone, elliptione, isozeylinone.
32	*Portulaca oleraceae*	Portulaceae	Stem, leaves, seeds.	Oleracins I and II, acylated betacyanins, carbohydrate, galacturonic acid, mucilage.
33	*Pterocarpus marsupium*	Fabaceae	leaves, flower, gum Heartwood,	Alkaloids, gum, essential oil, semi-drying fixed oil.
34	*Solanum melongena*	Solanaceae	Roots, leaves, tender fruits.	Ascorbic acid, alanine, arginine, caffeic acid.
35	*Solanum nigrum*	Solanaceae	Whole plant.	Solenin, solasodine.
36	*Stereopermum suaveolens*	Bignoniaceae	Roots, flower	Mucilage, albumin, sugar, wax, lapachol, dehydrotectol, β-sitosterol, *n*-triacontanol.
37	*Tephrosia purpurea*	Fabaceae	Whole plant	Tephrosin, betulinic acid, lupeol, rutin.
38	*Terminalia chebula*	Combretaceae	Mature, immature fruits.	Ascorbic acid, gallic acid, ellagic acid, chebulic acid.
39	*Thespesia populnea*	Malvaceae	Whole plant	Gossypol, herbacetin, kaempferol.

40	*Thespesia populneoides*	Malvaceae	Whole plant	Populneol, gossypol, kaempferol, quercetin-5-glucoside, calycopterin, kaempferol-5-glucoside, kaempferol-3-gluoside.
41	*Tinospora cordifolia*	Menispemaceae	Stem	Alkaloids, starch.
42	*Vernonia cinerea*	Asteraceae	Whole plant	Linoleic acid, lupeol, vernolic acid.

Other plant species with anti-inflammatory properties have already been described in the literature. However, the parts of the plants used and the compounds responsible for the anti-inflammatory activity have not yet been fully elucidated.

Phytochemical studies carried out with the species *Myracroduo nurundeuva* Allemão, *Schinus terebinthifolius* Raddi, *Spondias mombin* L., *Spondias purpurea* L. and *Spondias tuberosa* Arruda, belonging to the Anacardiaceae family, detected the presence of several secondary metabolites. The most abundant are phenols, triterpenes, flavonoids, and cinnamic acid, which are responsible for their anti-inflammatory action [53][54][55][56][57].

The plants that make up the Euphorbiaceae family, such as the species *Euphorbiaceae Acalypha* hispida Burm. f., *Acalypha indica* L., *Phyllanthus niruri* L., are rich mainly in phenolic compounds, saponins, tannins, and triterpenes, which are responsible for their anti-inflammatory action [58][59][60].

Research with the species *Ruellia asperula* (Mart. Ex Ness) Lindau (family Acanthaceae), Achyranthes *aspera* L., *Alternanthera brasiliana* (L.) Kuntze (family Amaranthaceae), *Himatanthus drasticus (Mart.) Plumel* (family Apocynaceae), *Matricaria chamomilla* L. (family Asteraceae), *Heliotropium indicum* L. (family Boraginaceae), *Momordica charantia* L. (family Cucurbitaceae), *Mimosa tenuiflora* (Willd.) Poir (family Leguminosae), *Borreria verticillata (L.) G.Mey*. (family Rubiaceae), *Solanum paniculatum* L. (family Solanaceae), and *Zingiber officinale Roscoe* (family Zingiberaceae) also indicates the existence of compounds with anti-inflammatory activity [61][62][63].

It is important to note that the extraction of plant materials is the first major step to test biological activities, presenting many advantages and some disadvantages compared to the isolation of pure active compounds [50]. When an entire extract is used, there is a good chance of synergism between active components that can be lost when each of these components is isolated. This synergism was discovered in several medicinal tests, including those for anti-inflammatory activity. On the contrary, the mixture of different compounds together may also lead to inhibitory effects, namely, that one component may reduce the biological activity of the other. In line with this assumption, some studies have shown that the anti-inflammatory activity of pure compounds (such as amentoflavone, pseudohypericin, and hyperforin) is higher than that of the extracts [64][65].

Medicinal plants are used instead of Non-steroidal anti-inflammatory drugs (NSAIDs) as the use of non-steroidal anti-inflammatory drugs is associated with several side effects, among which are unwanted effects on the gastrointestinal tract and the renal system. The biggest disadvantage of recently available potent synthetic drugs is concerning their toxicity and the reappearance of symptoms after discontinuation. Therefore, the screening and development of drugs with anti-inflammatory activity are necessary and there are many efforts to find anti-inflammatory drugs from medicinal plants .

Inflammation is a huge challenge for human kind. Although many anti-inflammatory drugs are available, it is believed that these drugs, such as opioids and analgesia inducing drugs like NSAIDs, are not useful in all cases and these drugs also produce side effects, so to overcome these problems, new drug molecules need to be discovered from plants. Plants have many phytoconstituents helpful in reducing inflammation and fewer side effects .

The objectives of the use of plants as therapeutic agents are: to concentrate and/or isolate bioactive substances for direct use as drugs; to produce bioactive compounds of novel or already known structures for semi synthesis to produce patentable entities of higher activity and/or lower toxicity; to use agents as pharmacological tools; and to use the whole plant or part of it as a herbal remedy [66].

It is worth mentioning that for the acquisition of new drugs, molecular diversity and biological function distinguish products of natural origin from synthetic products. The molecular diversity of natural products is far superior to that derived from synthesis processes, which, despite technological advances, are still restricted. This fact makes it possible for the chemical compounds present in plants to become potential drugs for different diseases .

An example of a phytotherapeutic anti-inflammatory agent is Acheflan®, indicated for the local treatment of inflammatory processes, and Daflon 500 mg®, a drug composed of a purified flavonoid fraction that presents venotonic and vasoprotective action . Therefore, the study of the immunopharmacological activities of plant species has provided evidence on different extracts/fractions and chemical classes with high therapeutic potential, which represents a promising alternative to the inflammatory processes and diseases related to them, as well as a form of validation of their ethnobotanical use. Besides, data from the scientific literature have shown that molecules of plant origin present important anti-inflammatory activities and that many of their actions are related to the ability to inhibit the synthesis or action of cytokines, chemokines, and adhesion molecules, and arachidonic acid and nitric oxide pathways [67][68].

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