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Ethnopharmacology as Current Strategy in the Search of Novel Anti-Ulcerogenic Drugs: Case of a Brazilian Medicinal Plant (*Maytenus ilicifolia* Mart. ex. Reissek)

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1. Introduction

Several medical products of natural origin were conceived in traditional systems of knowledge and practice that has been transmitted over centuries and which continuously change. In actual scenario, researchers of many countries involved in the modern drug discovery processes are becoming increasingly aware of the value of their traditional knowledge, while global pharmaceutical industry is looking for alternative solutions to reduce the crescent innovation deficit and enhance the development of new products.

Has been systematically showed that aleatory screening of plants used traditionally by pharmaceutical industries in the search for new leads or drugs is vastly expensive and requires much time. On the other hand, ethnodirected approach to traditional knowledge has been extremely useful in screening and identification of plants with bioactive compounds with potential application in drug development. This approach consists in selecting species according to the indication of specific population groups in certain contexts of use. The ethnodirected approach has significantly increased the chances of discovery of new biomolecules with potential therapeutic application while reduce the cost and time involved in this process. Beyond this approach provide a shortcut to the discovery of active compounds that could serve as a basis for rational drug development, it also provides a mechanism for pre-screening on the therapeutic properties of the species collected. Most of these compounds are part of routinely used traditional medicines and hence their tolerance and safety are relatively better known than any other chemical entities that are new for human use. Thus, traditional medicine based on ethnodirected bioprospecting offers an unmatched structural variety as promising new leads.

In the context of ethnodirected studies, the ethnopharmacological research has shown a great contribution in selecting plants and discovery of compounds with pharmacological potential. Ethnopharmacology is a strategy used in the investigation of plants with medicinal properties, combining information acquired from users of medicinal plants (traditional communities and experts), with chemical and pharmacological studies. While in the past the typical industrial drug discovery process made the use of aleatory selection and systematic bioassays to find promising compounds for a particular target,

ethnopharmacology goes the opposite way, tries to understand the pharmacological basis of culturally important medicinal plants, testing their efficacy in the laboratory.
Currently, research centers and pharmaceutical industries have driven the search for new drugs of plant origin with effective activity to fight several diseases that today present a limited treatment, including gastrointestinal ailments. In the case of gastric ulcers, several plants extracts described in the specific cultural context are being investigated in the search for sources of effective biomolecules in reducing the damage to gastric mucosa.
Gastric hyperacidity and ulceration of the stomach mucosa due to various factors are serious health problems of global concern. Peptic ulcer disease (encompassing gastric ulcer and duodenal ulcer) affect a large portion of the world population and are triggered by several factors, including stress, smoking, nutritional deficiencies, and ingestion of non-steroidal anti inflammatory drugs. Today, there are two main approaches for treating peptic ulcer. The first deals with reducing the production of gastric acid and the second with re-enforcing gastric mucosal protection. Although a number of anti-ulcer drugs such as H_2 receptor antagonists, proton pump inhibitors and cytoprotective agents are available, all these modern pharmacological approach have side effects and limitations. Moreover, development of drug tolerance and incidence of recurrences make the efficacy of allopathic drugs arguable. Therefore, there is urgent need to find alternatives that have antiulcerogenic properties. This has been the basis for the development of new anti-ulcer agents, which include herbal substances that could serve as leads for the development of new drugs.
In view of the importance of finding new plant compounds for the management of gastric ulcers in the context of current health, this chapter aims to show plant species and crud drug preparations with antiulcer activity identified within the ethnopharmacological approach. Furthermore, will be described the main phytochemicals responsible for the antiulcer therapeutic properties of plant extracts. Finally, by analyzing the case of *Maytenus ilicifolia*, will address aspects from preliminary phytochemical analysis and experimental tests with different preparations of this plant, and the process of isolation of fractions of the ethanol extract of *Maytenus ilicifolia* for identification of bioactive constituents related to its gastroprotective action.

2. Contribution of ethnopharmacology in the selection of natural products with potential application in health care

Chemical substances derived from plants have been used to treat human diseases since the dawn of medicine. Currently, the health care based in natural products is still the mainstay of about 75 - 80% of the whole world population, and the major part of traditional therapy involves the use of plant extracts (Gilani & Atta-ur-Rahman, 2005). Recognizably, natural products remain an important source for the discovery of new drugs and is estimated that about 13000 plant species worldwide are known to have been used in drugs formulation. About 60% of anticancer and 75% of anti-infective drugs approved from 1981-2002 could be traced to natural origins (Patwardhan & Vaidyab, 2010). Studies on sources of new drugs from 1981 to 2007 reveal that almost half of the drugs approved since 1994 are based on natural products (Harvey, 2008). Currently, it is estimated that about 80% of molecules used in drugs sold worldwide are derived from natural products and that over hundred new natural product-based leads are in clinical development (Butler, 2008; Bhutani & Gohil, 2010). Moreover, despite the tremendous development of chemical synthesis today, 25% of prescribed drugs in the world are of vegetable origin (Balunas & Kinghorn, 2005; Bhutani &

Gohil, 2010). Aspirin, atropine, artimesinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine and vinblastine are a few important examples of what medicinal plants have given us in the past. Most of these plant-derived drugs were originally discovered through the study of traditional cures and folk knowledge of indigenous people and some of these could not be substituted despite the enormous advancement in synthetic chemistry (Sekar et al., 2010).

Due to growing drug discovery from natural products, researchers and pharmaceutical industries has been increasing interest in traditional health practices used around the world (Patwardhan, 2005). This interest has been renovated for decades due to systematic demonstrations that plants are the richest resource of drugs of traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates and chemical entities for synthetic drugs (Hammer et al., 1999). Since the reported data so far available on plants are comparatively meager before the number of plant population, ethnopharmacologists, botanists, microbiologists and natural-product chemists world over today, is constantly still in search of medicinal efficacy of plants and their phytochemicals. Furthermore, the wide spectrum of therapeutic activity makes the natural products attractive candidates for further research (Vlietinck & Van Den Berghe, 1991). In this context, a new recognition has been given to ethnopharmacology, traditional, complementary and alternative medicines, which re-emerging as new strategic options in health attention, has provided valuable clues of plants with bioactive compounds potentially usable in the production of new drugs (Harvey et al., 2010; Patwardhan & Vaidyab, 2010). The World Health Organization's Commission on Intellectual Property and Innovation in Public Health also has duly recognized the promise and role of traditional medicine in developing affordable drugs for the treatment of health problems (Patwardhan, 2005a; Patwardhan & Vaidyab, 2010).

The ethnopharmacological approach is currently employed to study numerous medicinal plants and vegetable preparations from traditional ethnic groups (Elisabetsky & Nunes, 1990). Although the clinical efficacy of these preparations is reported by traditional practices, they have not been scientifically validated. Thus, ethnopharmacologists typically develop working hypotheses derived from field observations having as one of its main goals to enhance the knowledge of local communities incorporating scientific findings to traditional accounts. In this context, the central questions that direct the ethnopharmacological research is if a specific plant extract used in the cultural context to cure some diseases present a pharmacological basis that explains the effects traditionally indicated. In this process, ethnopharmacological discoveries started with field observations and ended in new pharmacological insights (Gertsch, 2009). Therefore, ethnopharmacology research is transdisciplinary, touching on areas like anthropology, ethnobiology, and as the name implies, pharmacology (Raza, 2006; Gertsch, 2009).

The systematic screening ethnopharmacology-based of plant species with the purpose of discovering new potential bioactive compounds is a routine activity in many laboratories (Elisabetsky, 2002). Traditionally, the etnopharmacological research on the medicinal plants should be extended with the identification and isolation of specific phytochemicals. After these processes, only from the careful scientific examination of these isolated compounds could lead to standardization and quality control of the products to ensure their safety. It is after such evaluation that vegetable derivatives can be approved for the development of new products used in health care (Vlietinck & Van Den Berghe, 1991, Elisabetsky, 2002; Patwardhan, 2005b).

Several advantages can be achieved with the adoption of ethnodirected method for screening bioactive components. Due to traditional use of vegetable products in specific communities for the prevention or treatment of various health conditions, it is possible to meet preliminary criteria for safety for human consumption and any adverse effects of such use (Elisabetsky & Nunes, 1990; Vlietinck & Van Den Berghe, 1991). Coupled with better cultural acceptability of natural products and reduced cost is encouraging for both the consuming public and national health care institutions to consider plant medicines as a complementary practice to synthetic drugs (Elisabetsky & Nunes, 1990; Elisabetsky, 2002; Patwardhan, 2005a).

3. Peptic ulcers and herbal medicine

Peptic ulcer disease (PUD) is one of the most common, chronic gastrointestinal disorder in modern era. Now it has become a common global health problem affecting a large number of people worldwide and also still a major cause of morbidity and mortality (Sen et al., 2009). An estimated 15,000 deaths occur each year as a consequence of PUD (Dharmani & Palit, 2006).

Ulcer is an open sore that develops on the inside lining of the stomach (a gastric ulcer) or the small intestine (a duodenal ulcer). Both types of ulcers are also referred to as PUD and can be characterized by inflamed lesions or excavations of the mucosa and tissue that protect the gastrointestinal tract. The most common symptom of a peptic ulcer is a burning or gnawing pain in the center of the abdomen (stomach) (Tarnawski, 2005, Vyawahare et al., 2009).

In the past, it was mistakenly thought that the main causes of peptic ulcers were lifestyle factors, such as diet, smoking, alcohol and stress. While these factors may play a limited role, it is known that the leading cause of peptic ulcers is a type of bacteria called *Helicobacter pylori* (*H. pylori)* can infect the stomach and small intestine; and in some people, the bacteria can irritate the inner layer of the stomach and small intestine, leading to the formation of an ulcer (Dulcie et al., 1997). Peptic ulcer occurs due to an imbalance between the aggressive (acid, pepsin and *H. pylori*) and the defensive (gastric mucus, bicarbonate secretion, prostaglandins, nitric oxide, growth factors and innate resistance of the mucosal cells) factors (Falcão et al., 2008b). Painkillers known as nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin and ibuprofen, are the second most common cause of peptic ulcers that can irritate the lining of the stomach and small intestine in some people, particularly if they are taken on a long-term basis (Tarnawski, 2005; Vyawahare et al., 2009).

Traditionally, there are two main approaches for treating peptic ulcer. The first deals with reducing the production of gastric acid and the second with re-enforcing gastric mucosal protection (Sen et al., 2009). According to the old hypothesis, acid secretion was thought to be the sole cause of ulcer formation and reduction in acid secretion was thought to be the major approach towards therapy. However, in the light of recent evidences this concept has changed. The modern approach for the ulcer treatment mainly targets the potentiation of the gastrointestinal defensive system preventing ulceration by inhibiting acid secretion, increase gastroprotection, increase epithelial cell proliferation and stop apoptosis for effective ulcer healing process (Bandhopadhyay et al., 2002).

Recently, there has been a rapid progress in the understanding of the pathogenesis of peptic ulcer. Most of the studies focus on newer and better drug therapy for the prevention and treatment of peptic ulcer. These have been made possible largely by the availability of the proton pump inhibitors, histamine receptor antagonists, drugs affecting the mucosal barrier

and prostaglandin analogues (primarily misoprostol) (Hoogerwerf & Pasricha, 2006). However, the clinical evaluation of these drugs showed development of tolerance and incidence of relapses and side effects that make their efficacy arguable. Furthermore, most of these drugs produce several serious adverse reactions including toxicities, arrhythmias, impotence, gynaecomastia, arthralgia, hypergastrinemia, haemopoeitic changes and even may alter biochemical mechanisms of the body upon chronic usage (Vyawahare et al., 2009). This has been the rationale for the development of alternative approach in recent days for the research of new antiulcer drugs medicaments from traditional medicinal system, which includes herbal drugs.

For many years, herbal medicines were generally indicated only as coadjutant gastrointestinal therapy to conventional drugs and when these drugs presented adverse effects and are used during a long-term. Due to several plants encountered in many countries have been reported to poses marked antiulcerogenic activity, the role of natural medicine in management of gastrointestinal diseases has been rethought (Schmeda-Hirschmann & Yesilada, 2005). Thus, the investigation of traditional knowledge, popular medicine and the development of new medicaments based in natural products for the treatment of diseases like peptic ulcer have been indicated as a absolute requirement of our time (Sen et al., 2009).

Medicinal plants and their derivatives have been an invaluable source of therapeutic agents to treat various disorders including PUD (Borrelli & Izzo, 2000). The use of vegetable extracts used in popular medicine and their phyto-constituents as drug therapy to treat major ailments has proved to be clinically effective for the treatment of PUD (Dharmani and Palit, 2006). Furthermore, the use of plants and their phytoconstituents in the treatment of gastrointestinal diseases is promising due to the broad spectrum of action on various defensive mechanisms like antioxidant, antinflamatory, imunomodulatory, cytoprotective and antisecretory (Newall et al., 1996).

Although several plants have showed beneficial gastroprotective effects, earlier publications, and researchers from around the world, have pointed out that relatively little of the world's plant biodiversity has been extensively screened for bioactivity (Harvey et al., 2010), and this scenario extends to most plants that have traditional indication for the management of gastric ulcers.

4. Ethnopharmacological discovery of antiulcer crude drugs

Treatment of gastrointestinal ailments with natural products is quite common in traditional medicine worldwide. The importance of ethnopharmacological studies in the search for plants with gastroprotective activity is emphasized by the observation that the first drug effective against gastric ulcer was carbenoxolone, discovered as a result of research on a commonly used indigenous plant, *Glycyrrhiza glabra*. Also, studies on cabbage, previously employed as an anti-ulcer agent in folk medicine, has led to the development of gefarnate, a drug used for the treatment of gastric ulcers (Akhtar & Munir, 1989). Thus, a search among medicinal plants is still important, despite the progress in conventional chemistry and pharmacology in producing effective drugs (Harvey et al., 2010).

Currently, new therapeutic approaches with medicinal plants based in traditional knowledge and in ethnopharmacological screening have received particular attention in the prevention and/or treatment of gastric diseases such as PUD. In this context, there are reports of a large variety of plants species with antiulcerogenic potential in several countries. Examples of plants and their phytochemicals with antiulcer activity investigated in ethnopharmacological studies are sowed in table 1.

Botanical name	Parts used*	Actives phytochemicals	Ulcer model
Aclepiadaceae			
Hemidesmus indicus	root	alkaloids, tannins, phenols, saponins	aspirin, pylorus ligation, cyteamine
Anacardiaceae			
Anacardium occidentale	leaves	glycosylated quercetin, glycosylated myricitin, catechin, proanthocyanidin, biflavonoid amentoflavone	ethanol + HCl
Asteraceae			
Centaurea solstitialis	spiny flowers	sesquiterpene lactones, chlorojanerin 13-acetylsolstitialin A, solstitialin A	ethanol, HCl, indometacin cold stress, serotonin
Clusiaceae			
Calophyllum brasiliense	stem bark	flavones, flavonols, triterpenoids, xanthones, steroids	ethanol, indomethacin, cold stress, pyloric ligation
Combretaceae			
Anogeissus latifolia	bark	glycosides, leucocyanidin, ellagic and flavellagic acid, galic acid	ethanol, aspirin, cold stress, pylorus ligation
Euphorbiaceae			
Alchornea castanaefolia	leaves, bark	quercetin-3-O-β-D-galactopyranoside, quercetin-3-O-α-L-arabinopyranoside, myrecetin-3-O-α-L-arabinopyranoside, quercetin, galic acid, amentoflavone, glycolipids, free sugars	ethanol + HCl, acetic acid cold stress, pylorus ligation, indomethacin
Emblica officinalis	fruits	flavonoids, phenols, curcuminoides, phyllembelic acid, tannins,	ethanol, aspirin, cold stress, pylorus ligation,

Fabaceae			
Desmodium gangeticum	root	alkaloids, steroids, pterocarpanoids flavone, isoflavonoid glycosides, N-oxides, b-amyrone, tryptamines, phospholipids	ethanol, aspirin, cold stress, pylorus ligation
Spartium junceum	flowers	alkaloids, saponins, spartitrioside	ethanol, pylorus ligation, cold stress
Labiatae			
Ocimum sanctum	leaves	eugenol, carvacrol, caryophyllene, apigenin, luteolin, orientin, molludistin, ursolic acid	ethanol, acetic acid, aspirin, reserpine, pylorus ligation
Liliaceae			
Aloe vera	leaves	alkaloids, sterols, gelonins, saponins, fatty acid, glycoproteins	HCl, pylorus ligation
Asparagus racemosus	root	alkaloids, steroids, saponins, flavonoids, phenols, tannins, terpenes	ethanol, aspirin, cold stress, pylorus ligation,
Malphiaceae			
Byrsonima crassa	leaves	quercetin-3-o-b-D-galactopyranoside quercetin-3-o-a-L-arabinopyranoside amentoflavone, catechin, epicatechin	ethanol + HCl
Meliaceae			
Azadirachta indica	bark	phenols, phenolic diterpenoids, glycosides, isoprenoids, essential oils flavonoids, tannins	ethanol, aspirin, indomethacin, histamin
Oleaceae			
Jasminum grandiflorum	leaves	alkaloids, saponins, phenois flavonoids, carotenoids, glycosides	pylorus ligation + aspirin ethanol, acetic acid

Sapindaceae			
Allophylus serratus	leaves	ß-sitosterol, phenacetamide, flavonoids, glycosides	ethanol, aspirin, acetic acid, cold stress
Rhizophoraceae			
Rhizophora mangle	bark	polyphenols, catechin, epicatechin, chlorogenic, gallic and ellagic acids, gallotannins, elagitannins	diclofenac
Rubiaceae			
Rubia cordifolia	root	anthraquinones, iridoid glycoside, bicyclic hexapeptides, triterpenes	pylorus ligation
Scrophulariaceae			
Scoparia dulcis	aerial parts	cirsitakaoside and quercetin	pylorus ligation, histamine, bethanechol
Simaroubaceae			
Quassia amara	bark	alkaloids, b-carbonile, cantin-6, steroids, quassinoids, terpenes	ethanol, HCl
Solanaceae			
Solanum nigrum	Fruits	tannins, alkaloids, carbohydrates, anthocyanins	ethanol, indomethacin, pylorus ligation, cold stress
Utleria salicifolia	rhizome	steroids, alkaloids, terpenoids, saponins, tannins	ethanol, acetic acid cold stress, pylorus ligation
Zingiberaceae			
Zingiber officinalis	Root	alkaloids, flavonoids, phenols, monoterpenoids, sesquiterpenoids	methanol, acetone, HCl
Amomum subulatum	fruits	anthocyanins, aurone, flavone, essestial oils	ethanol, aspirin, pylorus ligation

Table 1. Plants with antiulcerogenic activity from ethnopharmacological studies.
*Gastroprotective effects were obtained using crude preparations of all the plants described

Important questions related with crude drugs are the necessary amount of plant part to provide a healing response, traditional way of preparation (infusion, decoction and maceration), concentration (plant/solvent ratio), frequency and duration of treatment. Unfortunately, this basic information is not always present in ethnopharmacological studies and this fact is surprising as there should be a realistic approach to the doses to confirm the reputed effectiveness of the crude drugs. Extraction yields and doses recommended in traditional medicine were not taken into account in most cases. This fact clearly suggested the need for guidelines when looking for gastroprotective crude drugs or gastroprotective compounds from medicinal plants (Schmeda-Hirschmann & Yesilada, 2005).

In anthropological and ethnobiological investigations of popular herbal therapies practices has been indicated that as a common way of preparation, plants are used in traditional medicine as infusions or decoctions, but in some localities also as macerates, either in water or in alcoholic beverages (Schmeda-Hirschmann & Rojas de Arias, 1990). In particular cases, the treatment may also be applied by direct ingestion of the material.

As a common popular practice, the plant material (in the range of 5–50 g of dry plant material per liter) is placed in a pot of solvent (most commonly hot or coldwater), while resinous materials which would not dissolve in polar solvents are directly swallowed. As the percent (w/w) extraction yields of plant material presents a great variability depending on the extraction solvent, processing temperature and time, doses corresponding to 5–50 g of dry plant material are about 0.5–10 g extract for an adult user (60–70 kg) corresponding to ca. 100–150 mg of crude extract per kg of body weight. In the current scenario, it has been observed that most studies have investigated the antiulcerogenic properties using different animal models at doses of plant extracts ranging from 5 to about 2000 mg/kg. However, the doses between 25 and 800 mg/kg have indicated great gastroprotective effect of crude plant extracts, range that is more realistic considering the tolerable human consumption. Higher doses may not be realistic since they will not be used or recommended in traditional medicine (Schmeda-Hirschmann & Yesilada, 2005).

Although crude drugs obtained through the use of herbal preparations with fresh or dried plants and concentrated plant extracts have broad applicability in folk medicine, the viability of this practice in the pharmaceutical industry is arguable. Is widely recognized that crude drugs exhibit a wide spectrum of phytochemicals with different biological activities. However, few of these compounds have pharmacological activities of interest for the treatment of specific health conditions, and although these compounds are present in crude drugs, can also be phytochemicals with antagonistic activity or even harmful to human health. Furthermore, another important aspect is the difficulty of standardization in the phytochemical composition of these crude drugs since there is a wide variation in levels of the chemical components related to where the raw material was obtained (Leite, 2009).

In this context, following the identification of the efficacy of crude herbal preparations in different health conditions, the method ethnopharmacological predicts the development of several research stages aiming to identify, concentrate and isolate phytochemical components to test the biological activities of each compound identified in the crude drug. In this process, it is possible to focus the investigations on the phytochemicals responsible for the desired biological effects (Fabricant & Farnsworth, 2001; Bhutani & Gohil, 2010). Thus, through this approach it is possible to achieve the level of control required in pharmacological studies in order to determine the therapeutic dose, toxicity and mode of use of specific phytochemicals, criteria that must be strictly defined where the intention is to discover and develop new pharmaceuticals derived from plants for commercial purposes

(Koehn & Carter, 2005). A basic scheme of the ethnopharmacological method is represented in the figure 1. Based in this method several phytochemicals with antiulcer activity were discovered, and was clearly demonstrated that the main benefits of these crude drugs are linked to alkaloids, flavonoids, saponins and tannins.

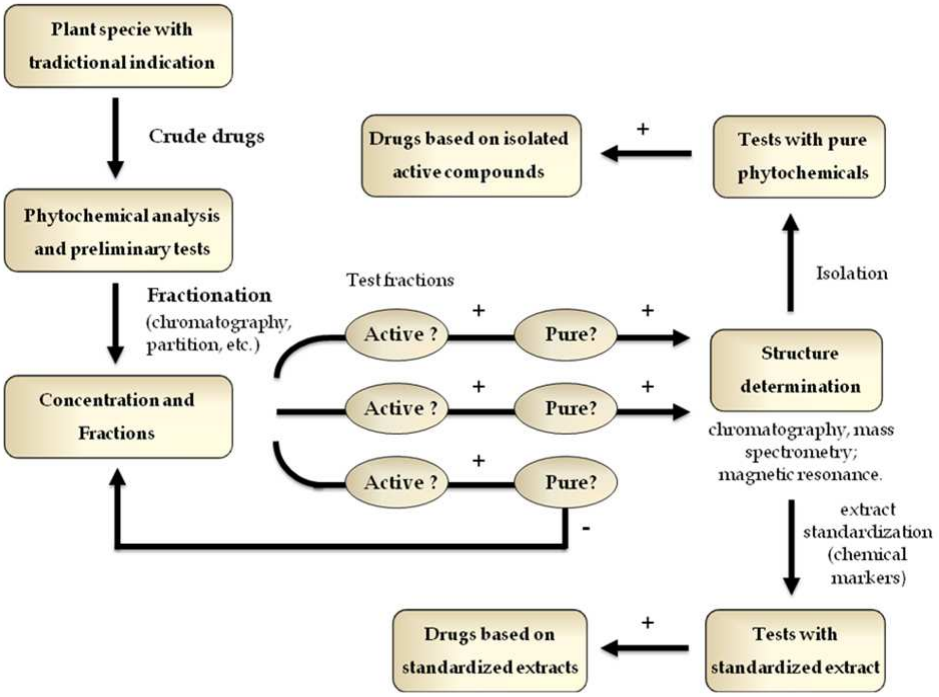


Fig. 1. Generic representation of ethnopharmacological method in a bioassay-guided fractionation for the investigation of phytochemicals with therapeutic properties used in drugs development (adapted from Koehn and Carter, 2005).

5. Antiulcer properties of specific phytochemicals

5.1 Alkaloids

The alkaloids are a diverse group of low molecular weight nitrogen-containing compounds derived mostly from amino acids. These secondary metabolites are found in about 20 % of plant species (Ziegler & Facchini, 2008). Plants containing alkaloids with antiulcer properties are showed in table 2. Furthermore, these phytochemicals represent a group of natural products that has had a recognized impact in medicine and are being used in management of gastrointestinal ailments. Clinically, alkaloids 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. In a previous literature review were identified fifty-five naturally derived alkaloids with antiulcer activity such as imidazole, indole, isoquinoline, non-nitrogen heterocycle alkaloid, phenylalkylamide, piperidine, pyrazine, pyridine, pyrrolidine, pyrrolizidine, quinolizidine and tropane alkaloids (Falcão et al., 2008a).

Botanical name	Parts used	Ulcer model
Apocynaceae		
Himatanthus lancifolius	bark	ethanol, pylorus ligation
Annonaceae		
Enantia chlorantha	bark	ethanol, HCl pylorus ligation
Apocynaceae		
Voacanga africana	fruits	ethanol, HCl, pylorus ligation, indomethacin
Asteraceae		
Mikania cordata	leaves	diclofenac
Senecio brasiliensis	flowers	ethanol, HCl, pylorus ligation, indomethacin
Buxaceae		
Pachysandra terminalis	leaves	cols stress
Flabaceae		
Sophora flavescens	leaves	acetic acid, cold stress
Ranunculaceae		
Coptis chinensis	rhizoma	ethanol, acetic acid pylorus ligation
Coptis japonica	rhizoma	ethanol
Rubiaceae		
Pausinystalia yohimbe	bark	cold stress
Rutaceae		
Galipea longiflora	bark	ethanol, HCl, bethanecol

Table 2. Plants containing alkaloids with anti-ulcer activity.

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 plants belonging to families Papaveraceae, Berberidaceae and Ephedraceae (Ziegler & Facchini, 2008). In murine model of gastric damage induced by reserpine, aspirin or indomethacin, morphine and ephedrine presented

significant antiulcer activity (Al-Shabanah et al., 1993; Sandor & Cuparencu, 1977). In addition, the alkaloid 7,8-dihydro-8-hydroxypalmatine obtained from the bark of *Enantia chlorantha* was effective to increase gastric mucus and accelerated ulcer-healing production after gastric lesions caused by acetic acid. Positive effect was also evidenced when ulceration of gastric mucosa was induced using HCl/ethanol and pylorus ligature (Tan et al., 2000). Other alkaloids isolated from *Coptidis* rhizome, coptisine and 8-oxocoptisine, showed protection of gastric mucosa similar to that offered by gastroprotective conventional drugs such as cimetidine and sucralfate (Hirano et al., 2000, 2001).

Alkaloids derived from *Voacanga africana* was assayed for cytoprotective, anti-secretory and ulcer healing actions. Through enteral administration, alkaloid fraction inhibited ulcer formation in a dose-dependent way in several models of gastric damage (HCl/ethanol, absolute ethanol, HCl/ethanol/ indomethacin, pylorus ligation, cold restraint stress, and histamine). These alkaloids have gastric anti-secretory effects similar to histamine receptor blockers and decreased the gastric acid secretion. Moreover, its cytoprotective and ulcer healing effects are associated to its property to strengthen gastric mucosal defenses by stimulating mucus synthesis (Tan & Nyasse, 2000). When combined with ranitidine, a synergistic anti-secretory effect was observed (Tan et al., 2002). In addition, alkaloids such as matrine, 13-alpha-hydroxymatrine and oxy-matrine isolated from *Sophora flavescens* were able to decrease the acid secretion and inhibited the gastric motility in experimental model of gastric ulcers induced by pylorus ligature (Zhu et al., 1993; Yamazaki, 2000).

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 this investigation, gastroprotective effects of alkaloids were associated to the stimulation prostaglandin synthesis in gastric mucosal and free mucus, reduction of exfoliation of superficial cells, hemorrhages and blood cell infiltration, events that can be mediated by increased expression of epidermal growth factors (Toma et al., 2004).

5.2 Flavonoids

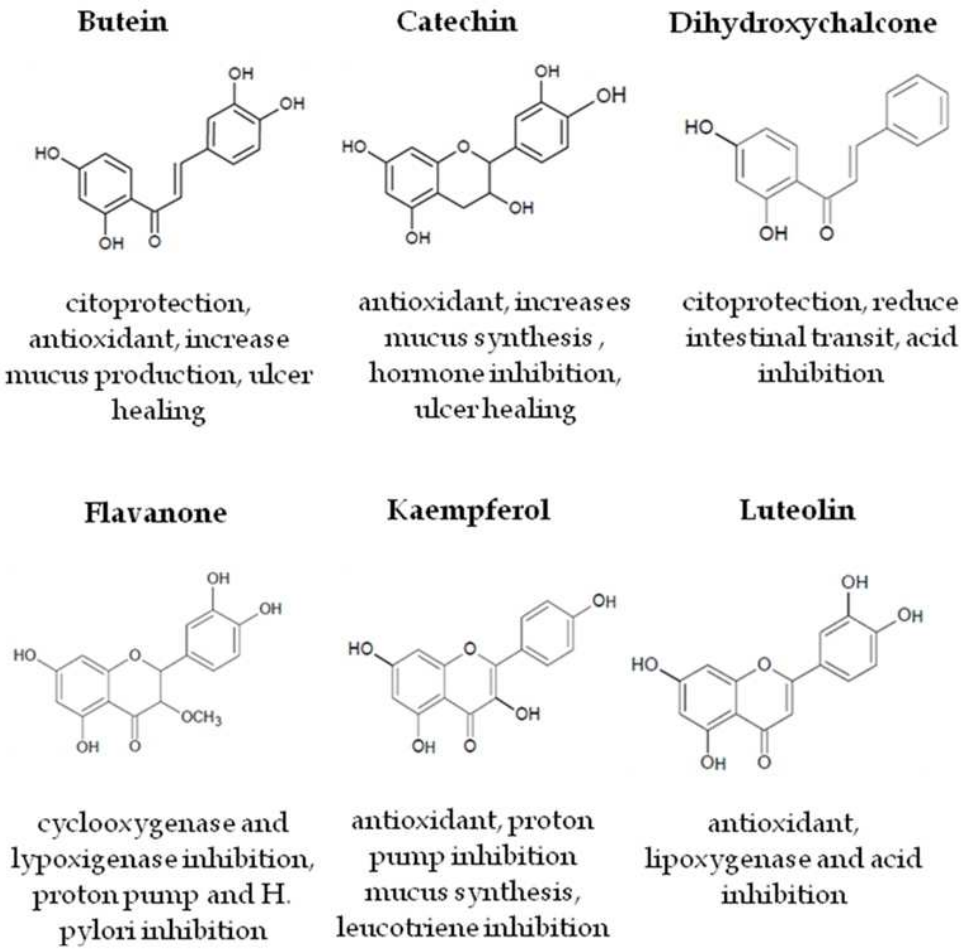
Flavonoids are important constituents in human diet that are also found in several medicinal plants used in popular medicine around the world (Di Carlo et al., 1999). These molecules represent a highly diverse class of secondary metabolites derived from vegetable material comprising about 9,000 structures with a wide range of biological effects, including antiulcer activity (Mota et al., 2009).

There are several studies with flavonoids naturally derived were found to be able to protect the gastric mucosa reducing the number and intensity of the lesions induced by a variety of ulcerogenic agents such as ethanol, HCl, acetic acid, aspirin, diclofenac, indomethacin, reserpine, cold stress and pylorus ligation (Borrelli & Izzo, 2000). Currently, the flavonoids catechin, flavanone, flavone, kaempferol, naringin, naringenin, quercetin, and rutin have been most commonly cited as having important gastroprotective effect in experimental models of duodenal and gastric ulcers.

Several mechanisms have been proposed to explain the gastroprotective effects of flavonoids; these include increase of mucosal prostaglandin content, decrease of histamine secretion from mast cells and inhibition of *H. pylori* growth (Beil et al., 1995). Furthemore, flavonoids have been found to be free radical scavengers with an important role in

protection against ulcerative and erosive lesions of the gastrointestinal tract. Due to low toxicity, flavonoids could have a therapeutic potential ideal for treatment of gastrointestinal diseases associated with *H. pylori* infection, i.e. type B gastritis and duodenal ulcer (Di Carlo et al., 1999, Martín et al., 2000). Common flavonoids with antiulcer activity are shown in Figure 2.

In experiments with murine model of ethanol-induced gastric ulcers, the flavonoids naringin and quercetin displayed marked antiulcerogenic effects. In particular, naringin at a dose of 400 mg/kg had a significant gastroprotective effect, reducing the number and severity of ulcerative lesions. It is suggested that the gastroprotective property of naringin occurs through a complex non-prostaglandin dependent mechanism that involved an increase in the mucus synthesis and their viscosity. Free-radical scavenging also seems to be implicated in this protective activity (Martín et al., 2000).



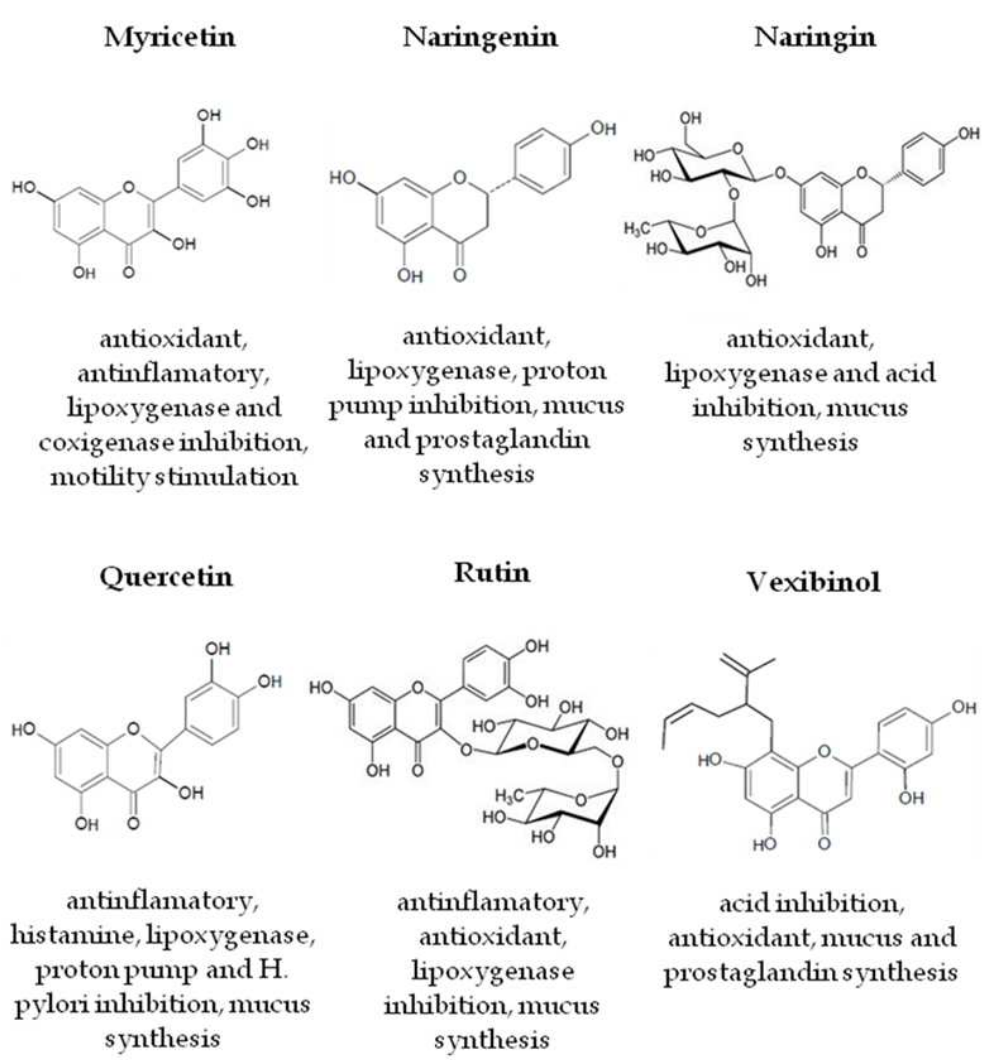


Fig. 2. Flavonoids with antiulcerogenic properties and their mechanisms of action.

Administration of Quercetin at a dose of 200 mg/kg also showed beneficial effects by reducing the occurrence of ulcers and increased the amount of glycoprotein content of gastric mucus. A proposed mechanism of action for the effects of Quercetin is a cytoprotective effect mediated by antioxidant properties, stimulation of prostaglandin and inhibition of leukotriene production, events that reinforce the defensive compounds of the gastrointestinal wall (Alarcon de la Lastra et al., 1994; Di Carlo et al., 1999). In a rat model of gastric damage induced by acidified ethanol, the antiulcer effects of flavone, quercetin, naringin, rutin and kaempferol were previously related to the synthesis of platelet activating factor (PAF), a recognized ulcerogenic agent (Izzo, 1996). In this study,

intraperitoneal administration of quercetin, rutin and kaempferol reduced tissue erosion in a dose-dependent manner (25-50 mg/kg), while naringin reduced gastric damage only at high dose levels (200-400 mg/kg) and flavone was inactive. Gastric mucosa of rats exposed to acidified ethanol presented large amounts of PAF and the treatment with flavonoids proved to have protective effects against the gastric damage when the doses utilized were able to reduce PAF synthesis. Although other protective mechanisms cannot be excluded, evidences indicate that the degree of PAF inhibition produced by flavonoids was an important factor associated with the reduction of gastric injuries (Izzo et al., 1994; Di Carlo et al., 1999).

The influence of flavonoids on gastric acid secretion, mucosal prostaglandin production and *H. pylori* growth were also previously investigated (Beil et al., 1995). In this study, the flavonoids Flavone, Flavanone and Quercetin reduced *H. pylori* growth and the acid production in response to histamine and dibutyryl cyclic AMP stimulation. All flavonoids tested also inhibited the gastric proton pump (H^+/K^+), however, no inhibitory action was observed on the formation of prostaglandin E. In this context, flavone and flavanone increased PGE release, and quercetin was inactive in this process. Thus, was possible concluded that due to low toxicity of flavonoids and the effective gastroprotective properties described (antisecretory action, stimulation of prostaglandins, inhibition of *H. pylori*), these compounds presented a promissory therapeutic potential for the direct treatment of ulcerative diseases or for the development of drugs with this purpose (Di Carlo et al., 1999).

5.3 Saponins

Saponins are largely distributed in plants and are characterized as a specific kind of glycosides. They exhibit haemolytic properties and are highly toxic in direct contact with the blood stream. According to the structure of the aglycone or sapogenin two forms of saponin are recognized, the steroidal and triterpenoid type, the latter form being found in high concentrations in many plant species (Samuelsson, 1992; Borrelli & Izzo, 2000).

Antiulcer activity of several plant species containing high amounts of Saponins has been continuously indicated in different experimental ulcer models. The main species investigated in ethnopharmacological studies are shown in Table 3. Was previously demonstrated that liquorice root contains about 2%-12% of glycyrrhizic acid and the seeds of the horse-chestnut up to 13% of aescin (Newall et al., 1996; Borrelli & Izzo, 2000). Among these, saponins isolated from the rhizome of *Panax japonicus* and the fruit of *Kochia scoparia* (with about 20% of saponins) showed significant gastro-protective properties by inhibiting the amount and severity of ulcerative lesions (Matsuda et al., 1998). Furthemore, oleanolic acid oligoglycosides extracted from the same plants showed antiulcer effects on ethanol- and indomethacin-induced gastric damage. In another study, methanol extract of *Panax japonicus* rhizome also was able to protect gastric mucosa against stress- or HCl-induced ulcers (Yamahara et al., 1987; Borrelli & Izzo, 2000).

Aescin, a mixture of saponins encoutered in the seeds of *Aesculus hippocastanum*, has been shown to possess a marked antiulcer property (Marhuenda et al., 1993). For this compound, the gastroprotective effect has been associated with an inhibition of gastric acid and pepsinogen secretion. However, in a model of gastric ulceration ethanol-inducedm aescin was also effective in preventing gastric lesions (Marhuenda et al., 1994; Borrelli & Izzo, 2000). As in this model acid and pepsin do not play a significant role, the evidences indicates that other protective mechanisms are involved in the antiulcer action of aescin Furthermore,

Botanical name	Parts used	Materials tested	Ulcer model
Araliaceae			
Polyscias balfouriana	leaves, roots	ethanolic extract	aspirin
Asteraceae			
Aster squamatus	aerial parts	hydroalcoholic extract	ethanol, pylorus ligation
Chenopodiaceae			
Kochia scoparia	fruits	isolated saponin	ethanol, indomethacin
Combretaceae			
Pteleopsis suberosa	bark	aqueous extract	indomethacin
Compositae			
Calendula officinalis	rhizome	isolated saponin	arsenic, butadione, pylorus ligattion
Dilleniaceae			
Davilla rugosa	stem	hydroalcoholic extract	acetic acid, ethanol, HCl, cold stress
Fabaceae			
Spartium junceum	Flowers	ethanolic extract	ethanol
Icacinaceae			
Pyrenacantha staudtii	Leaves	aqueous extract	indomethacin, serotonin, cold stress
Menispermaceae			
Rhigiocarya racemifera	Leaves	aqueous extract	indomethacin, serotonin, reserpine
Mimosaceae			
Calliandra portoticensis	Leaves	ethanolic, aqueous extract	cold stress, pylorus ligation
Sapindaceae			
Aesculus hippocastanum	seed	mix of saponins	ethanol, pylorus ligation cold stress
Sapindus saponaria	fruits, leaves	hydroalcoholic extract	cold stress
Sapotaceae			
Mimusops elengi	bark	hydroalcoholic extract	ethanol, pylorus ligation

Scarabaeoidea			
Panax binnatifidus	rhizome	isolated saponin	psychological stress
Theaceae			
Camellia sinensis	seed	methanolic extract	ethanol

Table 3. Plants containing saponins with anti-ulcer activity.

mucus synthesis mediated by prostaglandin seems not to be an able mechanism to explain the role of aescin-induced gastro-protection due to inability of saponin to stimulate the prostaglandin production in model of ethanol-induced gastric ulceration (Marhuenda et al., 1994; Borrelli & Izzo, 2000).

In a general context, the current information indicate that the antiulcer protective activities of the saponins are not due to inhibition of gastric acid secretion but probably due to activation of mucous membrane protective factors (Borrelli & Izzo, 2000).

5.4 Tannins

Plants produce tannins as protective substances, found in the outer and inner tissues. Tannins are by definition phenol compound with sufficiently high molecular weight and different chemical structures occurring in medicinal and food plants that are utilized world-wide. This phytochemical presents several remarkable biological and pharmacological activities and an important meaning for human health. Tannins are used in medicine primarily because of their astringent properties, which are due to the fact that they react with the proteins of the layers of tissue with which they come into contact (Samuelsson, 1992; Borrelli & Izzo, 2000). Moreover, the used of tannins against peptic ulcer, diarrhea and as an antidote in poisoning by heavy metals are described in medical literature.

Several plants with anti-ulcer activity containing high levels of tannins are showed in Table 4. In a previous investigation, a crude extract of *Linderae umbellatae* exhibited a marked anti-peptic and antiulcerogenic activity (Ezaki et al., 1985; Borrelli & Izzo, 2000). In this study, condensed tannins such as (+)-catechin, (-)-epicatechin, proanthocyanidin, cinnamtannin B1 and D1 (monomers, dimers, trimers and tetramers) have been isolated and their anti-peptic and anti-ulcer activity confirmed in experimental models of gastric lesions induced by pylorus-ligation in rats and stress in mice. Significant biological differences were observed between the chemicals structures of tannins. Monomers and dimers, did not presented inhibitory activity on peptic activity in vitro, while trimers exhibited higher inhibition of peptic activity compared to tetramers. In mice with pylorus ligation, trimers and tetramers markedly reduced the peptic activity of gastric juice. Furthermore, monomers and dimers slightly suppressed the peptic activity in this experimental model (Ezaki et al., 1985; Borrelli & Izzo, 2000). As monomers and dimers proved to be inactive in vitro, it is possible that their activity is not related to the direct inhibition of pepsin in vivo, but mainly related to influence on the secretion mechanism of pepsin.

Additional mechanisms have been related to the antiulcer action of tannins. This phytochemicals are known to coat the outermost layer of the mucosa and to render it less permeable and more resistant to chemical and mechanical injury or irritation (Asuzu & Onu, 1990; Borrelli & Izzo, 2000). When a low concentration of tannins is applied to the mucosa,

Botanical name	Parts used	Extract	Ulcer model
Anacardiaceae			
Myracrodruon urundeuva	bark	ethyl-acetate tannin fraction	ethanol, indomethacin
Schinus terebinthifolius	bark	aqueous	cold stress
Celastraceae			
Maytenus ilicifolia	leaves	aqueous	indomethacin
Combretaceae			
Combretum dolichopetalum	roots	ethanolic	indomethacin, cold
Pteleopsis suberosa	bark	chloroform, aqueous	Indomethacin, cold stress
Euphorbiaceae			
Excoecaria agallocha	bark	aqueous	diclofenac
Fabaceae			
Sesbania grandiflora	bark	ethanolic	indomethacin
Fagaceae			
Quercus suber *Quercus coccifera*	leaves	isolated tannins	ethanol
Lauraceae			
Linderae umbellatae	steam	isolated tannins	cold stress
Meliaceae			
Entandrophragma utile	bark	aqueous	ethanol
Menispermaceae			
Rhigiocarya racemifera	leaves	aqueous	reserpine, serotonin,
Myrtaceae			
Syzygium cumini	bark	isolated tannin	ethanol + HCl
Scrophulariaceae			
Veronica officinalis	aerial parts	hydroalcoholic	indomethacin, reserpine

Table 4. Plants containing tannins with anti-ulcer activity.

only the outermost layer is tanned, becoming less permeable and affording an increased protection to the subjacent layers against the action of bacteria, chemical irritation, and, to a

certain extent, against mechanical irritation. In another hand, high concentrations of tannins often cause coagulation of the proteins of the deeper layer of the mucosa, resulting in inflammation, diarrhea and vomiting. The discovery of the inhibitory effects of tannins on lipid peroxidation in rat liver mitochondria and microsomes was followed by the uncovering of several effects related to improving the several gastrointestinal symptoms, activity that may be related to inhibition of lipoxygenase products related to metabolism of arachidonic acid (Okuda, 2005; Borrelli & Izzo, 2000). In addition, gastroprotective protective effects are related to antioxidant, vasoconstricting and antihemorrhagic properties of tannins (Borrelli & Izzo, 2000), which has also been linked to inhibition of *H. pylori* growth by several hydrolysable tannins (Funatogawa et al., 2004).

6. Screening of the constituents from *Maytenus ilicifolia* with anti-ulcerogenic activity

The beneficial medicinal effects of plant materials typically result from the secondary products present in the plant, and usually are not attributed to a single compound but a combination of the metabolites. In an extensive literature review, was identified, in quantitative terms, that the gastroprotective properties of crude drugs plant-based are attributed mainly to the presence of flavonoids, being found about 53 flavonoid compounds with antiulcer activity (Mota et al., 2009). However, currently there are sufficient evidence that in crude vegetables preparations the gastroprotective effects are also deeply influenced by other phytochemicals such as alkaloids, saponins and tannins. Therefore, efforts should be directed towards isolation and characterization of the active principles and elucidation of the relationship between structure and activity, followed by attempts for modulation of its activity potential by chemical modification. Furthermore, detailed analysis of the active constituents of natural drugs should be directed towards clinical relevance and to maintain indispensable reproducible quality in biological evaluation.

The ethnopharmacology constitutes an important and reliable method in bioprospecting of phytochemicals with anti-ulcer activity. The case of the discovery of the gastroprotective activity of *Maytenus ilicifolia* constitutes an appropriate example that clearly demonstrates the important role of ethnopharmacology in elucidating the pharmacological basis that is associated with a large part of traditional knowledge about medicinal plants and that waiting to be discovered.

Maytenus ilicifolia Mart. ex. Reissek belongs to the Celastraceae, a pantropical family native to southern Brazil, Paraguay, Uruguay, and northern Argentina. The plant is a small medicinal evergreen shrub that grows to a height of five meters bearing leaves and berries that resemble holly and is popularly known as “espinheira santa” (holy spine), “cancerosa”, “cangorosa”, “maiteno” and “espinheira divina” (divine spine) (Cordeiro et al., 2006). *Maytenus ilicifolia* is widely used as a traditional medicine in many countries of South America and its leaves are traditionally used as a remedy for gastrointestinal diseases, including dyspepsia and gastric ulcers (Leite et al., 2001, 2010). They are found in the local commerce as capsules, powders, dried leaves, or as aqueous or aqueous-alcoholic preparations.

The antiulcerogenic activity of *Maytenus ilicifolia* leaves is well documented. Has been showed that its aqueous extract causes significant reduction in the number of gastric ulcers induced by both indomethacin and cold-restraint stress in rats. This protection was similar

to that observed with cimetidine, a well known histamine H2 receptor antagonist. Chemical constituents obtained from this plant extracts with solvents of different polarities are terpenoids, flavonoids, tannins and polysaccharides (Leite et al., 2001).

Souza-Formigoni et al., (1991) used boiling water extract of *Maytenus ilicifolia* leaves against ulcer lesions induced by indomethacin and cold-restraint stress in rats and found that both the oral and intraperitoneal administration of the extract had a potent antiulcerogenic effect against both types of ulcers. In this study, several phytochemicals were identified in crud extract of *Maytenus ilicifolia* and apparently polyphenols and flavonoids were the main compounds linked to gastroprotective effects evidenced. However, in a study conducted by Martins et al., (2003), antiulcer effects of *Maytenus ilicifolia* spray-dried powders obtained of an ethanol extract was mainly related to the tannins content in the crude extract. Thus, results of these studies suggested that a number of active constituents might be present in crude extract to control ulcerative lesions. However, of the major bioactive component of *Maytenus ilicifolia* that offers antiulcer effects remained still not well understood.

In a previous study, Baggio and collaborators reported the potent *in vivo* gastroprotective properties of a flavonoid-rich fraction separated from the leaves of *Maytenus ilicifolia*, *Maytenus ilicifolia*, containing epicatechin (3.1%) and catechin (2%) as major constituents, which was correlated with the in vitro inhibition of rabbit gastric H+,K+-ATPase activity (Baggio et al., 2007). Aiming to further the investigation on the bioactive constituents from *Maytenus ilicifolia* leaves, Leite et al., (2010) carried out a phytochemical investigation of an ethanol extract of *Maytenus ilicifolia* leaves for the isolation of compounds which were further used as chemical markers to monitorize an activity-guided fractionation of a lyophilized aqueous extract of *Maytenus ilicifolia* leaves. Finally, high performance liquid chromatography analyses of aqueous extract and its chromatographic fractions were carried out, aiming at establishing a correlation between gastroprotective effect and chemical composition. In this study, fractionation of aqueous extract led to 5 fractions containing different flavonoids such as the tri-flavonoid glycosides mauritianin, trifolin, hyperin, epi-catechin, a tetra-glycoside kaempferol derivate and the monosaccharide galactitol. Chemical structures of the phytochemicals identified are showed in Figure 3. These fractions were evaluated in rats for their effects on gastric secretion volume and pH in a model of pylorus ligation. Considering the results of the study it was possible to conclude that only fractions containing mauritianin and tetra-glycoside kaempferol derivate caused significant increase of gastric volume and pH, thus indicating that these glycosides play an important role on the gastroprotective effect of *Maytenus ilicifolia* leaves. Compounds identified in the other fractions had a less important contribution to gastroprotective effect since they have not disclosed significant activity on gastric volume and pH of rats. Gastric mucus is believed to play an important role in the defensive mechanism against gastric ulceration. The protective effect of mucus as an active barrier may be attributed to the glycoproteins, which have the property of holding water in the interstices, thus obstructing the diffusion of hydrogen ions. Stress has been shown to decrease the amount of mucus adhering to the gastric mucosa (Jorge et al., 2004). Hence, increase in synthesis of mucus, according to results obtained in this study with *Maytenus ilicifolia*, is consistent to those found by some authors (Bravo et al., 1990; Sairam et al., 2002), suggesting that such increase is an important factor for antiulcer protection.

Because of mucosa protection, extracts of *Maytenus ilicifolia* may represent an important clinical alternative in antiulcerogenic therapeutic, though, further studies are needed to

evaluate the real usefulness of this extract in the prevention and treatment of peptic ulcers. Thus, the screening of the constituents from *Maytenus ilicifolia* with antiulcer activity used in this study, clearly illustrate as a phytochemical investigation directed by an ethnopharmacologycal approach can be of great value in the search for compounds with potential use for the development of new and more efficient drugs used in management of ulcerative diseases and others health disorders. The occurrence of tetra-glycosylated flavonoids in this specie afford a valuable chemical marker for the quality control of the Brazilian *Maytenus* marketed as phytomedicines.

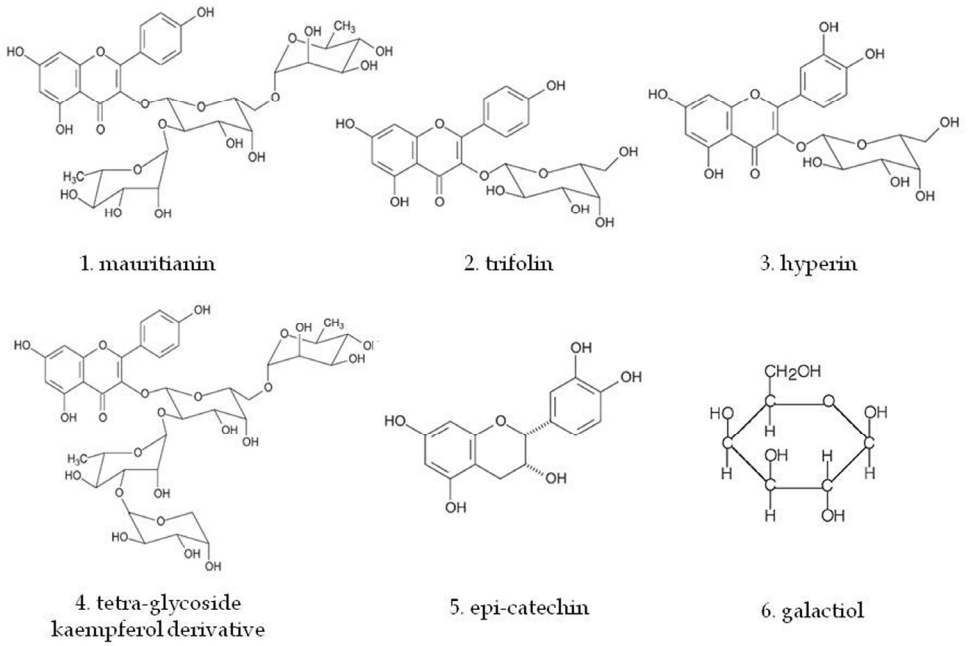


Fig. 3. Phytochemicals identified in a lyophilized aqueous extract of *Maytenus ilicifolia* leaves.

7. Conclusion

Currently, there is a positive trend in favor of traditional, complementar and integrative therapies both in scientific research and health care. Furthermore, in recent decades has been observed strengthening of approaches related to health care such as ethnopharmacology, reverse pharmacology, phytotherapy, systems biology and personalized medicine. Ethnopharmacology has already played recognized importance in the discovery of plants with medicinal potential and in the development of natural health care practices, and is likely to play more significant role in the years to come. It would not be surprising to see that the use of herbal medicines will be gradually accepted in the main stream of conventional medicine. Due to acceptance that the diversity of chemical substances found in vegetable materials may have different biological effects of interest with potential

applications in many different health conditions, it is believe that there will be a growing trend in the use of novel natural products and development of chemical libraries based on these products in drug discovery campaigns.

Plant resources have proved to be an important source for the discovery of new substances with antiulcer potential. Researches in this area have been targeted for both the isolation of active principles, such as to obtain standardized extracts. Polyphenolic compounds, including flavonoids, have been the subject of increasing interest since *in vitro* and *in vivo* biological assays indicated that flavonoids can mediate a range of mechanisms related to anticancer, antitumor, and anti-oxidant activities, among other. The contribution of the flavonoids to the dietary intake of polyphenolics compounds is considerable. In fact, cereals, legume seeds, fruits, wine, and tea contain significant amounts of flavonoids and their derivatives.

In Brazil, studies of the species *Maytenus ilicifolia* have advanced considerably, reinforcing the use in folk medicine, where preparations from the leaves of this species are used as an antiulcer treatment. This species is part of the cast of the Brazilian Pharmacopoeia, being the phenolic constituents used as chemical markers. After several chemical investigations, preclinical and clinical (Phase I, II and III) studies, herbal preparations that include this species obtained registration with the Health Surveillance Agency (ANVISA), the Brazilian agency that regulates the registration of these products. The species is also included in the list of herbal medicines that the Brazilian government provides in the pharmaceutical assistance of the Unified Health System (SUS), and their herbal medicine, therefore, proven by the government as to its effectiveness and safety. In *Maytenus ilicifolia* the 3-*O*-glycosides of quercetin and kaempferol are the most common group of flavonoids. It is known that the sugar moiety is an important factor for the bioavailability of the flavonoid derivatives.

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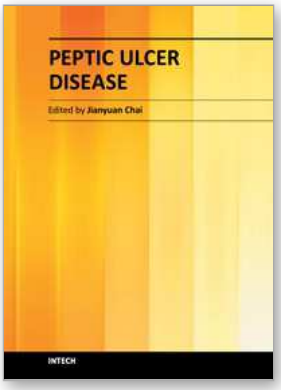

Peptic Ulcer Disease

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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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