



Development of effervescent medical powder containing *Maytenus ilicifolia* extract Mart. ex Reissek for treatment of gastric disorders

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Abstract

Brazil is the country with the biggest biodiversity on the planet, but it does not avail itself enough of this potential to produce herbal medicines. *Maytenus ilicifolia* Mart. Ex Reissek is popularly known as “Espinheira-Santa” and in Brazil is widely used in popular medicine to treat a number of diseases such as gastritis and dyspepsia, and also displays laxative, diuretic, analgesic, antiseptic and healing properties and antineoplastic and antimicrobial activities. Among the reasons that hinder a better exploration of such biodiversity, the absence of an innovative culture draws a lot of attention, besides the inherent difficulties in the characteristics of the research and the development of this product modality. The aim of this study was developing an effervescent powder containing medicinal extract of *M. ilicifolia*. The methodologies to determine quality of the plant and extract including the organoleptic characteristics, the moisture content and volatiles, total ashes, extractive content, pH, and the bulk density. In our experiments, we demonstrated that the plant has been identified and has displayed the appropriate organoleptic characteristics to the preparation of the extract; we also demonstrated that the extract has been incorporated into a formulation that maintained its organoleptic characteristics, pH and content, as well as the formation of stable gases. With these experiments, we demonstrate for the first time that the developed formulation can serve as a prototype for the development of pharmaceuticals effervescent product containing standardized extract of *M. ilicifolia*.

Keywords: Effervescent salt, *Maytenus ilicifolia*, gastritis.



Introduction

Gastric disorders are a major complaint of patients in the healthcare system worldwide, especially those changes related to the stomach and/or duodenum, indicating a proportion of two out of 10 people affected by problems ranging from transient malaise to gastritis, ulcer, and tumors.¹

Factors such as stress, *Helicobacter pylori* infection, smoking, poor nutrition, alcohol, continuous use of anti-inflammatory drugs, genetic predisposition, and endogenous aggressors (acid, pepsin, and bile) are associated with the etiology of this disease. It is generally accepted that gastric ulcer is established when the balance between aggressive and mucosal defending factors is disrupted.²

The Ulcer is a deep lesion of the gastric mucosa that affects the components of epithelial and connective tissue,

including subepithelial myofibroblasts, smooth muscle cells, vessels, and nerves. Such ulcerative lesions can be acute or chronic and most often appear in any portion of the gastrointestinal tract exposed to the aggressive action of peptic acid.³⁻⁵

Several drugs have been used in the treatment of gastric and duodenal ulcers, with gastric antisecretory agents such as H₂-type histaminergic receptor antagonists⁶ being of great importance protons such as omeprazole and lansoprazole.⁷

Maytenus ilicifolia belongs to the Celastraceae family, contains 98 genus and approximately 1264 species found mainly in tropical regions (Figure 1). Popularly known as “maiteno, espinheira-santa, cancerosa, salva-vidas,” this plant is originally from Brazil, its leaf is used. The “espinheira-santa” is a sub-shrub, its size can vary from 2 to 5 m in height. The stem is





Figure 1. *Maytenus ilicifolia* Mart. ex Reissek leaves and fruits.

woody and has pointed and jagged leaves 4 to 12 cm long. The primary chemical constituents reported for *Maytenus* spp. include terpenes (maytin, tringenone, isotenginone II, congorosins A and B, maitenoic acid), triterpenes (friedelanol and friedelin), essential oils (friedenelol), tannins, especially galics (epicatechin, epigallocatechin, and gallate of epigallocatechin), glycol monogalactosyldiacylglycerol, digalactosyldiacylglycerol, trigalactosyldiacylglycerol, tetragalactosyldiacylglycerol and sulphoquinovosyldiacylglycerol) and, lastly, alkaloids (maitein, maytinprine and maytol).⁸⁻¹² While Chiapetti et al¹³ established methods of analyzing the different plant extracts of *Maytenus ilicifolia* by the HPLC technique.

Maytenus ilicifolia can be used for gastritis, dyspepsia, and adjunctive treatment of peptic ulcers. It acts as a regulator of stomach functions and promotes the protection of the gastric mucosa.^{14,15}

This paper aims to develop an effervescent medicinal powder containing a standardized extract of *Maytenus ilicifolia*.

Methodology

Materials

In these experiments we use the following equipment: volumetric flask, analytical balance (explorer Ohaus), water bath, beaker, crucible, condenser, spatula, spectrophotometer, greenhouse, amber container, funnel, refrigerator, mortar, and pestle, warming blanket, muffle, filter paper, pH meter (Ohaus), rotavapor (Fisatom), test tube.

Methods

Plant Quality Control

The plant drug consists of dry leaves containing at least 2% of total tannins. Total tannins consist of at least 5% tanning fraction and at least 4% non-tanning fraction, as described in the Farmacopéia Brasileira. The tannins found in *Maytenus ilicifolia* were quantified by the gravimetric method through acetate precipitation of copper, method developed by Caldeira.¹⁶ The *Maytenus ilicifolia* samples used in the tests were from pharmacies

in the city of São Paulo, Brazil.

The determination of organoleptic characteristics, such as appearance, color, and odor, were visually evaluated.¹⁷ Briefly, the plant samples were processed according to the sensory characteristics evaluation, according to the monographs in the Farmacopéia Brasileira.¹⁸

Moisture/Volatile materials tests were performed as follows:

A dry, empty crucible was weighed, added 2 g of the dried plant, brought to the greenhouse at 105°C, weighed every hour until it was kept constant. A trial was done in triplicate.

In order to determine the % total ashes, after keeping the constant weight of the moisture/volatile materials test, it was taken to muffle for two hours after it was taken out and weighed. A trial was done in triplicate.

To determine the extractive content, 4 g of the plant was weighed and placed in a volumetric flask and made up to 100 mL of water, using the heating blanket and the condenser was kept at temperature for one hour, filtered to obtain the plant extract, then 10 mL was taken. The solution is placed in the oven at 105°C and weighed every hour to constant weight. A trial was done in triplicate.

Method of Preparing Extracts

The method used was maceration. 200 g of the dried plant was weighed. This was placed in an amber glass vial and made up to 2000 g with 77°GL cereal alcohol. This was kept in the dark environment and was shaken daily for 2 minutes for better extraction, and this was held for 7 days. Then the extract was filtered on filter paper. The obtained extract in rotavapor, to make a fractional distillation, thus removing the alcohol, leaving only the concentrated extract of the plant.²⁰

Sampling was performed according to the Farmacopéia Brasileira.²¹ All samples were evaluated in duplicate. Generic tannin extraction: we weighed 1g of the sample in a 100 mL beaker and added 25 mL of distilled water, boiled for 2 minutes; the supernatant was filtered using quantitative filter paper (Quality brand, weight 80 g/m², thickness 205 µm and gray 0.5%) to keep the powder at the bottom of the initial container; this process was repeated twice. At the end of the procedure, the extract was transferred to a 100 mL volumetric flask and made up to 100 mL (1:100) with distilled water.²²

The organoleptic characteristics, such as appearance, color and odor were visually evaluated, to perform the quality control of the extract.¹⁷

The determine pH as follows: the electrode was removed from the KCl solution, washed with distilled water jets, and then dried with filter paper. Calibration pH, the electrode was washed with distilled water and dried with filter paper.²³ Triplicate pH measurement.

Method of Preparing Effervescent Powder

To prepare the effervescent powder, tartaric acid was

weighed, placed in a porcelain mortar and ground to reduce the particle size of the powder. The citric acid was weighed and put to the same mortar, ground, and homogenized. The sodium bicarbonate was weighed and added to the same mortar, ground and homogenized. The prepared powder was used to add varying percentages of the *M. ilicifolia* extract, making the mixture with a dough consistency. This formed mass was passed through a sieve 60 to form granules and then placed in the oven to dry 45°C for 24 hours. This was removed from the greenhouse and re-sieved in the same mesh, obtaining an effervescent powder.²⁰ This effervescent powder was used as a base for the addition of organoleptic modifying agents such as flavoring and sweetening agents.

Stability Assessment Method

Cycle Testing

The stability of the *M. ilicifolia* extract powder was evaluated per sample, which was stored 24 hours at room temperature (25°C), 24 hours in the oven (45°C), and 24 hours in the freezer (-5°C), requiring a repetition of this procedure for 42 days. In the end, the organoleptic characteristics (appearance, color, taste, odor), effervescence time, pH, density were evaluated. Every 2 weeks a sample was taken from each temperature, and 24 hours later, it was evaluated.²⁴

Accelerated Stability Test

The stability of *M. ilicifolia* extract containing powder was evaluated under different temperature conditions for a period of 42 days. The prepared powder was packed in 16 amber vials. The samples were divided into four groups of four samples each, and each group was subjected to one of the following temperature conditions: room temperature (25°C), oven (45°C), freezer (-5°C) and refrigerator (+4°C). On the first day, the organoleptic characteristics, effervescence time, pH, and density were analyzed. Every two weeks a sample was taken from each temperature and 24 hours later it was evaluated.²⁰

Determination of Organoleptic Characteristics and Effervescence Time

The appearance, color, and odor of the effervescent powder and solution formed after being added to water were visually evaluated. Five grams of the powder was solubilized in 50mL of water. After the end of effervescence was assessed as to the appearance, color, odor, and taste of the formed solution.¹⁷

Five grams of the effervescent powder was solubilized in 50 mL of water. The effervescence time was observed and timed until all the powder was dissolved.

Determination of pH

The solution formed in the effervescence time evaluation was used for pH evaluation.¹⁷ The electrode was removed from the KCl solution, washed with distilled water jets,

and then dried with filter paper. Calibration was then performed by immersing the electrode in the pH 7.0 buffer solution, adjusting the pH value to the tabulated value by the calibration button. The procedure was repeated with pH 4.0 buffer. The electrode was washed with distilled water and dried with filter paper.²³ The pH reading was performed in triplicate by placing the electrode in the solution formed from the effervescent powder.

Determination of Bulk Density

A clean, dry, and previously calibrated metal pycnometer was used for density determination. Calibration consisted of determining the mass of the empty pycnometer and the weight of its contents with water already distilled at 20°C. The sample was placed on the pycnometer, and the excess substance was removed and weighed. The weight of the sample was obtained by the difference in the mass of the full and empty pycnometer. The ratio of net mass to water mass, both at 20°C, is the relative density.²³

Results

Plant Quality Control

The plant was identified as *M. ilicifolia*, according to the report analyzed from the supplier.

The result of organoleptic characteristics was aspect ground, color greenish brown, and odor plant characteristic.

In the moisture/volatile materials test, the sample presented a value of 8.12%, with a maximum reference value of 10% presented in the Farmacopéia portuguesa,²⁵ so there was no deviation in the result.

In the total ashes test, the sample presented the value of 6.18%, having as maximum reference value 8% shown in the Farmacopéia brasileira,²⁶ so there was no deviation in the result.

The value of the extractive content in the sample was 26%, with a minimum reference value of 15% presented in the British pharmacopeia,²⁷ so there was no deviation in the result.

Extract Quality Control

The result of organoleptic characteristics was aspect liquid, color greenish brown, flavor extremely bitter, and odor plant characteristic. The pH value was 5.29.

The final formulations and the degree of usual proportions in the formula for effervescent sodium phosphate are shown in Table 1.

The formulation was developed to contain 1 g of standardized dry extract of *M. ilicifolia* equivalent to 35 mg of total tannins expressed as *Maytenus* tannins distributed in a 50g sample of effervescent powder.

Discussion

According to some studies,²⁸⁻³¹ *M. ilicifolia* present action against peptic ulcer and gastritis. Coulaud-Cunha et al³⁰ report that the action of *M. ilicifolia* on the peptic ulcer and gastritis involves more than one mechanism of action, not

Table 7. Raw Material Quantity

Material	Quantity
Dibasic sodium phosphate dry and powdered	18%
Tartaric acid, dry powder	23%
Sodium bicarbonate	42%
Citric acid, monohydrate	15%
Standardized dry extract <i>Maytenus ilicifolia</i> Mart. ex Reissek	2%

yet conclusively elucidated, that both tannins, especially epigallocatechin, and essential oils, especially fridenelol, are responsible by the gastroprotective effects.

Carlini and Frochtengarten,²⁸ in studies with *M. ilicifolia* stuffy, report that the longer the treatment, the higher the gastroprotection without changes in pH. Such observation of *M. ilicifolia* in frogs proved that this has an inhibitory effect on histamine H₂ mediators in parietal cells. According to Gilman et al,³² when stimulated, cause the activation of adenylyl cyclase, initiating a series of complex morphological and biochemical alterations, which leads to increased gastric secretion, functioning as an H₂ antagonist, besides inhibiting the effect of gastrin. It has also been shown that both epigallocatechin (tannin) and fridenelol (essential oil) are responsible for part of the protective effect of the gastric mucosa.^{29,33}

The evidence of the synergistic effect between the components of *M. ilicifolia* was corroborated in studies by Queiroga et al,³⁴ which demonstrated that tannins, when used separately in indomethacin-induced ulcer models, have no activity.

Carlini and Frochtengarten²⁸ related the action of *M. ilicifolia* with its richness in tannins and those used. Several gallic tannins, including epigallocatechin, have been shown to inhibit the potassium-dependent membrane from offering a new product ATPase of gastric mucosa cells responsible for the secretion of hydrochloric acid in the stomach. This mechanism is processed by competitive inhibition. Later studies, such as Murakami et al³⁵ and Annuk et al³⁶ proved that there is a non-competitive inhibition, suggesting two distinct places of action. Still, according to Murakami et al,³⁵ epigallocatechin-3-gallate proved to be the most active compound. According to Annuk et al,³⁶ there is another mechanism of action related against *H. pylori*, frequently involved in clinical studies. Studies showed that gallic tannins of different medicinal plants had bacteriostatic action against *H. pylori* in vitro. Such action was mainly due to the change in membrane permeability, leading to electrolyte and water losses. It was also demonstrated that they acted to the bacteria's adhesion to the gastric mucosa, preventing its pathogenic action.

Clinical studies have shown *M. ilicifolia* antimicrobial activity, antiviral potential, antifungal, antiprotozoal, and anti-inflammatory activity.^{37,38}

According to Ferreira et al,³⁹ in a work carried out with

aqueous extract of *M. ilicifolia* leaves it was demonstrated the inhibition of histamine stimulated gastric secretion in frog gastric mucosa. After this experiment, it was concluded that the freeze-dried aqueous extract reduced the basal acid secretion in the frog's isolated gastric mucosa by the antagonistic effect of histamine H₂ receptors, as well as cimetidine and ranitidine.

According to studies carried out in ethanolic extract and freeze-dried aqueous extract of *M. ilicifolia*, the chemical components mauritianin, trifoline, hyperine, epicatechin, canferol, and galactiol were isolated. From these, it was proved by high-performance liquid chromatography that only the compounds mauritianin and kaempferol have activities on the volume and pH of gastric secretion of rats, being glycosides of great importance on the gastroprotective effect.⁴⁰

Isolation of friedelan-3β-ol and friedelin triterpenes from *M. ilicifolia* leaves confirmed that these two substances were not able to decrease indomethacin-induced gastric ulcers in rats.⁴¹

Several clinical studies have been performed with *M. ilicifolia* in the treatment of peptic ulcer and dyspepsia^{28,42,43,44} and corroborated the actions described in animal models.

“Espinheira-santa” (*M. ilicifolia*) is a phytotherapeutic of relevant therapeutic action, especially anti-ulcerogenic, given its pharmacological efficacy and safety. It is worth remembering that, due to lack of studies, it is not recommended for children and should not be used by pregnant women, since studies in mice (female and pregnant) indicated a significant decrease in the number of embryos, besides having estrogenic activity, which may interfere in the uterine receptivity of the embryo. Among its pharmacological activities, anti-ulcerogenic activity stands out, which can be compared to the action of ranitidine and cimetidine.⁴⁵

Tabach et al demonstrated in important preclinical⁴⁶ and clinical⁴⁷ studies the toxicological safety and therapeutic efficacy in humans following the use of standardized *M. ilicifolia* extract.

H₂ receptor antagonists like ranitidine, cimetidine, reversibly, and competitively inhibit histamine binding while proton pump inhibitors like omeprazole and pantoprazole by inhibiting gastric acid secretion. Generally, these drugs are well tolerated; however, occasional adverse effects may occur.

As noted throughout the paper, there are quite effective drugs for the treatment of gastric disorders, but there are always some exceptions to their use. The use of these drugs is widespread and used in chronic treatment, and these need to be monitored for any adverse effects that can only be observed with the abuse or long-term use of the drug.

The new product is a powder containing *M. ilicifolia* extract. Over time, various formulations were tested to meet market expectations.

Maytenus ilicifolia Mart. ex Reissek

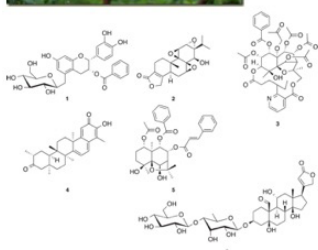
“Espinheira Santa”
 Family: Celastraceae



Normalizer of gastrointestinal functions.
 Gastritis and digestive ulcers
 Gastric ulcer protector
 Gastralgias, dyspepsias
 Atonic intestinal constipation

Gastroprotective effect mediated by
 phytocomplexes:

1. Reduces histamine activity in parietal cells.
2. Increases gastroprotective mucus secretion.
3. Micro-lesions healing in the gastric mucosa
4. Antioxidant and anti-inflammatory.
5. Antimicrobial against *H. pylori*.



Maytenus ilicifolia Mart. Ex Reissek envelope containing 50 g of effervescent formulation with 35 mg of total tannins, expressed in distributed maytenotannins.
 Dosage: 1 (one) envelope, 3 (three) times a day with meals.

Examples of isolated compounds from the Celastraceae family and their respective biological activity, are: (-)-epicatechin-5-O-β-D-glucosyl 3-benzoate (1) (antioxidant activity) (Hwang et al., 2001), triptolide (2) (insecticidal activity) (Luo et al., 2004), oppositine A (3) (cytotoxic activity against tumor cells in human colon) (Whitson et al., 2006), tingenone (4) (antimicrobial and antinociceptive activities) (Mena-Rejón et al., 2007; Veloso et al., 2014a, 2014b, 2015), 1-acetyloxy-9-benzoyloxy-8-cinamoyloxy-4,6-dihydro-β-agarofuran (5) (inhibition of photosynthesis) (Torres-Romero et al., 2008) and elaeodendroside W (6) (antiproliferative activity against human ovarian cancer) (Hou et al., 2009).

Figure 2. Pharmacological mechanisms of action to *Maytenus ilicifolia* on the digestive system. Adapted from Veloso, C.C. 2017 Rev Brasil Farmacogn. Vol. 24. 4. 4.

In this work, we demonstrate for the first time that an effervescent, stable, and effective formulation can be developed using a standardized extract of *M. ilicifolia* and may serve as a prototype for other herbal formulations (Figure 2).

With the information discussed above, it was possible to conclude that the product had good stability, keeping its organoleptic characteristics stable, with no change in pH, a slight increase in effervescence time, suffering only a change in density, but did not interfere with product quality.

Further quality control testing is also required, as we do not take the time to develop these tests in this paper. Study of the most suitable packaging for this product so that it can enter the market without stability problems.

Competing Interests

None.

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