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Newly Developed Antiulcer Capsules Based on *Gaertnera phanerophlebia* Baker (RUBIACEAE)

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Abstract

Gaertnera phanerophlebia Baker (Tsitsirontafika) is an endemic and medicinal shrub belonging to the RUBIACEAE family in Madagascar. Ethnobotanical studies have revealed its uses in treating war wounds during the colonial period. In the folk medicine, a decoction of the plant was used to treat pain and fever. An earlier study showed that an oral administration of 100 mg/kg of the aerial part extract to rats resulted in a high percentage of inhibition and curative ability against gastric ulcer formation without side effects. Based on these results, *G. phanerophlebia* extract was formulated into capsules and evaluated for its organoleptic, physicochemical and anti-ulcer properties according to European Pharmacopoeia standards. Gastrointestinal disorders are becoming one of the world's growing public health problems but many antiulcer medications are expensive and cause serious side effects. Thus, the aim of this study is to develop new, effective and affordable herbal gastric antiulcer capsules. The results confirmed the appropriate formulation of the plant extract as an active ingredient of gastric ulcering treatment. The obtained capsules are safe and an excellent antioxidant. It is also stable, non-toxic, complied to the good manufacturing practices with satisfactory physicochemical and pharmacotechnical qualities. All of values were found to be within acceptable limits. The weight variation test was successful. The excipients and extracts do not interact. Based on the findings achieved, this new herbal anti-ulcer remedy can be considered an improved traditional remedy for treating gastric ulcers. However, clinical trials are necessary before commercialization.

Keywords: *Gaertnera phanerophlebia*; Endemic; Aerial Part; Antiulcer; Formulation; Capsules

1. Introduction

The global rise in herbal medicine can be attributed to its natural origins, a perceived fewer side effects compared to pharmaceuticals, and integration into alternative and complementary medical practices. Dissatisfaction with conventional medicine, rising costs, and a growing interest in natural and holistic health approaches also contribute to its increased popularity worldwide [1]. It is worth noting that pharmacological treatments for non-communicable diseases, such as gastric ulcers, can be costly because they often require long-term use to achieve lasting results [2]. Consequently, healthcare professionals and patients often turn to traditional herbal medicines that have therapeutic and medicinal properties [3]. Despite the proven effectiveness of many traditional remedies, scientific research continues to confirm their benefits. However, the quality and safety of herbal products remain a concern due to potential contaminants, variability in active ingredient concentration, and possible adverse effects.

In Madagascar, a country rich in medicinal species, natural remedies have always been central to the traditional treatments adopted by its people [4]. The perpetuation of traditional culture and knowledge is a primary reason for the use of traditional medicine, which is also driven by economic factors like limited purchasing power and inaccessibility

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to modern healthcare facilities. This reliance is compounded by cultural beliefs, the lower cost of traditional remedies, and the long distances often required to reach rural health centers [5]. The virtues of medicinal plants have proven their worth time and again. Thus, Malagasy traditional medicine provides accessible healthcare where modern medicine is scarce or distrusted due to the long-standing use of medicinal plants [6].

The RUBIACEAE family is a cosmopolitan, found in diverse habitats ranging from deserts to rainforests around the world [7]. The family is particularly notable for its high level of endemism, which is especially prominent in regions such as Madagascar, Malaysia, New Caledonia, and the Antilles [8]. In Madagascar, the RUBIACEAE family is the second most abundant, after the ORCHIDACEAE family, with 70 to 80 genera, more than 30 of which are endemic [9]. This large family of plants is also known for producing phytobioactive compounds, such as alkaloids, terpenoids, and phenolics, which have remarkable therapeutic potential and a range of uses, from traditional medicine to modern pharmaceuticals [10,11,12].

Gaertnera phanerophlebia Baker (Tsitsirontafika), a species of the RUBIACEAE family, used in Malagasy traditional medicine is found in the humid and subhumid forests of Madagascar at various elevations [13]. Ethnopharmacological data on this genus have revealed its unique characteristic of containing lactones with a rare and specific chemical structure, with interesting cytotoxic properties [14]. The highest density of Gaertnera species is found in Madagascar, at 61.76 %. Many species are geographically restricted and/or poorly known, such as *G. phanerohlebia*. Previous studies have led researchers to conclude that Madagascar is likely the main distribution center for Gaertnera species [15,16]. Recent taxonomic revisions of Gaertnera species in Madagascar underscore the necessity of further research and conservation initiatives.

There is already scientific data available on *G. phanerophlebia*. A study by Rakotoarisoa *et al.* (2016) revealed various secondary metabolites in its leafy branches, including phenolic compounds (coumarins, flavonoids, anthraquinones, tannins, and polyphenols), as well as triterpenoids (triterpenes and steroids), which were identified as the biologically active compounds in the plant [17]. Earlier investigations have confirmed the wound-healing capacity of the plant leaf extract tested on rats [18]. Recently, an anti-ulcer experiment on the aqueous extract of the aerial parts revealed the plant extract's potential to prevent and cure gastric ulcers [19]. These findings corroborate the plant's immense health benefits and substantiate its medicinal value. *G. phanerophlebia* is now a promising candidate for use as an active ingredient in traditional remedies for treating gastric ulcers.

2. Materials and methods

2.1. Collection, Identification, Extraction of the plant material

Figure 1 *Gaertnera phanerophlebia* Baker (aerial part)

The aerial parts of *Gaertnera phanerophlebia* were collected in December 2019 from the Alaotra Mangoro region of Madagascar, Commune d'Ambohibary, Fokontany Ampitambe Ambatomainty and identified by The Botany Department at the National Center for Pharmaceutical Research Applications (CNARP)-Antananarivo, Madagascar (Fig.1). Then, a reference specimen was deposited in the herbarium of the CNARP under the registration number "ST380". To obtain the plant extract, 100 g of dried, homogenized powder of the aerial parts (ST380) was extracted by reflux (40° C) in

distilled water at a ratio of 1/10 (M/V) for 10 minutes. The extract was filtered and then vacuum-dried using a rotary evaporator.

2.2. Pharmacotechnical characterizations

Preformulation studies are essential for developing drug forms, particularly capsules and tablets. It is essential to determine the fundamental physical and chemical properties of the drug molecule, as well as the properties of the drug powder. This information influences many subsequent events and approaches in formation development [20].

2.2.1. Organoleptic parameters

The organoleptic properties of the extract powder were inspected and assessed using the senses of touch, smell, and taste.

2.2.2. Powder solubility

This parameter is important for drug absorption. The solubility test was evaluated using the flask method of OECD TG 105. The solubility was determined by gradually adding increasing volumes of water to approximately 100 mg of extract powder in a beaker containing 10 ml of reverse osmosis water at room temperature. After each addition of water, the mixture was stirred continuously for 10 minutes using a magnetic stirrer.

The solubility of the powder was visually verified. If the powder was insoluble, the test continued in a 100-ml beaker for 24 to 96 hours [21]. The solubility value was obtained using the following equation:

$$Solubility = \frac{(weight\ of\ initial\ powder) - (weight\ of\ dried\ residue)}{volume\ of\ solvent} x\ 100\ \%$$

2.2.3. Moisture Content

A 2 g sample of extract powder ST380 (m_{wet}) was finely ground, placed in an oven at 100-105° C for 3 hours, and its mass was recorded. The sample was then returned to the oven at 105° C and weighed hourly until the mass difference was less than 0.5 mg. The final mass obtained (m'_{dry}) is the last mass recorded. The moisture content (MC) was then calculated using the following formula after being determined by this gravimetric method [22,23].

$$MC\ \% = (m_{wet}\text{-}m'_{dry}/m_{wet})\ x\ 100$$

2.2.4. pH value

An aqueous dispersion containing 10 % *G. phanerophlebia* extract powder was prepared and filtered. The pH of the filtrate was then measured using a pH meter.

2.2.5. Particle size analysis

The fineness of the powder was determined by sieve analysis. A 10 g sample was separated into fractions using a series of sieves (600, 300, 200, 100, and 50 µm) and shaken for 30 minutes. The weight of the powder retained on each sieve was then measured to calculate the percentage by weight of each size fraction. This provides data on the powder's particle size distribution. The particle size and description were interpreted according to the British Pharmacopoeia 2013 [24].

2.2.6. Flowability

The angle of natural slope (α) is an important parameter for describing the fluidity of a powder. A specific apparatus was used to determine the angle of repose. A 100-gram sample of ST380 extract powder was introduced into a standardized funnel, and the flow time of the powder was measured once the funnel was open. The height (h) and radius (r) of the formed cone were also measured. The angle of the cone (α) was calculating using the following formula, and the relationship between the angle of repose (α) and powder flow is described in the table below [25,26].

$$Tan(\alpha) = h/r$$

Table 1 Interpretation of powder flowability

Angle of repose (α)	Type of flow	Angle of repose (α)	Type of flow
25	Excellent	30-40	Passable
25- 30	Good	> 40	Very poor

2.2.7. Tapped volume determination

A 100-gram sample of ST380 extract powder was placed in a graduated cylinder and lightly tamped down. The initial volume (V_0) was recorded, after which the sample was subjected to a series of tamping. Then, 10, 500, and 1250 tampings were performed, corresponding to V_{10}, V_{500}, and V_{1250}, respectively. The final tapped volume (V_f) is determined by comparing V_{500} and V_{1250}. If the difference between V_{500} and V_{1250} is less than 2 ml, then V_{1250} represents the final tamped volume. If the difference is greater than or equal to 2 ml, additional tampings are performed until the difference between V_{500} and V_n is less than 2 ml. The final volume (V_n) is then designated as the final tapped volume V_f. The obtained values were used to calculate the Carr's index (CI) and the Hausner index (IH) according to formulas (a) and (b) respectively [27,28].

$$IH = \frac{Vf}{V0}\ (a); \qquad IC\ \% = \frac{V0 - Vf}{V0} x\ 100\ (b)$$

2.2.8. Wettability measurement

To determine the minimum volume of reverse osmosis water needed for complete dispersion, a 2-gram sample of the powder is placed in a beaker, and reverse osmosis water is added incrementally with a pipette until the powder is fully dispersed. The wettability measurement is the total volume of water added at this point [29,30,31].

2.3. Capsules formulation

2.3.1. Dose per capsule

The dose of active ingredient in the *G. phanerophlebia* capsules is equivalent to the dose approved for treating gastric ulcers in a previous study on the anti-ulcer activity of the plant. The amount of aqueous extract (ST380) used in these capsules was set at 100 mg/kg, consistent with *in vivo* results in rats. Then, the dose administered to the rat was converted to a human dose, as shown in the table below. The daily dose was determined by calculating the Human Equivalent Dose (HED) using the following formula [32,33].

$$HED = (animal\ dose\ in\ mg/kg) x \left(\frac{animal\ weight\ in\ kg}{human\ weight\ in\ kg}\right)^{0.33}$$

Table 2 Dose conversion

Species	Cat 2 Kg	Monkey 4 Kg	Dog 12 Kg	Man 70 Kg
Mouse 20 g	29.231	61.53846	123.0769	384.6154
Rat 200 g	4.2222	8.888889	17.77778	55.55556
Guinea pig 400 g	1.4902	3.137255	6.27451	19.60784
Rabbet 1.5 Kg	1.0857	2.285714	4.571429	14.28571
Monkey 4 Kg	0.475	1	2	6.25
Dog 12 Kg	0.2375	0.5	1	3.125
Man 70 Kg	0.076	0.16	0.32	1

2.3.2. Capsule size

The capsule container contains an active ingredient, an aqueous extract of ST380, along with excipients. Using the conversion table, the volume of powder needed to fill a batch of capsules of the same size was determined (Table 3) [34].

Table 3 Sizes, volumes, weights, dimensions of capsule parts (body, cap), and the whole capsule

Size	**000**	**00EL**	**00**	**0EL**	**0**	**1EL**	**1**	**2EL**	**2**	**3**	**4**	**5**
Body length (mm)	22.2	22.2	20.2	20.2	18.4	17.7	16.6	16.7	15.3	13.6	12.2	9.3
Cap length (mm)	19.9	12.9	11.7	17.7	10.7	10.5	9.8	9.7	8.9	8.1	7.2	6.2
Capsule length (mm)	26.1	25.3	23.3	23.1	21.7	20.4	19.4	19.3	18.0	15.9	14.3	11.1
Weight (mg)	163	130	118	107	96	81	76	66	61	48	38	28
Volume (ml)	1.37	1.2	0.91	0.78	0.68	0.54	0.50	0.41	0.37	0.30	0.25	0.13

2.3.3. Manufactured capsules evaluation

Uniformity of weight

The determination of uniformity of weight was carried out according to the British Pharmacopoeia method [35]. It is necessary to calculate the average mass of the capsules, then the limiting deviation. Twenty capsules of the *G. phanerophlebia* aqueous extract were randomly selected and individually weighed using a precision balance. The capsules corresponding to each selection were then weighed. The difference between the two masses represents the mass of powder contained in each capsule. The limiting deviation (P) is obtained by: m ± 7.5 %. The mean (X) and confidence intervals (CI and CI') were calculated as follows:

$$CI = X \pm PX$$

$$CI' = X \pm 2PX$$

(P being the limiting deviation and varies according to the average mass of the contents of the capsules.)

Disintegration testing

This test determines if a solid dosage form breaks apart within a specified time when placed in a liquid medium under controlled conditions. The test is conducted using a disintegration apparatus (Fig. 3). Six capsules are randomly selected and placed individually into tubes in the basket-rack assembly. Reverse osmosis water at 37°C is used as the disintegration medium [36]. The apparatus is then operated and the time for each capsule to completely disintegrate (TD) is recorded. Complete disintegration is defined as a state in which any residue of the capsule, except for shell fragments, is a soft mass with no firm core.

Capsules stability

The manufactured capsules were stored in a glass bottle under different temperature conditions (25, 30, and 45° C) with a relative humidity (RH) of 70 %. Samples of capsules were taken from each site every 2, 6, 10, and 12 weeks and assessed for organoleptic properties. Then, the test capsules were compared with the capsules extract content before storage [37,38].

Capsules contents antioxidant activity

A DPPH free radical assay was performed to determine the antioxidant activity of the capsule contents [39,40]. This method quantifies the antioxidant capacity of a product at a single concentration (1 mg/ml) compared to the reference standard, α-tocopherol. A lower IC_{50} value indicates greater reducing power of the extract [41,42].

2.4. Statistical analysis

The results are presented as the mean ± SD. A Student's *t*-test was applied, and *P*-values less than 0.05 were considered significant. The correlation coefficient statistical tool in MS Excel software was used to analyze correlations between the acquired data.

3. Results and discussions

3.1. Extraction yield

The table 4 shows the yield of the aqueous extract (ST380) from the aerial part of *G. phanerophlebia*. A yield of 9.86 % was obtained using the decoction method.

Table 4 Yield of aqueous extract (ST380) of *G. phanerophlebia*

Weght of the dry powder (g)	Yield of the aqueous extract (%)
100	9.86

3.2. Pharmacotechnical characteristics

As shown in table 5, the physicochemical and organoleptic characteristics of the aqueous extract (ST380) are summarized.

Table 5 Pharmacotechnical properties of the aqueous extract (*G. phanerophlebia*)

Characteristics	Aqueous extract (ST380)
Physical appearance	Fine particle powder; pH= 5.2 ± 0.1
Organoleptic	Darck Brown coloured powder, distinctive smell, bitter taste
Solubility (g/l)	<1
Moisture Content (%)	4
Flowability (angle of repose°)	25.7
Hausner index	1.18 ± 0.12
Carr's Index (%)	12.8 ± 1.3
Wettability (ml)	2.3 ± 0.6

The above pharmacotechnical results made it possible to determine the key characteristics of the aqueous extract powder of *G. phanerophlebia* related to its suitability as an active ingredient in this formulation. Macroscopically, ST380 appears as a fine, dark brown powder with a characteristic odor and bitter taste (Fig.2). According to the ODCE method, it exhibits very low solubility in water (less than 1 g/l), but this does not affect the extraction yield of the plant's active substances by decoction. For oral solid dosage forms, aqueous solubility is a crucial factor that influences drug bioavailability [43].

Solubility testing results show that ST380 powder is soluble at a pH of approximately 5.2 ± 0.16.8 in an aqueous solution. This value is slightly acidic, but it may be compatible with the digestive tract, preventing potential gastric irritation [44].

Therefore, the powder extract exhibited good flow properties, with an angle of repose (α) of 25.7°. This implies that the active ingredient has excellent flowability for manufacturing capsule dosage forms.

The wettability rate of the extract powder was 2.3 ± 0.6 ml. This property suggests that the powder will not adhere to the walls of the equipment used. ST380's residual moisture content is very low (4 %), which ensures good capsule preservation at room temperature. Furthermore, it prevents clumping and limits potential enzymatic reactions as well as the proliferation of microorganisms [45]. The Carr (12.8 ± 1.3) and Hausner (1.18 ± 0.12) indices demonstrate the material's rheological properties. These values indicate good powder flow [46]. Satisfactory rheological properties are

crucial for uniform capsule filling, a key quality parameter in pharmaceutical manufacturing [47]. The powder's unpleasant taste is a drawback, but the capsule formulation masks the taste and makes administration easier.

Figure 2 Sieving method

3.3. Capsules manufacturing

For this antiulcer formulation, size 0 capsules were chosen and filled using the leveling method on a semi-automatic capsule filling machine (Fig. 3). To do this, 100 mg of the aqueous extract, mixed with the excipients (Microcrystalline Cellulose, Magnesium Stearate, Sodium Lauryl Sulphate, Starch), are placed in capsules, and then four capsules are taken daily to obtain the desired dose for a patient weighing approximately 60 kg.

Figure 3 Semi-automatic capsule filling machine and Disintegration apparatus (CNARP)

3.4. Capsules quality controls

3.4.1. Uniformity of weight

Weight uniformity was determined by calculating the deviation limit in capsule mass. The average mass of the capsules was found to be 578.5 ± 11.75 mg. The established limit of deviation was 578.5 ± 43.387 mg. Therefore, all capsule masses obtained fall within the calculated limit. According to the British Pharmacopoeia, uniform mass indicates that the *G. phanerophlebia* capsules conform to the specification.

3.4.2. Moisture level

After filling the capsules, the water content was measured again to see if it had changed during the manufacturing process. The result was 4 % water content after encapsulation, equal to the water content of the aqueous extract obtained during the pre-formulation study. This similarity suggests that the water content remained stable during manufacturing and that the extract was not significantly affected by moisture absorption during filling. Although hygroscopicity and moisture absorption were potential concerns, the water content remained constant.

3.4.3. Dissolution profile

The results of the dissolution studies on *G. phanerophlebia* capsules are shown in figure 4. The manufactured capsules disintegrated rapidly. It took 25 minutes for the capsules to completely disintegrate in water and release the active ingredient. This suggests that the granules contained within the capsules are released relatively quickly as they pass through the digestive tract [48].

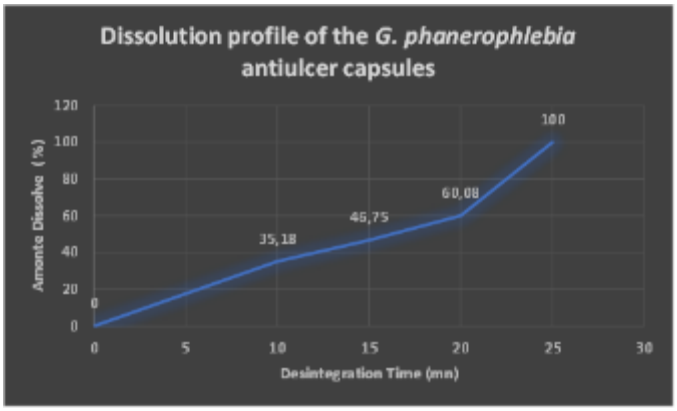

Figure 4 Disintegration time of the manufactured ST380 capsules

3.4.4. Capsules stability

The results of the stability tests on the anti-ulcer capsules made from the aqueous extract of *G. phanerophlebia* are presented in the table 6. All measured stability parameters were compared with the values obtained prior to storage.

Table 6 Capsules properties during storage

Antiulcers capsules of *G. phanerophlebia*- Storage conditions T (25° C, 30° C, 45° C); RH (70 %)					
Week n°	MC %	Size, Shape	Content aspect	Content color	Content odor
2	4.2	No change	Powder	Brown	No change
6	4.2	No change	Powder	Brown	No change
10	4.2	No change	Powder	Brown	No change
12	4.2	No change	Powder	Brown	No change

The objective of the capsule stability tests was twofold: first, to provide evidence of how the quality of the drug formulation and its contents varies over time under the influence of various environmental factors, such as temperature, humidity and light; and second, to establish a retest period for the drug substance or a shelf life for the drug. The results showed that there was no significant change in capsule properties during 12 weeks of storage under various conditions. This strongly suggests that the formulation stage complied with good manufacturing practices for capsules. However, these results are insufficient to determine the shelf life of this new product. Further stability studies are therefore warranted over periods of 3, 6 months, or even 1, 2, and 3 years.

3.4.5. Antioxidant activity of capsule contents

The free radical scavenging test yielded an IC_{50} of 23.66 ± 0.5 µg/ml for the contents of the anti-ulcer capsules, equivalent to 515.214 µM/mg for α-tocopherol. This result demonstrates the strong antioxidant potential of the mixture of the active ingredient and excipient against DPPH. The free radical scavenging activity of the aqueous extract of *G. phanerophlebia* (RUBIACEAE) can be attributed to the presence of polyphenolic substances, including tannins, flavonoids, saponins, terpenes, and polyphenols, which were identified in previous phytochemical studies [49].

In all cases, formulating the aqueous extract of *G. phanerophlebia* into an anti-ulcer capsule offers numerous advantages for both patients and the product itself. For an herbal tea treatment, as recommended in traditional medicine, it is difficult to ingest the entire dose in one day, which could negatively impact treatment adherence and increase the relapse rate among patients. On the other hand, capsule administration masks the bitterness of the extract powder and reduces the volume of water that must be swallowed with each dose, which could improve treatment adherence. Additionally, capsules are less bulky than herbal tea and can be easily carried.

The formulated antiulcer capsules have been packaged and labeled as presented in figure 5.

Figure 5 Antiulcer capsules based on *Gaertnera phanerophlebia* extract

4. Conclusion

The results showed that the aqueous extract of the aerial part of *Gaertnera phanerophlebia* was suitable for manufacturing anti-ulcer capsules. The preformulation study and stability parameters revealed that all values were within the acceptable limits. The manufactured capsules have high antioxidant potential. Based on these results, it can be concluded that the formulation and evaluation of the new anti-ulcer capsule are good. However, further studies are needed to investigate the product's shelf life and establish its clinical activity to confirm its use.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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