

# A pilot study of efficacy and safety of *Plantago lanceolata* and *Primula veris*, in the treatment of the common cold

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## Abstract

The ongoing coronavirus disease (COVID-19) pandemic has raised the need for new therapies to treat respiratory infections. A bibliographic review based mainly on the databases of the European medication agency (E.M.A) and the Department of Environment and Territorial Policy of the Basque Government (Spain) was carried out. From both databases, it was observed that 14 plant species of the 408 reviewed plants (3%) are approved for medicinal use at European level and that their use, coincides with the most common reasons for consultation in Primary Care. One of these pathologies (common cold) and 2 medicinal plants (*Plantago lanceolata* and *Primula veris*) have been selected for the present study. We will determine the efficacy and safety of the two plant species using one randomized multicenter open clinical trial. In the clinical trials, three treatment groups will run in parallel; two treatment groups with medicinal plants and another group with conventional treatment. The of the clinical trial will be: To objectify the therapeutic effects of the medicinal plants using parameters of usual clinical practice in primary care, to evaluate the side effects and the safety of the use of medicinal plants and to rationalize the mechanism of action of the possible benefits.

**Keywords:** *Plantago lanceolata*, *Primula veris*, Common cold, acute respiratory infections, Medicinal plants, Primary Care

## INTRODUCTION

Nowadays, viral infections are becoming a serious health problem [1-3]. The current coronavirus disease (COVID-19) pandemic has boosted/fueled the need for new therapeutic approaches/tools for the early treatment of acute respiratory infections.

A bibliographic study [4] was carried out on the existing medicinal plant species of Urdaibai, a natural area of the Basque Country, Biosphere Reserve since 1984, in northern Spain. As a result, it was observed that of the list of 408 vegetable species included in the Biodiversity Information System of the Department of the Environment, Territorial Planning, Agriculture and Fisheries, only 14 species (3%) have been included in the list of medicinal plants for human use registered and approved by the European Medicines Agency (EMA) up to the present time. Also, according to the results of the study [4], the use of Urdaibai medicinal plants coincides with the most common reasons for consultation in primary care. Therefore, it was decided to focus the study in primary care. As including all medicinal plants is not feasible, this study focuses on the treatment of

one pathology of high prevalence in primary care: the common cold with *Plantago lanceolata* and *Primula veris*.

*Plantago lanceolata* (Photograph 1) is known by the common names of ribwort plantain, narrow leaf plantain, English plantain, rib leaf, lamb's tongue, and buckhorn. It is a species of flowering plant in the plantain family Plantaginaceae. The plant is a perennial herb, with small

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flowers without petals that are grouped in a stalk at the end of a small white or purple stem. The lanceolate leaves are grouped forming a rosette at the basis of the plant. At Urdaibai, a Biosphere Reserve of Biscay (Basque Country, Spain), *Plantago lanceolata* can be found near the coast, in dry soils and roadsides<sup>[5]</sup>

The European Medicine Agency (EMA) recognizes the traditional use of ribwort plantain as follows: grinded or powder leaves, water-soluble dry extracts, and liquids that contain 20-40% ethanol, syrup, and juice obtained by squeezing the fresh plant.<sup>[6]</sup>

#### **Plantago lanceolata mainly contains<sup>[7]</sup>:**

1. **Mucilages (6%):** arabinogalactan, rhamnogalacturonan, glucomannan, and pectines. These compounds have an emollient action on the mucous membranes. An interesting study performed in pigs shows the adherence of mucilages to the oral mucous membranes and a consequent reduction of the cytolysis of these membranes.<sup>[8]</sup>
2. Phenolic acids like the p-hydroxybenzoic acid, the protocatechuic acid, gentisic acid, caffeic acid, and its derivatives: caffeic acid esters (chlorogenic acid), acteoside (verbascoside), etc...
3. **Iridoid glycosides:** mostly aucubin, catapol, and asperuloside. Different studies demonstrate that iridoid glycosides have anti-inflammatory activity. Moreover, *Plantago lanceolata* extracts anti-inflammatory activity was measured using the hen's egg-chorioallantoic membrane test (HET-CAM). Four different lyophilized liquid extracts (28% ethanol) were used. The anti-inflammatory activity of the extracts, at a ten times higher concentration, was similar to the hydrocortisone, phenylbutazone and diclofenac sodium anti-inflammatory activities<sup>[9]</sup>
4. **Flavonoids:** luteolin glycosides and apigenin.
5. **Others:** tannins, coumarins, salicylic acid, and mineral salts in particular of zinc and potassium.

The European Pharmacopoeia requires a minimum content of 1.5% of the orto-hydroxycinnamic acid derivatives, expressed/named as acteoside<sup>[6]</sup>

The E.M.A allows their use as Demulcent for the symptomatic treatment of oral or pharyngeal irritations associated with coughing.

In a prospective multicenter study<sup>[10]</sup> a cough syrup was administered (100 ml syrup contains 20 g of the extract of *Plantago lanceolata*) and its efficacy and safety in patients with acute respiratory diseases were evaluated. In total, 593 patients were included in the study, after 3-14 days of treatment, the intensity and frequency of the cough were reduced by 67% and 66%, respectively. Thoracic pain

decreased by 80%, irritating cough, and dyspnea by 69%. Overall efficacy was evaluated as good by the doctor in 62% of patients, and excellent by 26% of patients.

Moreover, its anti-bacterial and anti-viral activities have been analyzed/described in different studies. Abdin<sup>[11]</sup> observed the positive effects of the *Plantago lanceolata* leaves tea/infusion on an HIV patient, suggesting that further investigation could reveal the potential role of *Plantago lanceolata* as a treatment of HIV infections. On the other hand, the acteosides present anti-viral effects on the respiratory syncytial virus.<sup>[12]</sup> The aucubin, as a prodrug of aucubigenin, inhibited the DNA replication of the Hepatitis B virus in vitro<sup>[13]</sup>. Furthermore, the in vitro studies performed by Haznagy (1970) with *Plantago lanceolata* squeezed juice and aqueous extracts, showed antibacterial effects against *Staphylococcus aureus*, *Streptococcus β-hemolyticus*, *Proteus Vulgaris*, *Salmonella*, *Shigella*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Bacillus subtilis*<sup>[14]</sup>

*Primula veris* (Photography 2), whose name derives from the Latin term 'primulus' because it is one of the first flowers that bloom in spring, is an herbaceous perennial flowering plant in the primrose family Primulaceae. The deep yellow flowers grow in clusters of 10-30 blooms together on a single stem. The leaves are located on the basis and form a rosette. Characteristically it grows in cool environments. In Urdaibai *Primula veris* can be seen in meadows, hedges, and streamsides<sup>[5]</sup>.

The EMA acknowledges the experience of the traditional use of the grinded flowers in the form of tea and of the extracts that contain 25% of ethanol. Also of root liquid extracts that contain 10-70% of water, ethanol, and methanol as solvent.<sup>[15]</sup>

#### **Primula veris main components are<sup>[16]</sup>:**

##### **Root:**

1. **Phenolic glycosides (2.5%):** primveroside and primulaveroside that, during desiccation, undergoes enzymatic processing that releases primverose and the aglycones, 4- and 5- methyl methoxy salicylate respectively.
2. **Triterpenic saponins (5-10%) that derive from the olean:** primulasaponine.

##### **Flowers:**

1. **Flavonoids:** quercetin, kaempferol, luteolin, apigenin, isorhamnetin, gossypetin and quercetin, isorhamnetin, and kaempferol glycosides.
2. A small amount (2%) of saponins (mainly primulic acid A) at the sepals.

According to the EMA, *Primula veris* root and flowers derivatives have the following indications<sup>[15]</sup>:

In cold infective processes treatment as an expectorant. In that case, it is probably effective because of its anti-viral properties.

A study demonstrated *in vitro* that a mixture of *Primula veris* saponins had activity against V.influenza (A2 / Japan 305) producing 89% inhibition at a concentration of 6.2 µg / ml [17]. Another *in vivo* study performed in rabbits on the pharmacological/toxicological effects of extracts of the *Primula* flower showed a significant increase in the production of a bronchial secretion at the tested concentrations. The observed effect was in the range of the substances of reference bromhexine and acetylcysteine that were also tested [18].

In a double-blind, randomized, placebo-controlled, multicenter, prospective study, the clinical efficacy and tolerability of a fixed combination of thyme fluid extract and primrose root tincture (Bronchicum Tropfen) were investigated at a dosage of 30 drops (1 ml), taken orally five times daily. 150 outpatients suffering from acute, not previously treated bronchitis, lasting for less than 48 h, were randomized and treated with either verum or placebo for 7-9 days. At the end of the study, significantly more patients were symptom-free in the verum group (58.7%) than in the placebo group (5.3%) [19].

After an exhaustive bibliographic revision, we decided to carry out this study.

This study proposes the treatment with medicinal plants of one pathology: The common cold, usually treated with drugs excluded from social security and of limited efficacy.

Thus, the present study will guarantee an increase of knowledge of the use of medicinal plants in the sanitary field, which will ensure adequate and responsible use of these plants. Additionally, it will provide useful and necessary tools to be able to solve some of the most common health problems that we find in the community,

**Inclusion Criteria:**

Patients over 18 years of age, who complete and sign the informed consent before randomization with a medical diagnosis of the common cold and presence of the following clinical sign :

- nasal discharge
- nasal congestion
- sneezing
- sore throat

contributing to use the closest resources of the population, probably generating a more sustainable economic system

## METHODS

### Objectives

The main objectives of this project are to test the efficacy and safety of the use of *Plantago lanceolata* and *Primula veris* in the common cold treatment in patients over 18 years of age who visit the primary care of the Busturialdea Comarcas and Lea-Atibai (Bizkaia), the north of Spain.

### Secondary objectives

1. To objectify the therapeutic effects of the medicinal plants using parameters of usual clinical practice in primary care
2. Assess the side effects and safety of the use of medicinal plants
3. Rationalize the mechanism of action of the possible benefits

### Participants

- a) Target population: Patients over 18 years of age in the geographical area of the Comarca de Busturialdea and Lea-Artibai (Bizkaia), registered as users in the automated files of the participating Health Centers (Health Center of Munitibar-Mendata, Forua Health Center, Busturia Health Center). In the north of Spain.
- b) Study population: Target population that meets the inclusion criteria and does not have any criteria for exclusion, of the following:

**Exclusion criteria:**

- Pregnancy
- Use of antibiotics, antivirals, nasal steroids, decongestants or antihistamines
- Autoimmune diseases or immunodeficiencies,
- Asthma, bronchitis, Chronic Obstructive Pulmonary Disease
- Heart disease
- Chronic Renal Failure
- Hepatic Insufficiency
- Surgical Interventions scheduled during the study
- Medical and surgical emergencies
- Toxic consumption, allergy to the plant.
- Patients with a vital prognosis of less than a year

## Interventions

Patients will have a clinically confirmed diagnosis of the common cold. Three treatment groups of 100 patients each will be randomized

### - Group I *Plantago lanceolata*:

Dosage: Oral: 2 g of leaves in 150 ml of boiling water 3 times a day. During 1 week. The maximum duration prescribed in the monograph of the E.M.A (European Medicines Agency).

### - Group II *Primula veris*

Dosage: Orally: 1 g of the flower crushed in 150 ml of boiling water 3 times a day for 1 week. The maximum duration prescribed in the monograph of the E.M.A (European Medicines Agency)

### - Group III Paracetamol

Dosage: Via Oral: paracetamol 500mg 3 times a day for a week. The drug will be prescribed according to the National System of Health of Spain using recipes prescribed by the doctor.

## Outcomes

The study variables are:

- **MAIN VARIABLES:** Healing / Improvement (Yes / No), specifying the % improvement
- **SECONDARY VARIABLES:** Demographic data (age, gender, place of residence, etc ...), Type of treatment (conventional / phytotherapy), Time to cure / improvement, Reason for consultation, Pathological history (HBP, obesity, diabetes, AMI, etc), signs and symptoms, Habits of life (Toxic/alcohol consumption, diet, exercise, hobbies, etc ...), Regular treatment and other unconventional treatments (Homeopathy, Osteopathy, Acupuncture, etc.)

### Specifically, the variables will be:

- a) Sociodemographic. 1.1. Age (date of birth); 1.2. Gender (male / female); 1.3. Civil status; 1.4. Education level; (Primary Education, Secondary Education, Bachiller, Formation Professional, University) 1.5. Place of residence (population / district)
- b) Clinics. 2.1. Baseline situation (score), defined according to the scale of evaluation of signs and specific physical examination and designed for the study; 2.2. Visit 2 (score), in which the cynical situation is assessed at 5-7 days according to the scale of evaluation of signs and specific physical examination and designed for the study; 2.3. Healing / Improvement in 3rd visit (Yes / No), at

10-15 defined according to the scale of evaluation of signs and specific physical examination and designed for the study; 2.4. Type of treatment (conventional / phytotherapy); 2.5. Pathological antecedents (HBP, obesity, diabetes, AMI, etc); 2.6. Habits of life (Toxic/alcohol consumption, diet, exercise, hobbies, etc ...); 2.7. Current treatments; 2.8. Other unconventional treatments (Homeopathy, Osteopathy, Acupuncture, etc.).

## Sample size

Taking into account that there are 3 treatment groups (*Plantago*, *primula*, and paracetamol) and that the main variable is healing/improvement in 3rd visit (Yes / No), at 10-15 defined according to the scale of evaluation of signs and physical examination specifically designed for the study. And that a loss of 10% and a statistical power of 80% is assumed with a level of significance of 0.05. It is expected improvement of 13%% between the cure/improvement between the treatment group (*Plantago*, primrose) and the control treatment group (paracetamol), for this, it is necessary 100 patients in each treatment group, 300 in total and if we assume losses of 10% (dropouts, etc) will require 110 patients per treatment, 330 in total for this study.

## Randomization

A randomized list of both treatments (conventional/herbal medicine) has been prepared by the research department. This department kept proper allocation concealment and will be delivered to the nurse's station. In the list to each patient corresponds a number with a treatment. Once the doctor has made the diagnosis and filled out the data collection sheet, nursing, according to the list, will deliver treatment without the corresponding doctor knows.

## Masking

At the time of the evaluation, the data collection sheet will contain the number of the randomization list for each patient, without the treatment received. This way the doctor will blindly evaluate the patients.

## Statistical methods

A database or spreadsheet will be built to store all the information collected in the study. This information will be anonymized and controlled, following the current legislation.

To calculate the sample size, the proportions comparison procedure of the power prop. test function of the R package See 3.4.2 has been used. See Power Calculations for Two-Sample Test for Proportions, Peter Dalgaard. work by Claus Ekstrøm, <https://stat.ethz.ch/R-manual/R-devel/library/stats/html/power.prop.test.html>.

Before the statistical analysis, the quality control of the information will be checked, comparing it with the patient's clinical information.

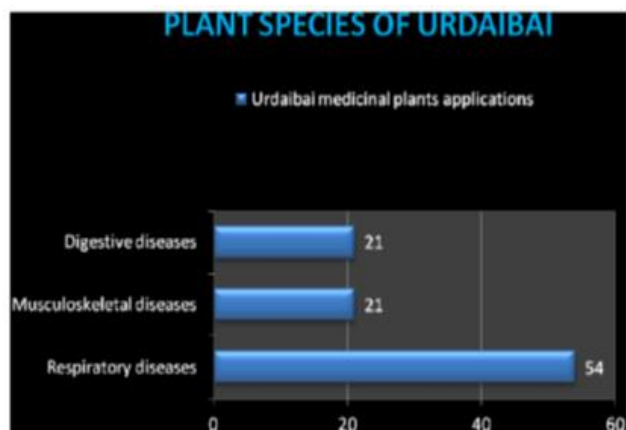


Before the statistical analysis, a Statistical Analysis Plan will be established, detailing the statistical methods, tables, and results of the final results report, as well as the suitability of analyzing different subgroups or subpopulations according to what is indicated in the study protocol. Descriptive analyzes of all the variables will be carried out according to their nature. Statistical analysis will be performed through an adequate test to compare the different symptoms of the disease between the baseline visit and each of the visits. If the symptoms measured are on an ordinal scale (no presence, little, much, etc.), the Mantel-Haenszel chi-square test will be used. However, if it is performed on a binary scale (presence/absence), the chi-square test will be used. When the frequencies observed are less than 5%, other alternative tests should be applied to the chi-square test, such as Fisher's exact test. All statistical analyzes will be performed with the SPSS package for Windows (version 21) and with R package v.3.1."

## DISCUSSION

The 14 plant species approved by the E.M.A., are authorized for use in the treatment of mild to moderate diseases. In no case, does it mention its usefulness for the treatment of serious diseases?

More than half of the Urdaibai medicinal plants approved by the EMA are used for (1): respiratory diseases, especially oral and pharyngeal in 53.8% (*Althaea Officinalis*, *Filipendula Ulmaria*, *Plantago Lanceolata*, *Polypodium vulgare*, *Potentilla erecta*, *Primrose veris*, *Salix Sp.*). It is followed in frequency by the treatment of arthralgias (*Filipendula Ulmaria*, *Salix Sp*, *Urtica dioca*) and digestive disorders (*Althaea Officinalis*, *Polypodium vulgare*, *Potentilla erecta*) by 21.4%. Finally, 14% is used for mild psychiatric disorders (*Humulus lupulus*, *Hypericum perforatum*), skin conditions (*Oenothera biennis*, *Urtica dioca*), and as diuretics (*Equisetum arvense*, *Urtica dioca*).



**Figure 1.** Urdaibai medicinal plants applications

The usefulness of medicinal plants of Urdaibai coincides with the most common reasons for consultation in Primary

Care. That is why, I think it convenient to conclude, that the place of medicinal plants is in Primary Care.

We would like to remark that one of the main roles of primary care in the early diagnosis and treatment of different diseases to reduce their progression to severe pathologies that should be treated in hospital facilities. During the COVID-19 pandemic, the lack of early therapeutic approaches has provoked the progression of the infection and the consequent collapse of the healthcare structures worldwide. In the present study, we introduce two new therapeutic tools (*Plantago lanceolata*, *Primula veris*) for the early treatment of acute respiratory infections that could avoid disease progression and solve the current problem.

Concerning trying to explain the mechanism of the pharmacological action of medicinal plants almost all studies focus on trying to explain which component is directly related to its therapeutic utility. However, until now it seems difficult to relate an isolated component with a single pharmacological action, as it usually happens in synthetic drugs. Further compounds not previously described can be isolated in subsequent studies. On a practical level, we should guide the research towards a more global vision, to try to achieve a rational use of the medicinal plants that surround us and to reintroduce them with more brevity in our usual clinical practice. Hence the need to conduct clinical trials that show the effectiveness of medicinal plants, so that the realization of this study arises.

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## Abbreviations

E.M.A: European Medicines Agency.

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**Photograph 1.** *Plantago lanceolata* (Llantén)



**Photograph 2.** *Primulaveris*