



## Cellular Rhinitis: A Therapeutic Proposal

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### Abstract

**Background:** Rhinitis, a common condition throughout the world, are classified in non-allergic (NAR) and allergic rhinitis (AR). The data collected by recent studies show that NAR affects more than 200 million patients world-wide, among which 8% to 10% suffer from NARES and NARESMA. Nevertheless, respiratory diseases, and in particular rhinitis, are not considered real and serious diseases, and, as a result, they remain frequently underdiagnosed and undertreated despite the heavy burden they place on patients, their families and society as a whole.

**Objectives:** This study aimed to investigate the therapeutic efficacy and safety of phytomedicine as an important alternative treatment option for patients with NARES and NARESMA.

**Methods:** A total of 79 subjects with NARES (80% of participants) and NARESMA (20% of participants) were included in the study and underwent nasal fibro endoscopy and physical examination. The Quality of life was evaluated thanks to the SNOT-20 questionnaire and associated to clinical and cytologic features collected by nasal cytology.

In order to determine the efficacy of herbal remedies in nasal inflammation, all these tests were performed before and after treatment with nasal saline (NaCl 0.9%) and with nasal spray consisted of *Calendula Officinalis* L., *Alnusglutinosa* Gaerth, *ribes Nugrum* L., *Abies Pectinata* D.C., *Rosa Canina* L., *Perilla Frutescens* L., Manganese Gluconate.

**Results:** The herbal spray produced a 50 % fall in nasal inflammation in all patients and a decreased of nasal mucosa edema and nasal secretions in 87.5 % of patients. According to SNOT-20, 87.5% of subjects treated with herbal spray showed an improvement in rhinitis total symptom score of baseline (pre-medical treatment values).

**Conclusions:** The herbal spray has been shown to suppress eosinophils and mast-cells infiltration in nasal tissues with significant difference in comparison to nasal saline as control. At the same time, treatment of patients with herbal remedy leads to a fall in the degree of the nasal mucosa edema and in nasal secretions, evaluated by nasal endoscopy.

Moreover, data collected by SNOT-20, indicated an improvement in nasal symptoms and, therefore, in quality of life, without side-effects.

### Abbreviations

NAR: non-allergic rhinitis; AR: allergic rhinitis; NARES: non-allergic rhinitis with eosinophils; NARNE: non-allergic rhinitis with neutrophils; NARMA: non-allergic rhinitis with mast-cells; NARESMA: non-allergic rhinitis with both eosinophils and mast-cells; SNOT-20: Sino Nasal Outcome Test 20; DPP: Dermatophagoides pteronyssinus; DPF: Dermatophagoides farina; SPT: Skin prick test; ALL: allergic children; NON-ALL: non-allergic children

### Background

Rhinitis is a common condition throughout the world and is defined as the presence of at least one of the following: congestion, rhinorrhea, sneezing, nasal itching and nasal obstruction. These symptoms are primarily induced by active mediators released from mast cells, basophils, eosinophils, lymphocytes and epithelial cells. Among these cells, mast cells and eosinophils are the most important cells in the allergic response such as AR: histamine release from resident mast cells is a major mediator in the inflammation of allergic rhinitis; eosinophils produce major basic protein (MBP), IL-5 and granulocyte macrophage-colony stimulating factor (GM-CSF), so they perpetuate their own survival and can induce tissue damage [1,2].

Rhinitis are classified in non-allergic (NAR) and allergic rhinitis (AR). In the former obstruction and rhinorrhea occurs in relation to non-allergic, noninfectious triggers and the lack of concomitant allergic disease is determined by negative skin prick test for relevant allergens and/or negative allergen-specific antibody tests [3]. Nasal cytology allows us to recognize different non-allergic rhinitis forms on the basis of the prevalent inflammatory cell infiltrates: non-allergic rhinitis with eosinophils (NARES), with neutrophils (NARNE), with mast-cells (NARMA) and with both eosinophils and mast-cells (NARESMA) [4,5].

The data collected by recent studies show that NAR affects more than 200 million patients world-wide, among which 8% to 10% suffer from NARES and NARESMA [6]. Nevertheless, respiratory diseases, and in particular rhinitis, are not considered real and serious diseases, and, as a result, they remain frequently under diagnosed and undertreated despite the heavy burden they place on patients, their families and society as a whole. The symptoms are distressing and adversely affect quality of life. Due to the resulting irritability, tiredness, inattention, lack of concentration, sleep disturbances and daytime sleepiness, rhinitis and its complications result in work and school day losses. Patients with rhinitis had a higher prevalence of comorbid diseases such as asthma, acute and chronic sinusitis, nasal polyposis, conjunctivitis, acute otitis media, chronic serous otitis media, sleep apnea, and fatigue [3-7].

Effective management of respiratory diseases is required to improve patient's quality of life, avoid more severe conditions and reduce their economic burden [8].

Despite the huge number of medication, such as corticosteroids, anti-histamines and leukotriene receptor antagonists, up to date there is no curative treatment for this disorder and most of the drugs used for treatment only can induce symptomatic relief and some of them have side effect and can cause withdrawal symptoms.

This study aimed to investigate the therapeutic efficacy and safety of phytomedicine as an important alternative treatment option for patients with NARES and NARESMA.

## Methods and Study Population

### Study population

Subjects suffering from rhinitis, after a detailed clinical history and otolaryngology examination, were divided in two groups, AR and NAR, according to the skin prick test positivity or negativity, respectively. Allergic patients were excluded; non-allergic rhinitis group was divided into the following 4 subgroups depending on nasal cytology result: NARES, NARMA, NARESMA and NARNE.

A total of 79 subjects with NARES (80% of participants) and NARESMA (20% of participants) were included in the study and underwent nasal fibro endoscopy and physical examination with special attention to the color of the mucous membranes of the nose, the type of nasal discharge and the degree of nasal obstruction. The Quality of life was evaluated thanks to the SNOT-20 questionnaire and associated to clinical and cytologic features collected by nasal cytology.

In order to determine the efficacy of herbal remedies in nasal inflammation, all subjects were divided in two groups and treated with nasal saline (NaCl 0.9%) and with nasal spray consisted of *Calendula Officinalis* L., *Alnus glutinosa* Gaerth, *ribes Nugrum* L., *Abies Pectinata* D.C., *Rosa Canina* L., *Perilla Frutescens* L., Manganese Gluconate. At the end of 1 month treatment, all patients coming to the follow-up, were evaluated with the same tests completed during the first visit.

An assessment of homogeneity of the socio-demographic and clinical characteristics of the 2 study groups were performed and, as the results indicated below, there were no significant differences between the 2 groups:

- Group A (Herbal spray): 50.5% males and 40.5% females, with a mean age of 45 years; according to the nasal cytology, 80% of patients were affected by NARES, 20% of patients by NARESMA
- Group B (Nasal saline): 49.9% males and 50.1% females, with a mean age of 43.7%; according to the nasal cytology, 80% of patients were affected by NARES, 20% of patients by NARESMA

### Methods

**Nasal cytology:** Nasal cytology represents a reliable method for the diagnosis of nasal inflammation as it is easy to perform, non-invasive and able to detect both the cellular modification of the nasal epithelium caused by either allergen exposure or irritative stimuli or inflammation. Such a consideration suggests the quality of a routine use of nasal cytology in the diagnostic work-up of upper and lower airways disorders, in order to reach a proper defined diagnosis and to study the airway inflammation: the diagnosis of nasal disorders through nasal cytology is based on the consideration that, in healthy subjects, the nasal mucosa is composed of 4 normal subsets of cells, which commonly characterize the pseudo-stratified epithelium; besides neutrophils, no other cells are detected in healthy individuals [2,9]. Therefore, on a rhinocytogram, the presence of eosinophils, mast cells, bacteria, spores and fungi has to be considered as a clear sign of nasal pathology.

In our study, nasal cytology was assessed in all patients, free of treatment (systemics antihistamine and/or nasal steroids) for at least 10 days' time, using these following steps:

- Sampling and processing: scraping the middle portion of the inferior turbinate by using Rhino-probe; placed the material on

a glass slide, fixed by air drying and stained by May-Grünwald-Giemsa method.

- Observation through a light microscopy able to magnify up to 1000X.

For the rhinocytogram analysis, the slide, divided into 10 microscopic fields, have to be read in order to detect eosinophils, mast cells, neutrophils, bacteria, spores and calculate their percentages comparing to the number of total leukocytes [10].

**Skin prick test:** SPT was performed with a panel of the most prevalent aeroallergens (birch, core, olive tree, grasses, ragweed, parietaria, dog, cat, house dust mite: DPP and DPF, mould: alternaria) and foods (cow lactalbumin, cow casein, egg white and yolk, peanuts).

Histamine hydrochloride, 10 mg/mL, and phenolated glycerol-saline served as positive and negative controls. The reaction was regarded as positive if the mean wheal diameter was at least 3 mm greater than negative control [11,12].

**SNOT-20:** The Sino-Nasal Outcome Test 20 (SNOT-20) is one of the most widely used quality-of-life instruments for sinonasal conditions, assesses a broad range of health and health-related quality-of-life problem. It is a self-administered multiple-choice 20-item test that is usually divided into four domains (rhinologic, ear and facial symptoms, sleep, and psychological domain), with a 5 point scale (from 0 = no problem, to 5 = as bad as it can be) [13].

The scores range from 0 to 100, with lower scores reflecting greater rhinitis control:

- 0-10 = no problem to mild problem
- 11-40 = moderate problem
- 41-69 = moderate to severe
- 70-100 = severe to "as bad as it can be"

**Nasal endoscopy:** Diagnostic nasal endoscopy enables clear visualization of all structures of the middle nasal meatus and of the ostiomeatal complex. It is a primary means for diagnosis of all anatomic variations and other pathogenic factors of the lateral nasal wall, which cannot be diagnosed by using anterior/posterior rhinoscopy. Furthermore, the effects of therapy can be endoscopically controlled [14].

## Results

### Nasal cytology before and after treatment

To examine the effect of herbal therapy against NARES and NARESMA, nasal cytology was performed before and after 1 month treatment in 2 groups of patients: one (group A 40 subjects) treated with herbal spray and the other one (group B 38 subjects) with saline spray (Table 1).

### Skin prick test

Negative in all patients.

### Nasal endoscopy before and after treatment

All participants underwent nasal fibro endoscopy in order to evaluate the color of the mucous membranes of the nose, the type of nasal discharge and the degree of nasal obstruction, before and after treatment.

- Group A: with the therapeutic dosage of 2 puff 3 time per day for

**Table 1:** In group A herbal spray produced a 50 % fall in nasal inflammation. The result was obtained in 5.26% of the patients treated with saline (group B).

	A		B	
	Before	After	Before	After
Eosinophils	+++	+	+++	+++
Mast cells	++	+	+	+
Neutrophils	+++	++	++	++
Bacteria	++	+	+	+

30 days, 87.5 % of patients showed a decreased of nasal mucosa edema and nasal secretions.

- Group B: in 7.89% of patients treated with nasal saline, the degree of nasal obstruction was lower than before treatment; the other subjects showed no differences before and after 1 month treatment. Nasal secretions showed a decreased in 94.7% of patients treated with nasal saline.

SNOT-20 was used for determining the presence and severity of nasal symptoms and patients' quality of life. Each subject completed the questionnaires before and after nasal treatment.

Our results indicated that herbal spray led to an higher level of improvement than nasal saline:

- Herbal spray→ 87.5% of patients showed an improvement in rhinitis total symptom score of baseline(pre-medical treatment values).
- Nasal saline→ 5.3% of patients showed an improvement in rhinitis total symptom score of baseline.

## Discussion

In spite of great progress in research into the causes and management of rhinitis in the last decades, NAR is grossly inadequately diagnosed and treated. Up to date there is no curative treatment for this disorder and most of the drugs used for treatment only can induce symptomatic relief sometimes with long-term side effects [1].

Phytomedicine has become an important alternative treatment option for patients, as they seek to be treated in a natural way after an unsatisfactory response to conventional drugs.

Blackcurrant (*Ribes nigrum* L.) represents a common medicinal plant used in the treatment of allergic rhinitis, joint and muscle pain and winter illnesses (such as headache, sore throat and upper airway diseases) due to its proven analgesics and anti-inflammatory effects via inhibition of prostaglandin and histamine synthesis and release. It has been shown with immunomodulatory characteristics through stimulation of adrenal cortex. Its antioxidant and anti-fungal effects are based on polyphenols, vitamins and sacuranetina. Its circulation property are clinically certified as well.

*Alnus glutinosa* Gaerthis attributed with anti-inflammatory, febrifugal and healing characteristics.

Marigold (*Calendula officinalis* L.) is well-known for its anti-inflammatory, anti-bacterial, anti-fungal and anti-oxidant effects due to flavonoids, essential oils and triterpene alcohols. This remedy is also an immunomodulatory agent and stimulates the phagocytosis and the collagen metabolism.

Dog. Rose (*Rosa canina* L.) is used against allergic rhinitis, otitis and common cold. It is the major natural source of vitamin C that exalts the flavanoids anti-oxidants effects, *Rosa canina* L. has been shown to improve the intestinal absorption of iron and calcium and to play a role in the production of hemoglobin and in the cholesterol regulation. Its anti-allergic effects is due to the activation of vitamin B9.

Silver fir (*Abies Pectinata* D.C.) is widely used in the treatment of eye and muscle diseases thanks to provitamin A and the essence of trimetina. It is certified as antirheumatic and diuretic as well.

Perilla (*Perilla frutescens* L.) has been described with anti-inflammatory and anti-allergic effects through changes in IgE synthesis and inhibition of lipoxigenase. According to this statement, in our study we investigated whether phytomedicinal agents could substitute a classic therapy considering efficacy and safety.

Remedy in this study was applied a combinations of several phytotherapeutics (*Calendula Officinalis* L., *Alnus glutinosa* Gaerth, *ribes Nugrum* L., *Abies Pectinata* D.C., *Rosa Canina* L., *Perilla Frutescens* L., *Manganese Gluconate*) and pharmacological effects are

considered to be the result of their synergistic interaction. Consistent with the observation that *Calendula officinalis* L. and *Ribesnigrum* L. have anti-inflammatory activity, we aimed to demonstrate that this herbal spray is effective in controlling upper airway inflammation in patients affected by NARES and NARESMA.

The herbal spray has been shown to suppress eosinophils and mast-cells infiltration in nasal tissues with significant difference in comparison to nasal saline as control. At the same time, treatment of patients with herbal remedy leads to a fall in the degree of the nasal mucosa edema and in nasal secretions, evaluated by nasal endoscopy [15].

Moreover, data collected by SNOT-20, indicated an improvement in nasal symptoms and, therefore, in quality of life, without side-effects.

These results should be interpreted in context and are subject to limitations.

Firstly, the number of participants at this study was quite low and it may therefore not be possible to generalize the data to the population as a whole.

Another aspect to consider is the fact that we separated AR and NAR patients only by the presence or absence of a positive SPT. Measuring specific and total IgE could have strengthened this separation, still the SPT seems to be a good measure for the serum IgE levels.

Thirdly, a 30-day treatment could not be able to investigate side-effects [16].

## Conclusions

In summary, this study provides evidence of therapeutic effect of this herbal spray which will greatly improve the quality of life, leading to a decreased of nasal inflammation, without side-effects in patients with NARES and NARESMA.

More than ever before, subjects demand to be treated in a natural way and phytomedicine has become an important alternative treatment option especially after an unsatisfactory response to conventional drugs.

It must be emphasized that recognition and application of phytomedicine into medicine will depend on credible (strong) evidence-based clinical data. For this purpose, it is mandatory to conduct future research in a large-sized, double-blind trial and a longer-term follow-up [15].

## References

1. Marone G, Triggiani M, Genovese A, De Paulis A (2005) Role of human mast cells and basophils in bronchial asthma. *Adv Immunol* 88: 97-160.
2. Sansone L, Gelardi M (2009) Progetto Naresma, corso di formazione a distanza promosso dall' A.I.C.NA., video conferenza del 28, Foggia.
3. Tran NP, Vickery J, Blaiss MS (2011) Management of rhinitis: allergic and non-allergic. *Allergy Asthma Immunol Res* 3: 148-156.
4. Maselli Del Giudice A, Barbara M, Russo GM, Fiocca Matthews E, Cassano M (2012) Cell-mediated non-allergic rhinitis in children. *Int J Pediatr Otorhinolaryngol* 76: 1741-1745.
5. Gelardi M (2004) *Atlante di Citologia Nasale*. Centro Scientifico Editore, Torino.
6. Gelardi M, Maselli del Giudice A, Fiorella ML, Fiorella R, Russo C, et al. (2008) Non Allergic Rhinitis with Eosinophils and Mast cells (NARESMA) constitutes a new severe nasal disorder. *Int J Immunopathol Pharmacol* 21: 325-331.
7. Progetto A.R.I.A. Allergic rhinitis and its impact on asthma, versione 2009
8. Erkkä Valovirta (2011) EFA Book on Respiratory Allergies: raise awareness, relieve the burden 2011, Available at <http://www.efanet.org>
9. Hellmich B, Ehlers S, Csernok E, Gross WL (2003) Update on the pathogenesis of Churg-Strauss syndrome. *Clin Exp Rheumatol* 21: S69-77.

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10. Gelardi M, Cassano P, Cassano M, Fiorella ML (2003) Nasal cytology: description of a hyperchromatic supranuclear stria as a possible marker for the anatomical and functional integrity of the ciliated cell. *Am J Rhinol* 17: 263-268.
  11. Demoly P, Piette V, Bousquet J (2003) In vivo methods for study of allergy: skin tests, techniques and interpretation. In: Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, Middleton's allergy principles and practice (6<sup>th</sup> edition) Mosby, St Louis 631-633.
  12. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, et al. (2012) Practical guide to skin prick tests in allergy to aeroallergens. *Allergy* 67:18-24.
  13. Pynnonen MA, Kim HM, Terrell JE (2009) Validation of the Sino-Nasal Outcome Test 20 (SNOT-20) domains in nonsurgical patients. *Am J Rhinol Allergy* 23: 40-45.
  14. Buljick-Cupic MM, Savovic SN (2007) Endonasal endoscopy and computerized tomography in diagnosis of the middle nasal meatus pathology. *Med Pregl* 60: 327-332.
  15. Ghazi-Moghadam K, Inancli HM, Bazazy N, Plinkert PK, Efferth T, et al. (2012) Phytomedicine in otorhinolaryngology and pulmonology: clinical trials with herbal remedies. *Pharmaceuticals (Basel)* 5: 853-874.
  16. Mølgaard E, Thomsen SF, Lund T, Pedersen L, Nolte H, et al. (2007) Differences between allergic and nonallergic rhinitis in a large sample of adolescents and adults. *Allergy* 62: 1033-1037.