

**Complementary treatment of allergic rhinoconjunctivitis: the role of the nutraceutical Lertal®**

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**Summary.** Nutraceuticals represent interesting therapeutic options in clinical practice. In this regard, a new compound has been designed: Lertal®. It contains quercetin, perilla extract, and vitamin D₃. These agents exert anti-allergic and anti-inflammatory activities. This article reports and discusses the results of four clinical studies conducted in adult and paediatric patients suffering from AR. Outcomes provided evidence that Lertal® may significantly prevent clinical worsening when prescribed as add-on to continuous antihistaminic treatment and also prevent clinical exacerbations, such as the need of rescue medication, when used alone as preventive strategy in AR patients. (www.actabiomedica.it)

**Key words:** allergic rhinoconjunctivitis, nutraceuticals, quercetin, perilla, vitamin D₃

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A new compound has been recently developed for the treatment of allergic rhinoconjunctivitis: Lertal®. Lertal® is an oral food supplement, containing: *Perilla frutescens* 80 mg (as dry extract), Quercetin 150 mg, and Vitamin D₃, 5 mcg (200 IU).

The dry extract of *Perilla frutescens* seeds contains rosmarinic acid and other flavonoids, such as luteolin, apigenin, and chrysoeriol; all of them have a well-documented *in vivo* and *in vitro* anti-allergic activity (1-5). Curiously, the leaves of *Perilla frutescens* are a popular garnish in Japan, as they are employed to antagonize fish and crab meat allergy, and also are used as a food colorant. Other medical indications include sedation and treatment of indigestion and food poisoning. About the anti-allergic activity of rosmarinic acid, a murine model demonstrated the significant suppression of passive cutaneous anaphylaxis reaction (5). A *Perilla*-derived methoxyflavanone also inhibited the *in vitro* IgE-mediated histamine release from a basophilic cell culture and *in vivo* prevented allergic rhinitis-like nasal symptoms in a murine model of Japanese cedar pollinosis (6). *Perilla* also has significant inhibitory activity against both 5-lipoxygenase and 12-lipoxygenase, key enzymes in one of the pathways of allergy and inflammation (7). Luteolin has been recognized as an antioxidant scavenger of damaging free radicals and inhibits protein kinase C, i.e. key regulator of inflammatory events and smooth muscle constriction (8). Luteolin is also a potent inhibitor of mast cell activation as could completely block the release of histamine and pro-inflammatory cytokines (9). Luteolin also reduced IL-4 and IL-5 and increased IFN-γ at bronchial level in an asthma model (10). Apigenin is another flavonoid able to suppress IgE and IL-4 production (11).

Quercetin is a bioflavonoid found in red wine, grapefruit, onions, apples, black tea, and, in lesser amounts, in leafy green vegetables and beans (12). Quercetin has a strong affinity for mast cells and basophils and tends to stabilize their cell membranes, so blocking degranulation, and inhibiting the release of pro-inflammatory mediators and cytokines implicated in allergic inflammation (13,14). In particular, a placebo-controlled study showed that 8-week querce-
tin course significantly reduced ocular symptoms in patients with Japanese cedar allergy (15). Using the same clinical model, a preventative activity was also documented on conjunctival symptoms (16). Quercetin significantly affected the nasal production of nitric oxide (17). Moreover, quercetin inhibited the in vitro activation of eosinophils (18). Therefore, all these outcomes confirm and underline its anti-allergic activity.

Vitamin D₃ is important for its contribution to the normal function of the immune system (19,20). In particular, it has been evidenced a relevant role in both prevention and potential treatment of AR, as it restores physiological T regulatory activity and exerts also anti-inflammatory activity as widely reported (21-24). In addition, it has been reported that Vitamin D₃ serum level is inversely correlated with immunological biomarkers of inflammation, such as IL-6 and IL-10 (25). Another intriguing anti-allergic mechanism of Vitamin D₃ has been demonstrated in mast cells: actually, mast cell can actively metabolize Vitamin D₃ to self-modulate IgE-mediated activation (26).

In addition, there is another interesting technological characteristic: Lertal® is formulated in bilayer tablets composed of a fast-release layer that allows the rapid antihistamine activity of Perilla, and a slow-release layer that enhances Quercetin and Vitamin D₃ bioavailability and anti-allergy activity spread over time. Thus, Lertal® could be considered as a fast-slow release compound.

The role of Lertal® in the treatment of Allergic Rhinoconjunctivitis

An important premise should be considered: nutraceuticals cannot replace completely standard pharmacological treatment to quickly relieve symptoms, but could be used to improve standard treatment or to prevent possible clinical relapse. Indeed, it is well known that a possible symptom worsening may occur also during the active antihistaminic treatment or after its suspension, as expression of insensitivity, tachyphylaxis, or excessive allergen exposure. Therefore, nutraceutical could be used as add-on strategy or preventative treatment.

At present, there are 4 published articles concerning Lertal® in patients with AR: two studies concern adult patients and two trials enrolled allergic children.

Adult studies

A recent open study, conducted in adult patients with seasonal AR, showed that Lertal® treatment induced a significant reduction of both symptom severity and consumption of anti-allergic drugs (27).

This clinical study was performed to demonstrate the efficacy of Lertal® for the relief of nasal and ocular symptoms and the reduction of anti-allergic medications use in patients with AR.

Twenty-three patients (16 women, mean age 44 years, and 7 men, mean age 46 years) were enrolled in this trial. Patients had history of AR symptoms for at least 1 year and were sensitized to Parietaria officinalis pollen. At baseline, patients were symptomatic.

A total symptom score (TSS) was used to score the daily symptoms’ episodes by a four-point scale (0=no episode; 1=1-5; 2=6-10; 3=≥11 episodes/day). Patients were visited at baseline, such as before the treatment, and after 1 month of the nutraceutical supplementation. Symptoms were assessed at both visits; the use of anti-allergic medications was also recorded. Lertal® was given to the patients together with indications of its use: to be taken twice a day, morning and evening, during or after meal, for 30 consecutive days. Pollen count was also carried out to document the related clinical feature during the study period.

There was a reduction of approximately 70% for symptom scores and 73% for the anti-allergic use. In particular, there was a significant reduction of both TSS (p<0.001) and single symptoms (p<0.0001 for all symptoms, i.e. sneezing, rhinorrhea, nasal obstruction, ocular itching, lacrimation, and conjunctival congestion). Notably, there were no noteworthy adverse events during the study.

Another study was conducted in patients suffering from seasonal allergic conjunctivitis (SAC) using an ophthalmological formulation, such as Ophthalmic Lertal® spray (28). This medical device contains Perilla frutescens extract, hyaluronic acid, and liposomes. Hyaluronic acid is a naturally occurring linear disaccharide
polymer with lubricating and rehydrating properties commonly used in the management of dry eye syndrome (29). Liposomal eye sprays may provide symptomatic relief for SAC, which often causes a tear film deficiency, by stabilizing the tear film lipid layer (30).

Therefore, this open-label clinical study aimed at investigating the efficacy and safety of ophthalmic Lertal® spray in patients with SAC. Concomitant use of anti-allergic medications, including topical or oral antihistamines or corticosteroids or topical decongestants, was permitted.

This was a 4-week, open-label, single-arm, uncontrolled trial. Patients (17 females and 13 males, mean age 43.4 years) were consecutively enrolled during the peak pollen season. Patients applied Lertal® spray to the closed eyelid three times daily (morning, midday and evening); additional doses were applied as needed for acute SAC signs and symptoms.

Patients underwent two clinical visits; a baseline visit (Visit 1) and an end of study visit (Visit 2; i.e. 4 weeks after starting study treatment). Ocular signs and symptoms were recorded using the Total Ocular Symptom Score (TOSS) scale (where 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms and 3 = severe symptoms) for the following nasal and ocular signs and symptoms: ocular itching, lacrimation, conjunctival congestion, ocular hyperemia and photophobia. Symptoms were assessed by clinicians at Visits 1 and 2.

The primary efficacy endpoint was the change in mean TOSS (i.e. ocular signs/symptoms) from baseline after 4 weeks of study treatment.

Secondary efficacy endpoints included: change from baseline in individual ocular symptom scores; change from baseline in the daily use of anti-allergy medications; and patient assessment of how ‘pleasant’ the spray application felt.

For the assessment of the changes in concomitant use of anti-allergy medications, patients were divided into two groups: the first group continued taking anti-allergy medications as needed, and the second (with lower baseline usage due to less severe and disabling symptoms) were instructed to discontinue anti-allergy medications (rescue treatment was permitted).

After 4 weeks of Lertal® spray administration, there was a significant reduction in all ocular signs and symptoms from baseline (mean ± SD TOSS 10.0 ± 3.24 at visit 1 vs. 3.7 ± 2.25 at visit 2; P<0.001) among patients with SAC, corresponding to a 63% reduction in mean total symptom score.

Mean scores for the individual ocular symptoms were all significantly reduced from baseline at the end of treatment, with reductions from baseline in mean symptom scores of 56% for ocular itching, 58% for lacrimation, 63% for ocular hyperemia, 66% for conjunctival congestion and 85% for photophobia. With regard to changes in TOSS scores for individual patients, 27 patients (90%) showed improvements from baseline at the end of the treatment, while three patients (10%) were considered non-responders.

Among patients who continued concomitant use of anti-allergy medications (n=15) due to the severity of their symptoms at the beginning of the study, there was a significant (P<0.001) reduction in the mean overall daily use of all medications and of each individual drug class with percentage reductions in mean daily usage scores of 64% to 100%. In a subjective assessment of how pleasant the spray application felt, 55% of patients answered ‘very pleasant’, 30% answered ‘pleasant’ and 15% answered ‘acceptable’. In particular, the majority of patients described a pleasant feeling of coolness in the ocular area and resolution of the itching a few minutes after the application of the spray.

No adverse events were observed during the 2-hour period following Lertal® spray administration. Overall, during 4 weeks’ treatment, no clinically relevant adverse effects were reported.

Paediatric studies

It is well known that AR is common mainly in childhood and in adolescents. The medical treatment is substantially the same used in adults. However, particular attention should be paid about medication overdosing and adverse events. In this regard, nutraceuticals could play an interesting role as complementary therapy in order to save medication use and so minimize adverse events. Therefore, two hypotheses should be tested to validate the usefulness of this nutraceutical in AR treatment: i) to investigate its capa-
bility to amplify the response to standard antihista-
minic AR medications and/or reduce the insensitivity
during the active treatment, and ii) to demonstrate its
potentiality to prevent possible relapse after standard
treatment suspension. To answer to these unmet needs,
a polycentric, randomized, Italian study has been per-
formed in two phases: the first as double blind, pla-
cebo-controlled trial during standard active AR treat-
ment and the second as an open-label, parallel-group,
extension study after the standard treatment withdraw.

First phase study

Thus, the aim of the first phase was to evaluate
the efficacy and safety of Lertal® as an add-on treat-
ment in children with AR (31). The first phase was
a 4-week, randomized, polycentric, double-blinded,
parallel-group, placebo-controlled trial. One hundred
and sixty patients suffering from AR were planned for
enrolment in 17 Italian Paediatric Allergy clinics. AR
diagnosis was performed, according to validated crite-
ria (32), such as if nasal symptom history was consist-
ent with documented sensitization.

Inclusion criteria were: age range 6-12 years, AR
diagnosis, sensitization to house dust mites or pollens,
Total Symptoms Score (TSS) ≥ 15 and at least 1 for
nasal congestion, written informed consent of patients
and of parents or legal guardians. TSS is the conven-
tional way to measure symptom severity as it is used in
all methodologically correct trials.

Exclusion criteria were: uncontrolled asthma,
secondary rhinitis to other causes, concomitant acute
or chronic rhinosinusitis, nasal polyps, current use of
topical or systemic corticosteroids, antihistamines, an-
tileukotrienes, inadequate washout of them, nasal ana-
tomic defect, respiratory infections in the last 2 weeks,
participation in other clinical studies in the last month,
documented hypersensitivity to the study product or
its excipients, and trip planned outside of the study
area.

After 2-week run-in period, eligible patients were
randomly (1:1 ratio) treated with Lertal® (1 tab/day
for 4 weeks) plus standard antihistamine therapy or
Lertal® placebo (1 tab/day for 4 weeks) plus standard
antihistamine therapy (Figure 1). Systemic or intra-
nasal corticosteroids, leukotriene antagonists, and so-
sodium cromoglicate were prohibited during the study.
Four visits were performed: Visit 1 at run-in, Visit 2 at
baseline (W0), Visit 3 after 2 weeks (W2), and Visit
4 after 4 weeks, i.e. end of treatment (W4). The study
protocol was approved by the Ethics Committees of
each center. The study was registered at ClinicalTrials.
gov ID NCT03365648.

Figure 1. Study design of the pediatric trial
The primary endpoint of this study was the TSS change from the baseline to the end of the treatment (4 weeks). The secondary objectives included: overall symptom control assessed by means of a VAS after 2 and 4 weeks of treatment, change from baseline of the Total Symptom Score (TSS) after 2 weeks of treatment, number of responders (at least 30% reduction of TSS) after 2 and 4 weeks of treatment, time to maximum effect on TSS vs placebo, change of TSS from 2 and 4 weeks (worsening was defined as at least 30% increase of TSS), use of rescue treatment, change from baseline of Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS) and Total Throat Symptom Score (TTSS) after 2 and 4 weeks of treatment, issues interfering with quality of life at baseline and after 4 weeks, duration of symptom-free or with mild symptoms.

Nasal symptoms (TNSS) included itching, sneezing, rhinorrhea, nasal congestion; ocular symptoms (TOSS): itching, hyperemia of conjunctiva, tearing; throat symptoms (TTSS): itching, coughing. With the help of their parents, patients scored symptoms severity on a 4-point scale: 0 = absent or irrelevant, 1 = mild, 2 = moderate, 3 = severe.

At Visit 3 and Visit 4 the patient was asked to indicate overall system distress on a 100 mm Visual Analogue Scale (VAS) were 0 is equal to no discomfort and 100 the worst possible discomfort.

The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) consists of 23 questions in 5 domains (nasal symptoms, ocular symptoms, practical issues, limitation of activities, other symptoms), that are answered on a 7-point scale (0-6), where 0 represents the absence of problems and 6 the greatest symptom distress. Children completed the questionnaire together with a parent at baseline and at Visit 4.

Safety was assessed on the incidence of adverse events for each treatment and on physical examinations.

The TSS at baseline was 15.9 (± 1.7) in Lertal®-group and 16.1 (± 1.2) in Placebo-group (p= n.s.). Both groups significantly (p<0.0001 for both) reduced TSS (last 12 hours) after 2 and 4 weeks, without between-group difference. In particular, TSS was at W4: 5.83 (± 4.5) in Lertal®-group and 6.39 (± 4.38) in Placebo-group (p=n.s.). There was a trend between groups about the percentage variation change: - 63.6% in Lertal®-group and - 60.7% in Placebo-group.

Notably, 24 children had total symptom score worsened (i.e. ≥30% increased TSS) between W2 and W4: 8 in Lertal®-group and 16 in Placebo-group, being the difference between treatments significant (P<0.05), as reported in Figure 2. In particular, the proportion of patients with maximum effect on TSS (i.e. the last 12 hours) at W2 was higher in the Placebo-group respect to the Lertal®-group (50.77% and 39.06% respectively). The proportion of patients with maximum effect on TSS (last 12 hours) at W4 was higher in the Lertal®-group respect to the Placebo-group (60.94% and 49.23% respectively). This trend in the differences of the proportions (time to maximum effect) is not due to a faster effect of the Placebo-group but to the fact that the proportion of worsened patients (i.e. >=30% increase of TSS between W2 and W4) was significantly higher from Week 2 to Week 4 in the Placebo-group than in the Lertal®-group.

Both treatments were well tolerated and no serious adverse events were reported.

It is well known that AR treatment is addressed to symptom relief and inflammation control. Antihistamines are the first-choice treatment in childhood, but, if they are ineffective, corticosteroids represent the second-level option, nevertheless many parents exhibit "steroid-phobia". As pharmacological medications are only symptomatic, and potentially may cause adverse
events, there is growing interest by both doctors and parents about complementary therapeutic strategies. This study confirmed that standard antihistaminic treatment improved the clinical feature in children with AR. Furthermore, it has been evidenced that Lertal®, used as add-on therapy, was able to tendentially improve the effect of the standard AR treatment. Actually, the Lertal®-group achieved a mean reduction of about 64% of symptom severity, whereas the Placebo-group 60%. However, it has to be noted that a relevant difference was not expected because of both the obviously antihistaminic activity and the intrinsic characteristics of the nutraceutical. Notably, Lertal® significantly reduced the possible occurrence of intercurrent clinical relapse during the standard treatment in children with AR. Indeed, the most important finding of this study was the capability of Lertal® to prevent symptom worsening during conventional antihistaminic treatment, mainly during the second period of the treatment (from week 2 to week 4). It is well known that some AR patients are partially responder, resistant, or develop tachyphylaxis to medications. In this regard, it is clinically relevant to identify the pathogenic mechanisms involved in these patients. In the current trial, 24 patients (8 in Lertal® group and 16 in Placebo group) had a clinical relapse between the third and the fourth week, despite an initial clinical improvement. Therefore, the possible explanation of this behaviour could depend on the common characteristic of these children, such as all of them had poly-allergy. It means that patients with allergy to more allergens, i.e. pollens and perennial allergens, usually present more severe symptoms than mono-allergic patients (33). Consequently, these poly-allergic children had clinical worsening, despite ongoing treatment, as exposed to multiple allergens and so developing more severe allergic reaction. Nevertheless, this study shows that the add-on Lertal® preserved clinical relapse in a larger number of poly-allergic children than standard therapy. This finding is particularly interesting if contextualized as part of a continuous effective antihistaminic treatment and this preventive activity may allow to avoid the recourse to corticosteroids.

This outcome could be explained by the multifaceted mechanisms of action exerted by Lertal®. In particular, Lertal® effects seem to be grounded in the complex anti-inflammatory and anti-allergic activity exerted on the immune response by the three compounds.

Another remarkable point was the interest, in other words the sensitivity, to perform a rigorous study before in childhood than in adulthood. This point deserves attention as there is relevant lack of paediatric studies that evaluate the efficacy and the safety of treatments in the paediatric age.

Therefore, the present study documented that add-on Lertal® treatment was able to: i) partially improve standard AR treatment in children, ii) significantly prevent the occurrence of clinical worsening in a subgroup of poly-allergic children, and iii) be safe.

Second phase study

The second phase was designed as open and parallel-group study and was conducted after the end of the blind-period (34). It was a 4-12-week open-label, parallel-group, extension study in which patients treated with study product in Period I continued treatment with Lertal® tablets, whereas patients initially treated with placebo received no further treatment.

Continuous treatment with systemic or intranasal antihistamines, corticosteroids, leukotriene antagonists and sodium cromoglicate were prohibited during the study. Two visits were scheduled during this period to collect efficacy, safety and quality of life data. Patients were asked to return their diaries at these visits in order to collect data concerning exacerbations and or adverse events.

The end-points of the Phase II were the length of time symptom-free or with mild symptoms, and the number, intensity, and duration of exacerbations. Exacerbation was defined as the need of restarting an antihistamine medication of any kind, at any dose and of any duration.

Safety was assessed by the incidence of adverse events for each treatment and by physical examinations.

The Phase II study included a total of 128 patients, of which 64 assigned to open Lertal® therapy (Lertal® Group: LG) and 64 to observation alone (Observation Group: OG).
The two groups were homogeneous as far as age, gender, BMI, type of allergy, time from diagnosis and symptom severity are concerned at baseline.

The LG showed a significant difference concerning the duration of symptom-free days in comparison with OG (Log-Rank test = 4.16; p=0.0413) with a HR 0.54 (CI 95% 0.29-0.99).

Considering the number of children who experience an AR exacerbation, there was a significant difference between groups as only 16 children (25%) in the LG had an AR exacerbation, whereas 27 children (42.2%) of OG had an AR exacerbation (p=0.039), as shown in Figure 3. Analysing only the children with AR exacerbation, the total number of days in which each patient took at least one rescue medication was significantly (p=0.018) lesser in LG than OG (9.6 ± 9 days and 28.5 ± 27.2 days respectively). Considering the global population, the cumulative days treated with rescue medication was significantly (p<0.0001) higher in OG than in LG (683 days and 153 days respectively).

Analysing only children treated with concomitant medications, LG children had tendentially less AR exacerbations than OG children (7 vs 12; p=0.051) and consequently used less antihistamines, such as had less days with antihistamines (Figure 4).

Lertal® treatment was well tolerated and no clinically relevant adverse events were reported.

Discussion of the outcomes

Noteworthy, it is important to consider that the clinical effect of a single dose of an antihistamine usually lasts until 24-36 hours, then symptoms reappear promptly (35). Similarly, the duration of intranasal corticosteroids effects is very short-lived after suspension, such as in a few days symptoms and inflammatory events recur (36). Moreover, both antihistamines and intranasal corticosteroids may be unable to completely inhibit allergic reaction in some circumstances, such as highly allergic patients, intense allergen exposure, or interfering disorders. Therefore, the use of add-on medications could be fruitful in such situations. Actually, the favourable effect, exerted by Lertal® in the first phase, was also evident in the second part of the active treatment, such as between the third and the fourth week, when some patients, after an initial response to drug treatment, showed a symptom worsening.

The outcomes of the Phase II not only confirmed indeed the favourable effects observed in the first phase, but also highlight a more relevant preventive activity consequent to the prolonged use of Lertal®. In particular, we would underline two main issues. The highly favourable HR value of 0.54: it means that the risk of AR exacerbation had been reduced in children taking Lertal® for a 4-12-week period by 46% in comparison with children without preventive intervention after the suspension of the standard 4-week antihistamine treatment. This finding is consistent with previous studies conducted in patients with asthma and in
children with allergic rhinitis (37-39). Therefore, the second part of present study evidenced that Lertal® treatment was able to approximately halve the risk of AR exacerbation after one-month of antihistamine treatment. This outcome is also supported by the larger number of Lertal®-treated children (75%) who did not experience AR exacerbation than untreated children (58%). Notably, the total number of days with rescue medication, such as use of antihistamines, was significantly higher in untreated children. Consistently, the severity of symptoms was lower in Lertal®-treated children.

In addition, these findings are consistent with outcomes documented in the first phase, such as Lertal®, used as add-on therapy, was able to tendentially improve the effect of the standard AR treatment and especially Lertal® significantly reduced the possible occurrence of intercurrent relapse during the standard treatment in children with AR. In this regard, it is noteworthy to consider that some children did not continue to be well controlled by antihistamines despite the fact that antihistamines have also an anti-allergic activity (40-45). Therefore, the current results could be envisaged as a proof of concept that Lertal® provides its preventive activity by an additional anti-allergic activity.

Another important aspect concerns the adverse events. In this regard, no patients experienced serious treatment-emergent adverse events or fatal adverse events. Only 2 children of the active group reported suspected treatment-related adverse events with temporarily discontinuation in the Phase I and only 1 of the Lertal® group in the Phase II. Anyway, all adverse events were mild and self-resolving.

The strength of this study was the methodological accuracy, based on the double-blinded, randomized, parallel-group, and placebo-controlled design of the first phase, the presence of a successive observational period, the sample size estimate.

From a clinical point of view, Lertal® could be considered a preventive compound that could be favourably prescribed both as add-on therapy during continuous antihistaminic therapy and as preventive strategy alone. As the safety profile is optimal, the duration of Lertal® treatment could be continued for prolonged periods as long as the pollination season in pollen-allergic patients or fall-winter in mite-allergic subjects.

In prospect, other potential aspects could be considered: the impact on asthma co-morbidity and the prevention of respiratory infections. Asthma is frequently associated with AR and it may be favourably improved by anti-allergic treatments that control respiratory inflammation (46,47). Moreover, allergic patients, as previously reported, may frequently contract infections that may be reduced by antiallergic treatments (48).

Another relevant issue should be considered: to document efficacy and safety of any AR treatment, evidence based medicine needs randomized controlled trials. So rigorous methodology has to be applied to the protocols, including patient’s characteristics, inclusion and exclusion criteria. In this regard, the age is frequently a sensitive parameter. However, AR pathogenic mechanism, clinical features, and responsiveness to medications are shared by children and adults in a specular manner. Actually, many trials, including pivotal clinical trials, have been conducted enrolling both children and adults. The findings were not conflicting after stratifying for age. Therefore, there is reliable consistency between paediatric and adult outcomes in randomized controlled trials.

On the basis of this background, it is conceivable that outcomes obtained by trials in children with allergic rhinitis can be extrapolated and applied in adults with allergic rhinitis.

Therefore, there is convincing rational and proof that the results provided by the Lertal® studies may be conveniently extended to adult patients suffering from allergic rhinitis.

Conclusions

Nutraceuticals will play a relevant role in the future treatment of AR, but their use cannot be separated from the proved evidence of their effectiveness and safety. In this context Lertal® meets these requirements. In particular, there is evidence that Lertal® may be favourably used to prevent clinical worsening as add-on strategy and to reduce clinical exacerbations as mere preventative strategy.
Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Yu H, Qiu JF, Ma LJ, Hu YJ, Li P, Wan JB. Phytochemical and phytopharmacological review of Perilla frutescens L. (Labiatae), a traditional edible-medicinal herb in China. Food Chem Toxicol. 2017;108(Pt B):375-391.

2. Shin TY, Kim SH, Kim SH, et al. Inhibitory effect of mast cell-mediated immediate-type allergic reactions in rats by Perilla frutescens. Immunopharmacol Immunotoxicol. 2000;22(3):489-500.

3. Imaoka K, Inouye S, Takahashi et al. Effects of Perilla frutescens extract on anti-DNP IgE antibody production in mice. Arerugi. 1993;42(1):74-80.

4. Ueda H, Yamazaki C, Yamazaki M. Luteolin as an anti-inflammatory and anti-allergic constituent of Perilla frutescens. J. Biol Pharm Bull. 2002;25(9):1197-202.

5. Makino T, Furuta Y, Wakushima H, et al. Anti-allergic effect of Perilla frutescens and its active constituents. Phytother Res. 2003;17(3):240-3.

6. Kamei R, Fujimura T, Matsuda M, et al. A flavanone derivative from the Asian medicinal herb (Perilla frutescens) potently suppresses IgE-mediated immediate hypersensitivity reactions. Biochem Biophys Res Commun. 2017;483:674-9.

7. Igarashi M, Miyazaki Y. A review on bioactivities of Perilla: progress in research on the functions of Perilla as medicine and food. Evid Based Complement Alternat Med 2013;2013:925342.

8. Kimata M, Shichijo M, Miura T, Serizawa I, Inagaki N and Nagai H. Effects of luteolin, quercetin and baicalein on immunoglobulin E-mediated mediator release from human cultured mast cells. Clinical and Experimental Allergy. 2000;30:501-508.

9. Theoharides TC, Kempraj D and Iliopoulos BP. Mast cells, T cells, and inhibition by luteolin: implications for the pathogenesis and treatment of multiple sclerosis. Adv Exp Med Biol. 2007;601:423-30.

10. Das M, Ram A and Ghosh B. Luteolin alleviates bronchoconstriction and airway hyperreactivity in ovalbumin sensitized mice. Inflammation Research. 2003;52:101-106.

11. Yano S, Umeda D, Yamashita T, Ninomiya T, Sumida M, Fujimura Y, Yamada K and Tachibana H. Dietary flavonones suppress IgE and Th2 cytokines in OVA-immunized BALB/c mice. European Journal of Nutrition. 2007;46:257-263.

12. Shaik YB, Castellani ML, Perrella A, et al. Role of Quercetin (a natural herbal compound) in allergy and inflammation. J Biol Regul Homeost Agents. 2006;20(3-4):47-52.

13. Chirumbolo S. The role of Quercetin, Flavonols and Flavones in modulating inflammatory cell function. Inflamm Allergy-Drug Targets 2010; 9(4):263-85.

14. Mlcek J, Jurikova T, Skrovankova S, Sochor J. Quercetin and its anti-allergic immune response. Molecules 2016;21,623.

15. Kawai M, Hirano T, Arimitsu J, et al. Effect of enzymatically modified isoquercetin, a flavonoid, on symptoms of Japanese cedar pollinosis: a rando,ized double-blind placebo-controlled trial. Int Arch Allergy Immunol 2009;149:359-68.

16. Hirano T, Kawai M, Arimitsu J, et al. Preventative effect of a flavonoid, enzymatically modified isoquercetin on ocular symptoms of Japanese cedar pollinosis Allergol Intern 2009;58:373-82.

17. Ebibara N, Takahashi K, Takemura H, et al. Suppressive effect of quercetin on nitric oxide production from nasal epithelial cells in vitro. Evidence-based Complement Altern Medicine 2018;ID 6097625.

18. Sakai-Kashiwabara M, Asano K. Inhibitory action of quercetin on eosinophil activation in vitro. Evidence-based Complement Altern Medicine 2013;ID 127105.

19. Mueheisen B, Gallo RL. Vitamin D in allergic disease: shedding light on a complex problem Allergy Clin Immunol. 2013;131(2):324-9.

20. Bozzetto S, Carraro S, Giordano G et al. Asthma, allergy and respiratory infections: the vitamin D hypothesis. Allergy. 2012;67(1):10-7.

21. Yepes-Nunes JJ, Brozek JL, Fiocchi A, Pawankar R, Cuello-Garcia C, Zhang Y, et al. Vitamin D supplementation in primary allergy prevention: systematic review of randomized and non-randomized studies. Allergy 2018;73:37-49.

22. Kim YH, Kim KW, Kim MJ, Sol IS, Yoon SH, Ahn HS, et al. Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis. Ped Allergy Immunol 2016;27:580-90.

23. Aryan Z, Rezaei N, Camargo CA. Vitamin status, allergic sensitization, and allergic rhinitis: a systematic review and meta-analysis. Int Rev Immunol 2017;36:41-53.

24. Loo EXL, Tham EH, Phang KW, Goh A, Teoh OH, Chong YS, et al. Associations between maternal vitamin D levels during pregnancy and allergic outcomes in the offspring in the first 5 years of life. Pediatr Allergy Immunol. 2018 Oct 19. doi: 10.1111/pai.12995.

25. Laird E, McNulty H, Ward M, Hoey L, McSorley E, Wallace JMW, Carson E, Mollov AM, Healy M, Casey MC, Cunningham C, Strain JJ. Vitamin D Deficiency Is Associated With Inflammation in Older Irish Adults The Journal of Clinical Endocrinology & Metabolism, 2014.

26. Yip KH, Kolesnikoff N, Yu C, Hauschild N, Taing H, Biggs L, Gottzman D, Colin CA, Anderson PH, Samuel MS, Galli SJ, Lopez AF, Grimbaldetson MA. Mechanisms of vitamin D3 metabolite repression of IgE-dependent mast cell activation. J Allergy Clin Immunol 2014.

27. Ariano R. Efficacy of a novel food supplement in the relief of the signs and symptoms of seasonal allergic rhinitis and in the reduction of the consumption of anti-allergic drugs. Acta Biomed. 2015;86(1):53-8.

28. Ariano R. Ophthalmic Lertal spray for seasonal allergic conjunctivitis: an open-label clinical study. In Focus 2017;10:3-7.
29. Rah MJ. A review of hyaluronan and its ophthalmic applications. Optometry. 2011;82:38-43
30. Böhm M, Avgitidou G, El Hassan E, Mosges R. Liposomes: a new non-pharmacological therapy concept for seasonal-allergic-rhinoconjunctivitis. Eur Arch Otorhinolaryngol. 2012;269:495-502
31. Marseglia GL, Licari A, Ciprandi G. A polycentric, randomized, double blind, parallel-group, placebo-controlled study on Lertal®, a multicomponent nutraceutical, as add-on treatment in children with allergic rhinoconjunctivitis: Phase I during active treatment. J Biol Reg 2019;33:617-622
32. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachtet C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017;140(4):950-958
33. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA, Pallestrini E. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? A population based study. Allergy 2005;60:882-7
34. Marseglia GL, Licari A, Leonardi S, Papale M, Zicari AM, Schiavi L, et al. A polycentric, randomized, parallel-group, study on Lertal®, a multicomponent nutraceutical, as preventive treatment in children with allergic rhinoconjunctivitis: Phase II. Ital J Ped 2019;45:84
35. Portnoy JM, Dinakar C. Review of cetirizine hydrochloride for the treatment of allergic disorders. Expert Opin Pharmacother. 2004 Jan;5(1):125-35
36. Ciprandi G, Ricci V, Ferrero P, Alessandra B, Riccio AM, Milanese M, et al. Duration of antiinflammatory and symptomatic effects after suspension of intranasal corticosteroid in persistent allergic rhinitis. Eur Ann Allergy Clin Immunol. 2004;36:63-6
37. Tonelli M, Bacci E, Dente FL, Bartoli ML, Cianchetti S, Di Franco A, et al. Predictors of symptom recurrence after low-dose inhaled corticosteroid cessation in mild persistent asthma. Resp Med 2006;100:622-9
38. Wirchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma. A randomized clinical trial. JAMA 2016;315:1715-25
39. Valovirta E, Petersen TH, Piotrowska T, Laurson MK, Andersen JS, Sorensen HF, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol 2018;141:529-38
40. Ciprandi G, Cosentino C, Milanese M, Mondino C, Canonica GW. Fexofenadine reduces nasal congestion in perennial allergic rhinitis Allergy 2001;56:1068-1070
41. Ciprandi G, Pronzato C, Ricca V, Varese P, Giacono GS, Canonica G. Terfenadine exerts antiallergic activity reducing ICAM-1 expression on nasal epithelial cells in patients with pollen allergy. Clinical Experimental Allergy 1995;25:871-878
42. Ciprandi G, Buscaglia S, Catrullo A, Pesce GP, Fiorino N, Montagna P, et al. Azelastine eye drops reduce and prevent allergic conjunctival reaction and exert anti-allergic activity. Clinical Experimental Allergy 1997;27:182-91
43. Ciprandi G, Tosca MA, Passalacqua G, Canonica GW. Long-term cetirizine treatment reduces allergic symptoms and drug prescriptions in children with mite allergy. Annals of Allergy Asthma Immunol 2001;87:222-6
44. Ciprandi G, Mora F, Cassano M, Gallina AM, Mora R. Visual analog scale (VAS) and nasal obstruction in persistent allergic rhinitis. Otolaryngol Head Neck Surg 2009;141:527-9
45. Ciprandi G, Cirillo I. The lower airway pathology of Rhinitis. Update Review J Allergy Clin Immunol 2006;118:1105-9
46. Ciprandi G, Tosca MA, Ricca V, Passalacqua G, Fregonese L, Facse L, et al. Cetirizine treatment of allergic cough in children with pollen allergy. Allergy 1997;52:752-4
47. Ciprandi G, Marseglia GL, Klersy C, Tosca MA. Relationships between allergic inflammation and nasal airflow in children with persistent allergic rhinitis due to mite sensitization. Allergy 2005;60:957-60
48. Ciprandi G, Ricca V, Tosca MA, Landi M, Passalacqua G, Canonica G. Continuous antihistamine treatment controls allergic inflammation and reduces respiratory morbidity in children with mite allergy. Allergy 1999;54:358-65

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