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Review Article

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An Oral Combination of Turmeric-Pomegranate (With Ginger) Prevents Viral (Cold/Flu) Episodes in Immunocompromised Patients

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Abstract

The aim of this pharma standard ("PS") supplement, registry was the evaluation – in a period of 3 months – of the effects of the use of a standardized combination (oral supplement including turmeric, pomegranate and ginger) in preventing common, winter, viral events (cold and flu episodes).

Results: *No safety or tolerability problem was observed with the supplement. The two resulting registry management groups – standard management (SM) and SM+the supplement combination – were comparable. The number of viral (cold/flu) episodes (lasting more than 3 days), and the total number of subjects with any episode was in favor of the group managed with the preventive supplement combination ($p<0.05$). The average number of days of disease and the lost working days were lower with the combination (Phyto Relief). The use of other OTC products and the number of complications were significantly lower (<0.05) with the supplement combination. The number of subjects with a clinical extension of the disease to more than 7 days with bronchial or tracheal complications was also lower ($p<0.05$) with the supplements in comparison with the SM group. Salivation was improved more in the supplemented group ($p<0.05$). The results of this concept, preliminary study in mildly immuno-compromised subjects shows that Phyto Relief may help prevent some episodes of cold/flu and help (by shortening the length of the episodes) the evolution of viral episodes when used early, when the initial symptoms can be identified. More specific evaluations and larger prevention studies are needed, in a more heterogenous population. The extension of this supplementary prevention to more subjects and for longer periods may indicate a more permanent effect of this supplement combination on improving local, mucosal immunity and resistance to viral spread.*

Conclusions: *The evaluation of immunocompromised subjects is significant in clinical conditions prevention (winter viral episodes) with this natural combination which may also avoid prolonged respiratory complications.*

Keywords: Turmeric, Pomegranate Extract, Ginger Extract, Cold, Flu, Viral Infections, Epidemiology, Lysozyme.

Introduction

Increased salivation – usually associated to an increase in lysozyme – may be produced by supplementary elements of natural origin (i.e., ginger or pomegranate) and can be theoretically useful in protecting the mucosal environment of the mouth from viral and bacterial contamination, in otherwise healthy subjects.1,2) A recent, pilot registry (a PS supplement study) indicates that the association of ginger, turmeric and pomegranate may be useful in the prevention of a number of cold episodes, possibly by increasing salivation [1, 2]. This combination appears to be effective on signs and symptoms associated to the viral episodes. The main activity of the combination appears to be an increase in salivation and, generally, an increase in the total content in lysozyme of the saliva. A dry mouth, without protection tend to be more frequently affected by local and systemic infections. Several attempts have been made – with different studies – to increasing salivation, improving immuno-responses (i.e., with systemic colostrum) and using an artificial saliva added with lisozyme to prevent cold and viral events by correcting mouth dryness that may cause a faster, more effective viral/bacterial mouth spreading and contamination [3-10]. A specific antioxidant complex – rapidly effective on the antioxidant power of the saliva – may also be effective in decreasing viral and bacterial spread in the mouth [5]. Lysozyme was increased during this registry with the active management

[5]. Prevention is even more important in immunocompromised subjects (Table 1). Immunodeficiency or immunocompromised conditions are characterized by a decreased function of the immune system that becomes unable to correctly fight infectious disease and/or cancer. The immune system may be compromised or even absent. Most cases of immunodeficiency are acquired (defined as "secondary") due to extrinsic factors that affect the patient's immune system. These factors may include HIV infection and environmental factors, such as nutrition, surgery or chemotherapy.

Table 1: The Two Types of Immunocompromised Subjects Evaluated in the Preventive Registry.

Neutropenia	Neutrophil	Chemotherapy	Enterobacte riaceae
	Granulocytes	Bone marrow	Oral Streptococci
		Transplantation	Pseudomonas aeruginosa
		Chronic granulomatous	Enterococcus species
		Disease	Candida species
			Aspergillus species
Asplenia	Asplenia	Splenectomy	Polysaccharide encapsulated
		Trauma	bacteria,7 particularly:
		Sickle-cell anemia	Streptococcus pneumoniae7
			Haemophilus influenzae7
			Neisseria meningitidis7
			Plasmodium species
			Babesia species
Source: https://www.healthline.com/health/neutrophils.			

Immunosuppression may be produced by some drugs (for instance, corticosteroids; this can be considered as an adverse effect or may be the main aim of the treatment. In organ transplants, anti-rejection measures are used to lower the efficiency of the immune system; in patients with an overactive immune system (autoimmune diseases), immunosuppression may be essential. Immunocompromised subjects are more vulnerable to opportunistic infections. Immunodeficiency may also decrease resistance to tumors.

Two types of immunodeficiency were considered in this registry, in otherwise healthy subjects (Table 1).

1. Subjects with granulocyte deficiency (decreased numbers of granulocytes, as granulocytopenia, particularly neutropenia). Granulocyte deficiencies may also include decreased function of individual granulocytes, such as in chronic granulomatous disease.
2. Asplenia, subjects without spleen (surgically removed, at least 5 years before, for traumatic events).

The aim of this pharma standard ("PS") supplement, registry was the evaluation of the preventive effects of the use of a standardized combination (an oral supplement including turmeric, pomegranate and a minimal quantity of ginger) in preventing common winter viral events (cold and flu episodes). Supplements should always be used in pharmaceutical standard (PS supplements) to evaluate and define a potential clinical value of the product [2]. The natural form of a product of natural origin, if not in pharmaceutical standard is very difficult to define. The main targets of the present registry study were the evaluation of the occurrence of episodes and the reduction of signs/symptoms, the reduction of days of disease, the reduction in use of specific medications, to control cold/flu and the evaluation and control of cold-related complications.

Subjects and Methods

Three gummy tablets/day were used as a prevention in the winter seasons (December to March). Two groups were formed: standard management and standard management + PhytoRelief. The tablets dissolve slowly in the mouth. Each tablet includes turmeric (50 mg), pomegranate (20 mg) and ginger extract in minimal quantity (5 mg); 3 tablets/day were regularly used as a single method for of prevention for 90 days. The standardized combination of PS supplements is produced in Switzerland and marketed by AlchemLife, Birmingham, UK). In the comparative group a generic, non-medicated mint caramel (Roshen, USA) was used at the same times. Safety and tolerability were assessed by weekly contacts and laboratory measurements (if and when needed). Adverse experiences – if reported or detected – were evaluated throughout the registry. All clinical adverse experiences were classified in terms of intensity: mild, moderate, or severe, also considering duration, seriousness, outcome, and relationship to the study product. Standard management was used by all subjects to prevent cold/flu. At the moment there is limited possibility of prevention (excluding vaccination, if and when effective considering the mutagenicity of the viruses). Prevention also included obvious measures: avoiding clear sources of contamination, washing hands after contacts, using 1 g/day of Vitamin C (Cebion, Bayer, Italy), a healthy lifestyle, open air exercise, avoiding, if and when possible, closed, crowded spaces with many individuals in the colder winter months. All subjects had normal, routine blood tests at inclusion (excluding a mild decrease in neutrophils), did not have any disease or risk condition and were not using any drug. Subjects were otherwise, healthy and without significant risk factors or risk conditions (i.e., diabetes). Their BMI (body-mass index) was <26

and their thyroid function was normal.

All supplement studies are aimed to define the field of activity of PS (pharmaceutical standard) supplements and possible preventive, preferably non-clinical applications [11-15]. They are planned and organized with the full attention and participation of the evaluation subjects. The included subjects may have significant benefits and no damages (all products used are defined RAS or 'recognized as safe'). The best fields of application for supplements are preclinical, preventive, borderline applications or the supplementary management of some risk conditions. Supplements, unless there are specific claims, are not generally used for treatment of signs/symptoms or clinical conditions. The aim of supplement studies is to produce supplementary data to be compared to "background" historical data (i.e., based on the best available management for comparable subjects) or to other management plans. In this type of study, PS supplements were used according to the following rules:

1. The use of the supplement is only suggested to the evaluation subjects; the supplement use is not formally prescribed but only suggested as an option, possibly capable of improving the management of the condition or risk condition.
2. The supplement is only used on top of what is considered at the time the "standard" or "best-management/care" available, if available for that condition, according to relative international guidelines.
3. The use of the supplement should not interfere with any other treatment or preventive measure.
4. The period of follow-up is considered variable, according to the needs and availability of the patients or registry subjects. The observation period could be therefore variable, not prefixed. Ideally, the supplementary administration should be used as long as needed to see results or changes;
5. The type of evaluation for these studies is always a registry.
6. In supplement studies there is no defined group allocation, no randomization organized by the investigators.
7. Subjects decide, after the initial briefing, the management group they want to join including the control (non-supplement) group. No placebo is used.

Open Label

Patients are informed about the supplement or any treatment and management. A possible placebo effect is also carefully explained and considered. Data and results are analyzed only after the observation period, ideally, when sufficient evidence is collected or when fund limitations would eventually stop the collection of the observations. The time needed to detect differences among groups is also considered an evaluation target. In this type of studies control groups, if present, are not necessarily parallel.

Characteristics of this Registry

This study was a small-scale, independent, pilot, registry study; the evaluation product was not prescribed but recommended. This registry is actually more corresponding to real, practical conditions than most clinical studies that artificially select groups of patients in defined conditions, often not corresponding to an epidemiological reality [16-23]. This type of supplement studies may be particularly suited for emerging countries and when expensive sponsorships are not available. Results and data were evaluated by an external reviewing panel, not in contact with the registry patients.

Sponsors/Cro

Commercial sponsorship from the producers of the tested supplement was not available.

Evaluation of Salivation.

Salivation was subjectively measured with a visual analogue scale line (VASL, range 0 to 4). The value of 4 indicated normal salivation. 3. Indicated mild, occasional decrease in salivation. 2. Indicated important, permanent decrease and some mucosal breaks. 1. Indicated important, persistent (>1 year) lack of salivation; small ulcerations were present. 0. Indicated a permanently dry mouth – with complications – requiring artificial saliva. Statistical analysis was used to evaluate the clinical efficacy of the supplement combination protection. On the basis of the model study at least two groups of more than 20 subjects would be needed to evaluate differences in the three target parameters after prophylaxis (supplementation). In this registry when 20 comparable subjects completed the registry period the study was considered statistically measurable. Non-parametric statistics was used to evaluate the differences between groups. The difference in occurrence of clinical events in the management groups was analyzed using the ANOVA.16 A specific, modified Sigma-Plot software was used.

Safety follow up: A safety and tolerability study was associated to the present registry. Subjects using PhytoRelief for a period of more than 3 months were monitored for possible tolerability problems and side effects.

Results

No safety or tolerability problem was observed with the supplementation or with the SM. The two resulting registry management groups were comparable (Table 2). The follow up for all subjects lasted more than 94 days. The total number of viral (cold/flu) episodes (lasting more than 3 days), the total number of subjects with any episode, the episodes in the first 2 weeks were all in favor of the group managed with the preventive supplement combination ($p<0.05$). Also, the average number of days of disease and the lost working days were lower ($p<0.05$) with the supplements combination (PhytoRelief). The use of other OTC products and the number of complications after 4 days were significantly lower (<0.05) with the supplements combination. The number of subjects with a prolongation and a clinical extension of the diseased Condition/event to more than 7 days – with bronchial or tracheal complications, requiring more complex management, including antibiotics – was also lower with the supplements in comparison with the SM group. Salivation was improved more in

the supplemented group (p<0.05; see Table 2).

Table 2: Observations in the two Groups (PhytoRelief Prevention and Standard Management).

	PHYTORELIEF CC	CONTROLS	
TOTAL subjects Age	12 (5 females) 46.7;3	14 (7 females) 47.4;3.2	ns
1. Episodes (>3 days) of cold	3/12 25%	8/14 57.1%	p<0.05
2. Total number of subjects (any episode)	3	8	p<0.05
3. Cold episodes (first 2 weeks)	2	6	p<0.05
4. Other parameters - Average days per episodes - Lost working days	3.3;2.1 1.8;0.5	3.7;1 2.2;0.5	p<0.05 p<0.05
5. Use of other OTC product (nasal drops, aspirin, Vitamin C, antihistamines, aerosols)	4/12 33.3%	10/14 71.4%	p<0.05
6. Number of complications	1	5	p<0.05
7. Disease event 'extension' (to >71 days with tracheal or bronchial complications)		5	p<0.05

At inclusion the VASL value was comparable in the two groups. At end study it was significantly improved in the supplement group in comparison with a significantly lower value (with a minimal variation) (p<0.05) in controls. The results of this concept, preliminary study in (mildly) immunocompromised subjects shows that PhytoRelief may help preventing some viral episodes of cold/flu and help (by shortening the length of the episodes) the evolution of cold/flu when used early, when the initial symptoms can be identified. More specific evaluations and larger prevention studies are needed, in a more heterogenous population. The extension of this supplementary prevention to more subjects and for longer periods may indicate a more permanent effect of this supplement combination on improving local, mucosal (lysozyme) and possibly, even systemic immunity.

Neutrophils

The neutrophil count in these included subjects was always <4000 WBC/mcl (as a definition of neutropenia). At inclusion, supplemented subjects had a count of 1578;112 neutrophils/mcl: at end study this value was increased to 1778;103/mcl. In controls, SM subjects, the values were 1596;144/mcl at inclusion and became 1679;148/mcl. The difference between the two groups was not statistically significant.

The increase in neutrophils cannot be correlated to the supplementation. Generally, a value of <1500 neutrophils/mcl indicates – by definition – mild neutropenia. Causes of immunocompromisation, in these subjects were previous oncological surgery with chemotherapy (at least 6 months before inclusion into the present study) without complications.

Safety Follow Up: 132 subjects (75 females) using PhytoRelief for more that 3 months (at least 3 lozenges daily) were monitored; the average follow up was 178;12 days (from 155 to 225 days). No safety issues and no side effects were observed. The tolerability was optimal with all subjects using the product until it was available.

Discussion

Turmeric (and curcumin, the most important active ingredients in turmeric), has shown potentials – with the right dose, consistent absorption and length of administration – in improving immune-modulation and, theoretically, it may help improving some immune functions (but only in a prolonged administration and with doses to be defined). However, there is no clinical evidence so far, in real patients, in clinical conditions. Curcumin has also shown to have – in vitro – potential antimicrobial, antiviral and antioxidant effects; again, it is very difficult to transfer these observations to real clinical models – as concentrations in vitro are completely different – and when evaluating symptoms associated with cold and flu. Pomegranate extract contains powerful antioxidants (as tannins, anthocyanins and ellagic acid) that may potentially boost the body's natural defenses against flu and cold viruses possibly by fighting off free radicals [2]. This effect requires time and cannot be provided by a few days of administration. In-vitro studies – particularly for PS supplements – have a very limited, indicative meaning if not associated to actual clinical observation in specific patients. Ginger in this combination is used at a very low dose (5 mg) that even locally has very minimal therapeutic or prophylactic antimicrobial or antiviral effects. However, its spicy taste tends to rapidly increase salivation and the availability of lysozyme in the mouth producing a passive effect not directly associated to the presence of ginger. Gingerol, the active ingredient found in ginger, has been shown to have potential anti-inflammatory effects (but not in clinical conditions) which can theoretically, positively impact symptoms (sore throat) and possibly even work to inhibit the spread of flu and cold viruses by an increase in the production of lysozyme. Prevention of even minimal viral events is essential in immunocompromised subjects (as indicated in Table

15.I). Immunodeficiency or immunocompromised conditions are characterized by a generally decreased function of the immune system that becomes unable to contrast infections (particularly viral contamination) and cancer. The immuno-system may be mildly compromised (with minimal risks) but in some subjects can be almost absent with serious risk even with minimal viral infections.

As seen in these patients, most cases of immunodeficiency are acquired (defined as secondary) i.e. as a consequence of extrinsic factors (surgery, blood loss, prolonged infections, splenectomy, radio or chemotherapy) that greatly affect the immune system. These extrinsic factors may include HIV infection and hepatitis and several environmental factors including such as nutrition or chronic poisoning (i.e. by sol vents). More specific evaluations and larger prevention studies are needed, also testing different dosages of the supplement combination. The extension of the prevention to more prolonged periods of administration may indicate a more permanent effect of this PS supplement on improving local, mucosal (lysozyme) and possibly, even systemic immunity. Also, the output of lysozyme and saliva (and oral oxidative stress) can be quantitatively measured. The accessory safety study showed no problems in using the lozenges for prolonged period of time. Recent studies have shown the specific activity of PhytoRelief in the mouth. This product is virucidal (against COVID) and also germicidal in a model study [21-23].

Conclusion

Normal levels of immunity are very difficult to improve and in-vitro concepts regarding supplements should be only translated into clinical suggestions (never to claims that are specific of drugs) if there is clinical evidence, evaluated in healthy subjects and in standardized conditions [2, 17, 18]. The effects of the components of this supplement combination need a more complete evaluation.19,20 At the moment there are no articles in Medline concerning the combination Turmeric and pomegranate. The evaluation of immunocompromised subjects is a very significant value in clinical conditions as the prevention of viral episodes may be of great benefit and avoid dangerous and prolonged complications.

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