## Lefter to the Editor

## COVID-19, food supplements and pediatricians. Knowledge of the products and their use: a national survey

Dear Editor,

Today some controversies still persist on the use or no-use of oral supplements for the treatment of pediatric populations. Physicians regularly accept to use these products in developing countries<sup>1</sup>, but their use is less accepted in the industrialized world<sup>2</sup>.

Some clarifications about nomenclature are necessary to introduce our topic to the readers.

"Oral supplement" defines a sterile liquid, semi-solid, or powder, which provides macro- and micro-nutrients that can be integrated into the diet but not exclusively<sup>3</sup>. The term "nutraceutical" is used to define any food component used for medicinal purposes that allegedly provides medicinal or health benefits, including the prevention and treatment of disease<sup>4,5</sup>.

Ghosh et al<sup>6,7</sup> supported the use of oral supplements and nutraceuticals in pediatric population. They<sup>6,7</sup> showed by two pediatric clinical trials that using oral supplements was possible to increase the body mass index (BMI) and reduce the incidence of upper respiratory infections (URI) both in short and long term.

Our group performed two clinical trials in Italy that showed the efficacy of nutraceuticals in reducing the episodes of recurrent tonsillitis<sup>8</sup> and improve the outcome of otitis media in children at different ages<sup>5</sup>. We tested nutraceuticals containing immune stimulating and immunomodulating molecules in association to natural anti-viral elements; the latter had efficacy against URI (the most common disease in the pediatric population)<sup>8,9</sup>.

SARS-CoV-2 pandemic has made necessary a new organization into several areas, so that also a rearrangement and a wider spread of knowledge and culture regarding nutraceuticals, functional foods and food supplements seem to be noteworthy<sup>10</sup>.

Several authors<sup>11,12</sup> have shown that oral supplementation with vitamin D can be useful to avoid severe infection and the use of the nutraceuticals has proved to both support the immune system and reduce the viral spread and its viral load<sup>13-15</sup>. Oral supplements and nutraceuticals have the capacity of stimulating and modulating the immune-response; this could benefit children, who are at higher risk of SARS-CoV-2 infection because not vaccinated yet. Currently, several concerns prevent the correct use and diffusion of such pharmaceuticals and limit their use in the pediatric field<sup>2</sup>. One of the major problems is the lack of information about these molecules which limits their use in the everyday practice. In addition, there is confusion about oral supplements and/or nutraceuticals effect on the immune system which discourages some physicians to use these molecules in children. Understanding the position of pediatricians on this topic may be useful to better inform professionals and increase the use of these precious elements for supporting children immune system especially in COVID-19 era.

To evaluate pediatricians' opinion on such issue, we created a specific questionnaire which was distributed through Pediatotem® platform. We used this platform because it allowed us to reach a wide number of physicians. The following four questions were asked to the readers: 1) "Are oral supplements and nutraceuticals one and the same?" 2) "Do you think using oral supplements is useful in your practice?" 3) "Do you think using nutraceuticals are useful in your practice?" 4) "Can immune-modulation and immune-stimulation be used as synonymous?". All questions asked had three possible answers: i) yes, ii) I am interested to have more info, iii) no.

699 pediatricians out of the 1300 registered on the platform answered to the four questions (Figure 1). 51.5% (360 subjects) were fully aware about the differences between oral supplements and nutraceuticals, 25.3% (177 doctors) believed that there was no difference between them, and 23.2% (162) professionals were interested in having more information on the differences between these pharmaceuticals.

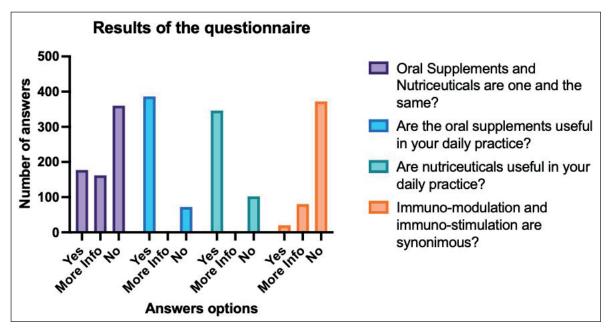


Figure 1. Results of the questionnaire.

Despite some of the participants were not fully aware of the differences between the two terms, the number of professionals interested in these natural molecules represented 74.7% (522 doctors) of the sample. 73.9% (386 subjects) pediatricians retained useful the prescription of the oral supplement and 66.3% (346) believed in nutraceuticals. Doctors were less confident with the efficacy of nutraceuticals (19.5%; 102 physicians) rather than oral supplements (13.8%; 72 professionals). We think that this data might suffer from the lower distribution and affordability of nutraceuticals compared to the oral supplements on the market. Most doctors (78.8%) were fully aware of the difference between the term immune-modulation and immune-stimulation, 17.7% (80 physicians) were interested in understanding more, and only a small percentage (4.2%; 20 doctors) believed the two words were synonymous. Although over 50% of pediatricians knew the differences between "oral supplement" and "nutraceutical", 49% of them wanted to learn more about the two types of products.

Our preliminary results showed that the majority of pediatricians believed in the efficacy and validity of the oral supplements or nutraceuticals to treat their patients. It was unclear, how they choose oral supplement or nutraceutical, if based on a strong clinical rationale or on information received by the pharmaceutical industry.

Overall, our survey showed that although both oral supplements and nutraceuticals were used, there was still confusion on their use. The use of these molecules has rapidly increased, and they are extremely useful to modulate and enforce the immune system, as shown by several clinical trials<sup>1,2,6-9</sup>. We think that after a pediatrician's adequate instruction, the oral supplements and nutraceuticals can be prescribed with the same confidence and frequency as they are used in adults and elderly. Moreover, additional surveys should be performed to understand if the molecules are administered as suggested by scientific literature<sup>1,2,6-9</sup>, since this is fundamental to obtain satisfactory results.

We believe the use of nutraceuticals and/or oral supplements could be useful to i) improve the efficiency of the immune system, ii) stimulate a better immune answer when associated with vaccine and iii) reduce the administration of antibiotics. In this pandemic, any efficient and safe product should be considered to protect weak population as children and elderly; oral supplements and nutraceuticals have, as largely shown<sup>1</sup>, these characteristics<sup>2,6-9</sup>, so we believe that they should be used in children to improve their immunity function and resistance to viral infection.

## **Conflict of Interest**

The authors declare that they have no conflict of interest.

## References

- Olsen MF, Iuel-Brockdorff AS, Yaméogo CW, Cichon B, Fabiansen C, Filteau S, Phelan K, Ouédraogo A, Michaelsen KF, Gladstone M, Ashorn P, Briend A, Ritz C, Friis H, Christensen VB. Impact of food supplements on early child development in children with moderate acute malnutrition: A randomised 2 x 2 x 3 factorial trial in Burkina Faso. PLoS Med 2020; 17: e1003442...
- 2) Agostoni C, Esposito S, Nobili A. Dietary Supplements in Infants and Children: Only Beneficial? J Pediatr Gastroenterol Nutr 2016; 63: 177-180.
- 3) Evans JM, Luby R, Lukaczer D, Rountree R, Stone PM, Guilliams TG, Yanuck S, Messier H, Ramsdell K, Hanaway PJ. The Functional Medicine Approach to COVID-19: Virus-Specific Nutraceutical and Botanical Agents. Integr Med (Encinitas) 2020; 19: 34-42.
- 4) Jensen GL. Oral nutritional supplementation. Am J Manag Care 2013; 19: 119-120.
- 5) Nastri L, Moretti A, Migliaccio S, Paoletta M, Annunziata M, Liguori S, Toro G, Bianco M, Cecoro G, Guida L, Iolascon G. Do Dietary Supplements and Nutraceuticals Have Effects on Dental Implant Osseointegration? A Scoping Review. Nutrients 2020; 12: 268.
- 6) Ghosh AK, Kishore B, Shaikh I, Satyavrat V, Kumar A, Shah T, Pote P, Shinde S, Berde Y, Low YL, Tan VMH, Huynh DTT. Effect of oral nutritional supplementation on growth and recurrent upper respiratory tract infections in picky eating children at nutritional risk: a randomized, controlled trial. J Int Med Res 2018; 46: 2186-2201.
- 7) Ghosh AK, Kishore B, Shaikh I, Satyavrat V, Kumar A, Shah T, Pote P, Shinde S, Berde Y, Low YL, Tan VMH, Huynh DTT. Continuation of oral nutritional supplementation supports continued growth in nutritionally at-risk children with picky eating behaviour: A post-intervention, observational follow-up study. J Int Med Res 2018; 46: 2615-2632.
- 8) Di Stadio A, Della Volpe A, Korsch FM, De Lucia A, Ralli M, Martines F, Ricci G. Difensil Immuno Reduces Recurrence and Severity of Tonsillitis in Children: A Randomized Controlled Trial. Nutrients 2020; 12: 1637.
- 9) Della Volpe A, Ricci G, Ralli M, Gambacorta V, De Lucia A, Minni A, Pirozzi C, Paccone M, Pastore V, Di Stadio A. The effects of oral supplements with Sambucus nigra, Zinc, Tyndallized Lactobacillus acidophilus (HA122), Arabinogalactans, vitamin D, vitamin E and vitamin C in otitis media with effusion in children: a randomized controlled trial. Eur Rev Med Pharmacol Sci 2019; 23: 6360-6370.
- 10) Buonsenso D, Onesimo R, Valentini P, Chiaretti A, Gatto A, Attinà G, Conti G, Vento G, Cambieri A, Mercuri E, Zampino G; pedCOVID-team. Children's Healthcare During Corona Virus Disease 19 Pandemic: the Italian Experience. Pediatr Infect Dis J 2020; 39: e137-e140.
- 11) Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, Quesada Gomez JM. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". J Steroid Biochem Mol Biol 2020; 203:105751.
- 12) Annweiler C, Beaudenon M, Gautier J, Simon R, Dubée V, Gonsard J, Parot-Schinkel E. COVIT-TRIAL study group. COvid-19 and high-dose VITamin D supplementation TRIAL in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial. Trials 2020; 21: 1031.
- 13) Di Stadio A, Ishai R, Gambacorta V, Korsch F, Ricci G, Della Volpe A, Bernitsas E. Nutraceuticals as immune-stimulating therapy to fight COVID-19. Combination of elements to improve the efficacy. Eur Rev Med Pharmacol Sci 2020; 24: 9182-9187
- 14) Mrityunjaya M, Pavithra V, Neelam R, Janhavi P, Halami PM, Ravindra PV. Immune-Boosting, Antioxidant and Anti-in-flammatory Food Supplements Targeting Pathogenesis of COVID-19. Front Immunol 2020; 11: 570122.
- 15) McCarty MF, Iloki Assanga SB, Lewis Luján L, O'Keefe JH, DiNicolantonio JJ. Nutraceutical Strategies for Suppressing NLRP3 Inflammasome Activation: Pertinence to the Management of COVID-19 and Beyond. Nutrients 2020; 13: 47.

A. Della Volpe<sup>1</sup>, L. D'Ascanio<sup>2</sup>, A. Di Stadio<sup>3</sup>

<sup>1</sup>Department of Otolaryngology, Santobono-Pausilipon Children Hospital, Naples, Italy <sup>2</sup>Department of Otolaryngology, AORMN, Fano, Italy <sup>3</sup>Department of Otolaryngology, University of Perugia, Perugia, Italy