European Review for Medical and Pharmacological Sciences 2021; 25: 4156-4162

Randomized clinical trial "olfactory dysfunction after COVID-19: olfactory rehabilitation therapy *vs.* intervention treatment with Palmitoylethanolamide and Luteolin": preliminary results

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Abstract. – OBJECTIVE: Approximately 30% of patients with confirmed COVID-19 report persistent smell or taste disorders as long-term sequalae of infection. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is associated with inflammatory changes to the olfactory bulb, and treatments with anti-inflammatory properties are hypothesized to attenuate viral injury and promote recovery of olfaction after infection. Our study investigated the efficacy of a supplement with Palmitoylethanolamide (PEA) and Luteolin to support recovery of olfaction in COVID-19 patients.

PATIENTS AND METHODS: We conducted a randomized-controlled pilot study in outpatients with history of confirmed COVID-19 with post-infection olfactory impairment that persisted ≥ 90 days after SARS-CoV-2 negative testing. Patients were randomized to two times a day olfactory rehabilitation alone or weekly olfactory rehabilitation plus daily oral supplement with PEA and Luteolin. Subjects with preexisting olfactory disorders were excluded. Sniffin' Sticks assessments were performed at baseline and 30 days after treatment. Data on gender, age, and time since infection were collected. Kruskal-Wallis (KW) test was used to compare variances of Sniff scores between groups over time, and Spearman's correlation coefficients were calculated to assess for correlations between Sniff Score and gender or duration of infection.

RESULTS: Among 12 patients enrolled (n=7, supplement; n=5, controls), patients receiving supplement had greater improvement in olfactory threshold, discrimination, and identification score versus controls (p=0.01). Time since infection was negatively correlated with Sniff Score, and there was no correlation between gender.

CONCLUSIONS: Treatment combining olfactory rehabilitation with oral supplementation with PEA and Luteolin was associated with improved recovery of olfactory function, most marked in those patients with longstanding olfactory dysfunction. Further studies are necessary to replicate these findings and to determine whether early intervention including olfactory rehabilitation and PEA+Luteolin oral supplement might prevent SARS-CoV-2 associated olfactory impairment.

Key Words:
COVID-19, SARS-Co-V-2, Coronavirus, Anosmia, Hyposmia, Olfactory dysfunction, Olfactory rehabilitation, Olfactory training, Olfaction, Smell, Taste, Gustatory, Quality of life, Palmitoylethanolamide, PEA, Luteolin, Supplements, Clinical trials, Post-viral.

Introduction

Impaired smell (olfactory dysfunction) is a common presenting symptom of Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) infection, and 33.9-68% of patients suffer from anosmia or hyposmia during the course of COVID-19[1-3]. Although the majority of patients

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spontaneously recover olfactory function within weeks[2,3], approximately 10-20% of patients report persistence of moderate or severe smell impairmenT[3,4], which has a negative impact on COVID-19 survivorship[5]. Few therapies for post-infectious olfactory dysfunction have been scientifically-validated[6]. Recommendations for persistent (>2 weeks) anosmia/hyposmia include safety counseling (maintaining smoke/gas detectors and monitoring expiration dates on foods), olfactory training/rehabilitation, and use of intranasal vitamin A and systemic omega-3[6].

Currently, olfactory training is the only intervention with proven efficacy for the treatment of post-infectious olfactory impairment[7]. Repetitive stimulation of peripheral olfactory neurons using different odors is thought to enhance the regenerative capacity of superior olfactory pathways, improving the olfactory threshold, identification, and discrimination of odors[8]. Unfortunately, olfactory rehabilitation is not effective in all patients, limiting the success of the therapy.

Studies of patients with COVID-19-induced anosmia demonstrate neuroinflammation, which is evident in histopathological findings of microglial activation along olfactory pathways and radiologic observations of necrosis of the olfactory bulb[9-13]. Reducing neuroinflammation may therefore alleviate anosmia, and we hypothesized that this approach would complement the salutary effects of olfactory rehabilitation, thereby promoting olfactory recovery. We conducted a randomized pilot trial of the putative neuroprotective and anti-inflammatory agents Palmitoylethanolamide (PEA) and Luteolin in a group of patients affected by persistent olfactory dysfunction after COVID-19.

Patients and Methods

Study Population

This study was conducted in respect of CONSORT rule for Clinical Trials (Figure 1). This single blinded randomized-clinical trial was conducted at Santa Croce Hospital AORMN (Fano-Pesaro, Italy) from November, 2020 to March 2021.

Inclusion criteria were: outpatients, ages 18 to 90 years, with confirmed history of COVID-19 (positive nasopharyngeal swab for SARS-CoV-2), and anosmia/hyposmia persisting ≥ 90 days after negative COVID-19 nasopharyngeal swab.

Exclusion criteria were: previous history of olfactory-gustatory disorders, impaired cognitive function, history of neurodegenerative disease, medical therapy with possible effects on olfactory function, presence of rhinological disorders (sinusitis, rhinosinusitis, sinonasal polyposis, atrophic rhinitis, allergy), history of chemo-radiotherapy of the head and neck region, history of stroke or neurotrauma, severe nasal blockage from stenosis of deformity, severe psychiatric illness (e.g., schizophrenia, bipolar disorder, olfactory hallucination), or previous sinonasal or nasopharyngeal tumors.

The following demographic data were collected: sex, age, major disease, tobacco/alcohol use, and time elapsed since negative COVID-19 test.

The study was approved by the Institutional Review Board (FN112020) and conducted in accordance with the Declaration of Helsinki. All patients signed a written consent before the inclusion in the study.

Experimental Design

After patient counseling and consent, the physician used a computer-generated for simple randomization of patients. Participants were assigned to rehabilitation therapy alone or rehabilitation with oral supplements (Figure 1).

The two study groups were defined as follows:

- Conventional therapy (control group; CG): olfactory training/stimulation through Sniffin' Sticks, administered twice every day (10-minute session) for 30 days.
- Intervention (treatment group; TG): olfactory training/stimulation through Sniffin' Sticks, administered as in control *plus* daily treatment with PEA/Luteolin oral supplement.

All patients underwent the following interventions at T0 (baseline) and T1 (30 days after treatment):

- Nasal endoscopic examination;
- Evaluation of smell function by Sniffin Sticks.

The T0 nasal endoscopic examination was performed to evaluate for presence of polyps, masses, anatomic blockage, or other pathology, which would result in exclusion from the study.

All patients (CG and TG) were evaluated for olfactory function by Sniffin' Sticks (Burghardt®, Medisense, Winschoten, The Netherlands). This initial olfactory evaluation was performed at the outset of the study (T0), before starting olfactory training, without or with supplement treatment.

Both study groups received olfactory training, and patients in TG additionally received a daily oral tablet that contained PEA 700 mg and Luteolin 70 mg (Glialia®, Epitech pharmaceutical,

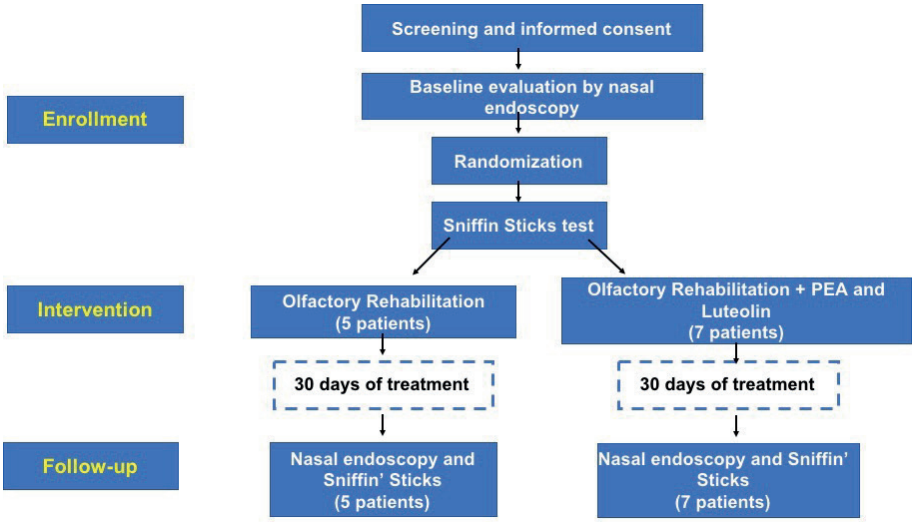

Figure 1. Consort Diagram shows the enrollment, intervention and follow-up we used.

Milano, Italy). Nasal endoscopy and assessment of olfactory function were repeated at 30 days, corresponding to the experimental endpoint of the study (T1).

Assessment of Olfactory Dysfunction

The Sniffin' Sticks battery was administered following a previously established protocol[14], using pen-like devices filled with odorants. Clinicians conducting the scoring were blinded to the treatment group of patients. Three score subtests were conducted to measure olfactory function:

(1) detection threshold ("T", the lowest concentration at which an odor can be perceived),

(2) odor discrimination ("D", ability to distinguish between odors) and

(3) odor identification ("I" ability to assign names to odors).

Possible scores ranged from 1-16 for the detection threshold subtest and 0-16 for both the discrimination and identification subtests. Adding these the subtests yielded a TDI "Sniffin score." Anosmia was defined as a score of <17, hyposmia by a score 17 to 30.75, and normosmia by a score of ≥31.

In the first test, odor detection threshold was determined using a three-option, yes-no staircase, forced-choice procedure with the odorant n-butanol. Participants were presented with triplets of odorant pens and asked to identify the pen containing n-butanol when presented with two blank distractor pens. In the second subtest, odor discrimination ability was assessed using 16 triplets of odorants: within each triplet, two pens contained the same odorant, while the third pen contained a different odorant. In a forced-choice procedure, the participants were asked to detect the odd pen for each triplet. During the odor identification task, participants were presented with 16 common odors. Using a multiple-choice answering format, they were asked to select which of 4 odor labels matched the presented odor.

Study Outcomes

The primary outcome was the change over time in Sniffin scores for the control versus intervention group. The secondary outcome was to evaluate for correlation between months since COVID-19 resolution (based on negative test) and Sniff' score.

Statistical Analysis

Two-tailed *t*-test (τ) was used to analyze statistical differences in Sniffin Stick score (TDI score) between Control and Treatment at T0 and at T1. Kruskal-Wallis (KW) test was performed to compare variances of scores between CG and TG. Spearman (S) test was used to analyze the effect of period without treatment on the severity of smell disorders (Sniffin score) (T0 only), and evaluate for association of age with Sniffin score, both before (T0) and after treatment (T1). We also used Pearson correlation coefficient to evaluate for association between gender and Sniffin scores, with significance set at $p < 0.05$. All analyses were performed using Stata® (Stata Software for Statistics and Data Science, College Station, TX, USA) .

Table I. Demographic characteristics of our sample.

Gender	12 patients 8 women, 4 men	
Age	42.2 + 14.1	
		Months of Smell Disorders
Control	5 patients: 3 women, 2 men	4.6 + 3.6
Treatment	7 subjects: 5 women, 2 men	9.7 + 2.5

Results

No patients were excluded based on nasal endoscopy screening. All study participants (n=12) had hyposmia or anosmia confirmed at T0 olfactory assessment, consistent with subjective reports of persistent smell disorders at the start of the study (Table I). All study participants (n=12) completed the study, including olfactory training sessions and adhering to the supplement regimen in the treatment group (Figure 1).

Patients taking supplement had greater improvement in Sniffin score than controls (mean change in Sniffin score = 2 for CG and 4 for TG; KW: $p = 0.01$) (Figure 2).

The length of time elapsed from negative COVID-19 test and the presence of smell alteration were not significantly associated with Sniffin Score, with the caveat of a negative trend and small sample size (S: *rs*: -0.5, $p= 0.08$) (Figure 3). Age, gender, and severity of anosmia were not associated with extent of recovery in either group. Baseline characteristics differed between groups. Patients randomized to TG had suffered from anosmia for an average of 9.7 months *vs.* only 4.6-months for CG. Also, patients in TG had significantly lower baseline Sniffin' scores (mean: 21.1; SD: 5.5; CI 95%: 15-31.7) compared to CG (28.8; SD:1.2; CI 95%: 27-30) (τ: $p=0.01$) (Figure 2). Mean Sniffin' score at conclusion of the study were 25.2 (SD:5.9; CI95%:14-32.5) and CG 31.1 (SD:5.5 CI 95%: 25-37.2). Patients in TG demonstrated two-fold improvement in Sniffin' scores relative to patients in CG, with no significant difference in Sniffin' score at 30 days (25.2 for TG [SD: 5.9; CI 95%: 14-32.5]; 31.1 for CG [SD: 5.5 CI 95%: 25-37.2]; T1, τ: $p=0.1$).

Discussion

These data support feasibility of randomizing patients with persistent olfactory dysfunction to treatment arms involving olfactory training with or without supplements (PEA and Luteolin). Furthermore, the study provides interesting pilot data on the treatment interventions. The quest for evidence-based regimens for olfactory dysfunction after SARS-CoV-2 infection is ongoing; however, given the few options for rehabilitation available to patients with hyposmia and anosmia, this study provides an impetus for further investigation. Amelioration of olfactory dysfunction with PEA/Luteolin supplementation coincides with mechanistic understanding of the pathogenesis of olfactory injury. The finding of a modest benefit from olfactory training alone

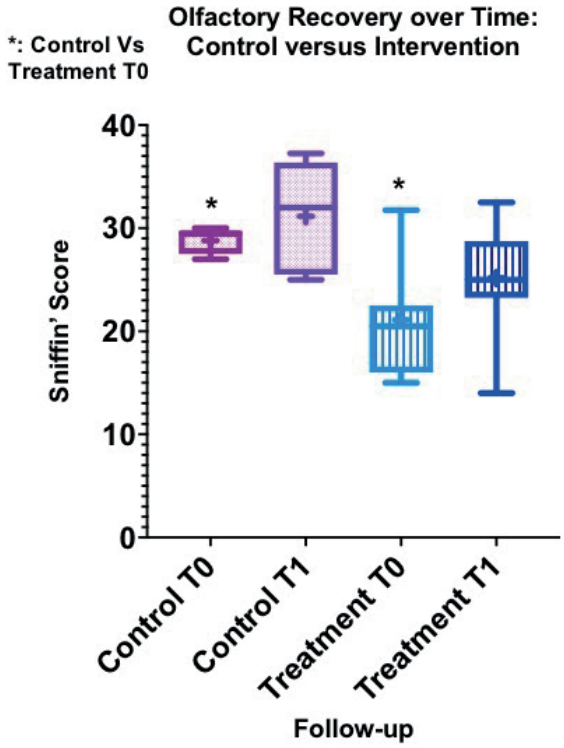

Figure 2. The graph shows the variation of Sniffin score at T0 and T1 in control and treatment. The scores statistically significant different at T0 (p=0.01), don't show any statistical difference after 30 days (T1). The lines of the boxes show the minimum and maximum value of Sniff score.

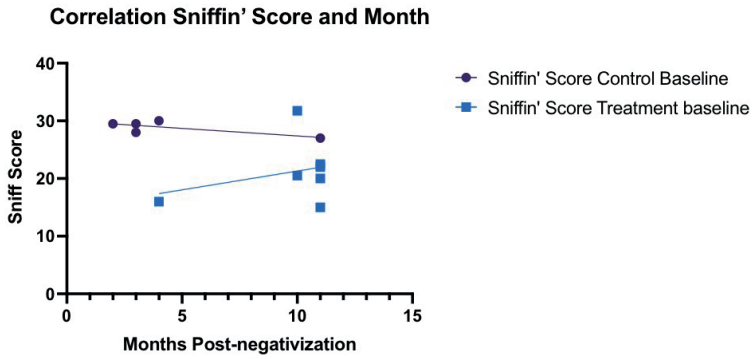

Figure 3. The graph shows the correlation between the elapsed months after Sars-CoV2 negativization and the Sniffin score at T0 in control and treatment. Longer was the time of persistence of smell disturbances after COVID-19 resolution lower were the scores of the Sniff test.

is consistent with other work in postinfectious olfactory dysfunction.

While the mechanism of olfactory dysfunction in patients with COVID-19 remains incompletely understood, currently available evidence implicates damage to the olfactory neuroepithelium[10] and the olfactory bulb[9]. Histological and radiological studies show that after traversing the olfactory mucosa, SARS-CoV-2 reaches the olfactory bulb[11,12], causing direct damage to neural tissue[11]. Systemic infection induces hypo-perfusion, brain inflammation, and microglial activation[11,13]. Post-mortem histopathological investigation of patients with anosmia and COVID-19 reveal necrotizing olfactory bulbitis[15] and ischemia[16], providing a rationale for combining olfactory rehabilitation with oral therapeutics that reduce neuroinflammation[17-19].

PEA and Luteolin, both of which are well-tolerated and without known toxicity, have distinct proposed mechanisms of reducing neuro-inflammation[17-19]. PEA is an endogenous fatty acid amide, produced and hydrolyzed by microglia, able to downregulate mast cell activation, and reduces neuroinflammation[20]. PEA attenuates activation of M1 microglia in brain and increases activation of M2 phenotype[21], thereby reducing the inflammatory milieu[20,21]. Due to its downregulating-mast-cells characteristics PEA is under-investigation as potential candidate to modulate lung inflammation from SARS-CoV-2[22,23].

Luteolin, the other component of the supplement, is naturally occurring flavonoid, with brain antioxidant, anti-inflammatory and neuroprotective characteristics[17]. The molecule improves motor and sensory impairments and inhibited neuronal cell degeneration reducing the activation of bad microglia. It antagonizes the activation of the Toll-like receptor 4 (TLR4)/TNF receptor-associated factor 6 (TRAF6)/nuclear transcription factor-κB (NF-κB) signaling pathway reducing inflammation[24].

PEA, which has anti-inflammatory effects on neural tissue, may reduce inflammation in the olfactory bulb[15,20,21]. PEA modulates the polarization of microglia in M2 protective phenotype[21], supporting neural regeneration and potentially supporting recovery of smell. Luteolin in addition is able to block the polarization of bad microglia inhibiting neural cell degeneration[17,24]. The major mechanism of Luteolin is its anti-inflammatory activity, which derives from its regulation of transcription factors such as STAT3, NF-κB, and AP-1[25]. These effects may mediate anti-inflammation and antioxidant effects to protect neural tissue and other organs from inflammation[16,24].

Limitations

This study has several limitations. The major limitation is small sample size, which predisposed to an underpowered analysis. In addition, despite randomization the baseline characteristics of CG and TG patients differed, with marked differences in severity and duration of olfactory dysfunction at T0. Patients in CG with higher Sniffin Score and shorter mean duration of smell alteration might have benefitted from spontaneous recovery. Conversely, patients in treatment group, despite improvement, may have required longer durations to recover olfactory functions. Finally, the study lacks a placebo control; because olfactory disorders adversely impact patient quality of life, the use of placebo or withholding treatment would not be equipoise. Nonetheless, absence of placebo control remains an important caveat when interpreting findings of this study.

One of the minor limitations of the study is that COVID-19 has complex survivorship implications, and not all patients are inclined to embark on olfactory training; the potential selection bias in patients who enrolled may affect generalizability. Furthermore, we did not investigate supplements individually or establish a dose response. In addition, using negative COVID-19 testing as a proxy for resolution of SARS-CoV-2 infection may have underestimated disease- by PCR free periods, as inert or dead virus may remain detectable after patients are no longer infectious or acutely ill[6]. Additional work in larger populations is necessary to validate our preliminary results, to identify optimal timing and dosing regimens, and to evaluate pharmacokinetics. The non-significant findings with respect to patient age, gender, and severity of olfactory illness may reflect absence of association, although small sample size with underpowered analyses is also possible.

An important consideration for future work includes identifying the optimal timing for initiating treatment. While olfactory neurons have regenerative capacity, neuronal cell body death is permanent. Therefore, while a 90-day washout period following a negative COVID-19 test may have minimized confounding form spontaneous recovery, it also precluded early intervention. Reducing central inflammation earlier in the course of disease warrants further study.

Conclusions

PEA and Luteolin are potential adjunctive treatments for treating olfactory dysfunction after COVID-19. While their clinical use remains investigative, we observed in our pilot study that the intervention group (supplements + olfactory training) experienced significantly greater recovery of olfactory function than a comparison group (olfactory training alone). Further research is needed to characterize the anti-inflammatory and anti-oxidative effects of these therapeutics. Future studies may clarify the optimal timing and dosing parameters. Improvement over time in the conventional therapy group is consistent with literature documenting benefits of olfactory training.

Trial Registration Information

The study was authorized by the IRB of Fano Hospital in November 2020 with number FN112020, and it was registered at Clinicaltrials.gov in April 2021 with Number: 20112020PGFN.

Conflict of Interest

The authors have no conflicts of interest and nothing to disclose (the authors have received no proceeds and have no relation to manufacture of palmitoylethanolamide or luteolin).

References

1) Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in covid-19 patients: a systematic review and meta-analysis. Otolaryngol Head Neck Surg 2020; 163: 3-11.
2) Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: a review based on up-to-date knowledge. Am J Otolaryngol 2020; 41: 102581.
3) D'Ascanio L, Pandolfini M, Cingolani C, Latini G, Gradoni P, Capalbo M, Frausini G, Maranzano M, Brenner MJ, Di Stadio A. Olfactory dysfunction in COVID-19 patients: prevalence and prognosis for recovering sense of smell. Otolaryngol Head Neck Surg 2021; 164: 82-86.
4) Sampaio Rocha-Filho PA, Voss L. Persistent headache and persistent anosmia associated with COVID-19. Headache 2020; 60: 1797-1799.
5) Pandian V, Brodsky MB, Brigham EP, Parker AM, Hillel AT, Levy JM, Rassekh CH, Lalwani AK, Needham DM, Brenner MJ. COVID-19 survivorship: how otolaryngologist-head and neck surgeons can restore quality of life after critical illness. Am J Otolaryngol 2021; 42: 102917.
6) Whitcroft KL, Hummel T. Olfactory dysfunction in COVID-19: diagnosis and management. JAMA 2020; 323: 2512-2514.
7) Levy JM. Treatment recommendations for persistent smell and taste dysfunction following COVID-19--the coming deluge. JAMA Otolaryngol Head Neck Surg 2020; 146: 733.
8) Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. Rhinology 2017; 55: 17-26.
9) Ralli M, Di Stadio A, Greco A, de Vincentiis M, Polimeni A. Defining the burden of olfactory dysfunction in COVID-19 patients. Eur Rev Med Pharmacol Sci 2020; 24: 3440-3441.
10) Vaira LA, Salzano G, Fois AG, Piombino P, De Riu G. Potential pathogenesis of ageusia and anosmia in COVID-19 patients. Int Forum Allergy Rhinol 2020; 10: 1103-1104.
11) Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, Laue M, Schneider J, Brünink S, Greuel S, Lehmann M, Hassan O, Aschman T, Schumann E, Chua RL, Conrad C, Eils R, Stenzel W, Windgassen M, Rößler L, Goebel HH, Gelderblom HR, Martin H, Nitsche A, Schulz-Schaeffer WJ, Hakroush S, Winkler MS, Tampe B, Scheibe F, Körtvélyessy P, Reinhold D, Siegmund B, Kühl AA, Elezkurtaj S, Horst D, Oesterhelweg L, Tsokos M, Ingold-Heppner B, Stadelmann C, Drosten C, Cor-

man VM, Radbruch H, Heppner FL. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 2021; 24: 168-175.

12) Chiu A, Fischbein N, Wintermark M, Zaharchuk G, Yun PT, Zeineh M. COVID-19-induced anosmia associated with olfactory bulb atrophy. Neuroradiology 2021; 63: 147-148.

13) Laurendon T, Radulesco T, Mugnier J, Gérault M, Chagnaud C, El Ahmadi AA, Varoquaux A. Bilateral transient olfactory bulb edema during COVID-19-related anosmia. Neurology 2020; 95: 224-225.

14) Oleszkiewicz A, Schriever V.A, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol 2019; 276: 719-728.

15) Stoyanov GS, Petkova L, Dzhenkov DL, Sapundzhiev NR, Todorov I. Gross and histopathology of COVID-19 with first histology report of olfactory bulb changes. Cureus 2020; 12: e11912.

16) Lee MH, Perl DP, Nair G, Li W, Maric D, Murray H, Dodd SJ, Koretsky AP, Watts JA, Cheung V, Masliah E, Horkayne-Szakaly I, Jones R, Stram MN, Moncur J, Hefti M, Folkerth RD, Nath A. Microvascular injury in the brains of patients with Covid-19. N Engl J Med 2021; 384: 481-483.

17) Nabavi SF, Braidy N, Gortzi O, Sobarzo-Sanchez E, Daglia M, Skalicka-Woźniak K, Nabavi SM. Luteolin as an anti-inflammatory and neuroprotective agent: a brief review. Brain Res Bull 2015; 119: 1-11.

18) Skaper SD, Facci L, Giusti P. Glia and mast cells as targets for palmitoylethanolamide, an anti-inflammatory and neuroprotective lipid mediator. Mol Neurobiol 2013; 48: 340-352.

19) Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol 2016; 82: 932-942.

20) Muccioli GG, Stella N. Microglia produce and hydrolyze palmitoylethanolamide. Neuropharmacology 2008; 54: 16-22.

21) Guida F, Luongo L, Boccella S, Giordano ME, Romano R, Bellini G, Manzo I, Furiano A, Rizzo A, Imperatore R, Iannotti FA, D'Aniello E, Piscitelli F, Sca Rossi F, Cristino L, Di Marzo V, de Novellis V, Maione S. Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. Sci Rep 2017; 23: 375.

22) Pesce M, Seguella L, Cassarano S, Aurino L, Sanseverino W, Lu J, Corpetti C, Del Re A, Vincenzi M, Sarnelli G, Esposito G. Phytotherapics in COVID19: Why palmitoylethanolamide? Phytother Res 2020 Dec 9. doi: 10.1002/ptr.6978. Epub ahead of print.

23) Gigante A, Aquili A, Farinelli L, Caraffa A, Ronconi G, Enrica Gallenga C, Tetè G, Kritas SK, Conti P. Sodium chromo-glycate and palmitoylethanolamide: A possible strategy to treat mast cell-induced lung inflammation in COVID-19. Medical Hypotheses 2020; 143: 109856.

24) Yang Y, Tan X, Xu J, Wang T, Liang T, Xu X, Ma C, Xu Z, Wang W, Li H, Shen H, Li X, Dong W, Chen G. Luteolin alleviates neuroinflammation via downregulating the TLR4/TRAF6/NF-κB pathway after intracerebral hemorrhage. Biomed Pharmacother 2020; 126: 110044.

25) Aziz N, Kim MY, Cho JY. Anti-inflammatory effects of luteolin: a review of in vitro, in vivo, and in silico studies. J Ethnopharmacol 2018; 225: 342-358.