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SHORT COMMUNICATION

Preventing COVID-19 Infection by Complementary Medicine and Oral Health

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Abstract

It's possible that the mechanisms of natural phytotherapeutic remedies used in dental care can prevent the SARS-COV2 virus infection or minimize its clinical manifestations through the modulation of the immune system and counteract viral absorption at the cellular level.

Uncaria Tomentosa and Echinacea are plants with antiviral, antibacterial and immunomodulatory properties. Their main active components are alkaloids, glycosides, triterpenes, polysaccharides which favor immunological, anti-inflammatory, vulnerary activity.

Uncaria Tormetosa acts on a biochemical level as a competitor of the SARS-COV2 virus; Echinacea enhances and modulates the immune response and inhibits viral replication thanks to the flavonoid quercetin.

The use of natural substances could represent a considerable help in countering the coronavirus pandemic. Appropriate clinical studies are desirable to confirm what has been described.

Introduction

COVID-19 is a disease caused by the SARS-COV-2 virus which can lead to a severe acute respiratory coronavirus syndrome. Today's treatments exist [1-4] but, if not applied with criteria and speed, the coronavirus causes an acute respiratory distress syndrome followed by anemia, acute cardiac injury, and secondary infections [4] with a Fatality Rate of 1,4% [5].

The use of preventive protocols such as distancing, wear the mask and accurate hand hygiene has not prevented a global scaremongering [6-8]. Vaccines effectiveness against contagion was found null, protection against symptomatic infection with the omicron variant rapidly decreases over time after two doses [9-13].

Beyond the already existing allopathic therapies, natural preventive approaches can also be taken into consideration to prevent the disease [14,15].

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The coronaviruses, which include COVID 19, are opportunistic infections. Indeed, respiratory viruses infect the human upper respiratory tract, mostly causing mild disease. However, in vulnerable populations, such as neonates, infants, elderly people and immunocompromised individuals, these opportunistic pathogens can also affect the lower respiratory tract, causing more severe disease (e.g., pneumonia) [16].

Furthermore, COVID-19 has oral manifestations of relevant interest in 68% of cases: dysgeusia is the first recognized oral symptom, following ulcer, erosion, bullae, vesicles, pustules, fissured or depapillated tongue, macula, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most common sites of involvement in descending order were the tongue (38%), labial mucosa (26%) and palate (22%).

Oral lesions were nearly equal in both sexes (49% female and 51% male). Older patients with higher severity COVID-19 disease had more diffuse and separate oral lesions. Lack of oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and hyperinflammatory response secondary to COVID-19 are the most important predisposing factors for the occurrence of oral lesions [17].

There is sufficient evidence in literature to endorse an association between the presence of periodontal disease and the development and course of respiratory illnesses [18]. There are direct and indirect mechanisms that explain this relationship: from a direct aspiration of periodontal pathogens into the lungs, to the mucosal surfaces' modification by virulence factors and enzymes released by periodontopathogens that facilitate colonization; or the respiratory epithelium modification via cytokines to promote infection [19].

If periodontal disease is both reflective and deterministic of systemic health [20] some effective natural remedies known and used in the treatment and prevention of periodontitis could also provide valid help in the prevention of viral infections such as SARS-COV-2.

The increase of the immune system, in all its components, should be considered as a prevention of primary importance in the fight against the virus [21].

In this work, some relevant scientific literature concerning two well-known plants in complementary medicine are analyzed: Uncaria Tomentosa (*Uncaria T.*) also called Una de gato and Echinacea in its variants.

Discussion

To date, the literature about the interaction of the plant and its chemical components in relation to Covid-19 such as Allium sativum, Camellia sinensis, Zingiber, Nigella sativa, Echinacea spp. Hypericum perforatum, Glycyrrhiza glabra, Scutellaria baicalensis, led to the conclusion that these plants can enhance the immune response [22]. It appears that different types of terpenoids (active chemical components of plants) have promising effects in inhibiting viral replication. In addition, some alkaloid structures (also active chemical components of plants) have strong anti-coronavirus effects. Natural products can inhibit several coronavirus targets such as protein S (Spike protein: allows the virus to anchor itself to human cells via its receptor Angiotensin-converting enzyme 2 (ACE2)) and the replication of viral enzymes such as 3CLpro, PLpro [23] (3-Chymotrypsin-Like proteases and Papain-Like protease: they cleave cellular polyproteins as vital role in viral replication), Helicase [24] (initiates RNA unwinding and potentially contributes to other key functions during viral replication) and RdRp (nonstructural protein 12 RNA-dependent RNA polymerase: viral protein target for antiviral development) [25].

A brief literature analysis was conducted to collect some of the most recent scientific works regarding the specific use of *Uncaria T.* and Echinacea in the infection of COVID 19 due to their traditional ability to promote overall immune function and to reduce inflammation. These plants have therapeutic indications also in periodontal diseases. The effectiveness of Echinacea has been verified in gingivitis and periodontal disease in combination with sage, peppermint oil, menthol and chamomile [26] and it has been recently proposed as a mouthwash too [27].

Uncaria T. is an anti-inflammatory, antiresorptive, and potential bone anabolic product to be considered as a therapeutic alternative to control bone diseases like periodontitis [28] and to inhibit oral cavity microorganisms [29,30].

The search results are summarized in table 1.

It should be considered that periodontitis, independently of any other pathology, raises IL-6 the same one that is overproduced in COVID 19 disease [31].

Table 1: Articles selected for Uncaria T and Echinacea

	Authors	Year	Journal	Title	Mecanism of action	Conclusions
Uncaria Tormentosa	Anderson O. Ferreira , Hudson C. Polonini and Eli C. F. Dijkers	2020	Journal of Personalized Medicine	Postulated Adjuvant Therapeutic Strategies for COVID-19	Contributes to reduce the oxidative stress; one tetracyclic alkaloid of Uncaria tomentosa could have an effect on thrombosis, as it has been reported as a potent inhibitor of platelet aggregation and venous thrombosis. Is rich in oxindole alkaloids and polyphenols, including phenolic acids and proanthocyanidins (procyanidins, flavalignans, and propelargonidins), which show positive correlation with the antioxidant capacity. Uncaria tomentosa pentacyclic oxindole alkaloids stimulate endothelial cells to produce a lymphocyte-proliferation-regulating factor.	Can act on some of the referred mechanism of the COVID-19. Thus, it could provide a beneficial role in the prevention or improvement of the COVID-19-associated symptoms.
	Andres F. Yepes-Perez, Oscar Herrera-Calderon and Jorge Quintero-Saumeth	2020	JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS	Uncaria tomentosa (cat's claw): a promising herbal medicine against SARS-CoV-2/ACE-2 junction and SARS-CoV-2 spike protein based on molecular modeling	Potential association of constituents of cat's claw to the SARS-CoV-2 spike protein. This approach also could conduce to block the SARS-CoV-2 spike protein interaction with human receptor ACE-2.	26 constituents of U. tomentosa were docked on the binding interface of the RBD–ACE-2 and inside SARS-CoV-2 RBD spike protein of novel corona virus. U. tomentosa can be performed as an herbal supplement in the treatment of novel coronavirus disease (COVID-19).
	Andres F. Yepes-P´erez, Oscar Herrera-Calderon, Jos´e-Emilio S´anchez-Aparicio, Laura Tiessler-Sala, Jean-Didier Mar´echal and Wilson Cardona-G	2020	Evidence-Based Complementary and Alternative Medicine	Investigating Potential Inhibitory Effect of Uncaria tomentosa (Cat's Claw) against the Main Protease 3CLpro of SARS-CoV-2 by Molecular Modeling	Most of the proanthocyanidins of the Cat's claw extracts show the higher binding affinities to 3CLpro. The ethanolic extracts of Cat's claw, at least cadambine and speciophylline are predicted to present very good inhibition to the SARS-CoV-2 main protease. Because these components are found in the ethanolic extract of Cat's claw, it may position itself as possible therapeutic herbal for COVID-19.	Due to the remarkable presence of these compounds in the Cat's claw extracts, we believe that this in silico study at least points at Uncaria tomentosa as a whole as an interesting herb opening novel therapeutically horizons for COVID-19 treatment.
Echinacea	Shaden A.M. Khalifa, Nermeen Yosri, Mohamed F. El-Mallah, Reem Ghonaim et al.	2021 Rview	Phytomedicine	Screening for natural and derived bioactive compounds in preclinical and clinical studies: One of the frontlines of fighting the coronaviruses pandemic	Shows significant effect via inhibition of the 3CLpro enzyme. Potent activity against HCoV-229E, SARS-CoV and MERS-CoV with IC50 values of 3.2, 50 and 50 µg/ml respectively.	

	Susana A. Llivisaca-Contreras , Jaime Naranjo-Morán, Andrea Pino-Acosta et al.	2021	Molecules	Plants and Natural Products with Activity against Various Types of Coronaviruses: A Review with Focus on SARS-CoV-2.	Active Principles: Caphtharic acid, cichoric acid and echinacoside. Antiviral activity: MERS-CoV, 229E/ The extract non-specifically and irreversibly interferes with viral docking receptors (eg, influenza) to block infectivity of pathogens. Echinacea purpurea howed dosedependent inhibition of 229E infectivity in respiratory epithelial cells and this extract irreversibly inactivated the virus. Its multicomponent extract non specifically and irreversibly interfered with viral docking receptors to block the infectivity of pathogens. Echinacea has also been proposed as a suppressor of the immunoinflammatory cascades observed in COVID-19, thanks to the plant's ability to activate the anti-inflammatory cannabinoid-2 (CB2) receptors and peroxisome proliferatoractivated receptors gamma (PPAR)	Combining E. purpurea with vitamin D, vitamin C, and zinc has been suggested to reduce the risk of infection and death from SARS-CoV-2
	Motahareh Boozari and Hossein Hosseinzadeh	2020	Phytotherapy Research	Natural products for COVID-19 prevention and treatment regarding to previous coronavirus infections and novel studies	Can inhibit different coronavirus targets such as S protein (emodin, baicalin) and viral enzymes replication such as 3CLpro (Iguesterin)	Can improve the immune response and useful for COVID-19 prevention

Between periodontitis and COVID-19 disease there is the same high expression of ACE-2 and CD147 (also known as extracellular MMP inducer. In periodontitis it has been indicated that regulate the collagenolytic balance [32]) and the similar overexpression of several cytokines [33].

Since the past centuries *Uncaria T.*, also called cat's claw, is a plant considered immunomodulatory by the Curanderos in the South American continent. Many scientific studies confirmed a lot of properties of this phytocomplex [34,35]. Its main components are pentacyclic oxindole alkaloids, glycosides of quinovic acid, polyhydroxylated triterpenes, tannins. The main activity of the drug has been defined as antiphlogistic, immunomodulatory, antiviral.

The antiphlogistic activity seems to be carried out mainly by quinovic acid adjuvanted by alkaloids and procyanidins [36], consequentially Cat's claw inhibits the production of proinflammatory cytokines such as TNF-alpha [37,38].

The ability of its alkaloids to fight the Dengue Virus is recognized [39] as well as the antiviral capabilities [40,41]. Mechanisms of the antiviral activity of the hydroalcoholic extract of *Uncaria T.* have been elucidated: its alkaloids (pentacyclic alkaloids) induced apoptosis of infected cells and reduced inflammatory mediators such as TNF-α and IFN-α with similar effects to dexamethasone [39] and herpes simplex virus type 1 (HSV-1) [42]. It has recently been demonstrated in an in vitro study that *Uncaria T.* possesses the anti-HIV property [43].

Disease-active periodontitis contains high loads of reactivated herpesviruses and tends to be associated with latent herpesviruses and with high-titer cytomegalovirus IgG serum antibody [44], that explains the *Uncaria T.*' use in medicine and oral diseases especially by gels or mouthwashes [45]. Lima, et al. [28] demonstrated that administration of *Uncaria T.* extract reduce inflammatory-induced bone loss in periodontitis animal model by means of direct effect on osteoclastogenesis. It not only acts as an antiresorptive agent by inhibiting osteoclasts formation but also osteoclasts function by blocking the expression of Cathepsin K [28] (enzyme that efficiently cleaves type I collagen at the triple helical regions at pH values between 4.5 and 6.6).

Uncaria T. is mentioned in a recent review [46] where twelve therapeutic agents are discussed, they could play a role in the prophylaxis and amelioration symptoms associated with COVID-19 (as adjunctive substances). In this article specific anti-inflammatory capacities are attributed to *Uncaria T.* in the improvement of symptoms. The initial disease stage occurs at the time of viral inoculation and incubation with symptoms typically nonspecific (e.g., cough, fever, diarrhea). Just before this phase, the strengthening of the immune defenses should be concentrated. The authors advise 800 mg/day in order to inhibits the release of cytokines (IL-, IL-6, IL-8, and TNF-), chemokines (CCL2, CCL3, and CCL5) and the expression of NF-kβ inflammatory enzymes (COX-1, COX-2, PLA2, iNOS) [47,48].

Yepes-Pérez et al. [49] based research on the virus-cell receptor coupling relationship. The SARS-COV-2 "hooks" the target cell through the spike protein, which binds to the specific receptor ACE -2. Structural bioinformatics approaches identified several bioactive compounds of *Uncaria T.* with potential therapeutic effect by double strong interaction with the interface of RBD-ACE-2 and ACE-2 binding site on the viral spike of SARS-CoV-2 RBD.

The same author publishes a multilevel computational study [50] to evaluate the potential antiviral properties of components of the medicinal herb, focusing on the inhibition of the 3CLpro protease, which is an essential enzyme of SARS-CoV-2, which plays a key role in viral replication and transcription within the cell. The results suggest the potential efficacy of *Uncaria T.* as a complementary and/or alternative medicine for the treatment of COVID-19.

Main components of Echinacea are alkylamides, alkaloids, polyphenolic compounds, flavonoid glucosides, glycoproteins, essential oils, polyins, polysaccharides and other minor components that are part of the phytocomplex such as betaines, triterpenes, sesquiterpenes, inulin. The main activity of the drug has been defined immunological, anti-inflammatory, and vulnerary [51,52].

Clinical studies have shown that the administration of arabinogalactans (polysaccharide components of Echinacea) favors the increase of lymphocytes, the phagocytic activity of macrophages, enhancing any immune response against bacterial, viral, or other external agents [53].

Echinacea extracts stimulate the immune system and bioavailable alkamides are key players by interacting with immunomodulatory cannabinoid receptors [54].

The most present molecule in Echinacea is Quercetin, the major polyphenolic flavonoid found in various vegetables and fruits, such as berries, lovage, capers, cilantro, dill, apples, and onions [55]. Quercetin is one of the most important plant molecules, showing pharmacological activity such as antiviral, anti-atopic, pro-metabolic, and anti-inflammatory effects. Smith and Smith [56] demonstrated for quercetin a theoretical, but significant, capability to interfere with SARS-CoV-2 replication as it was identified as ligands for the S protein: ACE2 receptor interface. The quercetin dose-dependently anti-inflammatory properties decrease the mRNA and protein levels of ICAM-1(a cell surface glycoprotein expressed at a low basal level in immune, endothelial and epithelial cells, but is up-regulated in response to inflammatory stimulation [57]), IL-6, IL-8, and MCP-1 (Monocyte chemoattractant protein-1) [58]; this mechanism favors the prevention of strong inflammatory cascade triggered during SARS-CoV-2 infection, but also the periodontal overproduction of proinflammatory cytokines and matrix metalloproteinases.

Extensive scientific literature describes the potential antiviral role of quercetin administered at very high dosages (1,000 mg/dose) for 12 weeks reducing the days of illness in middle-aged and elderly subjects [59].

A recent study [60] indicates Echinacea as a bioactive substance against SARS-COV-2 infection.

It shows significant effects via inhibition of the 3CLpro enzyme. The plant has a potent activity against HCoV-229E, SARS-CoV and MERS-CoV with IC50 values of 3.2, 50 and 50 µg/ml respectively.

Flavonoids stand out among the blockers of the ACE2 receptor, but they have also shown anti-replication activities; the inactivation of the viral particles is an effect of Echinacea: the multicomponent extract non-specifically and irreversibly interfere with viral docking receptors to block the infectivity of pathogens and combining with vitamin D, vitamin C, and zinc has been suggested to reduce the risk of infection and death from SARS-CoV-2 [61,62].

Conclusion

There are natural substances capable of increasing the immune system, nature provides a huge reservoir of anti-infective compounds [54]. The *Uncaria T.*

and Echinacea's immunomodulatory properties, combined with the non-toxicity of these plants, make it advisable to spread the use of these elements of complementary medicine.

Between Periodontitis and SARS-COV-2 infection there are some similar mechanisms which makes the hypothesis of etiopathogenetic correlations plausible [20,31]. Periodontitis has been shown to be a risk factor for: cardiovascular disease, diabetes mellitus, respiratory disease, rheumatoid arthritis and other conditions [63]. Periodontopathic bacteria were found in the bronchoalveolar lavage fluid of patients suffering from pneumonia and the association of periodontitis and diabetes could multiply the risk of pneumonia even in the absence of the SARS-CoV-2 infection [31]. SARS-COV-2 is a respiratory virus that mainly affects the middle-aged and elderly, as well as people with underlying diseases such as hypertension, diabetes, obesity or with heart and kidney problems.

Another similarity is represented by the fact that periodontitis has an excellent prognosis if intercepted early but can cause severe damage to the dentition with delay in therapy; the same pathogenetic mechanism develops for the SARS-COV-2 infection.

Considering the studies, an analysis of the risk of periodontitis cross-referenced with the presence of systemic noncommunicable diseases and with the risk to develop COVID-19 disease or other coronavirus diseases, might suggest the use of natural preventive approaches to help the body to a correct immune-inflammatory response in the fight against both diseases.

Certainly, more basic and clinical investigations into this issue are necessary for effective therapeutic approaches.

Conflict of Interest

Authors declare that there is no financial interest or conflict of interest.

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