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REVIEW ARTICLE

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Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue

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Abstract

COVID-19 leads to severe respiratory problems, but also to long-COVID syndrome associated primarily with cognitive dysfunction and fatigue. Long-COVID syndrome symptoms, especially brain fog, are similar to those experienced by patients undertaking or following chemotherapy for cancer (chemofog or chemobrain), as well in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) or mast cell activation syndrome (MCAS). The pathogenesis of brain fog in these illnesses is presently unknown but may involve neuroinflammation via mast cells stimulated by pathogenic and stress stimuli to release mediators that activate microglia and lead to inflammation in the hypothalamus. These processes could be mitigated by phytosomal formulation (in olive pomace oil) of the natural flavonoid luteolin.

KEYWORDS

brain fog, chemotherapy, coronavirus, COVID-19, cytokines, fatigue, inflammation, mast cells, microglia

1 | INTRODUCTION

Infection with the recent coronavirus (severe acute respiratory syndrome [SARS]-CoV-2) leads to COVID-19, the severity of which derives from the host's inflammatory response that involves release of a storm of pro-inflammatory cytokines,[1–7] especially interleukin-6 (IL-6),[8–11] but also IL-1.[12,13]

Even though symptoms associated with SARS-CoV-2 infection in children are mild, a number of recent publications reported a multisystem inflammatory syndrome (MIA-C) in older children[14–16] and adolescents,[17] often presenting with symptoms reminiscent of Kawasaki disease.[16] Symptoms in MIA-C typically occur 4–6 weeks after infection and the disease is characterized by elevated markers of inflammation[18] and the presence of multiple autoantibodies.[18] A similar disease in adults,

Abbreviations: AD, Alzheimer's disease; ACE2, angiotensin converting enzyme 2; BBB, blood–brain barrier; CNS, central nervous system; CRH, corticotropin-releasing hormone; DAMPs, damage-associated molecular patterns; HPA, hypothalamic–pituitary–adrenal; MCAS, mast cell activation syndrome; MCI, mild cognitive impairment; mtDNA, mitochondrial DNA; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; PAMPs, pathogen-associated molecular patterns; PAF, platelet activating factor; SP, substance P; SM, systemic mastocytosis; TLCOVID-19, toll-like receptor.

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named multisystem inflammatory syndrome (MIA-A) has been recognized by the Center for Disease Control (CDC, USA) (https://www.cdc.gov/mis-c/). In fact, autoimmune and inflammatory diseases are now increasingly identified following COVID-19.[19] The etiology of MIA remains unknown.

Cytokine storms have also been implicated in a variety of "mystery" diseases.[20] One such disease affects COVID-19 survivors and is associated with severe fatigue and neuropsychiatric symptoms (https://www.health.harvard.edu/blog/the-tragedy-of-the-post-covid-long-haulers-2020101521173), especially impairment in cognitive functions known as "brain fog" (https://www.nytimes.com/2020/10/11/health/covid-survivors.html). Such patients have been called "long-haulers" (https://directorsblog.nih.gov/tag/post-covid-syndrome/) and the illness has been termed "long-COVID syndrome" (https://directorsblog.nih.gov/2021/01/19/trying-to-make-sense-of-long-covid-syndrome/). In fact, the National Institutes of Health (NIH, USA) recently devoted a 2-day conference on the epidemiology and pathophysiology of this illness (https://www.niaid.nih.gov/news-events/workshop-post-acute-sequelae-covid-19). Other names used for this illness include "chronic COVID syndrome," "post-COVID syndrome," or "long haulers COVID syndrome."[21]

In addition to the severe respiratory and inflammatory problems discussed above, infection with SARS-CoV-2 can also contribute to neurological[22–25] and mental[26–30] disorders. For this reason, NIH held an 1-day workshop on the effect of COVID-19 on the central nervous system (CNS) (https://www.ncbi.nlm.nih.gov/search/research-news/11277/) and recently launched a database to track neurological symptoms associated with COVID-19 (https://www.nih.gov/news-events/news-releases/nih-launches-database-track-neurological-symptoms-associated-covid-19). The importance of the effects of COVID-19 on the brain is highlighted by the blog recently posted by the NIH Director on this subject (https://directorsblog.nih.gov/2021/01/14/taking-a-closer-look-at-the-effects-of-covid-19-on-the-brain/).

However, few scientific publication has so far discussed long-COVID syndrome (https://www.nytimes.com/2021/01/21/magazine/covid-aftereffects.html) such as the one that reported the presence of persistent fatigue apparently independent of the severity of the initial symptoms.[31] Symptoms experienced by long-COVID syndrome patients (Table 1) are very similar[32] to those present in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),[33,34] mast cell activation syndrome (MCAS),[35,36] or systemic mastocytosis (SM)[37] in whom the unique tissue immune cells, mast cells, are stimulated by environmental, pathogenic, and stress stimuli. Moreover, IL-6 has not only been implicated in COVID-19[8,12] but was also elevated in ME/CFS[38] and SM.[39–41] To make matters worse, IL-6 promotes an increase in number of mast cells.[42]

TABLE 1 Symptoms present in long-COVID syndrome

- Angioedema
- **Brain fog**
- Confusion
- **Difficulty multitasking**
- Dizziness
- Dysautonomia
- **Fatigue**
- Gastrointestinal complaints
- Headache
- Hypotension
- Insomnia
- **Irritability**
- Lightheadedness (syncope)
- **Inability to find the right words**
- **Memory loss**
- Myalgias
- Palpitations
- Shortness of breath
- **Weakness**

Note: The symptoms listed, especially those bolded, are experienced, by many long-COVID syndrome patients and also patients undergoing or after having been administered chemotherapy.

2 | CHEMOTHERAPY

Patients undergoing chemotherapy are susceptible to infection with COVID-19.[43]

Moreover, more than 50% of patients on or following chemotherapy develop symptoms similar to those described above for long-COVID syndrome (Table 1), especially cognitive dysfunction,[44–47] a condition that has been termed "chemofog"[48,49] or "chemobrain,"[50–54] and has been associated with distinct neuroimaging findings.[55,56] A number of drugs have been implicated in "chemobrain" (Table 2) most notably doxorubicin,[57–59] methotrexate,[60,61] lenalidomide,[62] rituximab,[62] and trastuzamab.[63]

There have been intense efforts to understand the biochemical[64] or cellular[44,65,66] mechanisms responsible for chemobrain. These have included disrupted neurogenesis,[67] aberrant myelination,[6869] interference with prefrontal activity,[70] but most importantly neuroinflammation[66] with cytokine dysregulation.[69,71]

3 | INFLAMMATION OF THE BRAIN

Microglia have important functions in the CNS,[72] especially with respect to neuroinflammation[72–74] and neurodegenerative[75–77] diseases. Microglia express Toll-like receptors (TLRs),[78] activated by damage-associated molecular patterns (DAMPs) and were recently implicated in COVID-19.[79,80] COVID-19 can also affect the hypothalamic–pituitary–adrenal (HPA) axis,[81] which is typically activated by stress and can further affect the emotional state of individuals affected by COVID-19.[82,83] Microglia also express receptors for corticotropin-releasing hormone (CRH)[84] and could be further activated by stress, especially associated with COVID-19.[85]

Microglia interact with the unique immune cells, mast cells, in the brain[86] leading to their activation[87] and neuroinflammation.[88] Activation of mast cells[89,90] and microglia[91] in the hypothalamus[33] could lead to cognitive dysfunction[92] commonly also seen in patients with MCAS[93,94] (Figure 1). Psychological stress has pro-inflammatory effects[82,95] via stimulation of mast cells,[83] especially by CRH[96] leading to increased vascular permeability.[83] This process also leads to disruption of the blood–brain barrier (BBB),[97,98] via release of IL-6[99] and CRH,[100] further exacerbating brain inflammation by permitting the entry into the brain of more viral particles, cytokines, or other toxic substances (Table 1). A recent NIH study reported blood vessel damage and inflammation, but no infection, in brains of patients with COVID-19.[101] (https://www.nih.gov/news-events/news-releases/nih-study-uncovers-blood-vessel-damage-inflammation-

TABLE 2 Chemotherapeutic agents implicated in chemofog

• **Bleomycin**
• Carboplatin
• Cis-platin
• Cyclophosphamide
• Cytarabine
• **Doxetaxel**
• **Doxorubicin**
• Lenalidomide
• **Methotrexate**
• **Taxol**
• Trastuzumab

Note: The drugs listed, especially those bolded, have been reported to induce "chemofog" or "chemobrain".

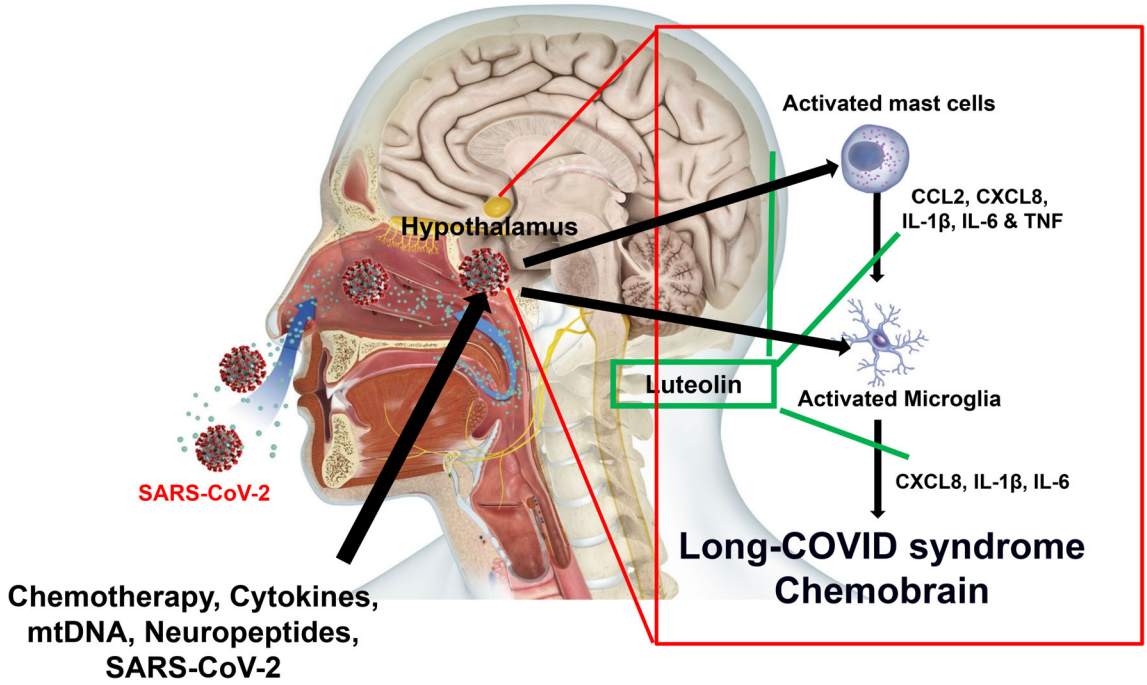

FIGURE 1 Diagrammatic representation of how SARS-CoV-2 could stimulate mast cells and microglia in the hypothalamus, inhibited by luteolin. SARS-CoV-2 could enter the brain via the olfactory nerve tract reaching the hypothalamus where it could activate brain mast cells and microglia to release pro-inflammatory molecules, thus contributing to brain inflammation and brain fog. The effect of SARS-CoV-2 could be exaggerated by chemotherapy, as well as cytokines and mtDNA, or neuropeptides released under stress (thunderbolt). These processed could contribute to the pathogenesis and symptoms of long-COVID syndrome and "chomobrain" and could be prevented by the flavonoid luteolin

covid-19-patients-brains-noinfection#:~:text=In%20an%20in%2Ddepth%20study,shortly%20after%20contracting%20the%20disease.) These findings may explain the recent comprehensive reports of significantly increased neurologic[102] and psychiatric[103] disorders in COVID-19 patients, as well as in long-COVID syndrome patients.[104]

Mast cells are ubiquitous in the body[37] and are critical for allergic diseases,[105] but also inflammation.[106] Mast cells are also present in the brain, especially in the median eminence of the hypothalamus, where they are located perivascularly close to nerve endings positive for CRH.[107] Mast cells are also triggered by viruses[108] including SARS-CoV-2.[109,110] A recent publication using normal oral cavity mucosa reported no gene expression of the SARS-CoV-2 receptor, angiotensin converting enzyme 2 (ACE2) in mast cells.[111] However, mast cells are "plastic" and their surface receptors can be induced by a variety of conditions. For instance, we reported that the neuropeptides neurotensin[112] and substance P (SP)[113] can induce CRHR-1. Moreover, SP can induce the ST2 receptor for IL-33.[114] In fact, ACE2 gene expression was recently shown to be induced by interferon,[115] and mast cells can elicit strong pro-inflammatory and type I interferon responses in response to viruses,[116] implying an autocrine action on ACE2 expression. Of course, it remains to be seen to what extent pulmonary and/or brain mast cells from deceased COVID-19 patients express ACE2.

Following stimulation, mast cells release pro-inflammatory mediators[117] such as histamine, tryptase, chemokines (e.g., CCL2, CCXL8)[118] and cytokines (IL-6,[119] IL-1β ,[120] and tumor necrosis factor [TNF][114]), especially when primed by IL-33.[121,122] Histamine can stimulate macrophages to release IL-1,[123] which stimulates mast cells to release IL-6.[119] Mast cells can also secrete mitochondrial DNA (mtDNA),[124] which was recently reported to be increased in the serum of COVID-19 patients and correlated with disease severity.[125] Extracellular mtDNA serves as an alarmin and stimulates pro-inflammatory mediator secretion from immune cells.[126,127] Moreover, mast cells synthesize and release platelet activating factor (PAF), which has been implicated in the inflammation[128] and microthromboses[129] characterizing COVID-19.

4 | TREATMENT APPROACHES

Unfortunately, there are no clinically effective interventions for long-COVID syndrome[1,130] or brain fog associated with either chemobrain, ME/CFS,[131] or MCAS.[36] It is also hard to decide whether it would be best to stimulate or suppress the immune system,[132,133] since antibody production and T cells appear to be protective, while pro-inflammatory cytokines are destructive.[1,134,135] A reasonable approach especially for brain fog associated with long-COVID syndrome, ME/CFS, MCAS, and chemotherapy-induced "chemobrain" would be inhibition of mast cell-associated neuroinflammation.

Even though inhibition of mast cells could be beneficial in COVID-19 or long-COVID syndrome,[38] there are no effective mast cell inhibitors.[136] Instead, mast cells could be inhibited with the structurally related natural flavonoids luteolin and quercetin,[137–141] which are readily available and are generally considered safe[142–146] (Figure 1). Both flavonoids have broad anti-viral properties, inhibit entry of the virus into host cells,[108,147,148] inhibit neuroinflammation,[149] and reduce cognitive decline.[150] Furthermore, luteolin better penetrates into the brain, inhibits both microglia[151,152] and mast cells,[153,154] and has been reported to reduce neuroinflammation[145,155,156] and cognitive dysfunction,[157,158] including Alzheimer's disease in humans[159,160] and in animal models.[161]

Luteolin and quercetin are difficult to absorb after oral administration,[162] but their pharmacokinetics are greatly improved in liposomal preparations using olive pomace oil.[163] In fact, a luteolin formulation in olive pomace oil (NeuroProtek®) has been used effectively for improving autism spectrum disorder,[144,164] while another one (BrainGain®) reduced brain fog.[157] These liposomal formulations not only improve oral absorption and bioavailability but also provide the additional neuroprotective[165–170] and anti-inflammatory[171,172] actions of

TABLE 3 Important facts and outstanding issues concerning long-COVID syndrome

- Long-COVID syndrome is a serious concern
- Symptoms of long-COVID syndrome are similar to those present in ME/CFS, MCAS and during or after chemotherapy
- The most vexing symptoms are chronic physical and mental fatigue (brain fog)
- The mechanism underlying these symptoms is presently not known
- Stress-related neuropeptides and interferons could induce ACE2 expression on mast cells and microglia
- Stimulation of hypothalamic mast cells and microglia by SARS-CoV-2 could lead to release of pro-inflammatory mediators
- Focal inflammation of the brain may be prevented/reduced by appropriate liposomal luteolin formulations

Abbreviations: ACE2, angiotensin converting enzyme 2; MCAS, mast cell activation syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome.

olive pomace oil polyphenols, as well as the increase in memory provided by the olive hydroxytyrosol[169,173] present in BrainGain®.

However, one should be aware of the fact that luteolin is now present in numerous dietary supplements with misleading names (e.g., "luteolin complex") and wide variations in the source, content, and purity (often not disclosed at all) of luteolin.[163]

5 | CONCLUSION

The number of COVID-19 cases may turn out to be fewer and the associated burden to the health system more by the long-COVID syndrome.[174] Obviously, there are many outstanding issues to be investigated (Table 3). In the meantime, the brain fog associated with long-COVID syndrome and use of chemotherapy may be prevented/reduced with appropriate luteolin formulations.

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AUTHOR CONTRIBUTIONS

Theoharis C. Theoharides conceived the concept, critically reviewed the literature and wrote the manuscript. Christos Cholevas and Konstantinos Polyzoidis assisted with the review of the literature.

CONFLICT OF INTEREST

Theoharis C. Theoharides is the Scientific Director of and shareholder in Algonot, LLC (Sarasota, FL), which develops and markets flavonoid-containing dietary supplements. He is also the recipient of US Patent No. 8,268,365, "Anti-inflammatory compositions for treating brain inflammation." The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

No data.

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