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Could St John's Wort have a protective effect on Brain Injury caused by COVID-19?

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Abstract : There are no organs that are not affected by SARS-CoV-2, known as COVID-19, which is the most critical health problem for last one and a half years. Angiotensin-Converting Enzyme-2 (ACE-2) and transmembrane protease serine 2 (TMPRSS2), which are responsible for virus invasion, are also secreted in the brain. Therefore, it suggests that this virus may invade brain tissues. The studies and clinical findings revealed that the virus could penetrate the brain tissues to an undeniable extent and cause neurodegeneration with inflammation-mediated cell death due to cytokine storm. Anti-oxidant and anti-inflammatory properties of the compounds extracted from St John's Wort (SJW) are used in the treatment of depression. Besides, SJW has a protective effect on neurodegenerative diseases such as schizophrenia and anxiety, as well as depression. Increasing the enzymatic and non-enzymatic antioxidants plays a vital role in the anti-oxidant properties of this drug. In its anti-inflammatory feature, it is effective by suppressing various inflammatory pathways. In additional studies, its antiviral activity is also mentioned. Therefore, in light of these findings, we think that SJW's both regulating neurotransmitter levels and preventing inflammation-mediated apoptosis with its antioxidant and anti-inflammatory properties can reduce the brain damage that may occur during COVID-19.

Keywords -Brain injury, COVID-19, Neurodegeneration, SARS-CoV-2, St John's Wort

I. BACKGROUND

There are no organs that are not affected by SARS-CoV-2, caused COVID-19, which emerged in December 2019. Although the virus affects the lungs at first, the presence of the Angiotensin-Converting Enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) enzymes responsible for the invasion in the endothelial cells, and glia in the brain indicate that it will be affected by COVID-19[1]. It has been reported there is a link between the SARS-CoV-2 in the cerebrospinal fluid is present the fatigue and headache that occurs in the early period of COVID-19 and the impairment of consciousness that occurs in the late period of the disease[1,2].

II. ACE-2 and COVID-19

In particular, the decrease in post-replication levels of ACE-2 enzyme, which is responsible for the invasion of the virus, increases the activation of NADPH oxidase, which is responsible for the formation of free oxygen radicals, and the activation of the ACE1 enzyme, which is responsible for the stimulation of inflammatory pathways[3]. Thus, the level of enzymes such as antioxidant glutathione peroxidase(GPx), superoxide dismutase(SOD), and catalase(CAT) decreases, the level of free oxygen radicals increases and the oxidant / antioxidant balance is disturbed. Besides, cytokine levels such astumour necrosis factor-alpha (TNF-α), interleukins(IL-1β, IL-6, -7, -8 and -17), interferon-gamma (INF-γ), are increased during COVID-19. These increased cytokines may contribute to both acute lung injury and neurotoxicity[4–6].

III. ST. JOHN'S WORT

Traditionally, St John's Wort (SJW) is used for the i) treatment of many disease states such as nerve pain, malaria, viral and antibacterial infections in the world thanks to its flavonoid, bioflavonoid, phloroglucinol compounds, ii) topically for wounds, burns, insect bites and iii) internally as a sedative, anxiolytic and

antidepressant.In preclinical studies using rodents, besides its antischizophrenic, anticonvulsant and analgesic effects, beneficial effects have been demonstrated with the addictive behaviour models[7,8]. Besides, SJW is used as an antioxidant and anti-inflammatory agent and for stress reduction, immune system booster, and menopausal symptoms[9]. It demonstrates by regulating the activity of neurotransmitters such as serotonin, dopamine, noradrenaline, gamma-aminobutyric acid (GABA), and L-glutamate[10].

St John's Wort has an antibacterial effect against gram-positive and negative bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Corynebacterium diphtheriae* and *Pseudomonas aeruginosa*. It also has antiviral effects against viruses such as infectious bronchitis viruses and HIV[11–15].

St John's Wort achieves its neuroprotective effect by regulating the oxidant/antioxidant balance. It shows its protective effect by suppressing reactive oxygen and reactive nitrogen species that may occur, especially during viral infection and trauma. In this effect, it achieves both enzymatic levels such as GPx, CAT, SOD, and non-enzymatic antioxidant levels such as α-tocopherol, carotenoids, and ubiquinone10, glutathione, histone-peptides, dihydrolipoic acid, melatonin, uric acid, and ascorbic acid[16]. This effect of SJW is provided by both enzymatic levels such as glutathione peroxidase, catalase, superoxide dismutase, and non-enzymatic antioxidant levels such as α-tocopherol, carotenoids and ubiquinone10 glutathione, histone-peptides, dihydrolipoic acid, melatonin, uric acid and ascorbic acid. It has also been shown to reduce the level of inflammatory mediators with its enzyme induction feature[17]. In additional studies, it has been shown that SJW extracts inhibit interferon IFN-γ-induced STAT-1 and NF-kB activation. It has also been found that they slow down apoptosis by reducing the activations of IL-1β and TNF-α responsible for inflammation-mediated neural apoptosis, and thus have a neuroprotective effect[17–20].

IV. CONCLUSION

In conclusion, it has been found that it causes inflammation in brain tissue, such as encephalitis and meningitis, in a certain population infected with COVID-19. Disruption of the blood-brain barrier by the increased cytokine expression plays an important role in the formation of this damage. SJW, which is used as an antidepressant in the clinic, has also been shown to have antimicrobial, antioxidant and anti-inflammatory properties thanks to the compounds present in its content.Therefore, we think that SJW 'can reduce the brain damage that may occur by preventing the cytokine storm that may occur during COVID-19 and by providing neuromediator regulation. Besides, when its enzyme induction feature is known, we believe that it can contribute to the treatment by reducing the adverse effects of the drugs used in routine treatment.

Author Contribution Statement

All authors have equally contributed to the study.

Conflict of interest

The authors have no conflicts of interest to declare.

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