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Research International Journal of Endocrinology and Diabetes

Mini Review

Effects of Quadruple Therapy: Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected with COVID-19

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Received: 01 August 2020; **Accepted:** 28 August 2020; **Published:** 29 August 2020

Citation of this article: Ahmed AK, Albalawi YS, Shora HA, Abdelseed HK, Al-Kattan AN (2020) Effects of Quadruple Therapy: Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected with COVID-19. Rea Int J of End and Diabe. 1(1): 018-021. DOI: 10.37179/rijed.000005.

ABSTRACT

COVID-19 emerged in Wuhan, China in December 2019, reached epidemic proportions and spread globally as a serious life-threatening pandemic. SARS- Cov-2 is the causative virus that causes severe acute respiratory distress, pneumonia, respiratory failure, and septic shock leading to increased mortality. High risk patients include those with chronic non-communicable diseases such as diabetes, hypertension, coronary heart disease and cancers. No specific treatment is available and supportive care all that could be done to rescue patients. Quadriple therapy consisting of Zinc, Quercetin, Bromelain and Vitamin C showed promising results in improving clinical outcome among COVID-19 patients.

Keywords: COVID-19, Cytokines, zinc, Quercetin, Bromelain, Vitamin C.

Introduction

A novel infectious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), was detected in Wuhan, China, in December 2019. The disease (COVID-19) spread rapidly, reaching epidemic proportions in China, and 27 other countries. No specific therapeutics are available, and current management includes travel restrictions, patient isolation, and supportive medical care. There are several pharmaceuticals already being tested [1].

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease that can lead to respiratory failure and death. Patients with chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, would be anticipated to have an increased risk of infection and a more severe disease [2].

The pathogen, a novel coronavirus (SARS-CoV-2), was identified by local hospitals using a surveillance mechanism for "pneumonia of unknown etiology" that was established in the wake of the 2003 SARS outbreak with the aim of allowing timely identification of novel pathogens [3].

The immune system plays a critical role in protecting the human body from infectious diseases [4]. T-cell counts are reduced significantly in COVID-19 patients, and the surviving T-cells appear functionally exhausted. Non-ICU patients with total T cells counts lower than 800/μ L may still require urgent intervention, even in the immediate absence of more severe symptoms due to a high risk for further deterioration in condition [5]. Further research on the severity of comorbidities and all medication received by the patients is mandatory to shed light on these associations [2] (Figure 1).

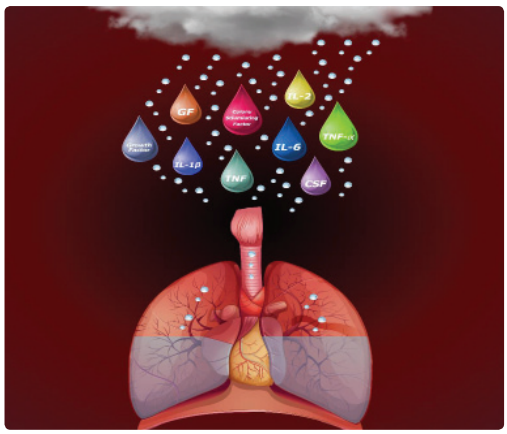

Figure 1: Cytokine storm.

Discussion

The role of Zinc:

Since the discovery of the first reported case with zinc-deficiency in Iran by Prasad et al. in 1961 [6], we have learned a lot about Zinc, and we have much more left to learn. Zinc is the second most abundant common trace mineral in the human body, with vital biological functions from cell growth and development to cell homeostasis and immune response [7].

Mechanical ventilation is a necessary intervention to support patients with lung injury and the acute respiratory distress syndrome (ARDS) but can also exacerbate injury through mechanical stress-activated signaling pathways. It is showed that stretch applied to cultured human lung cells, and to mouse lungs in vivo, induces robust expression of metallothionein, a potent antioxidant and cyto-protective molecule critical for cellular zinc homeostasis. Furthermore, genetic deficiency of murine metallothionein genes exacerbated lung injury caused by injurious mechanical ventilation, identifying an adaptive role for these genes in limiting lung injury.

Stretch induction of metallothionein required zinc and the zinc binding transcription factor MTF-1. We further show that dietary zinc-deficiency in mice potentiates ventilator-induced lung injury, and that plasma zinc levels were significantly reduced in human patients with ARDS compared to healthy and non-ARDS ICU controls [8].

Vit c

Vitamin C exerts its antiviral properties by supporting lymphocyte activity, increasing interferon-α production, modulating cytokines, reducing inflammation, improving endothelial dysfunction, and restoring mitochondrial function [9].

There are also suggestions that vitamin C may be directly viricidal. The in vitro effects constitute a reflection of both the supra-physiological concentrations of ascorbate and the interaction between vitamin C and metal-containing culture media—both of which are pro-oxidant, generating reactive oxygen species [10].

Quercetin (Que)

Quercetin (Que), (also known as 3,3',4'5,7-pentahydroxyflavone), is a widely distributed plant flavonoid, found in several vegetables, leaves, seeds, and grains, where it is conjugated with residual sugars to form Que glycosides. Studies suggest that Que supplementation may promote antioxidant, anti-inflammatory, antiviral, and immunoprotective effects. Quercetin has been studied in various types and models of viral infection due to its promising antiviral effects in inhibiting polymerases, proteases, reverse transcriptase, suppressing DNA gyrase, and binding viral capsid proteins [11].

Recently, Que has been shown to inhibit in vitro production of cyclooxygenase (COX) and lipoxygenase (LOX) which are typically induced by inflammation. The anti-inflammatory effect has been supported by in vivo experiments as well. Examples of Que's inhibitory qualities include the significant blocking of pro inflammatory cytokines in cultured fibroblasts. 10 μM Que down regulated the production of COX-2, the Nuclear Factor kappa B (NF-κB), and NO. 10–25 μM Que inhibited the level of NO and TNF-α.

Other properties of 50 and 100 μM Que include reducing the secretion of IL6 and TNF-α in LPS-stimulated RAW 264.7 microphages, while at 25 and 50 μM it proved to be the most efficient blocker of TNF-α secretion in macrophages. Finally, at low concentrations, Que (less than 50 μM) also stimulated anti-inflammatory cytokine IL-10. Similarly, 25μM Que blocked IL-1β, IL-6, IFN-γ, and TNF-α secretion in human whole blood induced by LPS [12].

Quercetin can also inhibit pro inflammatory cytokines. A six-week regiment of 150 milligrams of Que taken daily by human subjects significantly lowered cytokine TNF-α serum concentrations [12]. Quercetin effectively inhibited LPS-induced DC activation by reducing the production of proinflammatory cytokines/chemokines and the expression levels of MHC class II and costimulatory molecules. In addition, quercetin uniquely blocked endocytosis by Dendritic Cells DCs and the LPS-induced DC migration was diminished by quercetin treatment [13].

Quercetin has been shown clinically to block human mast cell cytokine release, possibly inhibiting the clinical manifestation of cytokine storm. Severe COVID-19 disease progression is associated with increased levels of C-Reactive protein, D-Dimer, Ferritin, IL-2, and IL-6. Quercetin has been shown in studies to reduce all these markers [14].

Balancing systemic iron levels within narrow limits is critical for maintaining human health. There are no known pathways to eliminate excess iron from the body and therefore iron homeostasis is maintained by modifying dietary absorption so that it matches daily obligatory losses. Several dietary factors can modify iron absorption. Polyphenols are plentiful in human diet and many compounds, including Que – the most abundant dietary polyphenol – are potent iron chelators [15].

Quercetin is a zinc ionophore and could have similar antiviral activity of chloroquine but described as safe choice in the treatment of viral infections [16].

Bromelain

Bromelain activates the inflammatory mediators, including interleukin (IL)-1β, IL-6, interferon (INF)-γ and tumor necrosis factor (TNF)-α in mouse macrophage and human peripheral blood mononuclear cells (PBMC) (Barth). These results indicated that bromelain potentially activates the healthy immune system in association with the rapid response to cellular stress. Conversely, bromelain reduces IL-1β, IL-6 and TNF-α secretion when immune cells are already stimulated in the condition of inflammation-induced over production of cytokines [17].

It was also found that bromelain upregulated p53 and Bax with consequent activation of Caspase 3 and Caspase 9 with concomitant decrease in BCL2. Marked inhibition of cyclooxygenase 2 (COX2) expression with inactivation of NF Kappa B by blocking phosphorylation and degradation of IK B α were blocked by bromelain. Furthermore, bromelain ameliorated extracellular signal of regulated protein kinase ERK1/2, P38 mitogen activated protein kinase MAPK and Akt activity. So, it modulated defective cellular signaling cascades [18].

Bromelain prevents or minimizes the severity of angina pectoris and transient ischemic attack (TIA). It is useful in the prevention and treatment of thrombophlebitis. It may also break down cholesterol plaques and exerts a potent fibrinolytic activity. A combination of bromelain and other nutrients protect against ischemia / reperfusion injury in skeletal muscle. Bromelain influences blood coagulation by increasing the serum fibrinolytic ability and by inhibiting the synthesis of fibrin, a protein involved in blood clotting [19, 20] (Figure 2).

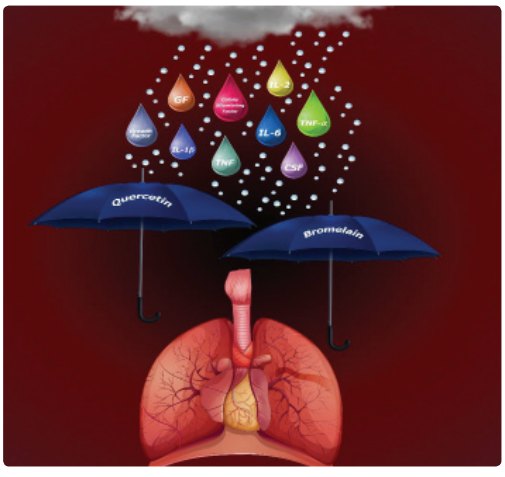

Figure 2: Quercetin and bromealin for blocking the interleukin.

Conclusion

The dreadful pandemic caused by SARS-CoV2 led to extremely high morbidity and mortality worldwide. There is no specific therapy and only supportive treatment to rescue patients' life is the only available option. A novel Quadriple therapy consisting of Zinc, Quercetin, Bromelain and Vitamin C shows a promising positive therapeutic effect. This mini review is the basis of our running clinical controlled trial and results will be available nearly.

References

1. Haibo Z, Josef MP, Yimin Li, Nanshan Z, Arthur SS (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target Intensive Care Med 46: 586-590. Link: https://bit.ly/3lrcRu5
2. Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A (2020) Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med 8: 436-438. Link: https://bit.ly/3bgv8FX
3. Qun Li, Xuhua G, Peng W, Xiaoye W, Lei Z, et al. (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 382: 1199-1207. Link: https://bit.ly/3jnQ4gK
4. Aysooda H, Omid S, Akram NB, Sepideh S, Gabriel SB, et al. (2019) Immunomodulatory Effects of Flavonoids: Possible Induction of T CD4+ Regulatory Cells Through Suppression of mTOR Pathway Signaling Activity. Front Immunol 10: 51. Link: https://bit.ly/3lnEMem
5. Diao B, Wang C, Tan Y, Xiewan C, Ying Liu, et al. (2020) Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19) Front. Immunol 11: 827. Link: https://bit.ly/3gFYAWK
6. PRASAD AS, HALSTED JA, NADIMI M (1961) Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. Am. J. Med 31: 532–546. Link: https://bit.ly/3hD2fWz
7. Roohani N, Hurrell R, Kelishadi R, Schulin R (2013) Zinc and its importance for human health: An integrative review. J. Res. Med. Sci 18: 144–157. Link: https://bit.ly/2QB4LRa
8. Englert J, Boudreault F, Pinilla-Vera M, Alvin TK, Colleen I, et al. (2016) ID: 60 Zinc deficiency primes the lung for ventilator-induced injury. Journal of Investigative Medicine 64: 973. Link: https://bit.ly/2Qx0hLx
9. Carr AC, Maggini S (2017) Vitamin C and Immune Function. *Nutrients.* 9: 1211. Link: https://bit.ly/31CvDGM
10. Furuya A, Uozaki M, Yamasaki H, Arakawa T, Arita Koyama MAH (2008) Antiviral effects of ascorbic and dehydroascorbic acids *in vitro*. *Int J Mol Med.* 22: 541–545. Link: https://bit.ly/31yX98d
11. Colunga BRML, Berrill M, Catravas JD, Marik PE (2020) Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). Frontiers in Immunology 11: 1451. Link: https://bit.ly/2QxVppr
12. Chen S, Jiang H, Wu X, Fang J (2016) Therapeutic Effects of Quercetin on Inflammation, Obesity, and Type 2 Diabetes. *Mediators Inflamm* 2016: 9340637. Link: https://bit.ly/2EzcZaf
13. Huang RY, Yu YL, Cheng WC, OuYang CN, Fu E, et al. (2010) Immunosuppressive effect of quercetin on dendritic cell activation and function. *J Immunol.* 184: 6815-6821. Link: https://bit.ly/3jzRh51
14. Zuyi W, Bodi Z, Shahrzad A, Nikolaos S, Alan Butcher, et al. (2012) Quercetin Is More Effective than Cromolyn in Blocking Human Mast Cell Cytokine Release and Inhibits Contact Dermatitis and

Photosensitivity in Humans. PLoS One 7: e33805. Link: https://bit.ly/32wunUZ

15. Lesjak M, Rukshana H, Sara B, Vernon S, Edward S, et al. (2014) Quercetin Inhibits Intestinal Iron Absorption and Ferroportin Transporter ExpressionIn Vivo and In Vitro. PLoS ONE 9: e102900. Link: https://bit.ly/2YI9SUu

16. Dabbagh-Bazarbachi H, Gael C, Isabel MQ, Mayreli O, Ciara KOH, et al. (2014) "Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model." J Agric Food Chem. 62: 8085-8093. Link: https://bit.ly/2EzfuJF

17. Onken JE, Greer PK, Calingaert B, Hale LP (2008) Bromelain treatment decreases secretion of pro-inflammatory cytokines and chemokines by colon biopsies in vitro. Clin Immunol 126: 345-352. Link: https://bit.ly/3gCCrsz

18. Pavan R, Jain S, Shraddha, Kumar A (2012) Properties and therapeutic application of bromelain: a review. *Biotechnol Res Int.* 2012: 976203. Link: https://bit.ly/3b4COdY

19. Rathnavelu V, Alitheen NB, Sohila S, Kanagesan S, Ramesh R (2016) Potential role of bromelain in clinical and therapeutic applications (Review) Biomed. Reports 5: 283-288. Link: https://bit.ly/3hDc0UO

20. Hu PA, Chen CH, Guo BC, Kou YR, Lee TS (2020) Bromelain Confers Protection Against the Non-Alcoholic Fatty Liver Disease in Male C57BL/6 Mice. Nutrients. 12: 1458. Link: https://bit.ly/3gCeGRh