SUPPLEMENTS

a. VITAMIN C AND QUERCETIN

Beatrice S. Vicente Pascual, MD, Caroline T. Gloria, MD, Cesar Joseph C. Gloria, MD

Introduction

There is current evidence that Vit C and quercetin co-administration exerts a synergistic antiviral action. This is attributed to the overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin, increasing its efficacy.

Mechanism of Action

Quercetin-3B-galactoside binds SARS-CoV-3CL protease (3CLpro) and inhibits its proteolytic activity. This inhibitory action on 3CLpro is dependent on the hydroxyl group of quercetin which recognizes Gln189 as a crucial site on 3CLpro responsible for binding of quercetin[2].

Quercetin exerts a synergistic antiviral action with Vit C. Quercetin spontaneously oxidizes to form O-semiquinone and O-quinone/quinone methide (QQ), which can bind protein thiols forming toxic compounds[3]. This process of both anti- and pro-oxidant effects has been named the "*quercetin paradox*"[4]. However, QQ can be recycled into quercetin by electron donors like NADH or ascorbate, or form together, with glutathione either 6-glutathionyl-quercetin or 8-glutathionyl-quercetin (GSQs)[5,6]. Importantly, if ascorbate or glutathione levels are *insufficient*, quercetin may be shunted to QQ and exert prooxidant effects. Therefore, we stress the importance for its co-administration with vitamin C[7,8].

Clinical Studies

No clinical studies are available at this time.

Recommended Dose

	Quercetin	Vitamin C
Prophylaxis	250 – 500 mg BID	500 mg BID
Mild cases	250 – 500 mg BID	500 mg BID
Severe cases*	500 mg BID	3 gr q6 for 7 days

*ARDS-like presentation, require assisted ventilation/intubation, ICU hospitalization.[1]

Adverse Effect

Oral supplementation with quercetin up to 1 g/day for 3 months has not resulted in significant adverse effects[9]. In a randomized placebo-controlled study, 30 patients with chronic prostatitis were supplemented with oral quercetin (1 g/day) and reported only two mild adverse reactions (headache and temporary peripheral paresthesia)(10). Intravenous administration of quercetin in a phase I clinical trial for cancer patients resulted in nausea, vomiting, sweating, flushing, and dyspnea at doses >10.5 mg/Kg (756 mg per 70 Kg individual)[11]. Only higher intravenously administered doses up to 51.3 mg/Kg (around 3,591 mg per individual) were associated with renal toxicity[9]. The safety of quercetin-based oral supplementation during pregnancy and breastfeeding has not been established.

Conclusion

Safe, cheap interventions which have a sound biological rationale should be prioritized for experimental use in the current context of the global health pandemic. The use of Vitamin C and quercetin both for prophylaxis in high-risk populations and for the treatment of COVID-19 patients as an adjunct to promising pharmacologic agents such as Remdesivir and convalescent plasma seem promising. Clinical trials in humans are needed to establish its efficacy and safety.

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b. VITAMIN D

Beatrice S. Vicente Pascual, MD

Introduction

Vitamin D is a fat-soluble vitamin that needs to undergo 2 hydroxylation processes to become active. The first occurs in the liver where Vitamin D is converted to 25-hydroxyvitamin D [25(OH)D], or calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol.[1]

Mechanism of Action

Vitamin D enhances the cellular innate immunity through induction of cathelicidin by 1,25 dihydoxyvitamin D and defensins. The cathelicidins kill the invading pathogens by perturbing their cell membrane and neutralize the biological activity of endotoxin. [2,3]

It reduces TNFα and Interferon gamma,[4] as well as other inflammatory cytokines such as IL-2.[5]

Calcitiriol, (1,25$(OH)_2D_3$) promotes cytokine production by the T helper type 2 (Th2) cells, which helps enhance the indirect suppression of Th1 cells by complementing this with actions mediated by a multitude of cell types.[6] Furthermore, calcitiriol promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes.[7]

The role of vitamin D in COVID-19 infection is twofold. First, vitamin D supports the production of antimicrobial peptides in the respiratory epithelium, thus making infection with the virus and development of COVID-19 symptoms less likely.[8] Second, vitamin D might help to reduce the inflammatory response to infection with SARS-CoV-2. Deregulation of this response, especially of the renin– angiotensin system, is characteristic of COVID-19 and the degree of overactivation is associated with poorer prognosis. Vitamin D is known to interact with a protein in this pathway—angiotensin converting enzyme 2 (ACE2)—which is also exploited by SARS-CoV-2 as an entry receptor. Vitamin D promotes expression of ACE2 contrary to the downregulation of ACE2 by the SARS-CoV-2.[8]

Clinical Studies

As of August 14, 2020, there are 24 clinical trials registered in clinicaltrials.gov investigating the role of Vitamin D in COVID-19. Fifteen are ongoing randomized controlled trials, 7 are ongoing observational studies and 2 are completed observational studies.

Recommended Dose: [1,9]

Infants:	8.5 to 10 ug/day or 400IU
1year to 70 years:	10ug/day or 600IU
>70 years:	20ug/day or 800IU

Adverse Effects

Vitamin D toxicity can cause anorexia, weight loss, polyuria, and heart arrhythmias. It can also raise blood levels of calcium which leads to vascular and tissue calcification, with subsequent damage to the heart, blood vessels, and kidneys.[10]

Conclusion

Studies on the use of Vit D on COVID-19 are ongoing and awaiting results of its benefits among COVID-19 patients.

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c. ZINC

Beatrice S. Vicente Pascual, MD

Introduction

Zinc (Zn) is an essential trace mineral with antiviral properties. There is no specialized Zn storage system in the body therefore a daily intake is needed to achieve a steady state.[1]

Mechanism of Action

Zinc inhibits the RNA synthesizing activity of SARS-COV replication and transcription complex (RTC). In vitro studies show Zn inhibits the SARS-COV RNA dependent RNA polymerase (RdRp) activity during the elongation phase of RNA synthesis by affecting template binding. It also inhibits both proper proteolytic processing of replicase polyproteins and RdRp activity.[1]

Clinical Studies

There is an ongoing study on the protective effects of IV zinc against organ damage in coronavirus. [2]

Recommended Dose

Not yet established for COVID-19.

Adverse Effects

Zinc toxicity can manifest as nausea, vomiting, loss of appetite, abdominal cramps, diarrhea and headache. Given in high doses it can affect copper status and reduced iron function.[3]

Conclusion

There is only one ongoing study on zinc for COVID-19. There is currently no evidence for the effectiveness of zinc as an adjunctive treatment in patients with COVID-19.

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d. MELATONIN

Pascualito I. Concepcion, MD and Radela Yvonne Ramos-Cortes, MD

Introduction

Melatonin (5 – methoxy – N – acetyltryptamine) is a main hormone secreted by pineal gland. It is given primarily for insomnia but recent researches showed that it has anti-inflammatory and anti-oxidant effects.

Mechanism of Action

As an anti-inflammatory, melatonin downregulates Nuclear Factor Kappa-B (NFK-B), and, through Sirtuin-1, down regulates proinflammatory polarization of macrophages, both resulting to an anti-inflammatory response.[1,2,3]

As an anti-oxidant, melatonin up-regulates anti-oxidative enzymes (superoxide dismutase), downregulates pro-oxidative (nitric oxide synthase), and functions as a free-radical scavenger.[5,6]

Lastly, melatonin improves proliferation and maturation of NK cells, T and B lymphocytes.[7]

Clinical Studies

There is one case series by Castillo, R. et al that looked at the effect of melatonin on 10 COVID-19 patients. This study concluded that high-dose melatonin may play a role as adjuvant therapy against COVID-19.[8] These findings are in conjunction with–published expert's recommendations to give melatonin to COVID-19 patients on the basis of its immunologic mechanism of action.

However, given the small sample size and methodological design, the results of this study must be taken with caution.

Recommended Dosing:

Though there are a lot of debates about the recommended dose of melatonin for treating COVID-19 patients, an approved dosage for this purpose does not yet exist.

Adverse Effects

Adverse effects include fatigue, changes in mood, psychomotor or neurocognitive performance.[9]

Conclusion

There are many published articles that recommend the giving of melatonin as adjunct treatment for COVID-19, however, there are no yet clinical studies that can conclusively support these claims.

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e. PROBIOTICS

Caroline T. Gloria, MD and Cesar Joseph C. Gloria, MD

Introduction

Probiotics are defined by the World Health Organization as living microbial agents of human origin that are able to tolerate the hostile gastrointestinal environment (acid and bile) such that they ultimately persist in the lower alimentary tract to confer health benefits to the host [1]

Probiotics are living microorganisms that confer health benefits to the host when administered in adequate amounts; however, dead bacteria and their components can also exhibit probiotic properties. Bifidobacterium and strains of lactic acid bacteria are the most widely used bacteria that exhibit probiotic properties and are included in many functional foods and dietary supplements.[2]

Probiotics have been shown to prevent and ameliorate the course of digestive disorders such as acute, nosocomial, and antibiotic-associated diarrhea; allergic disorders such as atopic dermatitis (eczema) and allergic rhinitis in infants; and Clostridium difficile-associated diarrhea and some inflammatory bowel disorders in adults. In addition, probiotics may be of interest as co-adjuvants in the treatment of metabolic disorders, including obesity, metabolic syndrome, nonalcoholic fatty liver disease, and type 2 diabetes.

In China, 58–71% of patients with COVID-19 were given antibiotics, and diarrhoea occurred in 2–36% of patients. When antibiotics are used, reinforcement of colonic flora using probiotics has been proposed to reduce susceptibility to subsequent infections.[3]

Mechanism of Action

The mechanisms of action of probiotics are diverse, heterogeneous, and strain specific, and have received little attention. One of the major mechanisms of action of probiotics is the regulation of host immune response. The immune system is divided into the innate and adaptive systems. The adaptive immune response depends on B and T lymphocytes, which bind to specific antigens. In contrast, the innate system responds to common structures, called pathogen-associated molecular patterns (PAMPs), shared by a majority of microbes.

The primary response to microbes, such as probiotics, is facilitated by pattern recognition receptors (PRRs), which bind to PAMPs. Toll-like receptors (TLRs), which are types of PRRs, are transmembrane proteins that are expressed on various immune and nonimmune cells, such as B-cells, natural killer cells, DCs, macrophages, fibroblast cells, epithelial cells, and endothelial cells. Activation of TLRs are known to facilitate activation of the innate immune response, and, consequently the adaptive immune response.

Probiotics help to preserve intestinal homeostasis by modulating the immune response and inducing the development of T-regs. Further research to elucidate the precise molecular mechanisms of action of probiotics is warranted.[2]

Clinical Studies

As of April 24, 2020, two randomized controlled trials showed that critically ill patients on mechanical ventilation who were given probiotics (*Lactobacillus rhamnosus* GG, live *Bacillus subtilis*, and *Enterococcus faecalis*) developed substantially less ventilator-associated pneumonia compared with placebo.[3,4]

Recommended Dose

2×10^9 colony-forming units (cfu) of Lactobacillus rhamnosus GG on a twice-daily basis[1]

Adverse Effects

The potential harms of probiotic therapy also requires investigation. Historically, the consensus has been that probiotic therapy was of questionable value but was safe.[1]

Conclusion

Not all probiotics are likely to be the same. *Lactobacilli* and *Bifidobacteria* are only two types of non-pathogenic bacteria and we must consider whether they can really tip the balance of a diverse gut ecosystem in combating COVID-19. When antibiotics are used, reinforcement of colonic flora using probiotics has been proposed to reduce susceptibility to subsequent infections.

To date, the rationale for using probiotics in COVID-19 is derived from indirect evidence. Blind use of conventional probiotics for COVID-19 is not recommended until we have further understanding of the pathogenesis of SARS-CoV-2 and its effect on gut microbiota. It is likely that a novel and more targeted approach to modulation of gut microbiota as one of the therapeutic approaches of COVID-19 and its comorbidities will be necessary.

However, the efficacy of probiotics in reduction of intensive care unit mortality and inpatient mortality is uncertain.[5]

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f. OMEGA 3 FATTY ACID AND DHA

Caroline T. Gloria, MD and Radela Yvonne Ramos Cortes, MD

Introduction

Omega-3 Fatty acid, including Docosahexaenoic acid (DHA) a long-chain omega-3 fatty acid, is predominantly sourced from fishes like salmon, tuna, and mackerel[1]. Increasing consumption is said to offer benefits to those with cardiovascular problems.

Studies have reported anti-inflammatory and immunomodulatory effects of DHA[2]

Mechanism of Action

DHA's anti-inflammatory action is by directly inhibiting pro-inflammatory transcription factors like Nuclear factor kappa beta that increases levels of IL-1beta,IL-6, TNF-alpha and chemokine MCP-1. DHA also inhibits inflammatory mediators such as : VCAM-1, ICAM-1,TNF-alpha,IL-6 and TLR-4.[3,4,5,6]

DHA increases the phagocytic property of macrophages [7] and neutrophils [8], decreased activation of basophils [9], mast cells[10] and T cells[11] and caused an increase in IgM production[12].

Recommended Dose

The American Heart Association recommends 4 g EPA+DHA to lower cholesterol[1], but there are no studies on the immunomodulatory dose.

Adverse Effects

Thromboxane A3 produced by DHA is a less potent platelet activator which may result to an altered platelet function[13]. There is also the possibility of intake of toxins or sea contaminants together with the DHA.[14]

Conclusion

There are no studies on the use of DHA for COVID-19. Human trials are needed to test for its efficacy and safety against COVID-19.

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