A Novel Combination of Vitamin C, Curcumin, and Glycyrrhizic Acid Has the Potential to Regulate Immune and Inflammatory Responses in Coronavirus Infections: A System Biology Perspective

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Abstract

In recent years, new Coronaviruses (CoV) have developed on a regular basis all across the world. CoVs are constantly proliferating, posing a threat to world health and the economy. Because there is no specific treatment for these CoVs, any effective method (including nutritional and dietary approaches) is worth looking into. A unique combination of vitamin C, curcumin, and glycyrrhizic acid (VCG Plus) was developed based on current breakthroughs in nutrients and phytonutrients research that offers potential against CoV infection. System biology methods were used to investigate the potential of VCG Plus in altering immune and inflammatory response targets and pathways. Along with network analysis, gene target acquisition, gene ontology, and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway enrichment were all done at the same time.

The findings demonstrate that VCG Plus has the ability to operate on 88 hub targets that are linked to immunological and inflammatory responses. VCG Plus has the ability to regulate the innate immune response by reducing PI3K/AKT, NF-B, and MAPK signaling pathways, as well as stimulate interferon production, activate and balance T-cells, and regulate the inflammatory response by inhibiting NOD-like and Toll-like signaling pathways. In studies of CoV infections, all of these biological mechanisms and pathways have been well described. As a result of our findings, VCG Plus may be useful in controlling immune responses to treat CoV infections and inhibiting excessive inflammatory responses to prevent cytokine storm. However, more in vitro and in vivo research is needed to confirm the current findings in system biology.

Keywords: Coronavirus • Vitamin C • Curcumin • Glycyrrhizic acid • System biology • Inflammatory response • Immune response

Introduction

Virus infection necessitates a well-coordinated immunological response. An out-of-control immune response, on the other hand, is linked to immune pathogenesis and an excessive inflammatory response, both of which can lead to adverse outcomes such severe lung injury and multi-organ failure [1-6]. CoV infections frequently generate severe public health hazards due to the difficulties in generating antiviral medicines and vaccines [7]. Infected persons must rely on their own immune defenses to keep the illness from spreading. These are self-limiting diseases, which means that an individual's immune function will determine whether early symptoms progress to severe acute respiratory tract symptoms (e.g., pneumonia) or infection recovery.

Phytonutrients are a class of bioactive non-nutrient plant chemicals with the ability to impact biochemical reactions and, as a result, human health after intake [8,9]. Flavonoids, anthocyanin, carotenoids, polyphenols, triterpenoids and phytosterols are common phytonutrients found in dietary supplements, and many of them have been shown to play key roles in human health and have therapeutic potential [10]. It is well known that a healthy diet rich in nutrients and phytonutrients can aid immune function by improving defense and resistance to infection while preserving tolerance.

It is well known that a healthy diet rich in nutrients and phytonutrients can aid immune function by improving defense and resistance to infection while preserving tolerance. Acerola berry (*Malpighia glabra L., M. emarginata D.C.*), roxburgh rose fruit (*Rosa roxburghii* Tratt), camu camu (*Myrciaria dubia* (Kunth) McVaugh), amla (*Phyllanthus emblica L.*), and sea buckthorn berry (*Hippophae rhamnoides L.*) are all known to be (VC). VC modulates immunity by boosting B- and T-cell differentiation and proliferation, and it aids in the prevention and treatment of respiratory and systemic infections. Due to its benefits on immunological function, VC may protect against infection induced by CoVs.

Glycyrrhizic Acid (GA) is a key phytonutrient found in licorice root (*Glycyrrhiza uralensis* Fisch. ex DC., *Glycyrrhiza inflata* Bat., *Glycyrrhiza glabra L.*), which is used as a culinary and medicinal ingredient in China. GA has antiviral, anti-inflammatory, and hepatoprotective properties. The National Health Commission of China suggested Traditional Chinese Medicine (TCM) therapies for SARS-CoV-2 infected pneumonia, and licorice root was one of the most often utilised TCM herbs. GA's potential to bind to Angiotensin Converting Enzyme 2 (ACE2) has recently been reported as a way to prevent SARS-CoV-2 infection. Intriguingly, clinical trials are being conducted to see how diammonium glycyrrhizinate mixed with vitamin C pills affects common pneumonia infected with SARS-CoV-2.

Curcumin (CC) and its analogues are the primary phytonutrients found in turmeric (*Curcuma longa* L.) and other *Curcuma spp*., which are widely used as culinary spices, traditional medicine, and a popular dietary supplement ingredient due to their wide range of health benefits, including anti-inflammation, anti-cancer, cardiovascular regulation, respiratory, and immune system benefits. Curcumin's ability to decrease numerous cytokines suggests that it could be a viable treatment for Ebola patients suffering from cytokine storm. Aminopeptidase N (APN), a cellular receptor for alpha CoV, was likewise inhibited by CC.

Because VC, CC, and GA are common in nutrition, as well as being used to modulate immune responses and recommended to intervene in CoV infections, a combination of VC, CC, and GA (VCG Plus) was proposed for its ability to prevent CoV infection. Our goal in this study is to use system biology methodologies to analyse biological processes and pathways regulated by VCG Plus, as well as to show how these biological processes and pathways may be linked to protection against CoV infections.

Materials and Methods

Gene target acquisition and screening: The comprehensive assessment of putative compound target interaction patterns is an important step in system biology study. Multiple databases/platforms, such as the Drug Bank Database, the Comparative Toxicogenomics Database (CTD), the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), and the Traditional Chinese Medicine Integrative Pharmacology based research platform (TCMIP), are currently used to find potential targets for small molecular compounds. Drug bank includes thorough information on FDA approved and investigational medications, including drug targets, pharmacological actions, and drug interactions [34]. CTD is a database of chemical gene interactions that has been hand curated from scholarly literature [35,36]. TCMIP uses MedChem Studio (version 3.0), an efficient drug similarity search engine to locate herbal chemical compounds with high structural similarity, to forecast possible targets for herbal chemical compounds.

Hub target identification and Protein–Protein Interaction (PPI) analysis

The following steps were taken to identify hub targets:

- Combine the VC, CC, and GA targets and delete any duplicates;
- Upload them to the CTD website, compare the gene databases for "viral disorders" and "immune system diseases," and choose the overlapping targets for further investigation.
- To do PPI analysis, map selected targets into STRING (Version 11.0), set the PPI cut-off degree to high confidence (0.700), and download the PPI information as TSV file format;
- Open the file in the Cytoscape programme (Version 3.6.1) Select the hub targets whose node degree is greater than the median value to study the topological properties of the interactions. Following these processes, STRING and Cytoscape are used to build and assess the model.

Distribution analysis of targets in tissues/system and Gene Ontology (GO) enrichment and analysis

The target-system location analysis was carried out using gene organizer. For the hub targets, DAVID bioinformatics resources 6.8 was used to perform GO analysis. GO's three main outputs were biological process, cell component, and molecular function. The p-value was modified using the Benjamini–Hochberg method after the cut-off value was set to 0.05. In addition, ClueGo (Version 2.5.6), a cytoscape plug-in that integrates the EBI-Uniport GO annotation database, was used to analyse specific GO annotation related in immune system functions. VC, CC, and GA targets were generally imported to ClueGo independently and represented by distinct colours. ClueGo analysis was set to "cluster" as the visual style. The GO term/ pathway was added to the list.

Pathway analysis from the Kyoto Encyclopedia of Genes and Genomes (KEGG): ClueGo was used to enrich and analyse KEGG pathways by connecting it with the KEGG database (updated in 17 February 2020). The approaches were similar to the GO word analysis for immune system processes, which is briefly discussed below:

- Separately import the VC, CC, and GA targets into ClueGo, each represented by a distinct colour;
- Set the visual style to "cluster," and the statistical approach to "two-side hypergenometric test with bonferroni step down correction," so that only paths with a p-value of less than 0.05 are displayed;
- Begin the study by downloading the protein-pathway interactions data in Excel format. Pathways are classified as (A) Metabolism, (B) Genetic information processing, (C) Environmental information processing, (D) Cellular processes, (E) Organismal systems, and (F) Human diseases, according to the KEGG database.

Results

Hub target identification and analysis

The probable targets for the three (phyto-) nutrients in VCG Plus were mined using three available datasets. There were 109, 146, and 65 eligible targets identified for VC, CC, and GA, respectively, and a total of 248 distinct targets identified for the VCG Plus (phyto-) nutrition combination. When the results were compared to the gene data for "viral diseases" and "immune system diseases" in CTD, it was discovered that 179 targets were present in both the "virus diseases" and "immune system disease" gene databases. PPI analysis and network topological analysis were then performed on these 179 targets. As a consequence, 88 densely related objectives (hub targets, node degree 12) were found to be worth investigating further.

Enrichment and analysis of target distribution in tissues and systems

Three datasets were used to mine the likely targets for the three (phyto-) nutrients in VCG Plus. For VC, CC, and GA, respectively, there were 109, 146, and 65 suitable targets found, with a total of 248 different targets identified for the VCG Plus (phyto-) nutrient combination. When the results were compared to gene data from CTD's "viral diseases" and "immune system diseases" gene databases, it was determined that 179 targets were present in both databases. These 179 targets were then subjected to PPI and network topological analyses. As a result, 88 tightly connected objectives (hub targets, node degree 12) were identified as being worth further investigation.

Discussion

The major determinant of such virions' attachment to human cells is the interaction between CoV spike (S) protein and its receptor. APN as the receptor for alpha CoV, Angiotensin Converting Enzyme 2 (ACE2) as the receptor for SARS-CoV, and Dipeptidyl-Peptidase 4 (DPP4) as the receptor for MERS-CoV have all been thoroughly described as CoV cellular receptors [1]. Inhibitors of S protein receptor binding are used to prevent and cure infection [7]. Although our findings did not reveal that VCG Plus (phyto-) nutrients operate on the CoV cellular receptor, GA binding to ACE2 has recently been shown. Furthermore, CC has been identified as an APN inhibitor with the potential to be used as a cancer chemoprevention agent.

When it comes to virus infection, the innate immune system is the first line of defense. An innate immune response that is quick and well coordinated when invading viruses are detected, with following signal transduction pathways focused to prevent infection. During a viral infection, the host's Pathogen-Recognition Receptors (PRRs), which are initially sensitized by viral pathogen-associated molecular patterns, are activated, resulting in the production of type 1 interferon's (IFNs). IFNs are the most common cytokines in the innate immune system, and they are hypothesized to boost the release of antiviral proteins to protect uninfected cells. Toll-like receptors, retinoic acid-inducible gene I (RIG-I)-like receptors, and nucleotide-binding and oligomerization domain (NOD)-like receptors are all capable of sensing CoV [4]. SARS-CoV and MERS-CoV accessory proteins can sometimes interfere with PRRs.

T-cells, especially CD4+ and CD8+ cells, have an antiviral role by not only attacking viruses but also preventing the emergence of autoimmunity or overwhelming inflammation [4]. CD4+ cells activate T-dependent B-cells to enhance the production of virus specific

antibodies, whereas CD8+ cells destroy virally infected cells. However, some CoVs are thought to cause T-cell apoptosis by activating apoptosis pathways, and CD4+ cell depletion in later phases is linked to immune-mediated interstitial pneumonitis and pathogen clearance delays [74]. Both CD4+ and CD8+ cell counts were lower in SARS-CoV-2 infected patients with severe pneumonia than in non-severe patients.

Conclusion

In conclusion, as there is no specific treatment for CoV infections, every conceivable method of protection against CoV infections is worth investigating and discussing. Using systems biology, this study looked into the potential protective impact of VCG Plus against CoV infections. Our findings show that VCG Plus may be useful in modulating the immune response to CoV infections and reducing excessive inflammatory responses to prevent cytokine storm. However, more in vitro/in vivo investigations are needed to confirm the findings. This study's analytical approach offers a fresh way of thinking about the formulation strategy for developing new dietary supplements with potential immunological advantages.

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