**Quercetina e vitamina C: una terapia sperimentale e sinergica per la prevenzione e il trattamento della malattia correlata alla SARS-CoV-2 (COVID-19)**

Ruben Manuel Luciano Colunga Biancatelli 1 2 3, Max Berrill 4, John D Catravas 1 2 5, Paul E Marik 1

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**Abstract**

La sindrome respiratoria acuta grave Coronavirus-2 (SARS-CoV-2) rappresenta una minaccia globale emergente che sta mettendo a dura prova la capacità sanitaria mondiale. A partire dal 27 maggio, la malattia causata da SARS-CoV-2 (COVID-19) ha provocato oltre 340.000 morti in tutto il mondo, di cui 100.000 solo negli Stati Uniti. È indispensabile studiare e sviluppare trattamenti farmacologici idonei alla prevenzione e al trattamento del COVID-19. L'acido ascorbico è una vitamina fondamentale necessaria per il corretto funzionamento del sistema immunitario. Svolge un ruolo nella risposta allo stress e ha mostrato risultati promettenti quando somministrato a pazienti critici. La quercetina è un noto flavonoide le cui proprietà antivirali sono state studiate in numerosi studi. È stato dimostrato che la co-somministrazione di vitamina C e quercetina esercita un'azione antivirale sinergica a causa della sovrapposizione di proprietà antivirali e immunomodulanti e della capacità dell'ascorbato di riciclare la quercetina, aumentandone l'efficacia. Nell'attuale contesto di una pandemia sanitaria globale, si dovrebbe dare la priorità agli interventi sicuri ed economici che hanno una solida logica biologica per l'uso sperimentale. Presentiamo le prove attuali per l'uso di vitamina C e quercetina sia per la profilassi nelle popolazioni ad alto rischio che per il trattamento di pazienti con COVID-19 in aggiunta a promettenti agenti farmacologici come Remdesivir o plasma convalescente.

**Discussione**

Un approccio multi-farmaco con quercetina e vitamina C può interrompere l'ingresso, la replicazione, l'attività e l'assemblaggio del virus e contemporaneamente fortificare la risposta immunitaria promuovendo la produzione precoce di IFN, modulando le interleuchine, promuovendo la maturazione delle cellule T e l'attività fagocitica. La co-somministrazione di quercetina e acido ascorbico rappresenta una strategia sperimentale per la profilassi e il trattamento di diversi virus respiratori, come SARS-CoV-2. Il blocco dell'ingresso del virus rappresenta una strategia chiave e la quercetina impedisce la fusione della membrana virale sia per l'influenza che per la SARS-Cov in vitro (98). La quercetina prende di mira anche le polimerasi virali e può interrompere la replicazione tramite l'inibizione degli enzimi della trascrittasi inversa. La quercetina inibisce ulteriormente la proteasi 3CL della SARS legandosi al suo sito GLN189 (102), che è espresso in modo simile da SARS-COV-2 (105) e fornisce un razionale meccanicistico diretto per il suo uso clinico sperimentale, oltre al suo immunostimolante e antinfiammatorio Azioni. Nonostante i limiti della ricerca in vitro, è interessante notare che i pochi modelli in vivo qui esaminati indicano una maggiore sopravvivenza da infezioni virali letali quando trattate con quercetina (42, 64). Alcuni studi suggeriscono che la somministrazione orale e l'elaborazione metabolica (metilazione, coniugazione, ecc.) È necessaria e hanno identificato i derivati ​​della quercetina, che mostrano una Tmax variabile, come responsabili di un'attività antivirale cooperativa (126-128).

La vitamina C esercita attività immunomodulante, aumentando la produzione di interferone attraverso la fosforilazione STAT3 (90), limitando il danno d'organo indotto dalle citochine (55), promuovendo la sopravvivenza nelle infezioni letali (54) e, cosa importante, è in grado di riciclare la quercetina ossidata (120), migliorandone effetti antivirali. L'infezione da virus SARS-Cov-2 può avviare una forte reazione infiammatoria e disregolata nel polmone con livelli aumentati di IL-6 e una "tempesta di citochine" (129) che ha dimostrato di provocare infezioni asintomatiche, lievi o gravi Questa disregolazione delle citochine può essere associata a trappole extracellulari dei neutrofili (130) e ad alterazioni dell'attività delle cellule T (131). Queste alterazioni immunologiche che hanno caratterizzato la nostra attuale comprensione del Covid-19 suggeriscono che gli agenti che prendono di mira la modulazione immunitaria, piuttosto che l'attività viricida diretta, possono presentare interessanti bersagli per l'intervento farmacologico. In questo scenario, la co-somministrazione di vitamina C e quercetina può rappresentare un approccio antivirale e immunomodulante sicuro, efficace e poco costoso sia per la profilassi delle popolazioni ad alto rischio che per il trattamento di casi sia lievi che gravi.

Inoltre è stato costantemente dimostrato che mostrano eccellenti profili di sicurezza e una considerazione dei rischi e dei benefici nel loro potenziale terapeutico dovrebbe essere inserita in questo contesto. La vitamina C è un integratore ampiamente disponibile che molti milioni di persone usano già e abbiamo evidenziato le sue proprietà antivirali in combinazione con la quercetina. A causa del suo uso su larga scala, la vitamina C in particolare sarebbe un intervento economico con cui accertare l'efficacia di questi composti come intervento profilattico. L'uso profilattico di integratori vitaminici da banco per combattere le infezioni è un comportamento con cui molte persone si impegnano già. La ricerca sulla potenziale somministrazione profilattica di vitamina C e quercetina nei gruppi ad alto rischio è quindi giustificata.

L'eccellente profilo di effetti collaterali di questi agenti suggerirebbe anche che possano integrare gli interventi che hanno mostrato potenziali benefici nel trattamento del Covid-19, come Remdesivir (132) e il plasma convalescente (133, 134), che riteniamo giustifichi il loro uso sperimentale in test clinici.

Esistono potenziali limitazioni del loro utilizzo negli studi clinici. Entrambi gli agenti sono presenti in varia misura nelle diete individuali e le raccomandazioni globali per l'assunzione di vitamina C variano ampiamente in tutto il mondo (135). Gli interventi profilattici nelle popolazioni generali all'interno della comunità saranno quindi confusi dalla quantità presente nelle diverse diete. Agenti come la vitamina C hanno anche effetti benefici ben caratterizzati oltre alle proprietà antivirali che abbiamo qui evidenziato. L'integrazione con questi agenti può quindi promuovere la salute generale e influenzare indirettamente la capacità degli individui di combattere le infezioni virali. Sebbene ciò ridurrebbe la capacità di identificare le proprietà antivirali dirette della vitamina C negli studi clinici, potrebbe avere benefici accessori nel promuovere la salute generale, che può essere particolarmente pertinente se somministrata in comunità con maggiore deprivazione o da paesi meno sviluppati economicamente.

**Conclusione**

La quercetina mostra una vasta gamma di proprietà antivirali che possono interferire in più fasi della virulenza del patogeno (ingresso del virus, replicazione del virus, assemblaggio delle proteine) e che questi effetti terapeutici possono essere aumentati dalla co-somministrazione di vitamina C.Inoltre, a causa della loro mancanza di gravi effetti collaterali e bassi costi, consigliamo vivamente la somministrazione combinata di questi due composti sia per la profilassi che per il trattamento precoce delle infezioni del tratto respiratorio, in particolare compresi i pazienti COVID-19.

Parole chiave: COVID-19; Coronavirus; SARS-CoV-2; antivirale; flavonoidi; immunonutrizione; quercetina; vitamina C.

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