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
PMID: 32636851 PMCID: PMC7318306 DOI: 10.3389 / fimmu.2020.01451
Articolo PMC gratuito

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.

References

1. Formica JV, Regelson W. Review of the biology of Quercetin and related bioflavonoids. Food Chem Toxicol. (1995) 33:1061–80. 10.1016/0278-6915(95)00077-1 [PubMed] [CrossRef] [Google Scholar]

2. Colunga Biancatelli RML, Berrill M, Marik PE. The antiviral properties of vitamin C. Expert Rev Anti Infect Ther. (2019) 18:99–101. 10.1080/14787210.2020.1706483 [PubMed] [CrossRef] [Google Scholar]
3. Marik PE. Vitamin C: an essential “stress hormone” during sepsis. J Thorac Dis. (2020) 12(Suppl. 1):S84–8. 10.21037/jtd.2019.12.64 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. Carr AC, Maggini S. Vitamin C and Immune Function. Nutrients. (2017) 9:1211. 10.3390/nu9111211 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
5. Leibovitz B, Siegel BV. Ascorbic acid and the immune response. Adv Exp Med Biol. (1981) 135:1–25. 10.1007/978-1-4615-9200-6_1 [PubMed] [CrossRef] [Google Scholar]
6. Dey S, Bishayi B. Killing of *S. aureus* in murine peritoneal macrophages by Ascorbic acid along with antibiotics Chloramphenicol or Ofloxacin: correlation with inflammation. Microb Pathog. (2018) 115:239–50. 10.1016/j.micpath.2017.12.048 [PubMed] [CrossRef] [Google Scholar]
7. Furuya A, Uozaki M, Yamasaki H, Arakawa T, Arita Koyama MAH. Antiviral effects of ascorbic and dehydroascorbic acids *in vitro*. Int J Mol Med. (2008) 22:541–5. 10.3892/ijmm_00000053 [PubMed] [CrossRef] [Google Scholar]
8. Li Y, Yao J, Han C, Yang J, Chaudhry MT, Wang S, et al. . Quercetin, inflammation and immunity. Nutrients. (2016) 8:167. 10.3390/nu8030167 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
9. Robaszkiewicz A, Balcerczyk A, Bartosz G. Antioxidative and prooxidative effects of quercetin on A549 cells. Cell Biol Int. (2007) 31:1245–50. 10.1016/j.cellbi.2007.04.009 [PubMed] [CrossRef] [Google Scholar]
10. Uchide N, Toyoda H. Antioxidant therapy as a potential approach to severe influenza-associated complications. Molecules. (2011) 16:2032–52. 10.3390/molecules16032032 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
11. Nair MP, Kandaswami C, Mahajan S, Chadha KC, Chawda R, NairandSchwartz SAH. The flavonoid, quercetin, differentially regulates Th-1 (IFNgamma) and Th-2 (IL4) cytokine gene expression by normal peripheral blood mononuclear cells. Biochim Biophys Acta. (2002) 1593:29–36. 10.1016/S0167-4889(02)00328-2 [PubMed] [CrossRef] [Google Scholar]
12. Shinozuka K, Kikuchi Y, Nishino C, Mori A, Tawata S. Inhibitory effect of flavonoids on DNA-dependent DNA and RNA polymerases. Experientia. (1988) 44:882–5. 10.1007/BF01941188 [PubMed] [CrossRef] [Google Scholar]
13. Bachmetov L, Gal-Tanamy M, Shapira A, Vorobeychik M, Giterman-Galam T, Sathiyamoorthy P, et al. . Suppression of hepatitis C virus by the flavonoid quercetin is mediated by inhibition of NS3 protease activity. J Viral Hepat. (2012) 19:e81–8. 10.1111/j.1365-2893.2011.01507.x [PubMed] [CrossRef] [Google Scholar]
14. Spedding G, Ratty A, Middleton E, Jr. Inhibition of reverse transcriptases by flavonoids. Antiviral Res.(1989) 12:99–110. 10.1016/0166-3542(89)90073-9 [PubMed] [CrossRef] [Google Scholar]
15. Cushnie TP, Lamb AJ. Antimicrobial activity of flavonoids. Int J Antimicrob Agents. (2005) 26:343–56. 10.1016/j.ijantimicag.2005.09.002 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
16. Debiaggi M, Tateo F, Pagani L, Luini M, Romero E. Effects of propolis flavonoids on virus infectivity and replication. Microbiologica. (1990) 13:207–13. [PubMed] [Google Scholar]
17. Winkel-Shirley B, Flavonoid Biosynthesis. A colorful model for genetics, biochemistry, cell biology, and biotechnology. Plant Physiol. (2001) 126:485. 10.1104/pp.126.2.485 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

18. Burger MC. ChemDoodle web components: HTML5 toolkit for chemical graphics, interfaces, and informatics. J Cheminform. (2015) 7:35. 10.1186/s13321-015-0085-3 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
19. Gábor M. Szent-Györgyi and the bioflavonoids: new results and perspectives of pharmacological research into benzo-pyrone derivatives. Commemoration on the 50th anniversary of the award of the Nobel Prize. Prog Clin Biol Res. (1988) 280:1–15. [PubMed] [Google Scholar]
20. Khoo NK, White CR, Pozzo-Miller L, Zhou F, Constance C, InoueandParks DAT. Dietary flavonoid quercetin stimulates vasorelaxation in aortic vessels. Free Radic Biol Med. (2010) 49:339–47. 10.1016/j.freeradbiomed.2010.04.022 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Andres S, Pevny S, Ziegenhagen R, Bakhiya N, Schäfer B, Hirsch-Ernst KI, et al. . Safety aspects of the use of quercetin as a dietary supplement. Mol Nutr Food Res. (2018) 62:1700447. 10.1002/mnfr.201700447 [PubMed] [CrossRef] [Google Scholar]
22. Brown JP. A review of the genetic effects of naturally occurring flavonoids, anthraquinones and related compounds. Mutat Res. (1980) 75:243–77. 10.1016/0165-1110(80)90029-9 [PubMed] [CrossRef] [Google Scholar]
23. Awad HM, Boersma MG, Vervoort Rietjens JIM. Peroxidase-catalyzed formation of quercetin quinone methide-glutathione adducts. Arch Biochem Biophys. (2000) 378:224–33. 10.1006/abbi.2000.1832 [PubMed] [CrossRef] [Google Scholar]
24. Terao J. Dietary flavonoids as antioxidants *in vivo*: conjugated metabolites of (-)-epicatechin and quercetin participate in antioxidative defense in blood plasma. J Med Invest. (1999) 46:159–68. [PubMed] [Google Scholar]
25. Abdelmoaty MA, Ibrahim MA, Ahmed NS, Abdelaziz MA. Confirmatory studies on the antioxidant and antidiabetic effect of quercetin in rats. Indian J Clin Biochem. (2010) 25:188–92. 10.1007/s12291-010-0034-x [PMC free article] [PubMed] [CrossRef] [Google Scholar]
26. Nabavi SM, Nabavi SF, Eslami S, Moghaddam AH. *In vivo* protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. Food Chem. (2012) 132:931–5. 10.1016/j.foodchem.2011.11.070 [CrossRef] [Google Scholar]
27. Gormaz JG, Quintremil S, Rodrigo R. Cardiovascular disease: a target for the pharmacological effects of quercetin. Curr Top Med Chem. (2015) 15:1735–42. 10.2174/1568026615666150427124357 [PubMed] [CrossRef] [Google Scholar]
28. Pace-Asciak CR, Hahn S, Diamandis EP, Soleas G, Goldberg DM. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. Clin Chim Acta. (1995) 235:207–19. 10.1016/0009-8981(95)06045-1 [PubMed] [CrossRef] [Google Scholar]
29. Cai Q, Rahn RO, Zhang R. Dietary flavonoids, quercetin, luteolin and genistein, reduce oxidative DNA damage and lipid peroxidation and quench free radicals. Cancer Lett. (1997) 119:99–107. 10.1016/S0304-3835(97)00261-9 [PubMed] [CrossRef] [Google Scholar]
30. Erden Inal M, Kahraman A. The protective effect of flavonol quercetin against ultraviolet a induced oxidative stress in rats. Toxicology. (2000) 154:21–9. 10.1016/S0300-483X(00)00268-7 [PubMed] [CrossRef] [Google Scholar]
31. Morikawa K, Nonaka M, Narahara M, Torii I, Kawaguchi K, Yoshikawa T, et al. . Inhibitory effect of quercetin on carrageenan-induced inflammation in rats. Life Sci. (2003) 74:709–21. 10.1016/j.lfs.2003.06.036 [PubMed] [CrossRef] [Google Scholar]
32. Dimova S, Mugabowindekwe R, Willems T, Brewster ME, Noppe M, Ludwig A, et al. . Safety-assessment of 3-methoxyquercetin as an antirhinoviral compound for nasal application: effect on

ciliary beat frequency. Int J Pharm. (2003) 263:95–103. 10.1016/S0378-5173(03)00363-6 [PubMed] [CrossRef] [Google Scholar]
33. Davies SP, Reddy H, Caivano M, Cohen P. Specificity and mechanism of action of some commonly used protein kinase inhibitors. Biochem J. (2000) 351(Pt. 1):95–105. 10.1042/bj3510095 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
34. Huang YT, Hwang JJ, Lee PP, Ke FC, Huang JH, Huang CJ, et al. . Effects of luteolin and quercetin, inhibitors of tyrosine kinase, on cell growth and metastasis-associated properties in A431 cells overexpressing epidermal growth factor receptor. Br J Pharmacol. (1999) 128:999–1010. 10.1038/sj.bjp.0702879 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
35. Agullo G, Gamet-Payrastre L, Manenti S, Viala C, Rémésy C, Chap H, et al. . Relationship between flavonoid structure and inhibition of phosphatidylinositol 3-kinase: a comparison with tyrosine kinase and protein kinase C inhibition. Biochem Pharmacol. (1997) 53:1649–57. 10.1016/S0006-2952(97)82453-7 [PubMed] [CrossRef] [Google Scholar]
36. Peet GW, Li J. IkappaB kinases alpha and beta show a random sequential kinetic mechanism and are inhibited by staurosporine and quercetin. J Biol Chem. (1999) 274:32655–61. 10.1074/jbc.274.46.32655 [PubMed] [CrossRef] [Google Scholar]
37. De Palma AM, Vliegen I, De Clercq E, Neyts J. Selective inhibitors of picornavirus replication. Med Res Rev. (2008) 28:823–84. 10.1002/med.20125 [PubMed] [CrossRef] [Google Scholar]
38. Itsuka H, Ohsawa C, Ohiwa T, Umeda I, Suhara Y. Antipicornavirus flavone Ro 09-0179. Antimicrob Agents Chemother. (1982) 22:611–16. 10.1128/AAC.22.4.611 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
39. Kaul TN, Middleton E, Jr. Ogra PL. Antiviral effect of flavonoids on human viruses. J Med Virol.(1985) 15:71–9. 10.1002/jmv.1890150110 [PubMed] [CrossRef] [Google Scholar]
40. Evers DL, Chao CF, Wang X, Zhang Z, Huong SM, Huang ES. Human cytomegalovirus-inhibitory flavonoids: studies on antiviral activity and mechanism of action. Antiviral Res. (2005) 68:124–34. 10.1016/j.antiviral.2005.08.002 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
41. Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR, Abubakar S. Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virol J. (2011) 8:560. 10.1186/1743-422X-8-560 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
42. Veckenstedt A, Béládi I, Mucsi I. Effect of treatment with certain flavonoids on Mengo virus-induced encephalitis in mice. Arch Virol. (1978) 57:255–60. 10.1007/BF01315089 [PubMed] [CrossRef] [Google Scholar]
43. Güttner J, Veckenstedt A, Heinecke H, Pusztai R. Effect of quercetin on the course of mengo virus infection in immunodeficient and normal mice. A histologic study. Acta Virol. (1982) 26:148–55. [PubMed] [Google Scholar]
44. Nieman DC, Henson DA, Gross SJ, Jenkins DP, Davis JM, Murphy EA, et al. . Quercetin reduces illness but not immune perturbations after intensive exercise. Med Sci Sports Exerc. (2007) 39:1561–9. 10.1249/mss.0b013e318076b566 [PubMed] [CrossRef] [Google Scholar]
45. Nieman DC, Henson DA, Davis JM, Angela Murphy E, Jenkins DP, Gross SJ, et al. . Quercetin's influence on exercise-induced changes in plasma cytokines and muscle and leukocyte cytokine mRNA. J Appl Physiol. (2007) 103:1728–35. 10.1152/japplphysiol.00707.2007 [PubMed] [CrossRef] [Google Scholar]
46. Nieman DC, Henson DA, Davis JM, Dumke CL, Gross SJ, Jenkins DP, et al. . Quercetin ingestion does not alter cytokine changes in athletes competing in the Western States Endurance

Run. J Interferon Cytokine Res. (2007) 27:1003–11. 10.1089/jir.2007.0050 [PubMed] [CrossRef] [Google Scholar]
47. Chen JY, Chang C-Y, Feng P-H, Chu C-C, So EC, Hu M-L. Plasma vitamin C is lower in postherpetic neuralgia patients and administration of vitamin C reduces spontaneous pain but not brush-evoked pain. Clin J Pain. (2009) 25:562–9. 10.1097/AJP.0b013e318193cf32 [PubMed] [CrossRef] [Google Scholar]
48. Marik PE, Hooper MH. Doctor-your septic patients have scurvy! Crit Care. (2018) 22:23. 10.1186/s13054-018-1950-z [PMC free article] [PubMed] [CrossRef] [Google Scholar]
49. Fowler AA, III, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. . Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. JAMA. (2019) 322:1261–70. 10.1001/jama.2019.11825 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
50. Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care. (2017) 21:300. 10.1186/s13054-017-1891-y [PMC free article] [PubMed] [CrossRef] [Google Scholar]
51. Anderson R, Smit MJ, Joone GK, Van Staden AM. Vitamin C and cellular immune functions. Protection against hypochlorous acid-mediated inactivation of glyceraldehyde-3-phosphate dehydrogenase and ATP generation in human leukocytes as a possible mechanism of ascorbate-mediated immunostimulation. Ann N Y Acad Sci. (1990) 587:34–48. 10.1111/j.1749-6632.1990.tb00131.x [PubMed] [CrossRef] [Google Scholar]
52. Lahiri S, Lloyd BB. The effect of stress and corticotrophin on the concentrations of vitamin C in blood and tissues of the rat. Biochem. J. (1962) 84:478–83. 10.1042/bj0840478 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
53. Manning J, Mitchell B, Appadurai DA, Shakya A, Pierce LJ, Wang H, et al. . Vitamin C promotes maturation of T-cells. Antioxid Redox Signal. (2013) 19:2054–67. 10.1089/ars.2012.4988 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
54. Valero N, Mosquera J, Alcocer S, Bonilla E, Salazar J, Álvarez-Mon M. Melatonin, minocycline and ascorbic acid reduce oxidative stress and viral titers and increase survival rate in experimental Venezuelan equine encephalitis. Brain Res. (2015) 1622:368–76. 10.1016/j.brainres.2015.06.034 [PubMed] [CrossRef] [Google Scholar]
55. Li W, Maeda N, Beck MA. Vitamin C deficiency increases the lung pathology of influenza virus-infected gulo-/- mice. J Nutr. (2006) 136:2611–16. 10.1093/jn/136.10.2611 [PubMed] [CrossRef] [Google Scholar]
56. Cai Y, Li Y-F, Tang L-P, Tsoi B, Chen M, Chen H, et al. . A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice. BioMed Res Int. (2015) 2015:675149. 10.1155/2015/675149 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
57. Banic S. Prevention of rabies by vitamin C. Nature. (1975) 258:153–4. 10.1038/258153a0 [PubMed] [CrossRef] [Google Scholar]
58. Kimbarowski JA, Mokrow NJ. Colored precipitation reaction of the urine according to Kimbarowski (FARK) as an index of the effect of ascorbic acid during treatment of viral influenza. Das Deutsche Gesundheitswesen. (1967) 22:2413–18. [PubMed] [Google Scholar]
59. Kim MS, Kim DJ, Na CH, Shin BS. A study of intravenous administration of vitamin c in the treatment of acute herpetic pain and postherpetic neuralgia. Ann Dermatol. (2016) 28:677–83. 10.5021/ad.2016.28.6.677 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

60. Kim GN, Yoo WS, Park MH, Chung JK, Han YS, Chung IY, et al. . Clinical features of herpes simplex keratitis in a Korean tertiary referral center: efficacy of oral antiviral and ascorbic acid on recurrence. Kor J Ophthalmol. (2018) 32:353–60. 10.3341/kjo.2017.0131 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
61. Hah YS, Chung HJ, Sontakke SB, Chung I-Y, Ju S. Ascorbic acid concentrations in aqueous humor after systemic vitamin C supplementation in patients with cataract: pilot study. BMC Ophthalmol. (2017) 17:121. 10.1186/s12886-017-0515-2 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
62. Gonzalez MJ, Berdiel MJ, Duconge J, Levy T, Alfaro I, Morales R, et al. High dose intravenous vitamin C and influenza: a case report. J Orthomol Med. (2018) 33:1–3. [Google Scholar]
63. Fowler Iii AA, Kim C, Lepler L, Malhotra R, Debesa O, Natarajan R., et al. . Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. World J Crit Care Med. (2017) 6:85–90. 10.5492/wjccm.v6.i1.85 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
64. Davis JM, Murphy EA, McClellan JL, Carmichael MD, Gangemi JD. Quercetin reduces susceptibility to influenza infection following stressful exercise. Am J Physiol Regul Integr Comp Physiol. (2008) 295:R505–9. 10.1152/ajpregu.90319.2008 [PubMed] [CrossRef] [Google Scholar]
65. Biskind MS, Martin WC. The use of citrus flavonoids in respiratory infections. Am J Dig Dis. (1954) 21:177. 10.1007/BF02886384 [PubMed] [CrossRef] [Google Scholar]
66. Liu S, Wu S, Jiang S. HIV entry inhibitors targeting gp41: from polypeptides to small-molecule compounds. Curr Pharm Des. (2007) 13:143–62. 10.2174/138161207779313722 [PubMed] [CrossRef] [Google Scholar]
67. Yang J, Li M, Shen X, Liu S. Influenza A virus entry inhibitors targeting the hemagglutinin. Viruses.(2013) 5:352–73. 10.3390/v5010352 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
68. Xia S, Liu Q, Wang Q, Sun Z, Su S, Duand L, et al. . Middle East respiratory syndrome coronavirus (MERS-CoV) entry inhibitors targeting spike protein. Virus Res. (2014) 194:200–10. 10.1016/j.virusres.2014.10.007 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
69. Wu W, Li R, Li X, He J, Jiang S, Liu S, et al. . Quercetin as an antiviral agent inhibits Influenza A Virus (IAV) entry. Viruses. (2015) 8:6. 10.3390/v8010006 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
70. Ganesan S, Faris AN, Comstock AT, Wang Q, Nanua S, Hershenson MB, et al. . Quercetin inhibits rhinovirus replication *in vitro* and *in vivo*. Antiviral Res. (2012) 94:258–71. 10.1016/j.antiviral.2012.03.005 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
71. Ganesan S, Faris AN, Comstock AT, Chattoraj SS, Chattoraj A, Burgess JR, et al. . Quercetin prevents progression of disease in elastase/LPS-exposed mice by negatively regulating MMP expression. Respir Res. (2010) 11:131. 10.1186/1465-9921-11-131 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
72. Nanua S, Zick SM, Andrade JE, Sajjan US, Burgess JR, Lukacs NW, et al. . Quercetin blocks airway epithelial cell chemokine expression. Am J Respir Cell Mol Biol. (2006) 35:602–10. 10.1165/rcmb.2006-0149OC [PMC free article] [PubMed] [CrossRef] [Google Scholar]
73. Rogerio AP, Kanashiro A, Fontanari C, da Silva EV, Lucisano-Valim YM, Soares EG, et al. . Anti-inflammatory activity of quercetin and isoquercitrin in experimental murine allergic asthma. Inflamm Res.(2007) 56:402–8. 10.1007/s00011-007-7005-6 [PubMed] [CrossRef] [Google Scholar]

74. Chiang LC, Chiang W, Liu MC, Lin CC. *In vitro* antiviral activities of Caesalpinia pulcherrima and its related flavonoids. J Antimicrob Chemother. (2003) 52:194–8. 10.1093/jac/dkg291 [PubMed] [CrossRef] [Google Scholar]
75. Ono K, Nakane H. Mechanisms of inhibition of various cellular DNA and RNA polymerases by several flavonoids. J Biochem. (1990) 108:609–13. 10.1093/oxfordjournals.jbchem.a123251 [PubMed] [CrossRef] [Google Scholar]
76. Ono K, Nakane H, Fukushima M, Chermann JC, Barré-Sinoussi F. Differential inhibitory effects of various flavonoids on the activities of reverse transcriptase and cellular DNA and RNA polymerases. Eur J Biochem. (1990) 190:469–76. 10.1111/j.1432-1033.1990.tb15597.x [PubMed] [CrossRef] [Google Scholar]
77. Vrijsen R, Everaert L, Boeyé A. Antiviral activity of flavones and potentiation by ascorbate. J Gen Virol. (1988) 69:1749–51. 10.1099/0022-1317-69-7-1749 [PubMed] [CrossRef] [Google Scholar]
78. Vrijsen R, Everaert L, Van Hoof LM, Vlietinck AJ, Vanden Berghe DA, Boeyé A., et al. . The poliovirus-induced shut-off of cellular protein synthesis persists in the presence of 3-methylquercetin, a flavonoid which blocks viral protein and RNA synthesis. Antiviral Res. (1987) 7:35–42. 10.1016/0166-3542(87)90037-4 [PubMed] [CrossRef] [Google Scholar]
79. Castrillo JL, Carrasco L. Action of 3-methylquercetin on poliovirus RNA replication. J Virol. (1987) 61:3319–21. 10.1128/JVI.61.10.3319-3321.1987 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
80. Li BW, Zhang FH, Serrao E, Chen H, Sanchez TW, Yang LM, et al. . Design and discovery of flavonoid-based HIV-1 integrase inhibitors targeting both the active site and the interaction with LEDGF/p75. Bioorg Med Chem. (2014) 22:3146–58. 10.1016/j.bmc.2014.04.016 [PubMed] [CrossRef] [Google Scholar]
81. Áy É, Hunyadi A, Mezei M, Minárovits J, Hohmann J. Flavonol 7-O-glucoside herbacitrin inhibits HIV-1 replication through simultaneous integrase and reverse transcriptase inhibition. Evid Based Complement Alternat Med. (2019) 2019:1064793. 10.1155/2019/1064793 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
82. Harakeh S, Jariwalla RJ, Pauling L. Suppression of human immunodeficiency virus replication by ascorbate in chronically and acutely infected cells. Proc Natl Acad Sci USA. (1990) 87:7245–9. 10.1073/pnas.87.18.7245 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
83. Xu HX, Wan M, Dong H, But PP, Foo LY. Inhibitory activity of flavonoids and tannins against HIV-1 protease. Biol Pharm Bull. (2000) 23:1072–6. 10.1248/bpb.23.1072 [PubMed] [CrossRef] [Google Scholar]
84. Gonzalez O, Fontanes V, Raychaudhuri S, Loo R, Loo J, Arumugaswami V, et al. . The heat shock protein inhibitor Quercetin attenuates hepatitis C virus production. Hepatology. (2009) 50:1756–64. 10.1002/hep.23232 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
85. Hosokawa N, Hirayoshi K, Kudo H, Takechi H, Aoike A, Kawai K, et al. . Inhibition of the activation of heat shock factor *in vivo* and *in vitro* by flavonoids. Mol Cell Biol. (1992) 12:3490–8. 10.1128/MCB.12.8.3490 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
86. Hosokawa N, Hirayoshi K, Nakai A, Hosokawa Y, Marui N, Yoshidaand M, et al. . Flavonoids inhibit the expression of heat shock proteins. Cell Struct Funct. (1990) 15:393–401. 10.1247/csf.15.393 [PubMed] [CrossRef] [Google Scholar]
87. Alvarez P, Alvarado C, Puerto M, Schlumberger A, Jiménez L, De la Fuente M., et al. . Improvement of leukocyte functions in prematurely aging mice after five weeks of diet supplementation with polyphenol-rich cereals. Nutrition. (2006) 22:913–21. 10.1016/j.nut.2005.12.012 [PubMed] [CrossRef] [Google Scholar]

88. Exon JH, Magnuson BA, South EH, Hendrix K. Effect of dietary chlorogenic acid on multiple immune functions and formation of aberrant crypt foci in rats. J Toxicol Environ Health A. (1998) 53:375–84. 10.1080/009841098159231 [PubMed] [CrossRef] [Google Scholar]
89. Cinatl J, Cinatl J, Weber B, Rabenau H, Gumbel H, Chenot J, et al. . *In vitro* inhibition of human cytomegalovirus replication in human foreskin fibroblasts and endothelial cells by ascorbic acid 2-phosphate. Antiviral Res. (1995) 27:405–18. 10.1016/0166-3542(95)00024-G [PubMed] [CrossRef] [Google Scholar]
90. Kim Y, Kim H, Bae S, Choi J, Lim SY, Lee N, et al. . Vitamin C is an essential factor on the anti-viral immune responses through the production of interferon-α/β at the initial stage of influenza A virus (H3N2) infection. Immune Netw. (2013) 13:70–74. 10.4110/in.2013.13.2.70 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
91. Mikirova N. Hunninghake R. Effect of high dose vitamin C on Epstein-Barr viral infection. Med Sci Monit. (2014) 20:725–32. 10.12659/MSM.890423 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
92. Kataoka A, Imai H, Inayoshi S, Tsuda T. Intermittent high-dose vitamin C therapy in patients with HTLV-I associated myelopathy. J Neurol Neurosurg Psychiatry. (1993) 56:1213–16. 10.1136/jnnp.56.11.1213 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
93. Nakagawa M, Nakahara K, Maruyama Y, Kawabata M, Higuchi I, Kubota H, et al. . Therapeutic trials in 200 patients with HTLV-I-associated myelopathy/ tropical spastic paraparesis. J Neurovirol. (1996) 2:345–55. 10.3109/13550289609146899 [PubMed] [CrossRef] [Google Scholar]
94. Stantic-Pavlinic M, Banic S, Marin J, Klemenc P. Vitamin C–a challenge in management of rabies. Swiss Med Weekly. (2004) 134:326–7. [PubMed] [Google Scholar]
95. Siegel BV. Enhanced interferon response to murine leukemia virus by ascorbic acid. Infect Immun. (1974) 10:409–10. 10.1128/IAI.10.2.409-410.1974 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
96. Siegel BV. Enhancement of interferon production by poly(rI)-poly(rC) in mouse cell cultures by ascorbic acid. Nature. (1975) 254:531–2. 10.1038/254531a0 [PubMed] [CrossRef] [Google Scholar]
97. Horvath CM. The Jak-STAT pathway stimulated by interferon gamma. Sci STKE. (2004) 2004:tr8. 10.1126/stke.2602004tr8 [PubMed] [CrossRef] [Google Scholar]
98. Yi L, Li Z, Yuan K, Qu X, Chen J, Wang G, et al. . Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J Virol. (2004) 78:11334. 10.1128/JVI.78.20.11334-11339.2004 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
99. Rota PA, Oberste MS, Monroe SS, Nix WA, Campagnoli R, Icenogle JP, et al. . Characterization of a novel coronavirus associated with severe acute respiratory syndrome. Science. (2003) 300:1394–9. 10.1126/science.1085952 [PubMed] [CrossRef] [Google Scholar]
100. Marra MA, Jones SJ, Astell CR, Holt RA, Brooks-Wilson A, Butterfield YS, et al. . The genome sequence of the SARS-associated coronavirus. Science. (2003) 300:1399–404. 10.1126/science.1085953 [PubMed] [CrossRef] [Google Scholar]
101. Snijder EJ, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LLM, et al. . Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineage. J Mol Biol. (2003) 331:991–1004. 10.1016/S0022-2836(03)00865-9 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
102. Chen L, Li J, Luo C, Liu H, Xu W, Chen G, et al. . Binding interaction of quercetin-3-beta-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): structure-activity relationship

studies reveal salient pharmacophore features. Bioorg Med Chem. (2006) 14:8295–306. 10.1016/j.bmc.2006.09.014 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
103. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. . A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. (2020) 579:270–3. 10.1038/s41586-020-2012-7 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
104. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. . Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. (2020) 395:565–74. 10.1016/S0140-6736(20)30251-8 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
105. Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L, et al. . Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science. (2020) 368:409–12. 10.3410/f.737592020.793572879 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
106. Atherton JG, Kratzing CC, Fisher A. The effect of ascorbic acid on infection chick-embryo ciliated tracheal organ cultures by coronavirus. Arch Virol. (1978) 56:195–9. 10.1007/BF01317848 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
107. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol. (2008) 585:325–37. 10.1016/j.ejphar.2008.03.008 [PubMed] [CrossRef] [Google Scholar]
108. Guo Y, Bruno RS. Endogenous and exogenous mediators of quercetin bioavailability. J Nutr Biochem. (2015) 26:201–10. 10.1016/j.jnutbio.2014.10.008 [PubMed] [CrossRef] [Google Scholar]
109. Murota K, Terao J. Antioxidative flavonoid quercetin: implication of its intestinal absorption and metabolism. Arch Biochem Biophys. (2003) 417:12–7. 10.1016/S0003-9861(03)00284-4 [PubMed] [CrossRef] [Google Scholar]
110. Graefe EU, Derendorf H, Veit M. Pharmacokinetics and bioavailability of the flavonol quercetin in humans. Int J Clin Pharmacol Ther. (1999) 37:219–33. [PubMed] [Google Scholar]
111. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. Food Chem Toxicol. (2007) 45:2179–205. 10.1016/j.fct.2007.05.015 [PubMed] [CrossRef] [Google Scholar]
112. Andrea J, Day JAR, Morgan RA. Characterization of polyphenols metabolites. In: Bao Y, Fenwick R. editors. Phytochemicals in Health and Disease. New York, NY: Marcel Dekker, Inc; (2005). p. 50. [Google Scholar]
113. de Boer VC, Dihal AA, van der Woude H, Arts IC, Wolffram S. Tissue distribution of quercetin in rats and pigs. J Nutr. (2005) 135:1718–25. 10.1093/jn/135.7.1718 [PubMed] [CrossRef] [Google Scholar]
114. Moon YJ, Wang L, DiCenzo R, Morris ME. Quercetin pharmacokinetics in humans. Biopharm Drug Dispos. (2008) 29:205–17. 10.1002/bdd.605 [PubMed] [CrossRef] [Google Scholar]
115. Shoskes DA, Zeitlin SI, Shahed A, Rajfer J. Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. Urology. (1999) 54:960–3. 10.1016/S0090-4295(99)00358-1 [PubMed] [CrossRef] [Google Scholar]
116. Ferry DR, Smith A, Malkhandi J, Fyfe DW, deTakats PG, Anderson D, et al. . Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for *in vivo* tyrosine kinase inhibition. Clin Cancer Res. (1996) 2:659–68. [PubMed] [Google Scholar]
117. Marik PE. Vitamin C for the treatment of sepsis: the scientific rationale. Pharmacol Ther. (2018) 189:63–70. 10.1016/j.pharmthera.2018.04.007 [PubMed] [CrossRef] [Google Scholar]

118. Awad HM, Boersma MG, Boeren S, van der Woude H, van Zanden J, van Bladeren PJ, et al. . Identification of o-quinone/quinone methide metabolites of quercetin in a cellular *in vitro* system. FEBS Lett. (2002) 520:30–34. 10.1016/S0014-5793(02)02754-0 [PubMed] [CrossRef] [Google Scholar]
119. Boots AW, Li H, Schins RP, Duffin R, Heemskerk JW, Bast A, et al. . The quercetin paradox. Toxicol Appl Pharmacol. (2007) 222:89–96. 10.1016/j.taap.2007.04.004 [PubMed] [CrossRef] [Google Scholar]
120. Askari G, Ghiasvand R, Feizi A, Ghanadian SM, Karimian J. The effect of quercetin supplementation on selected markers of inflammation and oxidative stress. J Res Med Sci. (2012) 17:637–41. [PMC free article] [PubMed] [Google Scholar]
121. Boots AW, Kubben N, Haenen GR, Bast A. Oxidized quercetin reacts with thiols rather than with ascorbate: implication for quercetin supplementation. Biochem Biophys Res Commun. (2003) 308:560–5. 10.1016/S0006-291X(03)01438-4 [PubMed] [CrossRef] [Google Scholar]
122. Bors W, Michel C, Schikora S. Interaction of flavonoids with ascorbate and determination of their univalent redox potentials: a pulse radiolysis study. Free Radic Biol Med. (1995) 19:45–52. 10.1016/0891-5849(95)00011-L [PubMed] [CrossRef] [Google Scholar]
123. Moalin M, van Strijdonck GPF, Bast A, Haenen GRMM. Competition between ascorbate and glutathione for the oxidized form of methylated quercetin metabolites and analogues: tamarixetin, 4′o-methylquercetin, has the lowest thiol reactivity. J Agric Food Chem. (2012) 60:9292–7. 10.1021/jf302068v [PubMed] [CrossRef] [Google Scholar]
124. Boots AW, Balk JM, Bast A, Haenen GR. The reversibility of the glutathionyl-quercetin adduct spreads oxidized quercetin-induced toxicity. Biochem Biophys Res Commun. (2005) 338:923–9. 10.1016/j.bbrc.2005.10.031 [PubMed] [CrossRef] [Google Scholar]
125. Awad HM, Boersma MG, Boeren S, Van Bladeren PJ, Vervoort J, Rietjens IM. Quenching of quercetin quinone/quinone methides by different thiolate scavengers: stability and reversibility of conjugate formation. Chem Res Toxicol. (2003) 16:822–31. 10.1021/tx020079g [PubMed] [CrossRef] [Google Scholar]
126. Roubalová L, Purchartová K, Papoušková B, Vacek J, Kren V, Ulrichová J, et al. . Sulfation modulates the cell uptake, antiradical activity and biological effects of flavonoids *in vitro*: an examination of quercetin, isoquercitrin and taxifolin. Bioorg Med Chem. (2015) 23:5402–9. 10.1016/j.bmc.2015.07.055 [PubMed] [CrossRef] [Google Scholar]
127. Ruotolo R, Calani L, Brighenti F, Crozier A, Ottonello S, Del Rio D. Glucuronidation does not suppress the estrogenic activity of quercetin in yeast and human breast cancer cell model systems. Arch Biochem Biophys. (2014) 559:62–7. 10.1016/j.abb.2014.03.003 [PubMed] [CrossRef] [Google Scholar]
128. Terao J, Murota K, Kawai Y. Conjugated quercetin glucuronides as bioactive metabolites and precursors of aglycone *in vivo*. Food Funct. (2011) 2:11–7. 10.1039/C0FO00106F [PubMed] [CrossRef] [Google Scholar]
129. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. . Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. (2020) 34:1. 10.23812/CONTI-E [PubMed] [CrossRef] [Google Scholar]
130. Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, et al. Neutrophil extracellular traps in COVID-19. JCI Insight. (2020) 5 10.1172/jci.insight.138999 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

131. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. . Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis. (2020) 221:1762–9. 10.1093/infdis/jiaa150 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
132. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. . Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med. (2020) 10.1056/NEJMoa2007764 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
133. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. . Treatment of 5 critically Ill patients with COVID-19 with convalescent plasma. JAMA. (2020) 323:1582–9. 10.1001/jama.2020.4783 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
134. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. . Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol. (2020). [Epub ahead of print]. 10.1002/jmv.25882 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
135. Carr AC, Lykkesfeldt J. Discrepancies in global vitamin C recommendations: a review of RDA criteria and underlying health perspectives. Crit Rev Food Sci Nutr. (2020) 1–14. 10.1080/10408398.2020.1744513 [PubMed] [CrossRef] [Google Scholar]