

Commentary

The Preventive Effect of Dietary Antioxidants on Viral Infection (Coronavirus Disease-2019, Influenza and Human Papillomavirus) and the Development of Cervical Carcinogenesis

Eri Ikuta, RN, MA¹; Masafumi Koshiyama, MD, PhD^{2*}; Miwa Nakagawa, RN, MA¹; Ayumi Ono, RN, MA¹; Yumiko Watanabe, CNM, MA²; Keiko Seki, RN, MA¹; Makiko Oowaki, CNM, PhD¹; Yuji Okuda, MD, PhD³

¹Graduate School of Human Nursing, The University of Shiga Prefecture, 2500 Hassakacho, Hikone, Shiga 522-8533, Japan

²Department of Women's Health, Graduate School of Human Nursing, The University of Shiga Prefecture, 2500 Hassakacho, Hikone, Shiga 522-8533, Japan

³Okuda Clinic, 5-9 Honmachi, Youkaichi, Shiga 527-0012, Japan

*Corresponding author

Masafumi Koshiyama, MD, PhD

Professor, Department of Women's Health, Graduate School of Human Nursing, The University of Shiga Prefecture, 2500 Hassakacho, Hikone, Shiga 522-8533, Japan; Tel. +81-749-28-8664; Fax +81-749-28-9532; E-mail: koshiyamam@nifty.com

Article information

Received: December 3rd, 2021; **Revised:** December 10th, 2021; **Accepted:** December 10th, 2021; **Published:** December 14th, 2021

Cite this article

Ikuta E, Koshiyama M, Nakagawa M, et al. The preventive effect of dietary antioxidants on viral infection (coronavirus disease-2019, Influenza and human papillomavirus) and the development of cervical carcinogenesis. *Women Health Open J.* 2021; 7(2): 34-37. doi: [10.17140/WHOJ-7-145](https://doi.org/10.17140/WHOJ-7-145)

Viral infections cause the production of radicals and reactive oxygen species (ROS) in cells. Disbalance between ROS generation and elimination results in oxidative stress. Oxidative stress plays an important role in pathogenesis.¹ Thus, oxidative processes cause virus replication in infected cells, decrease cell proliferation and induce cell apoptosis,² leading to chain reactions and subsequently damaging the cells of organisms.³ In contrast, an antioxidant is any substance that significantly inhibits or delays the oxidation of a substance.⁴ The role of antioxidants is also to complete chain reactions and prevent the damage of cellular components due to free radicals and associated chemical reactions.^{3,4} Beck also insisted that the antioxidant selenoenzyme, glutathione peroxidase-1, was found to be critically important, as glutathione peroxidase knockout mice developed myocarditis, when infected with a benign strain of myocarditis.⁵ This work points to the importance of host nutrition in not only optimizing the host immune response, but also preventing viral mutations that could increase viral pathogenesis.

Coronaviruses (CoVs) are single-stranded ribonucleic acid (RNA) viruses which cause respiratory, gastrointestinal, hepatic and neurologic disease.⁶ Above all, coronavirus disease-2019 (COVID-19) disease began to spread from Wuhan, China, in December 2019.^{7,8} On March 11, 2020, the World Health Organization (WHO) announced the world wide COVID-19 pandemic only 2-months after the official disclosure from the Chinese government. Oxidative stress and lipid oxidation are involved in the pathogenesis of COVID-19-related pulmonary damage.⁹

Curcumin, a polyphenol (one of antioxidants), has been shown to target multiple signaling molecules while also demonstrating activity at the cellular level, which has helped to support its multiple health benefits.¹⁰ Moreover, curcumin has been reported to bind to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); the virus that causes COVID-19 target receptor.¹¹ Curcumin could therefore be a potential treatment option for patients with COVID-19.¹² In addition, it has been reported that the combination of vitamin C, curcumin and glycyrrhizic acid, promotes the production of interferons and regulates the inflammatory response, suggesting that the combination of these compounds may be useful in modulating the immune response to counteract the SARS-CoV-2 infections.¹³ Vitamin D induces cathelicidins and defensins which can lower viral replication rates and reduce concentrations of pro-inflammatory cytokines, which produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increase the concentrations of anti-inflammatory cytokines can also reduce risk of infection.¹⁴ Therefore, vitamin D can reduce risk of viral infection. Grant et al¹⁴ suggested that vitamin D supplementation may decrease the risk of contracting influenza and COVID-19 infections. In a nutritional protocol for COVID-19 patients, the supplementation of 25-hydroxyvitamin D (25(OH)D) is planned.¹⁵

De Alencar et al¹⁶ reported a double-blind, randomized, placebo-controlled trial with N-acetylcysteine (NAC) as an antioxidant for the treatment of severe acute respiratory syndrome caused by COVID-19. However, no difference was observed in secondary endpoints between 67 patients in the placebo group and

68 patients in the NAC group. Thus, the administration of NAC in high doses did not affect the evolution of severe COVID-19.

It has been reported that influenza virus (IV) infection also leads to the induction of oxidative stress or ROS damage and the development of the clinical outcome.¹⁷ Mouse models and cell lines infected with IVs showed the enhanced ROS levels, together with an imbalance of antioxidant protection.^{18,19} These models indicated the relevance of the redox homeostasis induced by IVs.²⁰ During IV infection, the cellular metabolism of the host cells could be affected, leading to the dysregulation of redox homeostasis. Antioxidant therapies have been proposed to decrease the viral load and counteract the lung injuries caused by the overproduction of ROS induced by viruses.²¹ Some antioxidants are effective in this protection against infection through the nuclear erythroid 2-related factor 2 (Nrf2) pathway.²² However, the direct clinical use of antioxidation drugs for IV-infected patients has never been reported.

Persistent infection by high-risk human papillomavirus (HPV) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) genotypes has been recognized as a necessary step in the development, maintenance, and progression of cervical intraepithelial neoplasia (CIN) and cervical cancer.²³

HPV is a small, non-enveloped deoxyribonucleic acid (DNA) virus that infects the skin or vaginal mucosal cells.²⁴ The circular, double-stranded viral genome is approximately 8-kb in length.

During recent decades, the important role of antioxidants in preventing the development of cervical carcinogenesis has been received much attention.^{25,26} Antioxidants can act as efficient scavengers of free radicals and oxidants to prevent free-radical damage to DNA.²⁷ Moreover, if free radicals and oxidants are not neutralized by antioxidant molecules, the inflammatory processes caused by HPV infection could lead to extensive damage to DNA proteins.²⁸ The major product of DNA oxidation is also correlated with increased HPV infection, viral-host integration, and the development of dysplasia.²⁹ Thus, apoptosis is hindered by the disruption of many regulator pathways, which results in altered cellular proliferation.³⁰

Different antioxidants may have differing abilities to intervene in the natural history of cervical diseases associated with HPV infection. The intake of carotenoids may inhibit early events of cervical cancer development (HPV infection).^{31,32} The intake of vitamin A and D may also inhibit early events (from HPV infection to the development of CIN 1).³³⁻³⁶ The intake of folate was reported to potentially inhibit the events from HPV infection to the development of various grades of CIN.³⁷⁻³⁹ Furthermore, the intake of vitamin C and E may widely inhibit cervical cancer development (from HPV infection to the development of CIN 1, 2 and 3, as well as cervical cancer).^{23,40-42} However, the intake of antioxidants cannot inhibit cervical cancer development without chemotherapy and radiation therapy.²⁶

We suggest that the intake of antioxidants may prevent both RNA and DNA virus infection and persistent infection. However, we do not consider them to be sufficiently effective for the treatment of advanced stage disease.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Kuzmenko YV, Smirnova OA, Ivanov AV, Starodubova ES, Karpov VL. Nonstructural protein 1 of tick-borne encephalitis virus induces oxidative stress and activates antioxidant defense by the Nrf2/ARE pathway. *Intervirology*. 2016; 59: 111-117. doi: [10.1159/000452160](https://doi.org/10.1159/000452160)
2. Hejrati A, Nurzadeh M, Ruham M. Association of coronavirus pathogenicity with the level of antioxidants and immune system. *J Family Med Prim Care*. 2021; 10: 609-614. doi: [10.4103/jfmpc.jfmpc_1007_20](https://doi.org/10.4103/jfmpc.jfmpc_1007_20)
3. Salehi I, Martorell M, Arbiser JL, et al. Antioxidants: Positive or negative actors? *Biomolecules*. 2018; 8: 124. doi: [10.3390/biom8040124](https://doi.org/10.3390/biom8040124)
4. Young I, Woodside J. Antioxidants in health and disease. *J Clin Pathol*. 2001; 54: 176-186. doi: [10.1136/jcp.54.3.176](https://doi.org/10.1136/jcp.54.3.176)
5. Beck MA. Antioxidants and viral infections: host immune response and viral pathogenicity. *J Am Coll Nutr*. 2001; 20: 384S-388S. doi: [10.1080/07315724.2001.10719172](https://doi.org/10.1080/07315724.2001.10719172)
6. Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: What we know. *Int J Infect Dis*. 2020; 94: 44-48. doi: [10.1016/j.ijid.2020.03.004](https://doi.org/10.1016/j.ijid.2020.03.004)
7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395: 497-506. doi: [10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
8. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020; 382(8): 727-733. doi: [10.1056/NEJMoa2001017](https://doi.org/10.1056/NEJMoa2001017)
9. Lapenna D. Antioxidant therapy in coronavirus disease 2019: The crucial role of early treatment and antioxidant typology. *Clin Infect Dis*. 2021. doi: [10.1093/cid/ciab055](https://doi.org/10.1093/cid/ciab055)
10. Hewlings S, Kalman DS. Curcumin: A review of its effects on human health. *Foods*. 2017; 6: 92. doi: [10.3390/foods6100092](https://doi.org/10.3390/foods6100092)
11. Utomo RY, Ikawati M, Meiyanto E. Revealing the potency of citrus and galangal constituents to halt SARS-CoV-2 infection. *Preprints*. 2020; 2: 1-8. doi: [10.20944/preprints202003.0214.v1](https://doi.org/10.20944/preprints202003.0214.v1)

12. Lammi C, Arnoldi A. Food-derived antioxidants and COVID-19. *J Food Biochem*. 2021; 45: e13557. doi: [10.1111/jfbc.13557](https://doi.org/10.1111/jfbc.13557)
13. Chen L, Hu C, Hood M, et al. A novel combination of vitamin C, curcumin and glycyrrhizic acid potentially regulates immune and inflammatory response associated with coronavirus infections: A perspective from system biology analysis. *Nutrients*. 2020; 12: 1193. doi: [10.3390/nu12041193](https://doi.org/10.3390/nu12041193)
14. Grant WB, Baggerly CA, Lahore H. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020; 12: 988. doi: [10.3390/nu12040988](https://doi.org/10.3390/nu12040988)
15. Caccialanza R, Laviano A, Lobascio F, et al. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. *Nutrition*. 2020; 74: 110835. doi: [10.1016/j.nut.2020.110835](https://doi.org/10.1016/j.nut.2020.110835)
16. De Alencar JCG, Moreira CL, Miller AD, et al. Double-blind, randomized, placebo-controlled trial with N-acetylcysteine for treatment of severe acute respiratory syndrome caused by COVID-19. *Clin Infect Dis*. 2021; 72: e736-e741. doi: [10.1093/cid/ciaa1443](https://doi.org/10.1093/cid/ciaa1443)
17. Chen KK, Minakuchi M, Wuputra K, et al. Redox control in the pathophysiology of influenza virus infection. *BMC Microbiology*. 2020; 20: 1-22. 214. doi: [10.1186/s12866-020-01890-9](https://doi.org/10.1186/s12866-020-01890-9)
18. Amatore D, Sgarbanti R, Aquilano K, et al. Influenza virus replication in lung epithelial cells depends on redox-sensitive pathways activated by NOX4-derived ROS. *Cell Microbiol*. 2015; 17: 131-145. doi: [10.1111/cmi.12343](https://doi.org/10.1111/cmi.12343)
19. Yes S, Lowther S, Stambas J. Inhibition of reactive oxygen species production ameliorates inflammation induced by influenza A viruses via upregulation of SOCS1 and SOCS3. *J Virol*. 2015; 89: 2672-2683. doi: [10.1128/JVI.03529-14](https://doi.org/10.1128/JVI.03529-14)
20. Laghlali G, Lawlor KE, Tate MD. Die another way: Interplay between influenza A virus. *Viruses*. 2020; 12: 401. doi: [10.3390/v12040401](https://doi.org/10.3390/v12040401)
21. Fraternale A, Paoletti MF, Casabianca A, et al. Antiviral and immunomodulatory properties of new pro-glutathione (GSH) molecules. *Curr Med Chem*. 2006; 13: 1749-1755. doi: [10.2174/09298670677452542](https://doi.org/10.2174/09298670677452542)
22. Lee C. Therapeutic modulation of virus-induced oxidative stress via the nrf-dependent antioxidative pathway. *Oxid Med Cell Longev*. 2018; 2018: 6208067. doi: [10.1155/2018/6208067](https://doi.org/10.1155/2018/6208067)
23. Koshiyama M, Nakagawa M, Ono M. The preventive effect of dietary antioxidants against cervical cancer versus the promotive effect of tobacco smoking. *Healthcare*. 2019; 7: 1-6. doi: [10.3390/healthcare7040162](https://doi.org/10.3390/healthcare7040162)
24. World Health Organization (WHO). Human Papillomavirus (HPV). Web site. <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/human-papillomavirus>. Accessed August 17, 2021.
25. Guo L, Zhu H, Lin C, et al. Associations between antioxidant vitamins and the risk of invasive cervical cancer in Chinese women: A case-control study. *Sci Rep*. 2015; 5: 13607. doi: [10.1038/srep13607](https://doi.org/10.1038/srep13607)
26. Koshiyama M. The effects of the dietary and nutrient intake on gynecologic cancer. *Healthcare*. 2019; 7: 1-23. doi: [10.3390/healthcare7030088](https://doi.org/10.3390/healthcare7030088)
27. Salganik RI. The benefits and hazards of antioxidants: Controlling apoptosis and other protective mechanisms in cancer patients and the human population. *Am Coll Nutr*. 2001; 20: 464S-472S. doi: [10.1080/07315724.2001.10719185](https://doi.org/10.1080/07315724.2001.10719185)
28. Eiserich JP, van der Vliet A, Handelman GJ, Halliwell B, Cross CE. Dietary antioxidants and cigarette smoke-induced biomolecular damage: A complex interaction. *Am J Clin Nutr*. 1995; 62: 1490S-1500S. doi: [10.1093/ajcn/62.6.1490S](https://doi.org/10.1093/ajcn/62.6.1490S)
29. Visalli G, Riso R, Facciola A, et al. Higher levels of oxidative DNA damage in cervical cells are correlated with the grade of dysplasia and HPV infection. *J Med Virol*. 2016; 88: 336-344. doi: [10.1002/jmv.24327](https://doi.org/10.1002/jmv.24327)
30. Kgatle MM, Spearman CW, Kalla AA, Hairwadzi HN. DNA oncogenic virus-induced oxidative stress, genomic damage, and aberrant epigenetic alterations. *Oxid Med Cell Longev*. 2017; 2017: 3179421. doi: [10.1155/2017/3179421](https://doi.org/10.1155/2017/3179421)
31. Giuliano AR, Siegel EM, Roe DJ, Ferreira S, Baggio ML, Galan L, et al. Dietary intake and risk of persistent human papillomavirus (HPV) infection: The Ludwig-McGill HPV Natural History Study. *J Infect Dis*. 2003; 188: 1508-1516. doi: [10.1086/379197](https://doi.org/10.1086/379197)
32. Sedjo RL, Roe DJ, Abrahamsen M, et al. Vitamin A, carotenoids, and risk of persistent oncogenic human papillomavirus infection. *Cancer Epidemiol Biomarkers Prev*. 2002; 11: 876-884.
33. Yeo AS, Schiff MA, Montoya G, Masuk M, van Asselt-King L, Becker TM. Serum micronutrients and cervical dysplasia in Southwestern American Indian women. *Nutr Cancer*. 2000; 38: 141-150. doi: [10.1207/S15327914NC382_1](https://doi.org/10.1207/S15327914NC382_1)
34. Zhang YY, Lu L, Abliz G, Mijit F. Serum carotenoid, retinol and tocopherol concentrations and risk of cervical cancer among Chinese women. *Asian Pac Cancer Prev*. 2015; 16: 2981-2986. doi: [10.7314/apjcp.2015.16.7.2981](https://doi.org/10.7314/apjcp.2015.16.7.2981)
35. Huang X, Chen C, Zhu F, et al. Association between dietary

- vitamin A and HPV infection in American women: data from NHANES 2003-2016. *BioMed Research International*. 2020; 2020: 1-7. doi: [10.1155/2020/4317610](https://doi.org/10.1155/2020/4317610)
36. Ono A, Koshiyama M, Nakagawa M, et al. The preventive effect of dietary antioxidants on cervical cancer development. *Medicina*. 2020; 56: doi: [10.3390/medicina56110604](https://doi.org/10.3390/medicina56110604)
37. Hernandez BY, McDuffie K, Wilkens LR, Kamemoto L, Goodman MT. Diet and premalignant lesions of the cervix: evidence of a protective role for folate, riboflavin, thiamin, and vitamin B12. *Cancer Causes Control*. 2003; 14: 859-870.
38. Piyathilake CJ, Henao OL, Macaluso M, et al. Folate is associated with the natural history of high-risk human papillomaviruses. *Cancer Res*. 2004; 64: 8788-8793. doi: [10.1158/0008-5472.CAN-04-2402](https://doi.org/10.1158/0008-5472.CAN-04-2402)
39. Kwanbunjan K, Saengkar P, Cheeramakara C, et al. Low folate status as a risk factor for cervical dysplasia in Thai women. *Nutr Res*. 2005; 25: 641-654. doi: [10.1016/j.nutres.2005.05.004](https://doi.org/10.1016/j.nutres.2005.05.004)
40. Manju V, Kalaivani SJ, Nalmi N. Circulating lipid peroxidation and antioxidant status in cervical cancer patients: A case-control study. *Clin Biochem*. 2002; 35: 621-625. doi: [10.1016/s0009-9120\(02\)00376-4](https://doi.org/10.1016/s0009-9120(02)00376-4)
41. Cao D, Shen K, Li Z, Xu Y, Wu D. Association between vitamin C intake and the risk of cervical neoplasia: A meta-analysis. *Nutr Cancer*. 2016; 68: 48-57. doi: [10.1080/01635581.2016.1115101](https://doi.org/10.1080/01635581.2016.1115101)
42. Leekha A, Gurjar BS, Tyagi A, Rizvi MA, Verma AK. Vitamin C in synergism with cisplatin induces cell death in cervical cancer cells through altered redox cycling and p53 upregulation. *J Cancer Res Clin Oncol*. 2016; 142: 2503-2514. doi: [10.1007/s00432-016-2235-z](https://doi.org/10.1007/s00432-016-2235-z)