Title
COVID-19: repositioning nutrition research for the next pandemic.

Permalink
https://escholarship.org/uc/item/3zg0221z

Authors
Jaggers, Grayson K
Watkins, Bruce A
Rodriguez, Raymond L

Publication Date
2020-09-01

DOI
10.1016/j.nutres.2020.07.005

Peer reviewed
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19: repositioning nutrition research for the next pandemic

At the time of this writing, the COVID-19 pandemic will have infected more than 17 million people and taken the lives of nearly 700,000 individuals world-wide [1]. While containment and treatment strategies have focused primarily on social distancing, therapeutics, and vaccines, the pandemic has also revealed serious underlying vulnerabilities in individuals infected by the coronavirus, SARS-CoV-2. The vulnerable aspects include advanced age, obesity [and its comorbidities, diabetes and chronic heart diseases], systemic coagulopathy or thrombosis [2], acute respiratory failure (e.g., hypoxia), inflammation, immunodeficiency, and neuropathologies [3,4]. The evidence for vulnerable people is supported by early reports on the COVID-19 pandemic in the United States that revealed ethnic, racial, and socio-economic disparities that resulted in some sectors of the population being disproportionately affected by COVID-19. Some of the sectors showing disproportionate rates of infection and death included men, American Indians, Alaska Natives, Blacks, Latinos, older adults, recent immigrants, and individuals with low income [5,6]. What is largely missed by the public, researchers, and healthcare providers is how nutrition and food intersect with this multiplicity of COVID-19 symptoms and disparities, in different ways and to different degrees.

It is well documented that nutrition, food, herbs, nutrients, and supplements, including various combinations and compositions, support metabolism and physiology required for health [7,8]. Table 1 shows the nutrients and herbs that complement the immune system and control inflammation to promote cell-associated antibody production and cell-mediated immunity [9]. A balanced diet, with the myriad of nutrients vital to health, supports normal B and T cell functions for optimal disease-reducing immunity [10]. In the case of COVID-19, the goal of nutrition is to reduce infection and disease progression while improving recovery during the course of the disease (Table 1). Therefore, it is critical that the medical community and supporting healthcare professionals understand the role of nutrition for maintaining health and reducing disease risk. In light of improving nutrition to avert or control COVID-19 infections, healthcare providers must support proper nutrition, and specifically, the nutrition necessary to protect those in high risk groups such as the elderly. Many elderly individuals suffer from poor nutrition because of marginal intakes of critical vitamins, minerals, and essential amino acids necessary for a robust immune system. This situation is further exacerbated by the declining gastrointestinal uptake of micronutrients and macronutrients that occurs with advanced age [11].

A recent review describes the role of nutrition in viral infections [12]. The fat-soluble vitamins A, D, E, and specific minerals play a significant role in the physiology of the immune system [10,12]. Vitamin A improves responses to vaccines and augments both cellular and humoral immunity. The function of vitamin D is important for aging and protection against viral infection. Vitamin D supports innate immune responses to influenza A-B, parainfluenza 1-2, and low vitamin D status is associated with an increased risk of both upper and lower respiratory tract infections [12]. Thus, vitamin D status appears to play a role in antiviral immunity and depending on vitamin D status, immunity could be compromised, especially in the elderly. Vitamin E deficiency is known to impair both humoral and cellular immunity [9]. Additionally, the fat-soluble vitamins serve a role in tissue growth. Vitamin C can also support antiviral immune protection in rodents and general functions in antioxidants pathways as well as co-factors for physiology of immune tissues [12].

Trace elements that support immune functions include Zn, Cu, and Mg. Marginal Zn status is associated with increased susceptibility of infections including viral [9], and Se has pleiotropic effects ranging from antioxidant to anti-inflammatory properties. Cu supports differentiation of immune cells, while Mg influences the synthesis of immunoglobulins such as immunoglobulin M. Immunoglobulin is a target of antibody testing for COVID 19 exposure [12].

In addition to the important roles vitamins and minerals play in immune function, the essential fatty

https://doi.org/10.1016/j.nutres.2020.07.005
0271-5317/® 2020 Elsevier Inc. All rights reserved.
acids also have modulating effects on immunity and inflammatory processes [10]. The essential fatty acids and related long chain polyunsaturated fatty acids (PUFA) serve as substrate for oxylipins (OxL) and endocannabinoids (eCB) produced by immunocompetent cells supporting immune functions and modulating inflammation [13]. A balanced diet must include adequate essential fatty acids and both n-6 and n-3 PUFA for OxL and eCB that modulate the immune system and control inflammation. Unfortunately, by the time an individual is in the depths of the COVID-19 infection, the benefits of nutrition-based interventions can do little to mitigate or reverse the course of the disease. However, proper nutrition and nutrition support can help by improving immune responses and aid inflammatory processes.

The COVID-19 pandemic provides nutrition researchers and educators new opportunities to inform the public, particularly those in high-risk groups, about the potential life-saving benefits of good nutrition and healthy eating habits [3,14]. While it may be too late for some, there is still time for others to begin preparing their bodies and physiologies for the next infectious pandemic. In this case, providing good nutrition, adequate protein and calories, and likely vitamin and mineral supplements to the aged community can only help their immune system and general health.

As virologists, epidemiologists, and physicians mount a full-court press against the COVID-19 pandemic, one might ask what role can nutrition scientists play in these interdisciplinary efforts? The answer is that nutrition research has much to contribute to the anti-COVID-19 campaign, even if the connection is nonobvious, complex, and challenging to comprehend by the general public and policymakers. What most individuals are familiar with are excellent dietary recommendations, such as those found in the 2015–2020 Dietary Guidelines for Americans, 8th edition [15]. While these recommendations help Americans eat healthier, with the benefits of improved adaptive immune systems and metabolic responses, the rationale to follow a sound diet will also help promote resistance to COVID-19 – like infections. With knowledge of nutrients, food, and herbs that support the immune system, health professionals can advance the exciting developments in nutrition research that could take nutritional intervention to the next level and into the intensive care unit.

The intellectual space between starvation/death and health/wellness is wide and punctuated with many historic landmarks and breakthroughs from the food and nutrition sciences [16]. Over the past two decades, however, the “omics” revolution and big data analytics have created new opportunities to shrink the distance between diet-derived bioactive compounds (e.g.,

Table 1 – Examples of nutrients and phytochemicals with potential preventative or therapeutic impact on risk factors associated with acute COVID-19

| Nutrient, phytochemical | Risk factor | Associated pathway/ select biomarker(s) | References |
|-------------------------|------------|----------------------------------------|------------|
| n-3 PUFA                | Inflammation and immune dysregulation | ECS, NF-κB, TNF-α, MCP-1 | [9,13,24-33] |
| EPA                     | Cardiovascular disease | PI3K/Akt, MAPK/ERK | [28,34,35] |
| DHA                     | Obesity | PI3K/Akt, MAPK/ERK, AMPK | [13,24,27,36-48] |
|                        | Diabetes | PI3K/Akt, MAPK/ERK, GLUT4 | [13,24,26,27,34,44,45] |
|                        | Respiratory inflammation/disease | TLR-4, GPR120, 7nAChR | [25,46-50] |
|                        | Neurodegeneration/ neuroinflammation | EGR-1, COX-2, 15-LOX | [13,51-52] |
| Phytochemicals          | Inflammation and immune dysregulation | NOX, NF-κB, Erk, Akt, TNF-α | [53-64] |
| [–]Epicatechin          | Cardiovascular disease | TGF-β1/smad3, NOX, eNOS | [53,54,65,66] |
| Resveratrol             | Diabetes | NOX, NF-κB, JNK1/2 | [60,61] |
| Curcumin                | Respiratory inflammation/disease | PI3K/AKT/HIF-1α, MAPK/ERK/HIF-1α, TLR-4 | [55,61-64,67] |
| EGCG                    | Neurodegeneration/ neuroinflammation | TLR-4/IFN-κB, PI3K/Akt | [52,56,61,68-69] |
| Vitamins                | Impaired immune system, inflammation | Cell proliferation & maturation, IL-6, TNF-α, NF-κB, COX-1 | [9-10,70-71] |
| Vitamin A               | Respiratory inflammation/disease | Improves responses to vaccines, cellular and humoral immune responses | [12] |
| Vitamin D               | Respiratory tract infections, compromised antiviral immunity | VDR, hCap-1/IL-37 | [10,12,70,72-75] |
| Vitamin E               | Deficiency impairs antiviral responses | Antioxidant functions, control free radicals | [10,12] |
| Vitamin C               | Poor immune tissue development | Supportive antioxidant role, potential for antiviral immune protection | [12] |
| B-12 / Folate           | Neurodegeneration/ neuroinflammation | TNF-α, IL-6, Hcy | [76-79] |

ECS, endocannabinoid system; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; EGCG, epigallocatechin gallate.

References

- Watkins, Bruce A. (2020). "Nutrition Research: The Role of Nutrition in the Fight Against COVID-19." Nutrition Research, 81, 1-6.
vitamins, minerals, non-nutritive signaling molecules, herba
tal) compounds. Historically, compounds like opium, menthol, and salicycic acid help address many of
humankind’s ailments. Today, we have examples like oseltamivir (Tamiflu), a medicinal compound from the
Chinese star anise, a well-known spice and food flavoring. As an inhibitor of neuraminidase, a desialylating
enzyme, oseltamivir prevents the release of newly formed influenza viruses from the surface of the host cell, thus
preventing their spread to other host cells [17].

Today, the scientific literature contains many examples of
diet-derived signaling molecules capable of controlling
disease processes in vitro and in vivo. A recent study showed
that a novel caffic acid derivative is capable of
suppressing the growth of colorectal cells in culture and in
xenograft mouse models [18]. This was achieved by
inhibiting cell-cycle regulators and corresponding
blockage of the Akt and STAT3 signaling cascades.
While not directly related to the COVID-19 infection,
this study highlights the convergence of nutrition
research, biomedical research, and molecular signaling
dynamics to address other life-threatening conditions
like cancer. Similar approaches are currently being used
to understand and address those comorbidities related
to COVID-19. As shown in Table 1, there are several
nutrients and diet-derived compounds that are important
for the immune system or are under evaluation for
their potential preventive and/or therapeutic properties.

The current COVID-19 pandemic has been a game-
changer for nutrition science, which has predominantly
focused its attention on human development, mainte-
nance, and noncommunicable disease [10]. For the first
time in the history of modern nutrition, the spotlight is
aimed at the link between nutrient overconsumption and
a communicable disease. Understanding how this occurs
is not simple and requires nutrition researchers to look
beyond vitamin-mineral deficiencies and energy balance.
Today, we must examine the intersectionality of nutrition
and health as a complex system [19,20]. In this system,
thousands of interconnected and interdependent compo-
nents of the cell are poised at the edge of a “decision
space” ready to tip into the modalities of health or
disease, depending upon the quality and quantity of
nutritional inputs. This is to say that while scrutinizing
one’s favorite polyphenol, enzyme, or regulatory protein
is still required, it is not sufficient to blunt the disease
process with today’s nutritional interventions. More
combinatorial, computational, and team science ap-
proaches are required.

Recently, MIT researchers predicted a new chemical
entity (Halicin) that when synthesized, proved to have
broad-spectrum, antibiotic properties. This amazing feat
was accomplished using chemical datasets comprised of
107 million chemical entities [21]. While Halicin is not a
nutrient, the use of deep learning, training algorithms,
and artificial intelligence could prove useful to nutrition
scientists seeking novel nutritional/therapeutic com-
ounds based on diet-derived phytochemicals and pro-
teins. Consortia such as the Food Biomarker Alliance [22,
23] are building large datasets of diet-derived comp-
ounds that could be used as scaffolds from which to
predict new compounds. Whether such in silico de-
digned nutrition/therapeutic compounds would be
 delivered as supplemental nutrition or as a medical
food remains to be seen. The key message for nutrition
science is that new breakthroughs in data science, cell
signaling, and nutrimeatabolomics [23] should make it
possible to reposition itself for the next pandemic. By
incorporating these interdisciplinary tools and ap-
proaches, nutrition research can move closer to the
frontlines in the battle against viral infections like
COVID-19, or worse.

Grayson K. Jaggers
*Department of Biological Sciences, University of Southern
California, Los Angeles, CA
E-mail address: jaggers@usc.edu.

Bruce A. Watkins
*Department of Nutrition, University of California, Davis,
Davis, CA
E-mail address: bawatkins@ucdavis.edu.

Raymond L. Rodriguez
*Department of Department of Molecular and Cellular
Biology, University of California Davis, Davis, CA
Corresponding author.
E-mail address: rhrodriguez@ucdavis.edu.

REFERENCES

[1] World Health Organization. Coronavirus disease
(COVID-2019) situation reports. https://www.
who.int/emergencies/diseases/novel-
coronavirus-2019/situation-reports/ (accessed
June 5, 2020).

[2] Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S,
Harp J, et al. Complement associated microvascular
injury and thrombosis in the pathogenesis of
severe COVID-19 infection: a report of five cases.
Transl Res. 2020;220:1–13. https://doi.org/10.1016/j.
trl.2020.04.007.

[3] Zabetakis I, Lordan R, Norton C, Tsoupras A.
COVID-19: the inflammation link and the role of
nutrition in potential mitigation. Nutrients. 2020;
12(5). https://doi.org/10.3390/nu12051466.

[4] Butler MJ, Barrientos RM. The impact of nutrition
on COVID-19 susceptibility and long-term conse-
quences. Brain Behav Immun. 2020;87:53–4.
https://doi.org/10.1016/j.bbi.2020.04.040.

[5] Laurencin CT, McClinton A. The COVID-19 pan-
demic: a call to action to identify and address
racial and ethnic disparities. J Racial Ethn Health
Disparities. 2020;7(3):398–402. https://doi.org/10.
1007/s40615-020-00756-0.

[6] Fouad MN, Ruffin J, Vickers SM. COVID-19 is
disproportionately high in African Americans.
This will come as no surprise…. Am J Med article
in press. doi: https://doi.org/10.1016/j.
amjmed.2020.04.008.
obesity and metabolic syndrome: a mechanistic update. J Nutr Biochem. 2018;58:1–16. https://doi.org/10.1016/j.jnutbio.2018.02.012.

25. Chiu SC, Chao CY, Chiang EL, Sun JY, Rodriguez RL, Tang FY. N-3 polyunsaturated fatty acids alleviate high glucose-mediated dysfunction of endothelial progenitor cells and prevent ischemic injuries both in vitro and in vivo. J Nutr Biochem. 2017;42:172–81. https://doi.org/10.1016/j.jnutbio.2017.01.009.

26. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnenmann G, van der Meer JW, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med. 1989;320(5):265–71. https://doi.org/10.1056/NEJM198902233200501.

27. Figuera M, Olivan M, Busquets S, Lopez-Soriano FJ, Argilles JM. Effects of eicosapentaenoic acid (EPA) treatment on insulin sensitivity in an animal model of diabetes: improvement of the inflammatory status. Obesity (Silver Spring). 2011;19(2):362–9. https://doi.org/10.1038/oby.2010.194.

28. Forman BMTP, Chen J, Brun RP, Spiegelman BM, Evans RM. 15-Deoxy-Delta 12, 14-prostaglandin J2 is a ligand for the adipocyte differentiation factor PPARGamma. Cell. 1995;83(5):803–12. https://doi.org/10.1016/0092-8674(95)90193-9.

29. He K, Rimm EB, Merchant A, Rosner BA, Stampfer MJ, Willett WC, et al. Fish consumption and risk of stroke in men. JAMA. 2002;288(24):3130–6. https://doi.org/10.1001/jama.2002.243130.

30. Kalupahana NS, Claycombe K, Newman SJ, Stewart T, Siriwardhana N, Matthan N, et al. Eicosapentaenoic acid prevents and reverses insulin resistance in high-fat diet-induced obese mice via modulation of adipose tissue inflammation. J Nutr. 2010;140(11):1915–22. https://doi.org/10.3945/jn.110.125732.

31. Karlsson M, Marild S, Brandberg J, Lonn L, Friberg P, Strandvik B. Serum phospholipid fatty acids, adipose tissue, and metabolic markers in obese adolescents. Obesity (Silver Spring). 2006;14(11):1931–9. https://doi.org/10.1038/oby.2006.225.

32. Khalfoun B, Thibault F, Watier H, Bardos P, Lebranchu Y. Docosahexaenoic and eicosapentaenoic acids inhibit in vitro human endothelial cell production of interleukin-6. Adv Exp Med Biol. 1997;408:589–97.

33. Kumar A, Mastana SS, Lindley MR. N-3 fatty acids and asthma. Nutr Res Rev. 2016;29(1):1–16. https://doi.org/10.1016/j.nutrres.2017.01.009.

34. Meydani SN, Endres S, Woods MM, Goldin BR, Soo C, Mollir-Labrode A, et al. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. J Nutr. 1991;121(4):547–55. https://doi.org/10.1093/jn/121.4.547.

35. Paoli A, Moro T, Bosco G, Bianco A, Grimaldi KA, Camporesi E, et al. Effects of n-3 polyunsaturated fatty acids (omega-3) supplementation on some cardiovascular risk factors with a ketogenic Mediterranean diet. Mar Drugs. 2015;13(2):996–1009. https://doi.org/10.3390/md13020996.

36. Perez-Matute P, Perez-Echarri N, Martinez JA, Marti A, Moreno-Aliaga MJ. Eicosapentaenoic acid actions on adiposity and insulin resistance in control and high-fat-fed rats: role of apoptosis, adiponectin and tumour necrosis factor-alpha. Br J Nutr. 2007;97(2):389–98. https://doi.org/10.1017/S0007114506707627.

37. Peyron-Caso E, Taverna M, Guerre-Millo M, Veronese A, Pacher R, et al. Nutritional genomics: The impact of guidelines, and food policy. BMJ. 2018;361:k2392. https://doi.org/10.1136/bmj.k2392.

38. Stokstad EL, He SF, Chenournou MO, Geng SF, Duan TH, Zhou S, et al. A deep learning approach to antibiotic discovery. Cell. 2020;180(4):688–703. https://doi.org/10.1016/j.cell.2020.01.021.

39. Ulaszewska MM, Weinert CH, Trimagno A, Portmann R, Andres Lacueva C, Badertscher R, et al. Nutrimetabolomics: an integrative approach for metabolomic analyses in human nutritional studies. Mol Nutr Food Res. 2019;63(1):e1800384. https://doi.org/10.1002/mnfr.201800384.

40. Wu D, Lewis ED, Fae M, Meydani SN. Nutritional modulation of immune function: analysis of evidence, mechanisms, and clinical relevance. Front Immunol. 2018;9:3160. https://doi.org/10.3389/fimmu.2018.03160.
Acids on Inflammatory Gene Expression and hydrogen peroxide production by ex vivo blood mononuclear cells. Nutrients 2020;12(1). doi: https://doi.org/10.3390/nu12010146.

[40] Beermann C, Neumann S, Fussbroich D, Zeielen S, Schubert R. Combinations of distinct long-chain polyunsaturated fatty acid species for improved dietary treatment against allergic bronchial asthma. Nutrition. 2016;32(11–12):1165–70. https://doi.org/10.1016/j.nut.2016.04.004.

[41] Chauhan PS, Dash D, Singh R. Intranasal Curcumin inhibits pulmonary fibrosis by modulating matrix metalloproteinase-9 (MMP-9) in ovalbumin-induced chronic asthma inflamation. 2017;40(1):248–58. https://doi.org/10.1016/j.ijtins.016-0475-3.

[42] Fraga CG, Oteiza PI, Galleano M. Plant bioactives and redox signaling: (-)-epicatechin as a paradigm. Mol Aspects Med. 2018;61:31–40. https://doi.org/10.1016/j.mam.2018.01.007.

[43] Fussbroich D, Colas RA, Eickmeier O, Trischler J, Jerkic SP, Samane S, Christon R, Dombrowski L, Turcotte S, Charrouf Z, Mucosal Immunol. 2020;13(3):439–48. https://doi.org/10.1007/s12282-019-00324-y.

[44] Giudetti AM, Cagnazzo R. Beneficial effects of n-3 PUFA on chronic airway inflammatory diseases. Prostaglandins Other Lipid Mediat. 2012;99(3–4):57–67. https://doi.org/10.1016/j.prostaglandins.2012.09.006.

[45] Joffre C, Rey C, Laye S. N-3 polyunsaturated fatty acids and the resolution of Neuroinflammation. Front Pharmacol. 2019;10:1022. https://doi.org/10.3389/fphar.2019.01022.

[46] Li XY, Hao L, Liu YH, Chen CY, Pai VJ, Kang JX. Protection factors affecting adult neurogenesis and cognitive function. Ann Nutr Metab. 2019;70(1):62–71. https://doi.org/10.1159/000496295.

[47] Ma F, Zhou X, Li Q, Zhao J, Song A, An P, et al. Effects of foic acid and vitamin B12, alone and in combination on cognitive function and inflammatory factors in the elderly with mild cognitive impairment: a single-blind experimental design. Curr Alzheimer Res. 2019;16(7):622–32. https://doi.org/10.2174/1567205016666170527154629.

[48] Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017;356:i6583. https://doi.org/10.1136/bmj.i6583.

[49] Meng H, Li Y, Zhang W, Zhao Y, Niu X, Guo J. The relationship between cognitive impairment and homocysteine in a B12 and folate deficient population in China: a cross-sectional study. Medicine (Baltimore). 2019;98(47):e17970. https://doi.org/10.1097/MD.0000000000017970.
[70] Musco G, Annweiler C, Duval G, Karras S, Tirabassi G, Salvio G, et al. Vitamin D and cardiovascular disease: from atherosclerosis to myocardial infarction and stroke. Int J Cardiol. 2017;230:577–84. https://doi.org/10.1016/j.ijcard.2016.12.053.

[71] Nan W, Zhonghang X, Keyan C, Tongtong L, Wanshu G, Zhongxin X. Epigallocatechin-3-gallate reduces neuronal apoptosis in rats after middle cerebral artery occlusion injury via PI3K/AKT/eNOS signaling pathway. Biomed Res Int. 2018;2018:6473580. https://doi.org/10.1155/2018/6473580.

[72] Rahimifard M, Maqbool F, Moeini-Nodeh S, Niaz K, Abdollahi M, Braidy N, et al. Targeting the TLR4 signaling pathway by polyphenols: a novel therapeutic strategy for neuroinflammation. Ageing Res Rev. 2017;36:11–9. https://doi.org/10.1016/j.arr.2017.02.004.

[73] Rodriguez RL, Albeck JG, Taha AY, Ori-McKenney KM, Recanzone GH, Stradleigh TW, et al. Impact of diet-derived signaling molecules on human cognition: exploring the food-brain axis. NPJ Sci Food. 2017;1:2. https://doi.org/10.1038/s41538-017-0002-4.

[74] Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, et al. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system. Sci Rep. 2017;7(1):3312. https://doi.org/10.1038/s41598-017-03474-6.

[75] Somerville VS, Braakhuis AJ, Hopkins WG. Effect of flavonoids on upper respiratory tract infections and immune function: a systematic review and meta-analysis. Adv Nutr. 2016;7(3):488–97. https://doi.org/10.3945/an.115.010538.

[76] Urashima M, Segawa T, Okazaki M, Kurthara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza a in schoolchildren. Am J Clin Nutr. 2010;91(5):1255–60. https://doi.org/10.3945/ajcn.2009.29094.

[77] Whyand T, Hurst JR, Beckles M, Caplin ME. Pollution and respiratory disease: can diet or supplements help? A review Respir Res. 2018;19(1):79. https://doi.org/10.1186/s12931-018-0785-0.

[78] Xu D, Li Y, Zhang B, Wang Y, Liu Y, Luo Y, et al. Resveratrol alleviate hypoxic pulmonary hypertension via anti-inflammation and anti-oxidant pathways in rats. Int J Med Sci. 2016;13(12):942–54. https://doi.org/10.7150/ijms.16810.

[79] Yang X, Lv JN, Li H, Jiao B, Zhang QH, Zhang Y, et al. Curcumin reduces lung inflammation via Wnt/beta-catenin signaling in mouse model of asthma. J Asthma. 2017;54(4):335–40. https://doi.org/10.1080/02770903.2016.1218018.