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Comment on “Therapeutic target and molecular mechanism of vitamin C-treated pneumonia: a systematic study of network pharmacology” by R. Li, C. Guo, Y. Li, X. Liang, L. Yang and W. Huang, *Food Funct.*, 2020, 11, 4765

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This Comment raises concerns about the article “Therapeutic target and molecular mechanism of vitamin C-treated pneumonia: a systematic study of network pharmacology”.

Li *et al.* analyzed the overlap between vitamin C-related genes and pneumonia-related genes and found “90 primary presumptive targets of VC [vitamin C]-treated pneumonia”.¹ The premise of their analysis was the assumption that vitamin C influences pneumonia. To support that assumption, they write in the introduction: “sufficient VC supplementation may be used for preventing and managing infections in patients with different stages of pneumonia”. To justify this statement, Li refers to the paper by Gorton and Jarvis.² However, that reference is not valid.

First, Gorton and Jarvis did not study pneumonia and the word “pneumonia” does not appear anywhere in that paper. Instead, “students were asked to report any existing cold or flu symptoms” (p. 532, ref. 2).

Second, Gorton and Jarvis write even in the abstract that “Investigators tracked the number of reports of cold and flu symptoms among the 1991 test population of the facility compared with the reports of like symptoms among the 1990 control population.” Such a study design does not give any information about the effects of vitamin C on respiratory infections. There is variation in the distribution of viruses between different winters and there may be systematic differences in the set of students between those two years. Moreover, the assessment of symptoms was not consistent: “in 1991 the subjects were requested to report any sign of sore throat or nasal congestion on entering the facility, whereas no requests to report symptoms were made in 1990” (p. 532, ref. 2).

In addition, Li *et al.*¹ ignored studies that found no association between vitamin C intake and the risk of pneumonia. In one cohort study with 38 378 men in the USA,³ and in another with 83 165 women in the USA,⁴ dietary vitamin C intake and community-acquired pneumonia were not associated. These studies indicate that the variation in vitamin C intake in the ordinary population does not influence the risk of pneumonia. Thus, vitamin C does not have universal effects against pneumonia.

Vitamin C may influence the risk of pneumonia in special contexts. For example, in the older literature severe vitamin C deficiency was associated with a high risk of pneumonia.^{5,6} Nevertheless, the search for the genes which might explain the possible effects of vitamin C on infections by Li *et al.* may have limited relevance. Vitamin C is a major water-soluble antioxidant⁷ and nonspecific scavenging of various reactive oxygen and nitrogen species by vitamin C may explain a part of the effects on the immune system and on infections.

Furthermore, Li *et al.* found just 161 VC-treated targets.¹ However, it has been estimated that vitamin C may affect epigenetic regulation of over a thousand different genes in various cell types through its effects as a cofactor for regulation of hypoxia-inducible factor-1 α (HIF-1 α), ten eleven translocation enzymes (TETs) and histone demethylases.^{8–10} Thus, there seem to be many more genes that may be influenced by vitamin C than those analyzed.¹

Finally, at the end of the abstract, Li wrote that “More interestingly, the identified VC targets may act as biomarkers for the diagnosis and treatment of pneumonia”.¹ However, they do not give any evidence or argument that the identified targets might be specific for pneumonia. There are dozens of causative agents of pneumonia¹¹ and it seems unlikely that any biomarker is specific to the anatomically defined, yet etiologically diverse disease.

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Conflicts of interest

There are no conflicts of interest to declare.

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