Review Article
Open Access
CrossMark

Pyrroloquinoline Quinone (PQQ): a novel approach to managing chronic inflammatory response syndrome and mitochondrial dysfunction

Abstract

Chronic Inflammatory Response Syndrome (CIRS) is a complex, multi-system condition associated with persistent inflammation in response to biotoxins like mould or other environmental triggers. Mitochondrial dysfunction has been implicated in the pathophysiology of CIRS, contributing to chronic inflammation and exacerbating symptoms. Pyrroloquinoline quinone (PQQ), a redox cofactor, has gained attention for its potential neuroprotective, anti-inflammatory, and mitochondria-supporting properties. Additionally, CIRS shares overlapping features with cytokine storm effects observed in COVID infection, long COVID, and potential inflammatory reactions related to mRNA vaccine administration. This letter explores the role of PQQ in managing CIRS and addressing mitochondrial dysfunction caused by multiple potential triggers. However, further research is needed to confirm the effectiveness and safety of PQQ in addressing CIRS and related conditions.

Keywords: chronic inflammatory response syndrome, mitochondrial dysfunction, pyrroloquinoline quinone, Australian biotoxin inquiry, mould biotoxins, nutraceuticals, cytokine storm, endotoxins

Volume 11 Issue 1 - 2023

Cameron L Jones[1,2]
[1]Biological Health Services, Australia
[2]National Institute of Integrative Medicine, Australia

Correspondence: Dr. Cameron L. Jones, Biological Health Services, Level 1, 459 Toorak Rd, Toorak, Victoria, 3142, Australia, Tel +61414998900, Email cameron@drcameronjones.com

Received: April 01, 2023 | **Published:** April 10, 2023

Abbreviations: CIRS, chronic inflammatory response syndrome; PQQ, pyrroloquinoline quinone; ATP, adenosine triphosphate; ROS, reactive oxygen species; LNP, lipid nanoparticles; DMHS, dampness and mould hypersensitivity syndrome

Introduction

Chronic Inflammatory Response Syndrome (CIRS) represents a pressing health concern for numerous affected individuals worldwide. As a multifaceted condition, CIRS poses a unique challenge for both patients and healthcare professionals, leading to the urgent question: "How can I heal myself?" As a scientist with expertise in applied biomedical research, the aim of this paper is to provide an opinion of current understanding of CIRS and to discuss potential therapeutic strategies.

In recent years, a growing body of literature has sought to elucidate the underlying mechanisms of CIRS.[1–4] To further explore this complex condition, we will examine key findings from these studies and discuss their implications for diagnosis, treatment, and management of CIRS. Additionally, the Australian Biotoxin Inquiry has conducted a thorough investigation into the prevalence and impact of biotoxins, which may contribute to the development of CIRS.[5] This inquiry has provided valuable insights into the environmental factors that may exacerbate the condition and offers potential avenues for intervention.

Furthermore, mitochondrial dysfunction has been implicated in the pathogenesis of CIRS and other chronic inflammatory conditions.[6–8] A better understanding of the role of mitochondrial dysfunction in CIRS may pave the way for novel therapeutic approaches targeting cellular energy metabolism. One such approach involves the use of nutraceuticals, such as pyrroloquinoline quinone (PQQ), which is suggested to have potential benefits in addressing the complex nature of CIRS.[9,10] Additionally, it is worth noting that recent concerns have been raised regarding inflammation following SARS-CoV-2 vaccinations, which may warrant further investigation in the context of CIRS.

In summary, this paper will provide a comprehensive overview of the current understanding of CIRS, including insights from recent literature, the Australian Biotoxin Inquiry, and studies on mitochondrial dysfunction. Moreover, we will discuss the potential role of nutraceuticals like PQQ in addressing this multifaceted condition. By synthesizing the existing knowledge, we hope to provide a solid foundation for future research and contribute to the development of effective treatment strategies for CIRS.

Understanding CIRS and mould biotoxins

CIRS is a multi-system condition characterized by increased and persistent inflammatory responses to biotoxins or other environmental triggers.[11] These biotoxins can come from mould,[12,13] tick-borne infections,[14] marine toxins,[15] or other sources like endotoxins or *Actinobacteria*.[16] They often lead to a wide range of symptoms, including fatigue, cognitive impairment, and joint pain with an overarching inflammatory component. The Australian Biotoxin Inquiry, conducted in 2018, has played a crucial role in raising awareness of CIRS and mould-related illnesses in Australia,[5] emphasizing the need for improved diagnostic and treatment approaches to manage this condition. In fact, a recent integrative review in response to this governmental inquiry examined the impacts of mould-affected housing as risk factors for biotoxin-related illness.[17] Most recently, these ideas were further developed in reference,[18] where the importance of the inflammatory reaction as both a defense against "mould invasion" and as the cause of respiratory and non-respiratory system morbidities caused by mould exposure inside dampness-associated housing was emphasized. The applied context cited in these references states that indoor dampness and mould affect 10-50% of homes globally, with prevalence estimates ranging from 12.1% for dampness to 16.5% for multiple indicators in Europe, up to

Submit Manuscript | http://medcraveonline.com

©2023 Jones. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

47% in American homes, 12-78% in New Zealand homes, and up to 50% of homes in Australia.[17,18]

Mitochondrial dysfunction has been implicated in the pathophysiology of CIRS, as it contributes to the perpetuation of chronic inflammation and exacerbates symptoms.[19] Mitochondria, the cellular powerhouses, are responsible for generating energy in the form of adenosine triphosphate (ATP). When their function is impaired, energy production decreases, leading to a decline in overall cellular function and the onset of various age-related conditions[20] including cancer and other non-communicable diseases.[21,22] It is thought that Reactive Oxygen Species (ROS), the free radicals produced by mitochondria, when unchecked can damage mitochondria and tissues leading to inflammation.[23]

The promise of Pyrroloquinoline Quinone (PQQ)

Pyrroloquinoline quinone (PQQ) is an antioxidant and a cofactor for certain enzymes and known for its potential neuroprotective, anti-inflammatory, and mitochondria-supporting properties.[24–26] Nutraceuticals have emerged as a promising avenue for addressing mitochondrial dysfunction and related health issues.[27] PQQ is a redox cofactor that has garnered significant attention for its potential to improve mitochondrial function and alleviate age-related conditions. Jonscher et.al.,[28] make the case for the fact that PQQ shortage mimics vitamin deficiency and recovers dose-dependently with PQQ supplementation. PQQ supplementation may therefore enhance metabolic flexibility and offer immune and neuroprotection as well as Sirtuin-3 modulation and is a promising medicinal nutraceutical.

PQQ has been shown to stimulate the biogenesis of new mitochondria, enhance energy production, and protect against oxidative stress, all of which are crucial for maintaining optimal cellular health.[28] In fact dietary PQQ supplementation was shown to enhance mitochondria-related functions by decreasing levels of plasma C-reactive proteins and IL-6.[29] More recently, osteoarthritis, a degenerative disease of cartilage has shown that supplemental PQQ can relieve mitochondrion damage and increase the number of mitochondria, preserve ATP levels and reduce pro-inflammatory cytokines like tumor necrosis factor (TNF-α).[30] Related work on TNF-α has looked at how PQQ can delay inflammaging which is a low level pro-inflammatory state where inflammatory factors are released into tissues. Their work shows that PQQ can extend the lifespan of nematodes by reducing senescence and the expression and proliferation of TNF-α.[31]

Other research has demonstrated the potential of PQQ in promoting heart health and immunity. In animal studies, PQQ supplementation has been found to reduce the size of myocardial infarction and improve cardiac function by attenuating oxidative stress and inflammation.[32] Sirtuin 3, is upregulated in healthy hearts but downregulated in diseased hearts. Sirtuin 3 increases can improve heart pathologies, according to research.[33] Sirtuin 3 mostly deacetylates mitochondrial proteins involved in energy production. Sirtuin 3 regulates cardiac energetics, improving cardiac heath. In fact, PQQ was shown to prevent chronic heart failure by regulating the mitochondria in vivo and in vitro.[34]

The link between PQQ and its potential benefits in the context of mould exposure and CIRS lies in its ability to mitigate the consequences of chronic inflammation and oxidative stress, both of which are hallmarks of this syndrome. By improving mitochondrial function and bolstering the body's natural defenses, PQQ may help alleviate some of the symptoms associated with CIRS and enhance the body's resilience against mould-related biotoxins. Furthermore, PQQ has been shown to have immunomodulatory effects, including the regulation of pro-inflammatory cytokines and the enhancement of natural killer cell activity.[35]

In addition to PQQ, other nutraceuticals have shown promise in supporting mitochondrial function and addressing age-related health concerns.[36] These include coenzyme Q10,[37] curcumin,[38] and resveratrol,[9] all of which have demonstrated antioxidant, anti-inflammatory, and energy-enhancing properties.

Cytokine storm-like inflammatory reactions in CIRS, long COVID, and mRNA vaccine injury

Chronic Inflammatory Response Syndrome (CIRS), most commonly associated with mould exposure, shares overlapping features with cytokine storm effects observed in COVID infection and long COVID[39] and mRNA vaccine injury.[40–42] With over 13 billion doses of COVID-19 vaccine administered, mRNA vaccines have helped prevent hospitalization and severe disease, but they do not provide sterilizing immunity, resulting in reinfections. In fact, recent research[42] raises serious concerns about the immune tolerance induced by mRNA vaccines and the virus, which could exacerbate the outcome of COVID-19 infections. Multiple mRNA vaccine doses have been associated with elevated IgG4 levels, and rather than providing protection through immune regulation, this increase may contribute to spike-specific immune tolerance. This could make infection and replication of SARS-CoV-2 unopposed by inhibiting natural antiviral responses. In susceptible individuals, repeated vaccination induced IgG4 immune suppression and may also cause autoimmune diseases, malignancy growth, and autoimmune myocarditis.

These conditions are all characterized by an excessive and dysregulated immune response, leading to a cascade of inflammation and tissue damage. CIRS is typically triggered by exposure to mould and other biotoxins, while cytokine storms in long COVID patients result from persistent immune activation against SARS-CoV-2.[43] mRNA vaccine injuries may also lead to cytokine storm-like symptoms due to an overactive immune response to the vaccine components. Notably, post-vaccination side effects could be linked to the "spike hypothesis." This hypothesis suggests that the inflammatory properties of lipid nanoparticles or the mRNA in the vaccine, as well as the specific characteristics and proinflammatory actions of the antigens (e.g., the spike protein or its components) in human tissues and organs, may contribute to these adverse effects.[44] Other research finds that mRNA-containing lipid nanoparticles (LNPs) are highly inflammatory in mice. Both intradermal and intramuscular injections triggered strong inflammatory responses, including significant neutrophil infiltration, activation of various inflammatory pathways, and production of numerous cytokines and chemokines. The potent immune response and side effects observed with mRNA-LNP platforms may therefore be linked to the highly inflammatory nature of these nanoparticles.[45]

Despite the different distinct triggers, these conditions highlight the importance of understanding the complex interplay between the immune system and external factors in order to develop targeted therapies for mitigating the detrimental effects of immune dysregulation.

Emerging studies suggest there is potential for endotoxin contamination of commercial vaccines[46] as well as mRNA vaccines.[47]

Although officially considered unlikely due to stringent manufacturing processes, trace contaminants could potentially contribute to adverse reactions in some individuals. Another significant challenge with mRNA vaccines is maintaining their stability, which requires strict adherence to frozen storage conditions. If these storage requirements are not met, it is conceivable that the vaccines could undergo alterations in their properties, potentially affecting their efficacy and safety.[48] Efforts are underway to enhance mRNA vaccine stability to allow for more flexible storage options, but until these advancements are realized, proper cold chain management remains crucial to ensure the desired performance of these vaccines. Recent research has also looked at the role of the SARS-CoV-2 spike protein and how it can bind to bacterial lipopolysaccharides to boost pro inflammatory activity[49] and aggregation.[50] Endotoxins are toxic substances found in the outer membrane of Gram-negative bacteria and can elicit strong immune responses when introduced into the body. If endotoxins were to contaminate mRNA vaccines, they could trigger an excessive inflammatory response, leading to local or systemic symptoms.

The inflammatory potential of fungal mycotoxins and bacterial endotoxins

Endotoxins are lipopolysaccharides (LPS) found in the outer membrane of Gram-negative bacteria. They are released when the bacterial cell is disrupted or undergoes lysis and can also be shed during bacterial growth. Endotoxins are known to elicit strong immune responses in humans and animals, which can lead to inflammation, fever, and even septic shock in severe cases.

Moreover, it should be emphasized that mRNA vaccine manufacturers follow strict guidelines and quality control measures to ensure that their products are free from contaminants, including endotoxins. Therefore, the risk of endotoxin contamination in mRNA vaccines is minimal but could theoretically be a factor, especially if new study results are replicated elsewhere.[51–53] It is important to note that the potential benefits of PQQ in the context of endotoxin-contaminated mRNA vaccines are largely theoretical and based on extrapolation from in vitro and animal studies. Further research is needed to confirm the applicability of these findings to humans and to determine the optimal dosing and administration of PQQ in such cases.

Fungi, on the other hand, are a separate group of organisms distinct from bacteria. Fungi can release various toxic substances called mycotoxins, which can have detrimental effects on human health.[54] Some common mycotoxins include aflatoxins, ochratoxins, and trichothecenes, which are produced by different species of fungi. Mycotoxins can cause a wide range of health problems, from acute poisoning to chronic conditions such as immune suppression, liver damage, and even cancer. Fascinating new research even links mycoviruses in fungi in combination with mycotoxins in carcinogenesis and leukemia.[55]

While endotoxins and mycotoxins are produced by different types of organisms, they can both contribute to indoor air pollution and negatively impact human health. Exposure to endotoxins and mycotoxins can occur through inhalation, ingestion, or skin contact, and can lead to various health issues, particularly in individuals with pre-existing conditions or weakened immune systems. In some cases, endotoxins and mycotoxins can coexist in contaminated environments, such as water-damaged buildings with mould and bacterial growth. In such scenarios, the combined exposure to endotoxins and mycotoxins may lead to more severe health effects due to their synergistic or additive impacts on the immune system and other biological processes. It is essential to properly remediate contaminated environments and reduce exposure to both endotoxins and mycotoxins to protect public health.

PQQ could theoretically be beneficial in mitigating the effects of endotoxin or other contaminants in mRNA vaccines or for persons exposed to mould by:

a) Reducing inflammation: PQQ has demonstrated the ability to decrease the generation of pro-inflammatory cytokines, which are signaling molecules that promote inflammation. It also mitigates the activation of the nuclear factor-kappa B (NF-κB) pathway, a crucial component in the body's inflammatory response to harmful substances such as endotoxins.

b) Protecting mitochondria: Endotoxins (or LNP, and mycotoxins) can disrupt mitochondrial function, resulting in cell damage and reduced energy production. PQQ supports the growth and function of mitochondria, potentially mitigating the adverse effects of endotoxins on these cellular powerhouses.

c) Scavenging free radicals: The immune response to endotoxins frequently produces reactive oxygen species (ROS), which can lead to oxidative stress and cellular damage. PQQ possesses antioxidant capabilities that can counteract these free radicals, safeguarding cells from oxidative harm.

d) Enhancing immune response: Studies suggest that PQQ, with its anti-inflammatory and antioxidant properties, may contribute to the regulation of the immune system, encouraging a more balanced and well-coordinated response to endotoxins.

Inflammation and neurological symptoms after mould exposure and/or COVID

It is not uncommon for individuals who spend time in water-damaged buildings to attribute their health issues to sick building syndrome, typically characterized by a cumulative, potentially life-threatening exposure leading to irreversible dampness and mould hypersensitivity syndrome (DMHS). Recent research on DMHS in the context of antibodies reveals that affected individuals exhibit immune system dysregulation, hypersensitivity, and a marked loss of immunity, which manifests as increased susceptibility to common infections. DMHS is, therefore, a systemic, low-grade inflammation resulting from exposure to biotoxins.[56]

This research also demonstrates that autoantibodies are produced in response to the hypersensitivity induced by dampness, attacking myelin basic proteins and myelin-associated glycoproteins, which contribute to the mitochondrial damage associated with this mould-related illness. Studies have shown that neurological issues, most commonly presenting as brain fog, often include reduced cognition, difficulty concentrating and multitasking, and memory impairment. Patients with brain fog may be diagnosed with chronic fatigue syndrome, fibromyalgia, postural tachycardia syndrome, mild cognitive impairment, or display symptoms similar to early-onset Alzheimer's disease.[57]

Research suggests that brain fog may result from inflammatory molecules and histamine release from mast cells, causing focal brain inflammation. A Finnish study investigating workplaces with indoor air dampness found that brain fog symptoms were prevalent in 62% of individuals, compared to only 11% of those in non-water-damaged buildings.[58] More recently, COVID-19 survivors frequently experience lingering neurological symptoms resembling cancer therapy-related cognitive impairment, a syndrome where myelin loss

and white matter damage lead to neural dysregulation. It appears that those recovering from SARS-CoV-2 infection may exhibit cognitive impairments even after mild COVID-19 infection.[59] In conclusion, the connection between brain fog and autoimmunity resulting from mould exposure, as well as immune challenges following COVID-19 or mRNA nanoparticle exposure, underscores the need for a deeper understanding of the complex interplay between environmental factors, infections, and the immune system in order to better address these debilitating neurological symptoms.

Conclusion

In summary, targeting mitochondrial dysfunction with nutraceuticals like PQQ presents a potential avenue for helping those suffering from CIRS, adding to the existing therapeutic options mentioned in the literature.[60] By enhancing mitochondrial performance, such compounds may alleviate the chronic inflammation and oxidative stress associated with mould exposure, ultimately promoting overall health and well-being.

It's crucial to emphasize that, although the research on these nutraceuticals is encouraging, more in-depth studies, including randomized controlled trials, are necessary to confirm their effectiveness and safety in addressing CIRS. Moreover, individuals dealing with this condition should collaborate closely with their healthcare professionals to devise a thorough and customized treatment plan that caters to their specific needs and situations.

In conclusion, this opinion piece aims to inspire further research and discussion regarding the interplay between mitochondrial dysfunction, nutraceuticals, CIRS from mould, and inflammation caused by synthesized mRNA encoding specific viral proteins or nano-contaminants like LNP or endotoxins. By motivating new avenues of investigation, the goal is to advance understanding and ultimately benefit those affected by this complex condition.

Acknowledgments

None.

Conflicts of interest

The author declares there are no conflicts of interest.

Referneces

1. Hamilton D. Understanding mycotoxin-induced illness: part 1. *Altern Ther Health Med.* 2022;28(5):8–11 .
2. Shoemaker R, Meinhardt J, Heyman A, et al. Exposure to Actinobacteria resident in water-damaged buildings and resultant immune injury in Chronic Inflammatory Response Syndrome. *Med Res Archives.* 2021;9(10):1–28.
3. Bredesen DE. Inhalational Alzheimer's disease: an unrecognized- and treatable- epidemic. *Aging (Albany NY).* 2016;8(2):304–313.
4. Thomson DR. Chronic inflammatory response syndrome acquired after exposure to water- damaged buildings (CIRS-WDB). 2013:1–9.
5. Report on the Inquiry into Biotoxin-related Illnesses in Australia. Commonwealth Parliament; Parliament House. 2018.
6. Kong C, Song W, Fu T. Systemic inflammatory response syndrome is triggered by mitochondrial damage (Review). *Mol Med Rep*. 2022;25(4):147.
7. Islam MT, Mishra SK, Tripathi S, et al. Mycotoxin-assisted mitochondrial dysfunction and cytotoxicity: Unexploited tools against proliferative disorders. *IUBMB Life*. 2018;70(11):1084–1092.
8. Tonshin AA, Teplova VV, Andersson MA, et al. The Fusarium mycotoxins enniatins and beauvericin cause mitochondrial dysfunction by affecting the mitochondrial volume regulation, oxidative phosphorylation and ion homeostasis. *Toxicology*. 2010;276(1):49–57.
9. Rucker R, Jonscher K, Chowanadisai W. Comparative effects of Pyrroloquinoline Quinone (PQQ) and Resveratrol (RSV) on mitochondriogenesis in mice. *FASEB J*. 2021;35(S1).
10. Murray M. Pyrroloquinoline quinone (PQQ): the next essential nutrient and supplement superstar. *Nutrafoods.* 2018;17:125–129.
11. Mcmahon SW. An evaluation of alternate means to diagnose chronic inflammatory response syndrome and determine prevalence. *Med Res Archives*. 2017;5(3):1–18.
12. Kraft S, Buchenauer L, Polte T. Mold, mycotoxins and a dysregulated immune system: a combination of concern? *Int J Mol Sci*. 2021;22(22):12269.
13. Shoemaker RC, House D, Ryan J. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. *Health.* 2013;5:396–401.
14. Lochhead RB, Strle K, Arvikar SL, et al. Lyme arthritis: linking infection, inflammation and autoimmunity. *Nat Rev Rheumatol*. 2021;17(8):449–461.
15. Ryan JC, Wu Q, Shoemaker RC. Transcriptomic signatures in whole blood of patients who acquire a chronic inflammatory response syndrome (CIRS) following an exposure to the marine toxin ciguatoxin. *BMC Med Genomics.* 2015;8:15.
16. Shoemaker R, Neil V, Heyman A, et al. Newer molecular methods bring new insights into human- and building-health risk assessments from water-damaged buildings: defining exposure and reactivity, the two sides of causation of CIRS-WDB illness. *Med Res Archives.* 2021:9(3):1–36.
17. Coulburn L, Miller W. Prevalence, Risk factors and impacts related to mould-affected housing: an Australian integrative review. *Int J Environ Res Public Health*. 2022;19(3):1854.
18. Viljoen M, Claassen N. Pathophysiological aspects of exposure to dampness-associated indoor mould and mycotoxins: A mini-overview. *J Hazardous Mat Adv*. 2023;9:100228.
19. Zakharova VV, Pletjushkina OY, Zinovkin RA, et al. Mitochondria-targeted antioxidants and uncouplers of oxidative phosphorylation in treatment of the systemic inflammatory response syndrome (SIRS). *J Cell Physiol*. 2017;232(5):904–912.
20. Hwang AB, Jeong DE, Lee SJ. Mitochondria and organismal longevity. *Curr Genomics*. 2012;13(7):519–532.
21. Luo Y, Ma J, Lu W. The significance of mitochondrial dysfunction in cancer. *Int J Mol Sci*. 2020;21(16):5598.
22. Geto Z, Molla MD, Challa F, et al. Mitochondrial dynamic dysfunction as a main triggering factor for inflammation associated chronic non-communicable diseases. *J Inflamm Res*. 2020;13:97–107.
23. Andrieux P, Chevillard C, Cunha-Neto E, et al. Mitochondria as a cellular hub in infection and inflammation. *Int J Mol Sci*. 2021;22(21):11338.
24. Gao Y, Kamogashira T, Fujimoto C, et al. Pyrroloquinoline quinone (PQQ) protects mitochondrial function of HEI-OC1 cells under premature senescence. *NPJ Aging*. 2022;8(1):3.
25. Harris CB, Chowanadisai W, Mishchuk DO, et al. Dietary pyrroloquinoline quinone (PQQ) alters indicators of inflammation and mitochondrial-related metabolism in human subjects. *J Nutr Biochem*. 2013;24(12):2076–2084.
26. Shafiq M, Lone ZR, Bharati P, et al. Pyrroloquinoline quinone (PQQ) improves pulmonary hypertension by regulating mitochondrial and metabolic functions. *Pulm Pharmacol Ther*. 2022;76:102156.

27. Gupta SC, Kunnumakkara AB, Aggarwal S, et al. Inflammation, a double-edge sword for cancer and other age-related diseases. *Front Immunol*. 2018;9:2160.

28. Jonscher KR, Chowanadisai W, Rucker RB. Pyrroloquinoline-Quinone is more than an antioxidant: a vitamin-like accessory factor important in health and disease prevention. *Biomolecules*. 2021;11(10):1441.

29. Harris CB, Chowanadisai W, Mishchuk DO, et al. Dietary pyrroloquinoline quinone (PQQ) alters indicators of inflammation and mitochondrial-related metabolism in human subjects. *J Nutr Biochem*. 2013;24(12):2076–2084.

30. Han GT, Cai WS, Zhang YB, et al. Protective effect of Pyrroloquinoline Quinone on TNF-α-induced mitochondrial injury in chondrocytes. *Curr Med Sci*. 2021;41(1):100–107.

31. Hao J, Ni X, Giunta S, et al. Pyrroloquinoline quinone delays inflammaging induced by TNF-α through the p16/p21 and Jagged1 signalling pathways. *Clin Exp Pharmacol Physiol*. 2020;47(1):102–110.

32. Nakano M, Imamura H, Sasaoka N, et al. Novel antioxidant pyrroloquinoline quinone (PQQ) improves stress tolerance and exerts anti-inflammatory effects. *J Clin Biochem Nutri.* 2010;46(1):87–90.

33. Murugasamy K, Munjal A, Sundaresan NR. Emerging roles of SIRT3 in cardiac metabolism. *Front Cardiovasc Med*. 2022;9:850340.

34. Xu X, Chen C, Lu WJ, et al. Pyrroloquinoline quinone can prevent chronic heart failure by regulating mitochondrial function. *Cardiovasc Diagn Ther*. 2020;10(3):453–469.

35. Hara H, Hiramatsu H, Adachi T. Pyrroloquinoline quinone is a potent neuroprotective nutrient against 6-hydroxydopamine-induced neurotoxicity. *Neurochem Res*. 2011;32(3):489–495.

36. Singh AK, Pandey SK, Saha G, et al. Pyrroloquinoline quinone (PQQ) producing *Escherichia coli* Nissle 1917 (EcN) alleviates age associated oxidative stress and hyperlipidemia, and improves mitochondrial function in ageing rats. *Exp Gerontol*. 2015;66:1–9.

37. Mantle D, Heaton RA, Hargreaves IP. Coenzyme Q10, ageing and the nervous system: an overview. *Antioxidants (Basel)*. 2022,11(1):2.

38. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa). *J Altern Complement Med.* 2003;9(1) 161–168.

39. Desjarlais M, Wirth M, Lahaie I, et al. Nutraceutical targeting of inflammation-modulating microRNAs in severe forms of covid-19: a novel approach to prevent the cytokine storm. *Front Pharmacol*. 2020;11:602999.

40. Trougakos IP, Terpos E, Alexopoulos H, et al. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. *Trends Mol Med*. 2022;28(7):542–554.

41. Bellavite P, Ferraresi A, Isidoro C. Immune response and molecular mechanisms of cardiovascular adverse effects of spike proteins from SARS-CoV-2 and mRNA vaccines. *Biomedicines*. 2023;11(2):451.

42. Uversky VN, Redwan EM, Makis W, et al. IgG4 Antibodies induced by mRNA vaccines generate immune tolerance to SARS-CoV-2'spike protein by suppressing the immune system. *Preprints.org.* 2023;2023030441.

43. Queiroz MAF, Neves PFMD, Lima SS, et al. Cytokine profiles associated with acute COVID-19 and long COVID-19 syndrome. *Front Cell Infect Microbiol*. 2022;12:922422.

44. Trougakos IP, Terpos E, Alexopoulos H, et al. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. *Trends Mol Med*. 2022;28(7):542–554.

45. Ndeupen S, Qin Z, Jacobsen S, et al. The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. *iScience*. 2021;24(12):103479.

46. Geier MR, Stanbro H, Merril CR. Endotoxins in commercial vaccines. *Appl Environ Microbiol*. 1978;36(3):445–449.

47. McKernan DK. DNA contamination in 8 vials of Pfizer monovalent mrna vaccines. 2023.

48. Oude Blenke E, Örnskov E, Schöneich C, et al. The storage and in-use stability of mRNA vaccines and therapeutics: not a cold case. *J Pharm Sci*. 2023;112(2):386–403.

49. Petruk G, Puthia M, Petrlova J, et al. SARS-CoV-2 spike protein binds to bacterial lipopolysaccharide and boosts proinflammatory activity. *J Mol Cell Biol*. 2020;12(12):916–932.

50. Petrlova J, Samsudin F, Bond PJ, et al. SARS-CoV-2 spike protein aggregation is triggered by bacterial lipopolysaccharide. *FEBS Lett*. 2022;596(19):2566–2575.

51. Cinquegrani G, Spigoni V, Iannozzi NT, et al. SARS-CoV-2 Spike protein is not pro-inflammatory in human primary macrophages: endotoxin contamination and lack of protein glycosylation as possible confounders. *Cell Biol Toxicol*. 2022;38(4):667–678.

52. Samsudin F, Raghuvamsi P, Petruk G, et al. SARS-CoV-2 spike protein as a bacterial lipopolysaccharide delivery system in an overzealous inflammatory cascade. *J Mol Cell Biol*. 2023;14(9):mjac058.

53. Root-Bernstein R. From co-infections to autoimmune disease via hyperactivated innate immunity: COVID-19 autoimmune coagulopathies, autoimmune myocarditis and multisystem inflammatory syndrome in children. *Int J Mol Sci*. 2023;24(3):3001.

54. Paterson RR, Lima N. Toxicology of mycotoxins. *EXS*. 2010;100:31–63.

55. Tebbi CK. Mycoviruses in Fungi: carcinogenesis of fungal agents may not always be mycotoxin related. *J Fungi (Basel).* 2023;9(3):368.

56. Tuuminen T. The roles of autoimmunity and biotoxicosis in sick building syndrome as a "starting point" for irreversible dampness and mold hypersensitivity syndrome. *Antibodies (Basel)*. 2020;9(2):26.

57. Theoharides TC, Stewart JM, Hatziagelaki E, et al. Brain "fog," inflammation and obesity: key aspects of neuropsychiatric disorders improved by luteolin. *Front Neurosci*. 2015;9:225.

58. Hyvönen S, Lohi J, Tuuminen T. Moist and mold exposure is associated with high prevalence of neurological symptoms and MCS in a finnish hospital workers cohort. *Saf Health Work*. 2020;11(2):173–177.

59. Fernández-Castañeda A, Lu P, Geraghty AC, et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell*. 2022;185(14):2452–2468.

60. Hope J. A review of the mechanism of injury and treatment approaches for illness resulting from exposure to water-damaged buildings, mold, and mycotoxins. *Scientific World Journal*. 2013;2013:767482.