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Case Series

# Use of a Cysteine-Rich whey Protein Isolate as Adjuvant Therapy in Patients with COVID-19 Pneumonia: A Case Series

**Arturo Arias[1], Catalina Camacho[2], Maria Padron[2], Gilberto Bustamante[3], Fernando Villamizar[3], Eduardo Scholcoff[2] and Ruben D Restrepo[4]***

*[1]Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia*

*2Immunotec Incorporated, Victoria, BC, Canada*

*[3]Clínica Norte, Cúcuta, Colombia*

*[4]The University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA*

***Corresponding Author:** Ruben D Restrepo, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA.

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## Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 has infected more than 283 million people worldwide and is responsible for nearly 5.5 million deaths. While a significant number of people have recovered from this infection, nearly 40% of the patients who leave the ICU have important complications that compromise their activity of daily living. It is estimated that without a specific effective antiviral treatment, new waves due to emerging variants may further compromise healthcare systems and potentially delay herd immunity. Several previous studies have demonstrated that glutathione (GSH) deficiency may play an important pathophysiological role in severe COVID-19 morbidity and mortality. Historically, administration of N-acetylcysteine (NAC), a GSH precursor, has been found to significantly reduce the incidence of clinically apparent influenza and influenza-like episodes. Such benefits have created enormous interest in the use of NAC to target severe lung cell injury in patients with acute respiratory distress syndrome (ARDS). Despite the advent of vaccines against the virus, it has not yet been possible to identify a single agent or cocktail of drugs that effectively modulates the cytokine storm associated with SARS-CoV-2 infection. The addition of cysteine-rich whey protein isolate (CRWPI) supplementation as adjuvant therapy in treating patients with severe respiratory symptoms associated with COVID-19 pneumonia has not been reported in the literature. This article describes the results of adding a CRWPI to the treatment of four patients diagnosed with severe COVID pneumonia admitted to a medical ICU in Cucuta, Colombia.

***Keywords:*** *Cysteine-Rich; Protein Isolate; Adjuvant Therapy; COVID-19 Pneumonia*

## Introduction

On March 11, 2020, the World Health Organization (WHO) declared a pandemic due to the ß- coronavirus that causes severe respiratory distress syndrome (SARS-CoV-2) called COVID-19. By the last week of December 2021, the number of reported cases in the world exceeded 283 million and over 5.5 million deaths [1]. Colombia has reported over 5.1 million cases and nearly 130.000 deaths [2]. The widespread of this viral infection and the severity of critically ill patients led the WHO to declare COVID-19 a public health emergency that has resulted in compromised of healthcare systems in many affected countries. As a result of the overwhelming burden on health systems, research and development of other adjuvant therapies have become a strong focus.

It has been proposed that glutathione (GSH) deficiency is a very plausible explanation for serious manifestation and death in COVID-19 infected patients, particularly with moderate-to-severe illness [3,4]. It is well documented that oxidative stress contributes to hyper-

inflammation of the lung leading to adverse disease outcomes such as acute respiratory distress syndrome (ARDS), multiorgan failure and death [5]. In addition, GSH deficiency from either decreased biosynthesis and/or increased depletion is associated with oxidative damage of the lung, regardless of other factors associated with low GSH such as smoking, aging, and chronic disease comorbidity [6]. Several authors have proposed the prophylactic and therapeutic potential of glutathione augmentation as potential and novel adjuvant therapies, against coronavirus infection, given their powerful antioxidant effects and potential to modify the "cytokine storm" [6-8]. According to Lu, GSH can suppress the formation and enhance the elimination of reactive oxygen species (ROS) and repair intracellular oxidative damage [11].

Glutathione (L-γ-glutamyl-L-cysteinyl-glycine) or GSH is the most abundant non-protein thiol in mammalian cells and functions as an antioxidant to limit oxidant-induced damage to lipids, proteins, and genetic material. GSH has a leading role in maintaining the intracellular oxide-reduction (redox) balance and in regulating biochemical pathways affected by oxidative stress. Maintaining a high intracellular concentration of GSH is therefore critical for cellular defense against oxidative damage. Diotavelli., *et al.* suggested that certain genes responsible for natural immunity and antiviral activity require GSH as an essential molecule for their action [12].

While the National Library of Medicine provides access to over 165,000 articles in PubMed.gov relating to GSH to date, the efficacy of its oral administration appears to be limited [13]. Aging and other clinical conditions including pulmonary disease, diabetes, HIV/AIDS, cardiovascular disease, viral infections, cancer, liver disease, Parkinson's, Alzheimer's and renal disease, are associated with low levels of GSH [14-22].

Guloyan., *et al*. recently reported on the possible use of liposomal glutathione for the management of COVID-19 [23], while Horowitz., *et al.* suggested the use of GSH as part of their tripartite proposal for prevention, diagnosis, and treatment of COVID-19 [24]. The modulation of the "cytokine storm" seems to be an important key to decrease the mortality associated not only with COVID-19, but many other diseases associated with a significant reduction in GSH levels [24,25].

A key aspect in the synthesis of intracellular GSH and its biological properties as a tripeptide antioxidant is the availability of its precursors, the amino acids cysteine, glycine, and glutamate [26]. While uptake and absorption of glycine and glutamate typically do not represent any challenges in a regular diet, as a free amino acid L-cysteine given orally is rapidly oxidized during digestion, which significantly compromises its bioavailability and the ability of the cell to generate GSH [27,28]. Cysteine is recognized as the rate-limiting amino acid for synthesis of GSH. Improving cysteine availability within tissues using cysteine "prodrugs" like N-acetyl-cysteine (NAC) effectively increases GSH synthesis [29]. NAC is a well-known mucolytic and antidote for acetaminophen intoxication. The addition of the acetyl side chain has been shown to protect cysteine from oxidation and improves its cellular uptake to optimize GSH synthesis [30]. In addition, its role as a preventive and therapeutic agent in situations of oxidative stress, GSH depletion or, anecdotally, improvement of patients with influenza or similar diseases has also been reported [31]. Biwas and Rahman have proposed that substances related to cysteine such as NAC, carbocysteine or erdostein can be used as adjuvant therapeutic agents against medical conditions such as acute respiratory distress, asthma, pulmonary fibrosis, or chronic obstructive pulmonary disease (COPD) [32]. NAC supplementation has been found to significantly reduce the incidence of clinically apparent influenza and influenza-like episodes and thus, it has created enormous interest in targeting severe lung cell injury in patients with acute respiratory distress syndrome (ARDS) [33]. Administration of NAC is unfortunately not free from side effects [34].

Cysteine is available through dietary means, but to act efficiently as a glutathione precursor it survives oxidation best as the dimer "cystine" in larger folded proteins. Heating, mechanical stressors such as blending and other food preparation techniques unfolds (denatures) these proteins and expose the disulfide cysteine-cysteine link to oxidation [34-37]. Bovine whey protein isolates (WPI) are rich in cystine, the disulfide form of cysteine. Kent., *et al.* reported that the use of WPI increased intracellular GSH by 64%, compared with control

cells not receiving WPI. A similar increase was observed with NAC [38]. Supplementation of cysteine rich WPI (CRWPI) has been associated with increased intracellular GSH synthesis [39]. It has a very high biological value (BV), PER (protein efficiency ratio) and PDCAAS (protein digestibility-corrected amino acid score) [40-42].

The objective of this case series is to report the outcome of patients admitted with COVID-19 pneumonia by providing patients with CRWPI supplementation acting as a rich source of cystine (bioavailable cysteine) to support synthesis of intracellular GSH.

## Materials and Methods

### Participants

Four female patients between ages 55 and 86 years old diagnosed with COVID-19 via PCR testing were transferred from internal medicine to the Intensive Care Unit (ICU) due to progressive deterioration of their oxygenation status in the city of Cucuta, a large metropolitan city in Colombia, between November 3, 2020, and December 4, 2020. Their National Early Warning (NEW) scores were between 5 and 7, (Comorbidity, Age, Lymphocyte count, Lactic Dehydrogenase) CALL scores between 6 and 11, and partial pressure of arterial oxygen to fraction of inspired oxygen ($PaO_2/FiO_2$) ratio was less than 150 mm Hg. All subjects had elevated ferritin, C-reactive protein (CRP), and D-dimer levels, while only one had an elevated procalcitonin (0.5 ng/mL). Troponin was negative on all of them. All the patients were alert and conscious. Table 1 summarizes demographic information and laboratory profile upon admission to the ICU. Ethical informed consent was obtained from either the subjects or their legally responsible representatives before initiating this study. The Institutional Review Board approved this study.

| Case | 1 | 2 | 3 | 4 | Mean ± SD |
|---|---|---|---|---|---|
| Age | 55 | 86 | 53 | 60 | 63.5 ± 15.3 |
| ICU stay (days) | 7 | 3 | 5 | 7 | 5.5 ± 1.9 |
| NEWS | 6 | 7 | 5 | 5 | 5.75 |
| COVID GRAM | 178 | 208 | 198 | 152 | 194.6 ± 97.6 |
| CALL score | 9 | 11 | 6 | 9 | 8.75 ± 2.1 |
| NEWS | 6 | 7 | 5 | 5 | 5.75 ± 0.9 |
| LDH (units/L) | 884 | 508 | 646 | 568 | 651.5 ± 165 |
| CRP (mg/ml) | 48 | 48 | 96 | 6 | 49.5 ± 36.7 |
| D-dimer (ng/ml) | 835 | 1680 | 236 | 1323 | 1018.5 ± 626.2 |
| Ferritin (mcg/l) | 791 | 282 | 714 | 1200 | 746.8 ± 376.1 |

***Table 1:*** *ICU: Intensive Care Unit; NEWS: National Early Warning Score; CALL: Comorbidity, Age, Lymphocyte count, Lactic Dehydrogenase; CRP: C-reactive protein.*

### Treatment protocol

When similar patients with COVID-19 pneumonia were admitted to the ICU, they were placed on non-invasive ventilation (NIV) using a helmet as the interface, weaned to a high flow nasal cannula (HFNC) and later to a low-flow nasal cannula before being transferred to the floor. They also received included a daily intravenous infusion of 6 grams of N-Acetylcysteine (NAC) for 10 days.

### Dietary supplementation

In addition to the management protocol above, 20 grams of a cysteine-rich whey protein isolate (CRWPI) (Immunocal, Immunotec, Montreal, Canada) were orally administered three times daily (60 grams) for fourteen days to the patients on this report. This CRWPI dietary supplement is a highly undenatured whey protein isolate specially prepared to retain the cysteine in bioavailable form as cystine [43,44]. A regimen of 10 grams three times daily was administered after discharge for three consecutive months. No adverse effects were reported during the administration of the CRWPI.

### Case history one

This was a fifty-year old obese female evaluated in the emergency room (ER) for a 4-day history of productive cough, rhinorrhea, headache, nasal congestion, asthenia, and mild dyspnea. She was admitted to the internal medicine service with a diagnosis of COVID-related pneumonia. She received oxygen via nasal cannula at 2 L/min. Her initial PaO2/FiO2 was 418 (NEWS 6 - COVID-GRAM risk score 178, CALL score 9). A month after hospitalization, she presents with severe dyspnea and her PaO2/FiO2 drops to 148 and was transferred to the ICU for further management.

Her initial ICU $PaO_2/FiO_2$ was 135 mm Hg. Her chest computed tomography (CT) revealed bilateral and diffuse stained-glass infiltrates. She was placed on NIV and an awake proning protocol was ordered for the next 72 hours. The standard COVID-19 protocol was initiated along with the administration of the CRWPI as described in methods.

### Case history two

Eighty-six-year-old female was evaluated in the emergency room (ER) for a 6-day history of malaise, occasional cough, asthenia, and adynamia, but no fever. She had a history of diabetes mellitus, hypothyroidism, coronary artery disease, and chronic sinusitis. She was also admitted to the internal medicine service with a diagnosis of COVID-related pneumonia. She was placed on a non-rebreather (NRB) oxygen mask for pulse oximeter saturations ($SpO_2$) of 84% on room air. Her initial $PaO_2/FiO_2$ was 129. The subject rapidly deteriorated (NEWS 7 - COVID-GRAM risk score 208 - CALL score 11) with progressively worse dyspnea. She was transferred to the ICU, where her initial $PaO_2/FiO_2$ was 109. Her chest computed tomography (CT) revealed diffuse infiltrates, predominantly in the left hemithorax. She was placed on NIV and an awake proning protocol was ordered for the next 72 hours. The standard COVID-19 protocol was initiated along with the administration of the CRWPI as described in methods.

### Case history three

Fifty-nine-year-old female visited the ER for an 8-day history of fever, osteomyalgia, dry cough, anosmia, asthenia, and adynamia. Her mother had died due to COVID-19 three days before coming to the ER and the subject brought a positive COVID-19 test along. No history of comorbidities. A chest x-ray was negative and $SpO_2$ > 95% on room air. She was discharged for ambulatory care but returns six days later for persistence of symptoms and moderate dyspnea. Her initial PaO2/FiO2 was 328 mm Hg and it was decided to admit her to the internal medicine ward with a diagnosis of COVID-related pneumonia. Procalcitonin was 0.5 ng/mL. She started requiring higher FiO2 and her nasal cannula was replaced by a NRB mask (NEWS 5 - COVID-GRAM risk score 198 - CALL score 6). She was transferred to the ICU, where her initial $PaO_2/FiO_2$ was 130. Table 1 summarizes her laboratory profile. Her chest computed tomography (CT) revealed bilateral and diffuse stained-glass infiltrates. She was placed on NIV and an awake proning protocol was ordered for the next 72 hours. The standard COVID-19 protocol was initiated along with the administration of the CRWPI as described in methods.

### Case history four

Sixty-year-old female visited the ER for a 13-day history of rhinorrhea, malaise, sporadic dry cough, asthenia, and adynamia. Additionally, 2 days with fever, diarrhea, shortness of breath, and worsening cough. She has a history of hypertension, hypothyroidism, and resolved thyroid cancer. She was admitted to the internal medicine service for worsening dyspnea and $SpO_2$ below 92% on room air. Blood gases were obtained and her initial $PaO_2/FiO_2$ was 128, thus, a decision is made to transfer the patient to the ICU (NEWS: 5 - COVID-GRAM risk score 152 - CALL score 9). Her chest CT revealed multilobar pneumonia. She was placed on NIV and an awake proning protocol was ordered for the next 72 hours. Standard COVID-19 protocol was initiated along with the supplementation of the CRWPI as described before.

### Case progression and follow up

The ICU stay of these patients averaged 6 days. They never required invasive positive airway pressure and they were rapidly weaned to a nasal cannula after wearing the helmet. Figure 1 one shows the rapid improvement of $PaO_2/FiO_2$ ratios and the upward trend to day seven of hospitalization. Three months after discharge and thereafter, telephone interviews were conducted to evaluate the clinical condition of these patients. They all remain clinically stable and without any sequalae.

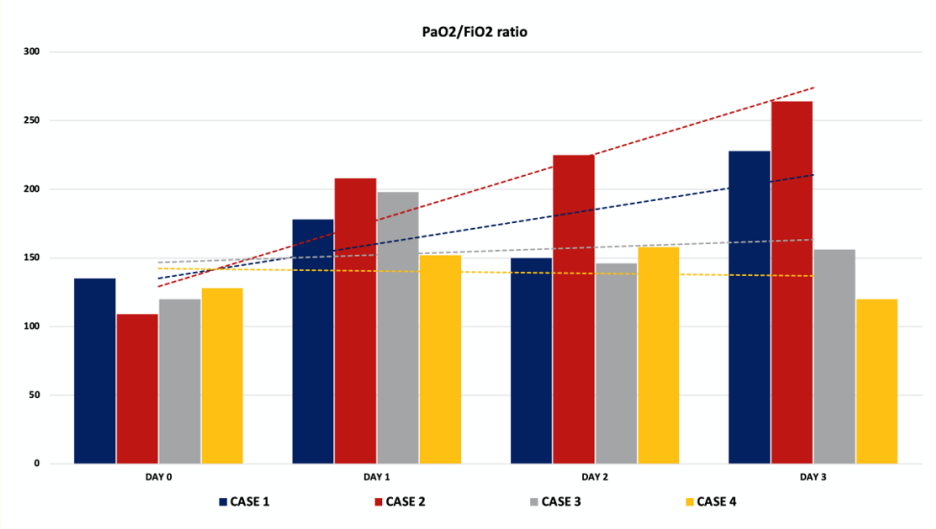


***Figure 1:*** *$PaO_2/FiO_2$ ratio changes over the first three days of ICU admission. Dotted lines indicate trends for each case.*

## Discussion

Nutritional supplements containing cysteine such as found in undenatured whey protein isolate have previously been found to increase GSH levels, and thus improving the immune response against a variety of infectious processes. The purpose of this paper was to evaluate the benefit of adding a CRWPI to an institutional management protocol in four patients admitted with COVID-19 pneumonia with medium to high risk of progression to severe COVID based on the clinical scores upon admission to the ICU. These four patients demon-

strated rapid clinical improvement of oxygenation status few hours after administration of the CRWPI, which is consistent with the results reported by Horowitz after oral and IV administration of glutathione plus oral N-acetylcysteine to two patients with COVID-19 pneumonia and respiratory distress. His trial resulted in improvement of dyspnea within 1 hour of administration. He describes this novel treatment as a method designed to block NF-κB and addressing the "cytokine storm syndrome" associated with COVID-19 infection. The positive effects of CRWPI on clinical and biochemical parameters that significantly impact the immune system and even muscular performance of individuals has been previously documented [45-52].

Kennedy and Bounous had described the use of the same CRWPI used in these case reports and its role on GSH modulation in cancer treatment by depleting tumor cells and making them more vulnerable to chemotherapy over 20 years ago [53,54].

The dietary supplement used in this group of patients is a protein supplement of high-quality since well-prepared whey protein isolates reportedly have the highest biological value and protein efficiency ratios of all dietary proteins [55,56]. This dietary supplement provided a rich source of cysteine (bioavailable cysteine) that could be used to synthesize glutathione and as found in an earlier study having demonstrated an ability to raise intracellular GSH values by 35% [46].

Cysteine-rich whey protein isolates have also been recently evaluated as alternative therapies for viral infections [46,57-62]. Fan., *et al.* recently evaluated the *In vitro* effect of WPI from human milk on viral infection and replication of SRAS-CoV-2 and pangolin coronavirus *In vitro*. They found all the skim breast milk from different donors effectively inhibited SARS-CoV pseudovirus with inhibition efficiency more than 98% [57]. Scarcella., *et al*. just reported the successful use of whey protein in reducing the ICU stay in critically ill COVID-19 patients [63].

This report has several limitations. The first, and main limitation, this is a small sample size. Lack of a case control group (e.g., COVID-19 patients without NAC or other protocols) does not allow the authors to establish a direct causality connection between the use of a CRWPI and the observed clinical outcome. The second limitation is that the cases came from a single center, not allowing to generalize these conclusions to other centers or protocols in COVID-19 patients. Third, the impact of using NAC in some subjects as a control group versus CRWPI should be evaluated separately to truly evaluate the full benefit of the oral supplement in increasing GSH and claim any clinical benefit. Nevertheless, these limitations are counterbalanced by the fact that clinical outcomes presented in these cases compare well to those with larger sample size studies where a CRWPI was administered.

## Conclusion

Administration of a cysteine-rich whey protein isolate for these patients with COVID-19 pneumonia was associated with a rapid clinical improvement. With the emergence of new variants of the COVID-19, such as delta and omicron, this case series using CRWPI suggests its potential as a novel natural coadyuvant. Further prospective and large-scale, controlled studies are needed to confirm these results.

## Disclosures

Arturo Arias, Catalina Camacho, Maria M Padron, Eduardo Scholc off, and Ruben D Restrepo are independent consultants for Immunotec.

## Correspondence

Ruben D Restrepo restrepor@uthscsa.edu.

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## Bibliography


1. World Health Organization Coronavirus (COVID-19) Dashboard (2022).
2. World Health Organization Coronavirus (COVID-19) Colombia (2022).
3. Polonikov A. "Endogenous Deficiency of Glutathione as the Most Likely Cause of Serious Manifestations and Death in COVID-19 Patients". *ACS Infectious Diseases* 6.7 (2020): 1558-1562.
4. Khanfar A and Al Qaroot B. "Could glutathione depletion be the Trojan horse of COVID-19 mortality?" *European Review for Medical and Pharmacological Sciences* 24.23 (2020): 12500-12509.
5. Cecchini R and Lourenço CA. "SARS-Co-V-2 infection pathogenesis is related to oxidative stress as a response to aggression". *Medical Hypotheses* 143 (2020): 110102.
6. Domej W., *et al*. "Oxidative stress and free radicals in COPD - implications and relevance for treatment". *International Journal of Chronic Obstructive Pulmonary Disease* 9 (2014): 1207-1224.
7. Poe FL and Corn J. "N-Acetylcysteine: A potential therapeutic agent for SARS-CoV-2". *Medical Hypotheses* 143 (2020): 109862.
8. Rangel-Méndez JA and Moo-Puc RA. "N-acetylcysteine as a potential treatment for novel coronavirus disease 2019". *Future Microbiology* (2020).
9. De Flora S., *et al*. "Antioxidants and COVID-19". *Journal of Preventive Medicine and Hygiene* 62.1-3 (2021) (2021): E34-E45.
10. Andreou A., *et al*. "COVID-19: The Potential Role of Copper and N-acetylcysteine (NAC) in a Combination of Candidate Antiviral Treatments Against SARS-CoV-2". *In Vivo* 34.3 (2020): 1567-1588.
11. Lu SC. "Regulation of hepatic glutathione synthesis: current concepts and controversies". *The FASEB Journal* 13.10 (1999): 1169-1183.
12. Diotallevi M., *et al*. "Glutathione Fine-Tunes the Innate Immune Response toward Antiviral Pathways in a Macrophage Cell Line Independently of Its Antioxidant Properties". *Frontiers in Immunology* 8 (2017): 1239.
13. Gould RL and Pazdro R. "Impact of Supplementary Amino Acids, Micronutrients, and Overall Diet on Glutathione Homeostasis". *Nutrients* 11.5 (2019): 1056.
14. Lang CA., *et al*. "Low blood glutathione levels in healthy aging adults". *Journal of Laboratory and Clinical Medicine* 120.5 (1992): 720-725.
15. Erden-Inal M., *et al*. "Age-related changes in the glutathione redox system". *Cell Biochemistry and Function* 20.1 (2002): 61-66.
16. Dröge W. "Oxidative stress and ageing: is ageing a cysteine deficiency syndrome?" *Philosophical Transactions of the Royal Society B: Biological Sciences* 360.1464 (2005): 2355-2372.
17. Gu F., *et al*. "Glutathione redox imbalance in brain disorders". *Current Opinion in Clinical Nutrition and Metabolic Care* 18.1 (2015): 89-95.
18. Sung CC., *et al*. "Oxidative stress and nucleic acid oxidation in patients with chronic kidney disease". *Oxidative Medicine and Cellular Longevity* (2013): 301982.

19. Traverso N., *et al*. "Role of glutathione in cancer progression and chemoresistance". *Oxidative Medicine and Cellular Longevity* (2013): 972913.

20. Ballatori N., *et al*. "Glutathione dysregulation and the etiology and progression of human diseases". *Journal of Biological Chemistry* 390.3 (2009): 191-214.

21. Valko M., *et al*. "Free radicals and antioxidants in normal physiological functions and human disease". *The International Journal of Biochemistry and Cell Biology* 39.1 (2007): 44-84.

22. Dröge W and Holm E. "Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction". *The FASEB Journal* 11.13 (1997): 1077-1089.

23. Guloyan V., *et al*. "Glutathione Supplementation as an Adjunctive Therapy in COVID-19". *Antioxidants* 9.10 (2020): 914.

24. Horowitz RI and Freeman PR. "Three novel prevention, diagnostic, and treatment options for COVID-19 urgently necessitating controlled randomized trials". *Medical Hypotheses* 143 (2020): 109851.

25. Horowitz RI., *et al*. "Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases". *Respiratory Medicine Case Reports* 30 (2020): 101063.

26. Meister A. "Glutathione metabolism". *Methods in Enzymology* 251 (1995): 3-7.

27. Bounous G. "Whey protein concentrate (WPC) and glutathione modulation in cancer treatment". *Anticancer Research* 20.6C (2000): 4785-4792.

28. Homma T and Fujii J. "Application of glutathione as anti-oxidative and anti-aging drugs". *Current Drug Metabolis* 16.7 (2015): 560-571.

29. Haddad JJ and Harb HL. "L-gamma-Glutamyl-L-cysteinyl-glycine (glutathione; GSH) and GSH-related enzymes in the regulation of pro- and anti-inflammatory cytokines: a signaling transcriptional scenario for redox(y) immunologic sensor(s)?" *Molecular Immunology* 42.9 (2005): 987-1014.

30. Tsuchiya T., *et al*. "Oral administration of the amino acids cystine and theanine attenuates the adverse events of S-1 adjuvant chemotherapy in gastrointestinal cancer patients". *The International Journal of Clinical Oncology* 21.6 (2016): 1085-1090.

31. Cai J., *et al*. "Inhibition of influenza by glutathione". *Free Radical Biology and Medicine* 34.7 (2003): 928-936.

32. Biswas SK and Rahman I. "Environmental toxicity, redox signaling and lung inflammation: the role of glutathione". *Molecular Aspects of Medicine* 30.1-2 (2009): 60-76.

33. De Flora S., *et al*. "Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment". *European Respiratory Journal* 10.7 (1997): 1535-1541.

34. Sandilands EA and Bateman DN. "Adverse reactions associated with acetylcysteine". *Clinical Toxicology* 47.2 (2009): 81-88.

35. Lu SC. "Regulation of hepatic glutathione synthesis: current concepts and controversies". *The FASEB Journal* 13.10 (1999): 1169-1183.

36. Bounous G and Gold P. "The biological activity of undenatured dietary whey proteins: role of glutathione". *Clinical and Investigative Medicine* 14.4 (1991): 296-309.

37. Bounous G and Molson JH. "The antioxidant system". *Anticancer Research* 23.2B (2003): 1411-1415.

38. Kent KD., *et al*. "Effect of whey protein isolate on intracellular glutathione and oxidant-induced cell death in human prostate epithelial cells". *Toxicology in Vitro* 17.1 (2003): 27-33.

39. Bounous G., *et al*. "Whey protein in cancer prevention". *Clinical and Investigative Medicine* 11.4 (1988): 271-278.

40. Gilani GS. "Background on international activities on protein quality assessment of foods". *British Journal of Nutrition* 108.S2-2 (2012): S168-S182.

41. Sarwar G and McDonough FE. "Evaluation of protein digestibility- corrected amino acid score method for assessing protein quality of foods". *Journal - Association of Official Analytical Chemists* 73.3 (1990): 347-356.

42. Reference Manual for U.S. Milk Powders. 2005 Revised Edition (2022).

43. Prescriber's Digital Reference. PDR Network, 2021 (2022).

44. Compendium of Pharmaceuticals and Specialties. Canadian Pharmacists Association (2022).

45. Tozer RG., *et al*. "Cysteine-rich protein reverses weight loss in lung cancer patients receiving chemotherapy or radiotherapy". *Antioxidants and Redox Signaling* 10.2 (2008): 395-402.

46. Lands LC., *et al*. "Effect of supplementation with a cysteine donor on muscular performance". *Journal of Applied Physiology* 87.4 (1999): 1381-1385.

47. Gillis C., *et al*. "Prehabilitation with whey protein supplementation on perioperative functional exercise capacity in patients undergoing colorectal resection for cancer: a pilot double-blinded randomized placebo-controlled trial". *Journal of the Academy of Nutrition and Dietetics* 116.5 (2016): 802-812.

48. Grey V., *et al*. "Improved glutathione status in young adult patients with cystic fibrosis supplemented with whey protein". *Journal of Cystic Fibrosis* 2.4 (2003): 195-198.

49. Chitapanarux T., *et al*. "Open-labeled pilot study of cysteine-rich whey protein isolate supplementation for nonalcoholic steatohepatitis patients". *Journal of Gastroenterology and Hepatology* 24.6 (2009): 1045-1050.

50. Prussick R., *et al*. "Psoriasis improvement in patients using glutathione-enhancing, nondenatured whey protein isolate - A Pilot Study". *The Journal of Clinical and Aesthetic Dermatology* 6.10 (2013): 23-26.

51. Tosukhowong P., *et al*. "Biochemical and clinical effects of Whey protein supplementation in Parkinson's disease: A pilot study". *Journal of the Neurological Sciences* 367 (2016): 162-170.

52. Bounous G., *et al*. "Whey proteins as a food supplement in HIV-seropositive individuals". *Clinical and Investigative Medicine* 16.3 (1993): 204-209.

53. Kennedy RS., *et al*. "Anticancer Research 15.6B (1995): 2643-2649.

54. Bounous G. "Whey protein concentrate (WPC) and glutathione modulation in cancer treatment (Review)". *Anticancer Research* 20.6C (2000): 4785-4792.

55. Gilani GS. "Background on international activities on protein quality assessment of foods". *British Journal of Nutrition* 108.2-2 (2012): S168S182.

56. Sarwar G and McDonough FE. "Evaluation of protein digestibility-corrected amino acid score method for assessing protein quality of foods". *Journal - Association of Official Analytical Chemists* 73.3 (1990): 347-356.

57. Fan H., *et al*. "The effect of whey protein on viral infection and replication of SARS-CoV-2 and pangolin coronavirus in vitro". *Signal Transduction and Targeted Therapy Peer-reviewed journal* 5.1 (2020): 275.

58. Nduati R., *et al*. "Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial". *The Journal of the American Medical Association* 283 (2000): 1167-1174.

59. Weller TH. "The cytomegaloviruses: ubiquitous agents with protean clinical manifestations". *The New England Journal of Medicine* 285 (1971): 203-214.

60. Elattar G., *et al*. "The use of whey protein concentrate in management of chronic hepatitis C virus - a pilot study". *Archives of Medical Science* 6 (2010): 748-755.

61. Florisa R., *et al*. "Antibacterial and antiviral effects of milk proteins and derivatives thereof". *Current Pharmaceutical Design* 9 (2003): 1257-1275.

62. Yu B., *et al*. "Nutrition acquisition by human immunity, transient overnutrition and the cytokine storm in severe cases of COVID-19". *Medical Hypotheses* 155 (2021): 110668.

63. Scarcella M., *et al*. "Effect of whey proteins on malnutrition and extubating time of critically ill COVID-19 patients". *Nutrients* 14 (2022): 437.

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