Potent NRF2-activating dietary supplements (like resveratrol, curcumin, sulforaphane, “Asea redox supplement” [ARS] etc.) should be clinically tested as adjuvants in all types of medium and severe cases of aggressive respiratory viral infections (including Influenza A/B/C, avian influenza, measles, Coronavirus-related SARS, MERS, COVID-19 etc.) based on their extraplated cytoprotective antioxidant effects (especially on vital organs), including the cytoprotection offered by ARS on the cardiac muscle of DMD patients which can be extrapolated to the lungs of the infected patients (very short medical communication)

DOI: 10.13140/RG.2.2.33764.12163

Paper version: 1.1 (26.03.2020) (no matter this current paper version, its latest variant can be always downloaded from this URL; version 1.0 released on 29.02.2020)

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For motivation of this Wikipedia-based paper format, see URL.

Abstract
(with some abbreviations further used in this paper)

This very short medical communication proposes that potent NRF2-activating dietary supplements (like resveratrol, sulforaphane, curcumin, “Asea redox supplement” [ARS] etc.) should be clinically tested as safe adjuvants (in various combinations) in all types of medium and severe cases of aggressive respiratory viral infections (including Influenza A/B/C, avian influenza, measles, Coronavirus-related SARS, MERS, COVID-19 etc.), including those patients who have important comorbidities like HIV/AIDS, tuberculosis [TB] etc.) based on their extrapolated cytoprotective antioxidant effects (especially on the main vital organs: brain, heart, lungs, kidneys and liver), including the extrapolated strong cytoprotection offered by ARS on the cardiac muscle of DMD patients (which can be extrapolated to the lungs), like the author of this paper has demonstrated in past papers [1, 2, 3, 4, 5].

Keywords: NRF2-activating dietary supplements, resveratrol, sulforaphane, curcumin, “Asea redox supplement” [ARS], respiratory viral infections, influenza A/B/C, avian influenza, measles, coronavirus, SARS, MERS, COVID-19, HIV/AIDS, tuberculosis [TB]

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I. Very short medical communication with main arguments and additional ideas

Introduction. Potent NRF2-activating dietary supplements (NADS) (like resveratrol, sulforaphane, curcumin, “Asea redox supplement” [ARS] etc.) stimulate the activity of NRF2, a master transcription factor (encoded by the NFE2L2 human gene), which activated NRF2 significantly increases the expression of antioxidant proteins (glutathione synthetase, glutathione peroxidase, [GPx], superoxide dismutase [SOD], catalase etc.) that strongly protect against oxidative stress (OS)/damage triggered by acute/chronic infectious (viral, bacterial etc) or non-infectious (toxic, autoimmune etc.) injury and inflammation at cellular and tissue level. Several NADS are being studied as treatment of diseases that are caused by OS (or which have an important OS component in their pathogenic chain) [URL1, URL2, URL3, URL4].

For a more detailed introduction to NRF2 and ARS see the main references of this paper [1, 2].

The author has also dedicated a separate online database [URL] to all known (natural or synthetic) NRF2 activators (see URL): www.nrf2.dragoii.com

The main proposal/suggestion of this short medical communication. In the context of recent various aggressive viral epidemics worldwide (including Influenza A/B/C, SARS, MERS, COVID-19, measles, avian influenza etc., including those patients which have important comorbidities like HIV/AIDS, tuberculosis [TB] etc.), this paper proposes that at least some of the previously listed NADS (including ARS) to be clinically tested in high doses (or even very high doses, close to their toxic lower bounds) as adjuvants (in combination with specific antiviral drugs or other types of medication) in all types of medium and severe children and adult cases of aggressive respiratory viral infections (as those previously enumerated), especially in those patients without prior vaccination against one or another specific disease (if, when and where it is the case).

Prediction / work hypothesis which needs to be clinically tested in hospitals and/or other medical research centers, under medical supervision (with arguments plus extrapolation). “ASEA redox supplement” (ARS) may plausibly show much stronger cytoprotective antioxidant effects than other NADS on vital organs (possibly affected by the aggressive viral infections previously listed) at average, high or very high ARS doses of 3.5-7ml/kg/bm/day (kgbm=kilogram of body mass). Argument (1). ARS has remarkable antioxidant and immunomodulatory effects (by NRF2 selective activation and NF-kB inhibition). In vitro studies showed that ARS is a very potent selective NRF2 activator, thus a very potent (indirect) cytoprotective antioxidant: the studies conducted in vivo also support this main pharmacological mechanism of ARS, with no toxicity up to high doses. Argument (2). In both cases of children with Duchenne muscular dystrophy (DMD) (treated with ARS) published until present [1, 2] (plus one additional third DMD child case, which is still under preparation to be also published in the near future), the author has demonstrated that the strong cytoprotective effect of ARS (on both cardiac and skeletal type of muscles) can be replicated in vivo, with excellent safety profile and NO measured adverse effects on the bone marrow and/or liver (by standard blood_count and serum levels/concentrations of liver enzymes): more specifically, even after only three months of starting ARS treatment, the main skeletal and cardiac rhabdomyolysis markers (with very high initial serum levels, especially CK, CK-MB, and myoglobin) dropped significantly (down to 2-3 times lower and even 5-6 times lower [in the case of myoglobin] than initial serum levels), with NO found blood marrow and/or liver and/or kidney toxicity until present.

Extrapolation (work hypothesis which needs to be clinically tested in hospitals and/or other medical research centers, under medical supervision). Given its high capacity of limiting myocardial damage (proved by significantly decreasing CK-MB in two DMD cases (also based on the high cytoplasmatic target-NRF2

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concentrations in these main vital organs: heart, lungs, kidneys and liver) AND its higher bioavailability in the central circulation system (which also serves those vital organs), this paper predicts (by extrapolation) that ARS may have strong cytoprotective antioxidant effects in the lung tissue too: furthermore, ARS has a strong additional advantage over the other NADS, because ARS can be administrated both orally and nebulized (as it remains stable in this nebulized form), thus ARS may reach even higher concentrations in the affected lungs of patients with moderate or severe respiratory infections (like those already listed in this paper) (see also next additional arguments). Additionally, ARS appears to significantly reduce the rate of rhabdomyolysis (which is relatively frequent in influenza but also in COVID-19), as demonstrated in DMD patients, thus ARS may indirectly prevent renal failure (RF) by acute tubular necrosis (ATN) partially secondary to rhabdomyolysis in COVID-19, with RF and ATN being important risk factors for multiple organ failure thus bad prognostic factors which increase mortality in both influenza and COVID-19.

**Additional argument (1) for the previous extrapolation.** A trial in patients with chronic obstructive pulmonary disease (COPD) using sulforaphane (a potent NADS, yet weaker than ARS) improved the initially reduced phagocytosis of bacteria (by alveolar macrophages from those patients with COPD) [URL1, URL2].

**Additional argument (2) for the previous extrapolation.** NADS may also have the additional benefit of improving resistance to viral entry and replication in cells infected with influenza A virus, thus may plausibly help in reducing COPD patient vulnerability to viral exacerbation [URL1, URL2].

**Additional ideas of clinical testing/research of ARS in combination with N-acetylcysteine (NAC).** (1) ARS stimulates the cellular synthesis of reduced glutathione (GSH) (by activation of glutathione synthetase via NRF2 pathway), which is a very potent endogenous antioxidant. On the other hand, N-acetylcysteine (NAC) serves as a prodrug to L-cysteine (which is a precursor of the same GSH): hence, oral and/or nebulized (and/or intravenous) administration of NAC replenishes GSH stores of human organism and that is why it may strongly enhance the beneficial effects of ARS (by plausible therapeutic synergy) in these type of aggressive infections but ALSO in many other type of diseases with an important oxidative stress (OS) component (infections, DMD etc.) [URL]. (2) Vitamine B6 is also a candidate that may be used in combination with ARS (plus/minus NAC, plus/minus any other NADS) [URL]. (3) Various combinations of two or more NADS may also be clinically tested. (4) ARS or other NADS can be also tested in combination with other types of immunostimulants (with potential synergic effect when combined with NADS) like for example: vitamin E, vitamin C, vitamin D, inosine pranobex (an analog of thymus hormones with indirect antiviral properties), inositol hexaphosphate, deoxycholic acid etc.

**Important note.** There are also several respiratory OS markers that can be used to assess the biological efficiency (if any) of ARS and NAC (in standalone or combined adjuvant therapies) [URL1, URL2, URL3].

**Conclusion.** Given their strong antioxidant effects (by NRF2 potent activation), at least some NADS (including ARS) deserve future cohort studies on acute/chronic diseases that imply high levels of tissue oxidative stress, especially some acute/chronic cardiovascular and respiratory diseases like: medium and severe infections (including aggressive infections like including influenza A/B/C, avian influenza, measles, Coronavirus-related SARS, MERS, COVID-19, etc., including those patients which have important comorbidities like HIV/AIDS, tuberculosis [TB] etc.), acute myocardial infarction with acute/chronic heart failure, stroke, chronic obstructive pulmonary disease (COPD), asthma etc. of both children and adults, so that NADS may help millions and even billions worldwide.

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**II. References**

(partially integrated as Wikipedia URLs in the main text of this paper)

[1] Andrei-Lucian Drăgoi (July 2019). (ASEA in DMD - CJBR article - 20.07.2019) The Remarkable Effects of ”ASEA redox Supplement” In A Child with Duchenne Muscular Dystrophy – A Case Report, Canadian Journal of Biomedical Research and Technology (CJBR) 2019; volume 1, issue 4.8. ISSN: 2582-3663. URLs: URL1a, URL1b, URL1c (CJBRT original sources); URL2a (Research Gate source); URL2b & URL2c (Academia sources); URL2d (Vixra source); URL3 (Research Gate preprint source). See also the newly released related add-on paper (RG preprint) The 1st case report on the remarkable effects of “ASEA Redox Supplement” (ARS) in a boy with Duchenne muscular dystrophy (DMD) – periodic updates released after 20.07.2019 (the date of the official case publication in a peer-reviewed journal) (DOI 10.13140/RG.2.2.23141.76002, URL to RG preprint).


