Review



# Neglected Effective Early Therapies against COVID-19: Focus on Functional Foods and Related Active Substances. A Review

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*Review*

# Neglected Effective Early Therapies against COVID-19: Focus on Functional Foods and Related Active Substances—A Review

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**Cover Letter:** The official recommendations for COVID-19 management in the outpatient setting focus on high-cost drugs, that show several problems and limitations. Therefore, other treatments may be considered, if they meet the following criteria: promising effectiveness, based on favorable randomized controlled trials (RCTs) of acceptable validity, provided the treatments are also: safe, convenient, biologically plausible, accessible and coming from researchers with no major conflict of interests. The focus is on some functional foods and their active ingredients, with further mention of a few other substances of different origin but meeting the above criteria. The supporting scientific evidence privileges meta-analyses of RCTs, the most valid study design, including the most solid outcome: all-cause mortality.

**Abstract:** The official recommendations to manage COVID-19 in the outpatient setting focus on high-cost drugs (remdesivir, nirmatrelvir-ritonavir, molnupiravir), suffering from many problems. Therefore, one may consider also other treatments meeting these criteria: (1) promising effectiveness, based on favorable randomized controlled trials (RCTs) of sufficient validity. Even without definitive evidence, physicians and informed patients can consider them if they are also: (i) safe, to the state of knowledge; (ii) with a very favorable opportunity cost; (iii) biologically plausible/not implausible; (iv) accessible; (v) without major commercial sponsors in the trials promoting them, and with researchers without major conflicts of interests. The main focus is on a limited group of functional foods and some their active ingredients, with further mention of other substances of different origin, yet fully meeting all the aforementioned criteria. The functional foods and substances described and discussed certainly do not cover all the known effective therapies for COVID-19 (in one case also for Long-COVID), but the only therapies proposed in this paper currently satisfy all the above criteria. The supporting scientific evidence will favor meta-analyses of RCTs that include the most definitive outcome: all-cause mortality, i.e., the outcome that most fully informed people tend to prioritize. Furthermore, the reported evidence favors clinical studies of the most valid design, i.e., RCTs.

**Keywords:** EB functional foods in COVID-19 early therapy; EB active ingredients of foods in COVID-19 therapy; EB active substance in Long-COVID-19 therapy; EB active substance for Post-COVID sequelae.

## 1. Introduction

### *1.1. Current gaps and problems*

Strategies to manage COVID-19, mainly in the outpatient setting, evolve as new data emerge about newer treatments. However, the official recommendations (e.g., by World Health Organization/WHO [1], or by American College of Physicians [2]) are chiefly focused on high-cost drugs, as remdesivir, but only for patients with high risk of hospitalization [1], or as nirmatrelvir-

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ritonavir and molnupiravir [1,2], to be taken within 5 days of the onset of symptoms and only by people at risk of progressing to severe disease.

Anyway, these drugs have several problems in addition to the very high cost. In particular, as regards remdesivir, the difficult and inconvenient administration, making it unsuitable for home therapy. As regards molnupiravir, the web site of European Medicine Agency (EMA) [3] reported that, on 21 June 2023, Merck Sharp & Dohme (MSD) withdrew its application for a marketing authorisation concerning this drug (Lagevrio) for the treatment of COVID-19 in adults. MSD stated that its decision was based on the view of the Committee for Medicinal Products for Human Use (CHMP) of EMA, that the data provided by MSD itself do not allow to conclude on a positive benefit-risk balance for Lagevrio. Indeed, based on the totality of data, CHMP was unable to conclude that Lagevrio either can reduce the risk of hospitalisation or death or shorten the duration of illness or time to recovery in adults at risk of severe disease. Furthermore, it was not possible to identify a specific group of patients for whom a clinically relevant benefit of Lagevrio had been demonstrated.

As regards nirmatrelvir-ritonavir, in addition to the numerous pharmacological interactions limiting its use [4], there are also other problems. E.g., its effectiveness was lowered during the Omicron surge [5]: it remained significant against hospitalization and death due to Covid-19 among patients 65 years of age or older, but no evidence of benefit was found in younger adults of 40 to 64 years [5], neither versus hospitalization among patients with previous immunity (Adjusted Hazard Ratio 1.13; 95% CI, 0.50 to 2.58), nor versus death due to Covid-19 (AHR 1.32; 95% CI, 0.16 to 10.75). It showed also a high virologic rebound: in a recent large cohort study [6,7], more than 1 in 5 people taking nirmatrelvir-ritonavir had a rebound, often without symptom, but associated with shedding of replication-competent viruses. Even the hypothesized effectiveness of nirmatrelvir-ritonavir against the development of Post-COVID-19 conditions (PCCs) was questioned, because it seems to reduce only combined thromboembolic events out of 31 potential PCCs [8] in a target trial emulation in US Veterans (82.5% vaccinated).

Highly specific monoclonal antibodies showed initial clinical trials evidence, soon becoming no longer applicable to covid-19 caused by the SARS-CoV-2 variants and subvariants that are currently circulating globally [1].

So, it is also useful to take into account *less specific* treatments, with potentially more durable and affordable effectiveness.

### *1.2. Materials and Methods - Inclusion criteria for proposed therapies*

The products or active substances addressed by this paper expand the range of COVID-19 remedies, effective also in the home setting. Of course, after having discussed them with one own's physician.

Such products or active substances have been chosen and included according the following criteria:

- very promising effectiveness, based on favorable randomized controlled trials (RCTs) of sufficient validity,* complemented by consistent observational studies, available on the major databases of biomedical literature. Even if the evidence is not definitive, attending physicians and informed patients can consider them to the extent that they are at the same time also:
- safe (*primum non nocere*!), to the state of knowledge
- affordable, with a very favorable opportunity cost, allowing resources to be saved for other valuable healthcare uses
- biologically plausible (or at least not clearly implausible)
- accessible (or capable of quickly granting accessibility)
- without major commercial sponsors in the trials promoting them, and realized by researchers without major conflicts of interests.

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The main focus is on a limited group of functional foods and related active substances, with mention also of other substances of different origin, yet fully meeting all the aforementioned criteria, including also a product with valid evidence of efficacy against long-COVID

(but also by closing the list with a negative didactic example, of an active ingredient among the most used and recommended worldwide, although it does not meet five of the six aforementioned *golden* criteria).

The substances that will be described and discussed in this review manuscript certainly do not cover all the known effective therapies against COVID-19 (including those approved or pending approval), but the only therapies proposed in this paper are those that currently satisfy all the above criteria.

Among the treated substances, the paper set a special focus on functional foods and on some of their active ingredients.

The supporting scientific evidence will favor meta-analyses of clinical trials that include the most definitive of outcomes, all-cause mortality. This is also the outcome that most fully informed people tend to prioritize. Furthermore, the scientific evidence reported will favor clinical studies of the most valid design, i.e., randomized controlled trials, as already specified in the inclusion criteria.

* Note that some cited references come from preprint articles. When there is also a good number of RCTs with favorable results on a substance, the choice was not to exclude preprint articles adding consistent information on the topic. It should be noted that there are also reasons other than the quality of scientific information why major biomedical journals do not publish or heavily delay the publication of some articles. There is an ongoing debate on this topic, and some authors with very high H Indexes have chosen to publish elsewere their scientific production [9].

## 2. Curcumin

Curcumin is a polyphenolic compound derived from the rhizomes of turmeric (Curcuma Longa). Its spices' yellow pigment has shown anti-inflammatory, antioxidant, immune modulating and anti-viral properties [10,11]. Its antiviral activity was observed against multiple viruses including hepatitis viruses, influenza viruses and arboviruses like the Zika or chikungunya virus; it has also been reported to inhibit human immunodeficiency virus, herpes simplex virus 2 and human papillomavirus [12]. Curcumin also favors fibrinolysis [13].

Both a systematic review and dose–response meta-analysis [14] and an umbrella meta-analysis [15] of randomized clinical trials (on nearly 6,000 participants) have suggested that turmeric/curcumin supplementation may be useful for improving inflammatory/oxidative status, and that curcumin is a promising agent in reducing inflammation as an adjunctive therapy in diseases

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with a high level of infammatory biomarkers. Indeed, curcumin supplementation significantly decreased levels of C-reactive protein (CRP), interleukin 6 (IL-6), and tumour necrosis factor $\alpha$ (TNF-$\alpha$) levels.

A problem may be caused by the low bioavailability of traditional forms of curcumin and turmeric, first of all related to their poor solubility [16], requiring bio-enhancers like piperine to considerably improve its absorption. RCTs has successfully used a dosage of about 500 mg or curcumin with piperine (2,5 mg) twice a day (e.g., [17]). Another substance substantially increasing the absorption of curcumin after oral administration is bromelain, isolated from the pineapple stem [13], in turn accredited with anti-inflammatory, fibrinolytic and anticoagulant properties, but affecting the absorption rate of several medications, potentially leading to drug interactions.

Both curcumin and bromelain might also inhibit viral entry into cells, with possible multiple synergistic actions. The absorption of curcumin is also favored by nano or liposomal formulations, available as over-the-counter oral supplements.

Curcumin has shown high safety and tolerability in clinical trials, even at high doses [18]; its potential adverse effects include diarrhea, headache, rash, and yellow stool, but no serious adverse effects have been reported to date [19]. 500 mg twice a day has shown

to be a safe and common dosage regardless of curcumin type [20].

Given that curcumin is about 10% in weight of curcuma, and that piperine is about 5%-8% in weight of black pepper, a home made dosage could consider (in agreement with one's doctor) about 5 grams of curcuma with 1-2 well-chewed black peppercorns twice a day.

A real time analysis of COVID-19 early (and late) treatments [21] shows for curcumin the following mortality results, all coming from single o double blind randomized controlled trials (RCTs)(Figure 1):

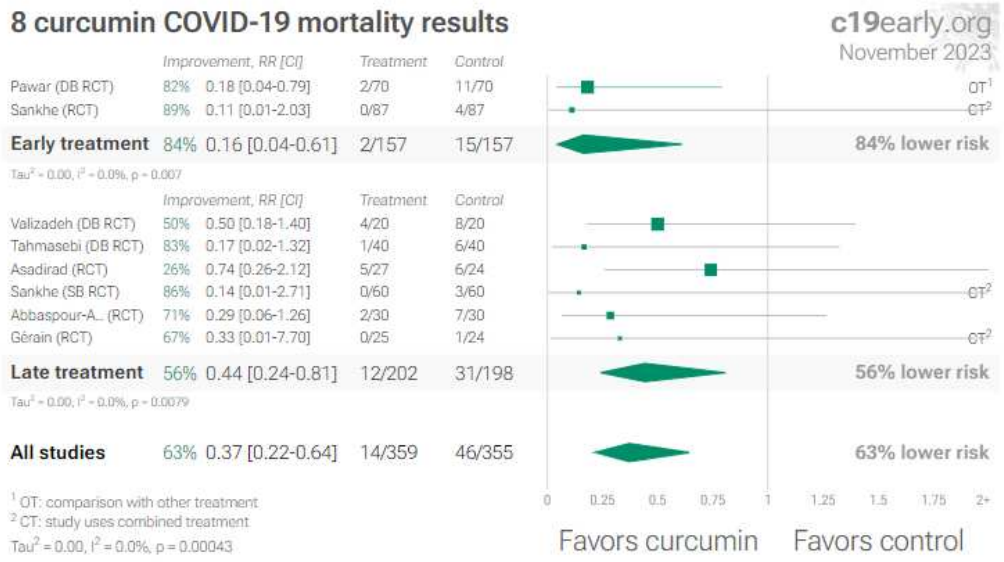


***Figure 4.*** Random effects meta-analysis for mortality results.

**Figure 1.** Random effects meta-analysis for all RCTs about curcumin mortality results in COVID-19 [17,22–28].

Note the consistency of the results of all the RCTs. They are not large, but some have a highly valid design (double blind), with very good results both in early and in advanced treatment phases.

Moreover, Figure 2 shows all the curcumin RCTs in COVID-19, studying several other outcomes in addition to mortality (hospitalization, ventilation, numbers of recovery or recovery time, progression of the disease, oxigen saturation, viral positivity, in both early and late treatments):

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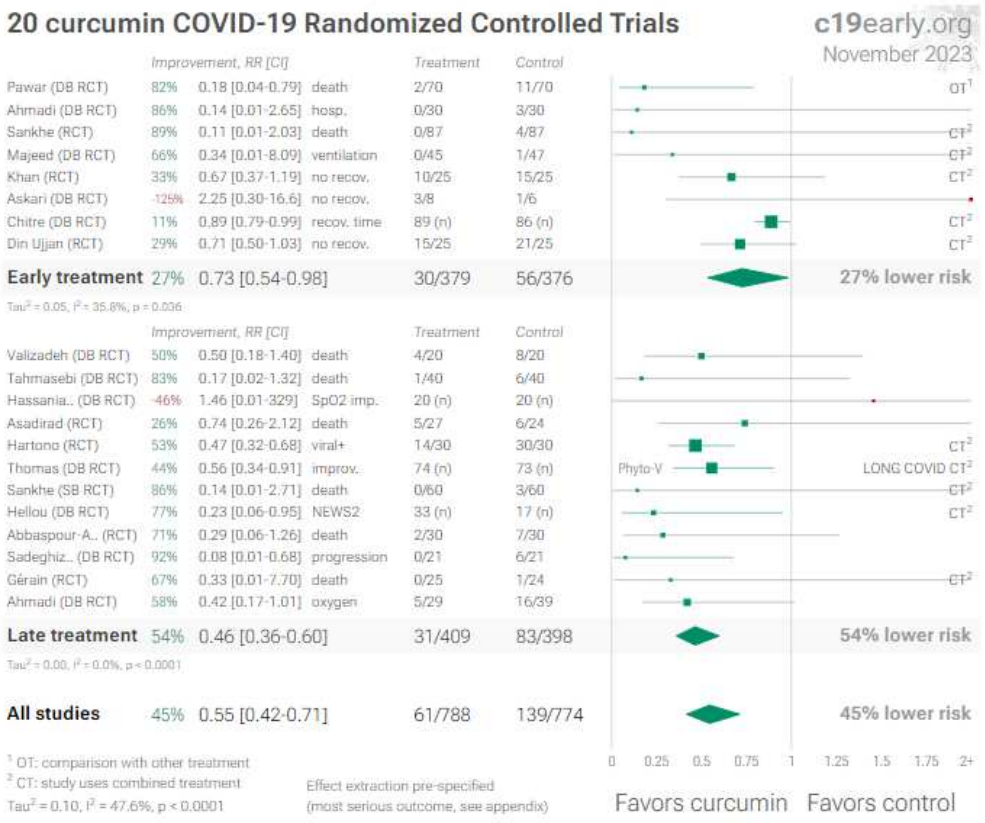


**Figure 2.** Random effects meta-analysis for all RCTs about curcumin in COVID-19 [17,22–40]. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section [21] for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix [21].

Interestingly, curcumin has offered antiinflammatory and prophylactic benefits also in healthy individuals with a history of prior COVID-19 infection who received the COVID-19 vaccine [41].

### 3. Nigella Sativa (Black Seed)

*Nigella* (*N.*) *sativa*, also known as black seed or black cumin seed, is a food spice with a medicinal value, with several active compounds, including thymoquinone and a radical scavenging property. The safety profile of thymoquinone has been documented in clinical trials (e.g., one in asthmatic patients [42]). A systematic review of RCTs that used *N. sativa* showed no serious adverse effects on hepatic and renal function [43]. Several preclinical and clinical studies have documented the antiviral activities of *N. sativa* against several viruses [44]. Some *N. sativa* compounds demonstrated potential inhibition of coronavirus replication in in silico models [45]. In several studies *N. sativa* has shown immunostimulant effects through the induction of multiple cellular mediators and immune responses to eradicate infections [45]. In studies on inflammatory conditions, *N. sativa* L. has demonstrated anti-inflammatory and immunomodulatory activities, reducing pro-inflammatory mediators [46]. It has also analgesic and antipyretic properties [47].

A real time analysis of COVID-19 early (and late) treatments [21] shows for nigella sativa the following mortality results, all coming from RCTs (Figure 3).

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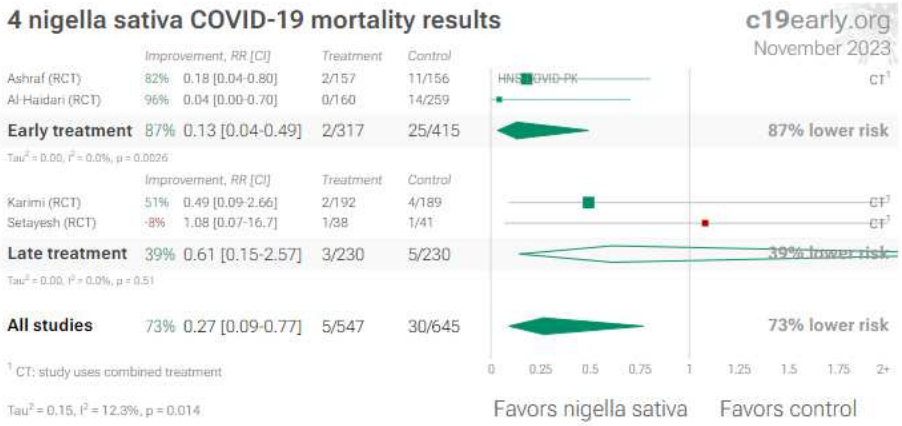


**Figure 3.** Random effects meta-analysis for RCTs with mortality results about nigella sativa [48–51].

Figure 4 shows all the nigella sativa RCTs in COVID-19, studying several other outcomes in addition to mortality (hospitalization, recovery, cases/viral positivity, symptomatic cases, both in early and in late treatments):

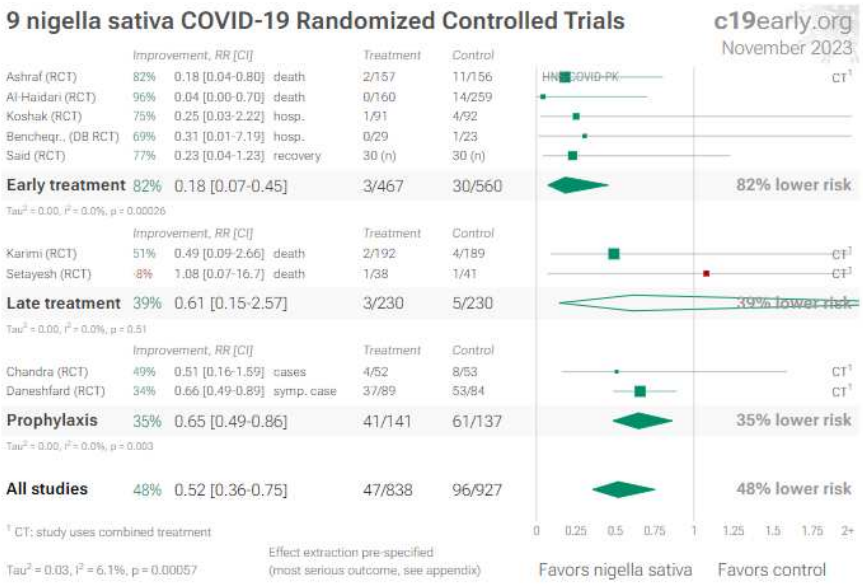


**Figure 4.** Random effects meta-analysis for all RCTs about nigella sativa [48–56]. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section [21] for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix [21].

However, only in one case the RCT is double blind, and the quality of some black seed trials is poor.

Doses of *N. Sativa* typically used in the RCTs have been 0.5 g twice daily of black seed oil for about two weeks, or 2-5 g of black seed, about 40 mg per kilogram of weight.

## 4. Quercetin

Quercetin is a plant flavonol, of the flavonoid class of phenolic compounds, with potent antioxidant activity, studied for its immunomodulatory and immune-boosting properties. It has been approved by the US Food and Drug Administration as GRAS (Generally Recognized As Safe) for use as an ingredient at levels up to 500 mg per serving.

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Important sources of quercetin, approximately expressed in mg per 100 g of each food, are: capers (200 mg); lovage (levisticum) leaves (170); eidelberry (sambucus) juice concentrate (110 mg); dill weed (anethum), fresh (55 mg); cilantro (coriandrum), fresh (55 mg); banana peppers (50 mg); juniper berries (50); onions (40 mg); radicchio and read leaf lettuce (30 mg); asparagus, kale, okra, bee pollen, cocoa powder, apples skin, chia seeds (20-25 mg).

Quercetin, like other flavonoids, reduces the production of pro-inflammatory mediators (Bhaskar, 57), promotes the relaxation of cardiovascular muscles, and neuroprotection (Khan, 58). Moreover, quercetin protects against both non-communicable diseases as cancer, coronary heart disease, atherosclerosis and hypercholesterolemia, rheumatic diseases, and infections thanks to its antioxidant properties and the regulation of cellular homeostasis (Batiha 59). It may benefit people with comorbidities like hypertension, diabetes mellitus, obesity, chronic obstructive pulmonary disease, coagulopathy and cytokine storm, all associated with COVID-19 seriousness (60 Xu). Quercetin also have shown a strong association with reduction in frailty onset in the 12 years follow-up of a prospective cohort study of individuals from the Framingham Heart Study without frailty at baseline (61). Every 10 mg/d of higher quercetin intake was associated with 35% lower odds of frailty onset (OR: 0.65; 95% CI: 0.48–0.88).

Antibacterial and antiviral activity of Quercetin has been known for decades [62].

In in vitro studies quercetin has inhibited the replication of various respiratory viruses, among which influenza virus [63], and severe acute respiratory syndrome (SARS) viruses [64]. This suggested possible clinical efficacy in COVID-19 [65–68].

A systematic review and meta-analysis of quercetin for COVID-19 patients [69] have found that quercetin significantly decreased the risk of intensive care unit admission (OR = 0.31; 95% confidence interval (CI) 0.10–0.99) and the incidence of hospitalisation (OR = 0.25; 95% CI 0.10–0.62), but did not [significantly] decrease the risk of all-cause mortality (OR 0.39; 0.10 to 1.54) and the rate of no recovery (0.55; 0.28 to 1.07). However, one should consider that even for these outcomes the tendency is in the direction of a benefit. The Authors [69] conclude: "Quercetin may

be of benefit in COVID-19 patients, especially if administered in its phytosome formulation which greatly enhances its bioavailability, but large-scale RCTs are needed to confirm these findings".

The already cited real time analysis of COVID-19 early (and late) treatments [21] shows for quercetin the following mortality results, all coming from single blind RCTs (Figure 5):

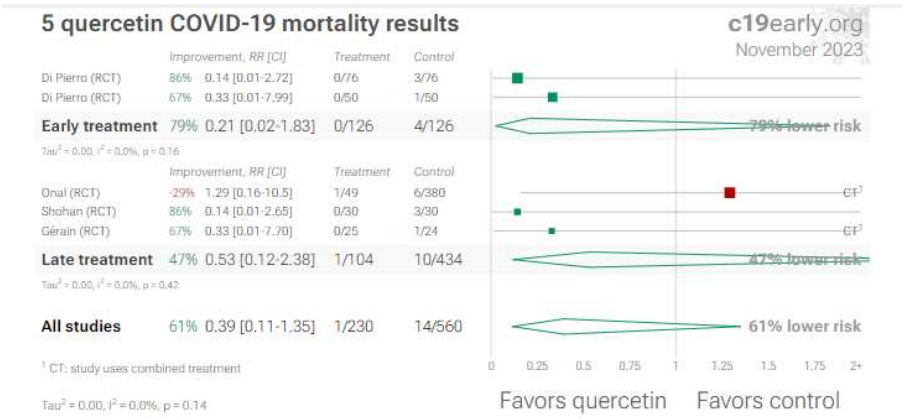


**Figure 5.** Random effects meta-analysis for RCTs with mortality results about quercetin [66–68,70,71].

Figure 6 shows all the quercetin RCTs in COVID-19, studying several other outcomes in addition to mortality (hospitalization, recovery, cases/viral positivity, symptomatic cases, both in early and in late treatments):

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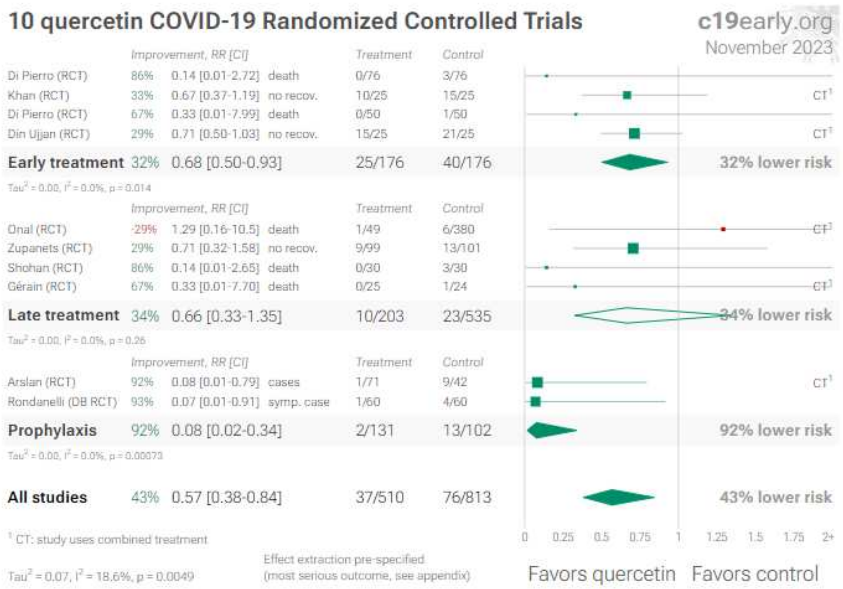


**Figure 6.** Random effects meta-analysis for all RCTs about quercetin in COVID-19 [66–68,70–76]. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section [21] for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix [21].

## 5. L-arginine

L-arginine is an amino acid that participates in the formation of almost all proteins. It is a semi-essential amino acid, i.e., produced by the body but also taken in from the outside with food (nuts, especially pine nuts, seeds, legumes…). It is a substrate for endothelial nitric oxide synthase, a key enzyme in endothelial cells [77,78], and it showed to significantly improve the endothelial function. It stimulates the synthesis of glutathione, thus preventing oxidative stress. L-arginine also showed beneficial effects on the regulation of immune responses [79].

Preclinical and clinical evidence shows that the endothelium is a target organ in COVID-19, explaining many of its systemic manifestations. In severe COVID-19 decreased plasma levels of L-arginine, and more arginase activity [80,81] have been reported.

L-arginine has beneficial effects on the endothelial function [78]. Therefore, in a double-blind RCT [82] on patients hospitalized for COVID-19 requiring oxigen support, after a mean of 7.8 days since the symptoms onset the standard therapy was supplemented with oral vials containing 1.66 g of L-arginine, twice a day (48 patients), or with an identical placebo (53 patients). The dose was the same as that used in a study in which this regimen was safe and effective in improving the oxidative metabolism in sportsmen [83]. The adherence was 100%.

The primary outcome of the reduction in respiratory support was significantly reached 10 days after randomization in the L-arginine group, but the result was no longer significant at 20 days (however, nearly twice the participants in the L-arginine group were already discharged at 20 days, and in hospital there remained only the sicker patients of their group). Indeed, the time to hospital discharge was significantly shorter with L-arginine (25 days) than with placebo (46 days), even in a fully adjusted multivariable analysis. Moreover, in the per protocol analysis 3 patients (6.7%) died in the placebo arm, vs no deaths in the L-arginine arm; in the intention to treat analysis the placebo group had 20.8% deaths, L-arginine 6.3%; p = 0.035.

Three serious adverse events were reported in the placebo arm and 1 in the L-arginine arm, though the investigators considered them unrelated to the study treatment.

It is noteworthy that L-arginine had no significant effect in the time to negativization of RT-PCR for SARS-CoV-2 on nasopharyngeal swab. This suggests that L-arginine acts improving the endothelial function, not against virus replication, which affects the negativization of RT-PCR for SARS-CoV-2. The COVID-19 pathogenesis includes first a viral injury, then an inflammatory immune

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response, which could culminate in a disfunctional hyperinflammation, leading to endothelitis, thromboembolism, and intravascular coagulation. L-arginine depletion has shown to increase the production of reactive oxygen species and to exaggerate the inflammatory response [84].

The promising results of this RCT indicate that L-arginine added to standard therapy in patients with severe COVID-19 can significantly improve their late treatment, leading to the conjecture of its possible use to treat Long-COVID symptoms.

*5.1. Long-COVID treatment*

Long COVID, also known as Post COVID-19 condition (PCC), or post-acute sequelae of SARS-CoV-2 infection (PASC), is the continuation or development of new symptoms in the period after acute infection with SARS-CoV-2. The World Health Organization (WHO) definition of PCC [85] states that these symptoms should be present three months after the initial SARS-CoV-2 infection and last for at least two months with no other explanation.

COVID-19 affects both the epithelial cells of the lung, and the endothelial cells in the whole body, causing a generalized endothelial damage.

Endothelial dysfunction, caused by the viral infection or by the resulting high inflammation, can increase permeabilization, tissue edema, possibly leading to thromboembolism. Endothelial dysfunction may affect smokers and subjects with hypertension, obesity, diabetes and cardiovascular disease, notoriously more prone to adverse outcomes in COVID-19. The favorable interim results of the RCT testing oral supplementation of L-arginine in COVID-19 hospitalized patients [82] led to the survey LINCOLN [86]. The aim was to verify wether L-arginine and Vitamin C could improve Long-COVID symptoms, administering a questionnaire to 1390 patients, with these inclusion criteria: COVID-19 diagnosis confirmed by RT-qPCR; its negativization confirmed by RT-qPCR from at least 4 weeks; COVID-19 sequelae extended more than four weeks after initial infection. The first group (521 patients) included patients who had received 2 vials/day of L-arginine 1.66 g associated with 500 mg of liposomal Vitamin C. The second group (alternative treatment) had been treated with a multivitamin combination of B Vitamins. At the questionnaire administration, both groups had already completed 30 days of treatment. The investigators asked to physicians administering the survey to maintain about a 2:1 ratio (L-Arginine + Vitamin C *vs* alternative treatment); therefore, they were not blinded. The physicians assessed 10 typical Long-COVID symptoms on a scale from 1 to 3 (1 means absence of the symptom, 2 presence of a mild symptom, 3 presence of a severe symptom). The results, shown in Table 1, were excellent:

**Table 1.** Survey results in the two groups of patients treated with multivitamin or L-Arginine + Vit. C [21].

| Outcome | | Alternative Treatment (N=521) | L-Arginine + Vitamin C (N=869) | p |
|---|---|---|---|---|
| **Asthenia** | absent (%) | 0,4 | 94,9 | |
| | mild (%) | 5,2 | 4,0 | <0.0001 |
| | severe (%) | 94,4 | 1,1 | |
| **Dyspnea** | absent (%) | 5,4 | 74,2 | |
| | mild (%) | 55,1 | 25,4 | <0.0001 |
| | severe (%) | 39,5 | 0,4 | |
| **Chest tightness** | absent (%) | 26,3 | 86,1 | |
| | mild (%) | 50,9 | 13,4 | <0.0001 |
| | severe (%) | 22,8 | 0,5 | |
| **Dizziness** | absent (%) | 66,6 | 87,3 | |
| | mild (%) | 25,9 | 11,6 | <0.0001 |
| | severe (%) | 7,5 | 1,1 | |
| **Gastrointestinal disorders** | absent (%) | 63,3 | 87,7 | |
| | mild (%) | 26,7 | 11,7 | <0.0001 |

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| | | | | |
|---|---|---|---|---|
| | severe (%) | 10,0 | 0,6 | |
| **Headache** | absent (%) | 39,2 | 81,8 | |
| | mild (%) | 44,1 | 16,8 | <0.0001 |
| | severe (%) | 16,7 | 1,4 | |
| **Anosmia** | absent (%) | 52,0 | 87,2 | |
| | mild (%) | 34,0 | 11,0 | <0.0001 |
| | severe (%) | 14,0 | 1,8 | |
| **Concentration difficulty** | absent (%) | 32,8 | 79,1 | |
| | mild (%)(%) | 46,8 | 19,4 | <0.0001 |
| | severe (%) | 20,4 | 1,5 | |
| **Sleeplessness** | absent (%) | 39,5 | 80,7 | |
| | mild (%) | 42,6 | 17,5 | <0.0001 |
| | severe (%) | 17,9 | 1,8 | |

A prospective study has demonstrated that endothelial dysfunction in COVID-19 patients remains significantly impaired compared to healthy controls even at a 6-month follow-up [87]. Circulating endothelial cells, probably detached from the vessels, correlate with the severity of COVID-19 outcome [88]. The non-respiratory symptoms of Long-COVID are strongly correlated to persistent endothelial dysfunction [89]. An already cited research demonstrated that reduced levels of L-arginine increase the generation of reactive oxigen species (ROS), worsening inflammation [84]. L-arginine level showed an inverse correlation with platelet activation [90], contributing to COVID-19 thromboembolic events.

Until the end of 2022, no research of valid design (RCT) had been published in the biomedical literature on a medicine capable of treating the symptoms of Long-COVID. The above survey stimulated the execution of a single-blind RCT on Long-COVID adult patients with persistent fatigue, attending a post-acute COVID-19 outpatient clinic [91].

The participants were randomized either to an oral combination of vials containing 1.66 g L-arginine plus 500 mg liposomal vitamin C twice-daily, or to an indistinguishable placebo for four weeks. Primary outcome: the distance paced on the 6 min walk test. Secondary outcomes: handgrip strength, fatigue persistence, flow-mediated dilation. 23 participants per group received the intervention and completed the study.

Results at 28 days showed significant improvement in 6 min walk distance (intervention +30 m, vs. placebo +0; $p = 0.001$), handgrip strength (+3.4 kg vs. +1 kg; $p = 0.03$), flow-mediated dilation (14.3% vs. 9.4%; $p = 0.03$). Above all, it reduced fatigue, reported only by two participants (8.7%) in the L-arginine vs 21 (80.1%) in the placebo group ($p < 0.0001$).

A systematic critical assessment [92] of the current evidence for the

management of long COVID rated "moderated evidence" for important benefits only for respiratory training for respiratory symptoms. The Authors cite a Living Systematic Review of Therapeutic Options for Post COVID-19 Condition [93]; last subsequent publication in August 2023], rating L-arginine + Vitamin C among some therapeutic options for PCC-related asthenia or fatigue, with a disappointing summary of findings: "Uncertainty in potential benefits and harms. Further research is needed", similar to the findings regarding Coenzime Q10, which really showed unsatisfactory results in a well conducted RCT [94].

However, as regards to L-arginine, I disagree, for the following reasons:

- it is true that the RCT [91] is not double blind, has only 4 weeks of follow-up and it is very small, with the possibility that a larger RCT would not confirm its excellent results, however
- one does not see valid reasons to speak of "uncertainty about potential harms", which the trial's results do not allow to hypothesize, even more so given that the active ingredients are introduced daily even with a healthy diet, albeit at doses lower than those effectively administered in the RCT. Moreover, the review [93] states "Adverse events and Severe adverse events: No information", but this is not true, because the Authors [91] report that "L-arginine

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plus vitamin C supplementation was safe and well tolerated, and no adverse events were recorded"; even more so because the retention was complete in both groups

- the problem of Long-COVID is widespread and socially very relevant, and currently lacks therapeutic options confirmed by valid research
- the product used in the RCT [91] still satisfies all the "Inclusion criteria for proposed therapies", and, although awaiting more definitive research, there are good reasons to inform doctors and to offer it to patients with persistent COVID-19 sequelae.

Furthermore, it is plausible that the results of this research [91], suggesting important benefits of a safe molecule such as L-arginine on endothelial disfunction, will also stimulate similar research in other pathologies where endothelial disfunction is believed to have an important pathogenetic role.

**6. Povidone-iodine (and other antiseptics for local use)**

The SARS-CoV-2 virus is usually transmitted in the air and settles in the nose (and in the pharynx, and/or in the ocular mucosa), and multiplies for days before it invades the body. The virus can be killed in those locations, and in any case the viral load can be significantly reduced with early targeted local interventions. Some studies have suggested that mouthwash and/or gargling with povidone-iodine (PVP–I) may have an antiseptic effect for SARS-CoV-2, reducing its viral load [95].

PVP-I is a water-soluble iodine compound that has long been used as a skin antiseptic and mouthwash. After free iodine dissociates from polyvinylpyrrolidone, it quickly enters microorganisms and destroys them by disrupting proteins and oxidizing nucleic acid structures [95]. No germ resists it or develops resistance to it.

PVP–I has previously been shown to have an antiseptic effect on SARS-CoV and MERS in vitro [96,97], and it was also effective against SARS-CoV-2 [98]. A single in vitro gargle with PVP–I reduced the salivary viral load in patients with a high salivary viral load [99].

It is now one of the most studied antiseptics against SARS-CoV-2, with overall excellent results.

The repeatedly cited living real-time analysis of over 3,500 studies [21] reports only two studies with mortality results for PVP-I: one is a retrospective observational study, with good results in late treatment [100]; the other is a rather large RCT, in early treatment, with excellent results [101], published in 2021.

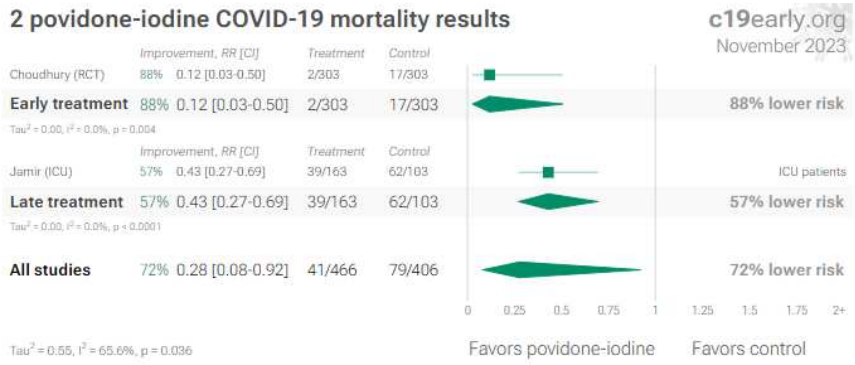


**Figure 7.** Random effects meta-analysis for RCTs with mortality results about povidone-iodine in COVID-19 [100,101].

In the Choudhury's RCT [101] in Bangladesh, 606 COVID-19 middle class patients were enrolled and randomized in 2 groups after taken consents. About 40% of patients were in the 31-50 years age group, and 35% in the 51-70 years age group. The treatment was taken at home.

The 303 patients in the experimental group underwent mouthwash/gargle, nasal drops and eye drops with 1% PVP-I every four hours for 4 weeks (but now we know that about ten days/two weeks can be more than enough for the large majority of patients) as well as symptomatic treatment according to need. In the control group, 303 patients were advised to do mouthwash/gargle, nasal cavity and eye wash with lukewarm water 4 hourly for 4 weeks and symptomatic treatment

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according to need. In Bangladesh 10% PVP-I was found all over the country, but 1% commercially available PVP-I was found only in a few cities. Most of the 1% PVP-I was formed from 10% PVP-I, diluting 1 mL of it in 10mL of purified water. The instructions were to introduce 1% PVP-I as mouth wash, distributing the solution throughout the oral cavity for 30 seconds and then gently gargled, or holding at the back of the throat for another 30 seconds before spitting out. Then 4-5 drops of 1% PVP-I were introduced to wash the nostrils by dropper and 2 drops in each eye. This application was done every 4 hours for 4 weeks. The same instructions were given for the control group, but with lukewarm water.

RT-PCR test was done every 3rd, 5th and 7th day and thyroid hormone level (TSH, T3, T4, FT4) was measured at 4th week for follow up, but excluding patients with thyroid diseases.

**Results:** on the 7th day only 2.64% (N. 8) of PVP-I patients were RT-PCR positive, whereas in the control group 70.30% (N. 213) were RT-PCR positive ($p>0.05$). Only 3.30% (N. 10) hospitalized patients of group A needed oxygen support (by mechanical ventilator and/or high flow nasal cannula and/or non rebreather mask and/or face mask and/or nasal cannula). On the contrary, 20.79% (N. 63) patients of group B needed oxygen support. Mortality rate was high 5.6% (N. 17) in the control group, and only 0.66% (N. 2) in PVP-I group ($P<0.05$) [101].

Therefore, the PVP-I group has dramatically reduced mortality, morbidity and hospitalization, as well as financial burden. Indeed, nose has the highest expression of $ACE_2$, the main receptor of COVID-19 virus. Local use of PVP-I 1% as drops in the nostrils, in the eyes, and as mouth wash/gargling showed to be a simple, rapid and cost effective treatment in reducing mortality and morbidity by COVID-19.

The fact that an RCT like this has not been replicated since then, and that this extremely effective, economical, affordable, convenient and safe treatment has not been disseminated worldwide suggests the weight and influences of commercial interests in health strategies and policies.

Figure 8 shows all the povidone-iodine RCTs in COVID-19, studying several other outcomes in addition to mortality (hospitalization, recovery, viral positivity, viral load, symptomatic cases, both in early and in late treatments):

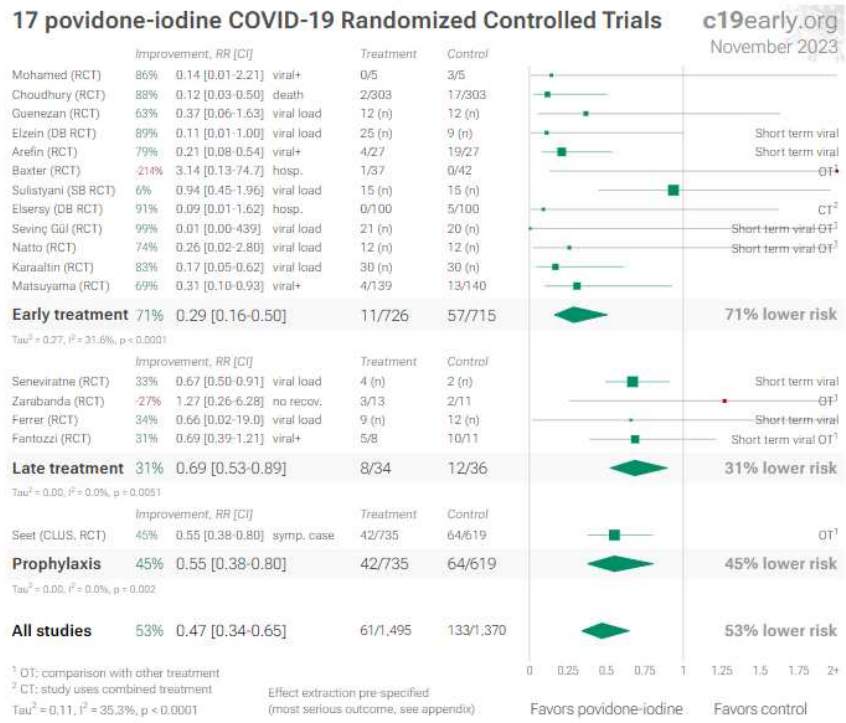


**Figure 8.** Random effects meta-analysis for all RCTs about povidone-iodine in COVID-19 [100–117]. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section [21] for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix [21].

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*6.1. Nose/oropharyngeal treatments*

Under this denomination the living real-time analysis c19early.org [21] lists other products in addition to PVP-I: **alkalinization** (with sodium bicarbonate, saline irrigation…), **chlorhexidine**, **hydrogen peroxide**, **iota-carrageenan**, and some others. The results are consistently good.

At least one systematic review and meta-analysis comparing PVP-I and chlorhexidine (CHX) deserves mention here [118]. It included 10 studies concerning 1,339 patients with COVID-19. Compared with the control group, both CHX and PVP-I reduced significantly the viral load in the COVID-19 patients. In subgroup analysis, compared with the control group, CHX had a pooled medium-to-large effect size of 0.69 (95% CI=0.02–1.37; p=0.04) for reducing the viral load, without evidence of heterogeneity across the studies ($I^2$=0.00). Similarly, the pooled effect size of PVP-I was 0.66 (95%

CI=0.04–1.27; p=0.04) for decreasing the viral load, without evidence of heterogeneity across the studies ($I^2$=0.00). PPVP-I was safe, and it does not cause tooth or tongue discoloration or taste disturbance. CHX can have adverse effects if used for 4 weeks or longer. Specifically, CHX mouthwash causes brown discoloration on the surface of the teeth which may be removed by a dental expert after scaling and polishing. CHX mouthwash causes no or minimal discoloration after 1 or 2 weeks of treatment, but may have taste disruption and mouth lining pain, albeit temporary and reversible after use has ceased. Therefore, both CHX and PVD-I seem similarly effective, but for longer time usage PVP-I seems to be safer.

Finally, early alkalization interventions (nasal irrigation and gargle and spit with sodium bicarbonate or simple saltwater) also deserve mention, for their effectiveness, simplicity, safety, cost-effectiveness and affordability.

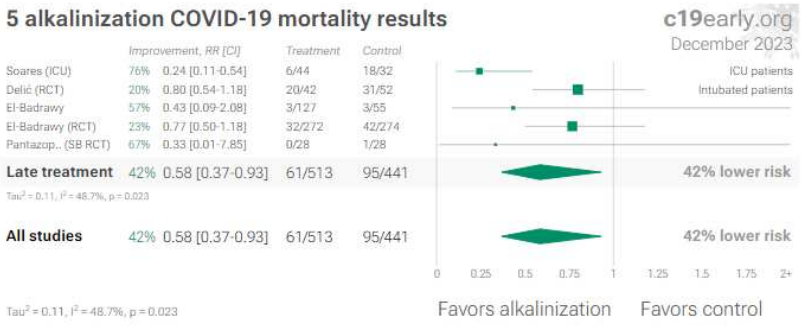


**Figure 9.** Random effects meta-analysis for RCTs with mortality results about alkalinization in COVID-19 [119–123].

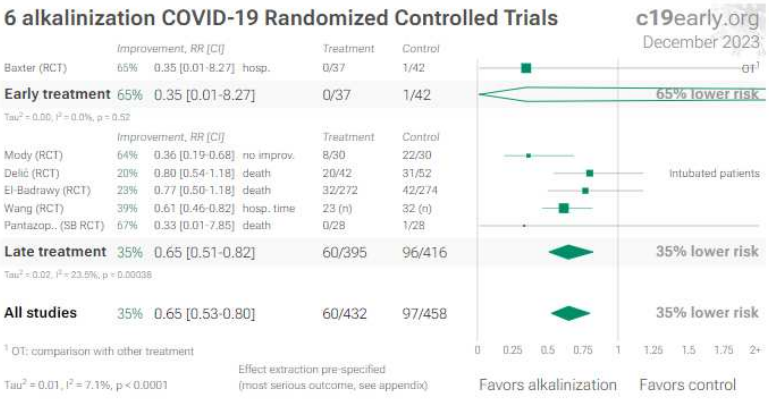


**Figure 10.** Random effects meta-analysis for all RCTs about alkalinization in COVID-19 [119–126]. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section [21] for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix [21].

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Topical nasal rinses acts in multiple ways [127]. First, they physically disrupt the viscous surface layer, removing the mucus and its associated particulate matter.

Additionally, nasal saline helps to increase hydration of the deeper aqueous layer, simultaneously improving the underlying ciliary beat frequency and reducing local inflammatory mediators. This can be particularly helpful during a viral respiratory infection, in which there is resultant mucociliary dysfunction and mucostasis, secondary to the inflammatory response.

The benefit of topical nasal saline has been well established, but the optimal saline tonicity level is less clear. Isotonic saline (IS) consists of a 0.9% wt/vol sodium chloride solution, close to the physiologic salt concentration of the body; hypertonic saline (HS) solutions are greater than 0.9% wt/vol. There is supportive evidence for both IS and HS efficacy in vivo [128]. It has been theorized that HS, having higher osmolarity, pulls water out of cells resulting in increased hydration of the aqueous portion of the mucus layer, improving mucociliary clearance and also decreasing epithelial edema. Indeed, a meta-analysis evaluating both IS and HS rinses for all sinonasal diseases concluded that HS, with a sodium chloride concentration of less than 5%, was more beneficial than IS for the management of sinonasal pathology. Moreover, a RCT evaluating HS in the common cold has given evidence of reduction duration of illness, over-the-counter medication use, transmission to household members, and viral shedding [129].

However, performing irrigations of the nasal cavities require hygienic precautions, because they may increase viral shedding and transmission. There is some concern about viral contamination of the nasal rinse bottle itself, with transmission through contact-induced infections. Viral contamination of surfaces may occur via rinsing: for instance rhinovirus was detected in nasal lavage [127].

**7. Melatonin**

Melatonin is an endocrine molecule secreted by the pineal gland. It is also synthesized in mitochondria throughout the body, in greater quantity. Melatonin has a well-known role in sleep and circadian rhythm regulation, but it is also an anti-inflammatory, anti-oxidant, and immunomodulatory agent [130]. It is alsto a cost-effective anti-viral with minor side effects, which makes it a potential adjuvant in the COVID-19 treatment ([131].

Many studies have highlighted the link between COVID-19 severity and cytokine storm, that causes excessive production of reactive oxygen species (ROS), leading to the over-activation of neutrophils, which produce myeloperoxidase (MPO). Melatonin is both a potent ROS scavenger and a potent MPO inhibitor, and this is one of the possible mechanisms by which melatonin can cure COVID-19 [132].

A systematic review of the clinical studies on melatonin's effects in COVID-19 patients [133] included 5 RCTs, 3 clinical trials (CTs) and 2 Cohort studies comparing the effect of melatonin in the treatment of COVID-19 with the standard of care therapy in patients older than 18. Both cohort studies were of good quality, while the others, although in theory of even more valid design, were of inferior quality, except for a good RCT [134] in patients with severe COVID-19, assessed at "low risk of bias". In this RCT, in the melatonin group 1 of 82 patients died (1.2%), while in the control group 13 of 76 patients died (17.1%), P-value 0.000, with significant differences also in thrombosis (11% vs 23.7%) and sepsis (8.5% vs 35.5%).

The Authors' of the systematic review [133] concluded that studies "demonstrate that melatonin supplementation at a dosage of 3–10 mg/day (or 2 mg of prolonged release in an Italian trial [135]) is associated with an improvement in clinical outcomes in COVID-19 patients". Moreover "melatonin could be a potential adjuvant in the treatment of COVID-19 patients if administered for two weeks and can possibly help to reduce recovery time, mortality rate, and the likelihood of coagulopathy disorder or sepsis. Furthermore, it can improve patient outcomes during intubation.". Anyway, more high-quality randomized clinical trials are needed.

The cited living real-time analysis of over 3,500 studies [21] reports the following tables:

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**Figure 11.** Random effects meta-analysis for RCTs with mortality results about melatonin in COVID-19 [133–141].

Figure 12 shows all the melatonin RCTs in COVID-19, studying several other outcomes in addition to mortality (hospitalization, recovery, symptomatic cases, progression, ICU, both in early and in late treatments):

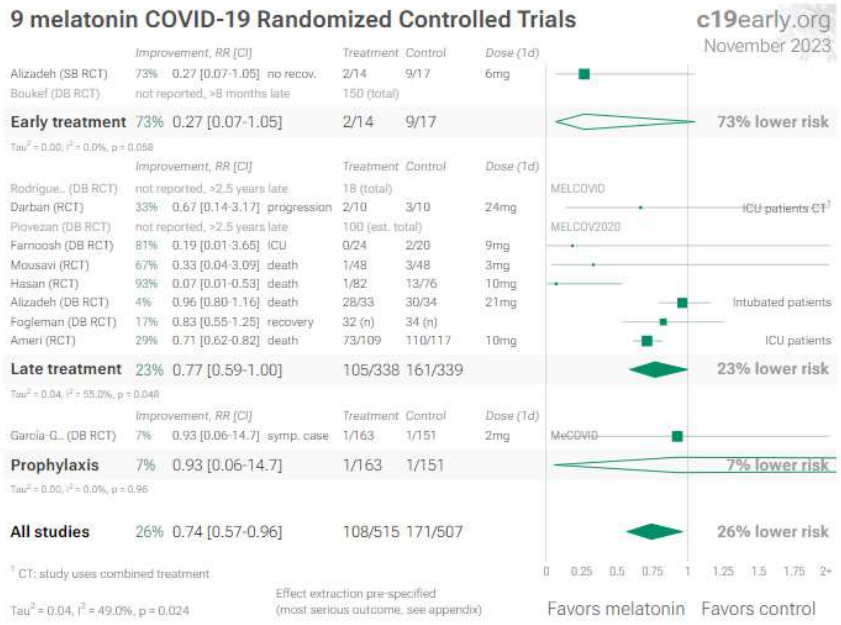


**Figure 12.** Random effects meta-analysis for all RCTs about melatonin in COVID-19 [133–146]. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section [21] for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix [21].

## 8. Discussion

A frequent criticism of RCTs like those supporting the substances proposed in this article is that (even with valid study designs) they are *small* RCTs, often *not double-blinded* and even *open-label*, that is with less guarantees of avoiding confounding factors, etc. Therefore, the evidence would never be definitive, and other large confirmatory RCTs would be needed... before such substances could be recommended.

Two considerations must be made.

First, what is stated in the previous paragraph is true... except the last six words. Indeed, when the effectiveness of a therapy is not yet conclusive, it *should not* be recommended if: it has safety issues, and/or a high opportunity cost, and/or it is biologically implausible, and/or unaffordable,

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and/or it is promoted by commercial sponsors and investigators with relevant conflicts of interest, making their proposal less credible. On the contrary, a therapy *can be offered legitimately* if it is at the same time: safe, as far as it is known, with a favorable opportunity cost, biologically plausible, accessible and without big commercial sponsors or researchers with relevant conflicts of interest. And, above all, if there are no more effective alternatives with most of the same characteristics.

Second, is the same strictness about the absence of conclusive evidence of effectiveness always applied by the Health Authorities? The answer is **no**.

The teaching example of paracetamol is telling.

*8.1. Acetaminophen (Paracetamol): a negative didactic example*

The World Health Organization (WHO) updated November 10, 2023, its guidelines on treatments for COVID-19 [147]: "For people at low risk of hospitalization, WHO does not recommend any antiviral therapy. Symptoms like fever and pain can continue to be managed with analgesics like ***paracetamol***."

The European Medicine Agency (EMA) March 18, 2020 [148] wrote: "When initiating treatment for fever or pain during COVID-19 illness, patients and healthcare professionals should consider all available treatment options, including ***acetaminophen*** and NSAIDs (Nonsteroidal Antinflammatory Drugs). Each medicine has its own benefits and risks as described in the product information and which need to be taken into consideration alongside European guidelines, many of which recommend ***paracetamol*** as a first-line treatment option for fever and pain.".

The Italian Drug Agency (Agenzia Italiana del Farmaco/AIFA) in its "Recommendations on drugs for home management of COVID-19", Update 10/03/2023 [149], states: "***Paracetamol*** or NSAIDs can be used in case of fever or joints or muscles pain (unless there is a clear contraindication to use)".

Accordingly, the Italian Ministry of Health still recommend ***paracetamol***, which appears 13 times among the 50 best-selling OTC drugs in Italy, and it occupies the 1st and 3rd position in this list [150]. This proves that, although the paracetamol is not expensive, the size of sales represents an important business for the big drug manufacturers (worldwide).

Unfortunately, there is no valid evidence of efficacy or safety for paracetamol in COVID-19. The repeatedly cited living real-time analysis of over 3,500 studies [21] reports the following Figure, showing that paracetamol has lost all comparisons, for any outcome:

Potential mechanisms of harm of paracetamol are highlighted in the box in Figure 13.

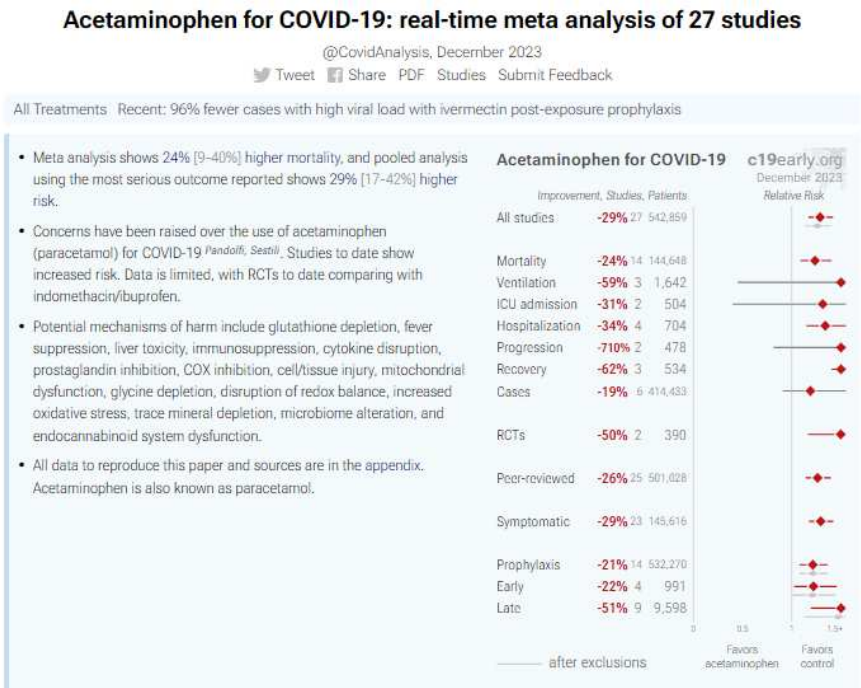

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**Figure 13.** No RCT (i.e., study of high validity design) reported mortality results for acetaminophen versus other comparators. Figure 14 gives the references of the various studies, showing its poor performance in virtually every comparison.

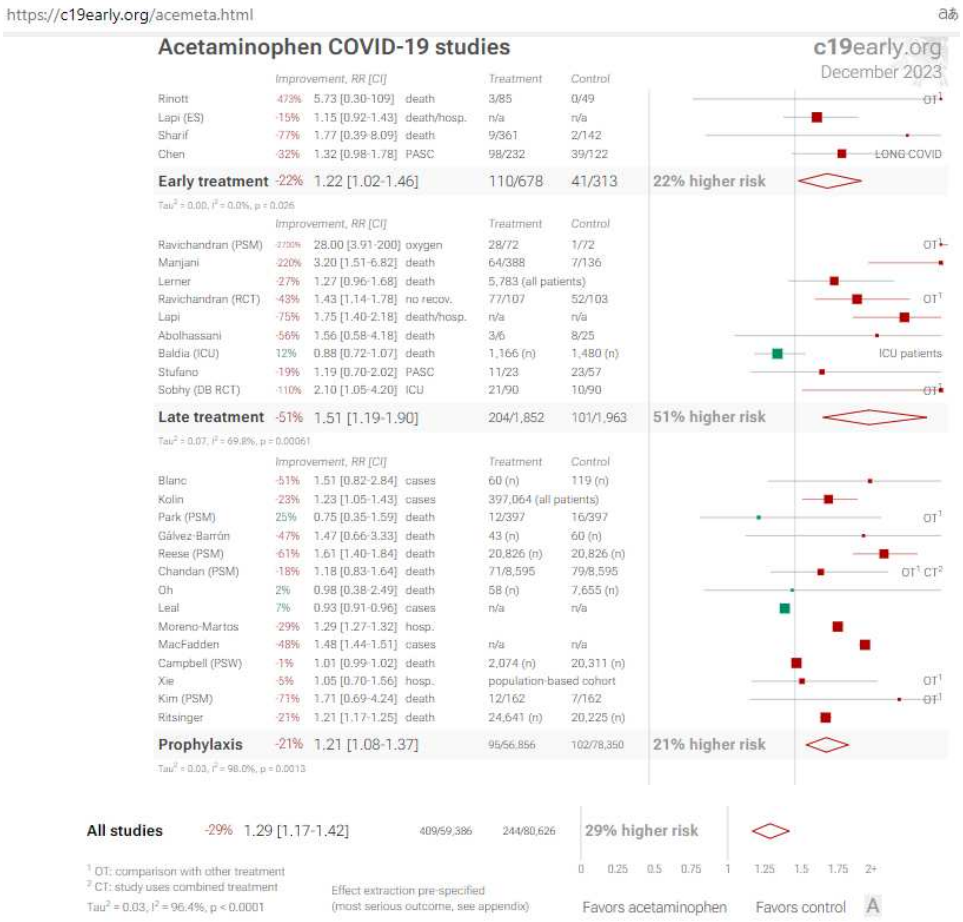


**Figure 14.** Random effects meta-analysis for studies about acetaminophen in COVID-19 [151–177].

One mechanism is the induction of oxidative stress and of glutathione depletion [178], leading to damage of several organs, notably liver and lungs.

Another mechanism is even paradoxical: the insistently pursued suppression of fever, one of the best universal defenses against infections [179]. Indeed, it can slow or inhibit the replication of practically all viruses, including the latest Omicron variants [180], favoring recovery.

Moreover, paracetamol is not as safe as it is thought [181], and it is associated with incident hypertension, cardiovascular and even gastrointestinal [182] adverse events, liver damage, possible acute poisoning and fatal overdoses (with a rather narrow therapeutic window).

All considered, it is clear that recommending a drug with the risks of paracetamol during infections cannot rationally be reconciled with strict preclusions towards the very promising substances described in the chapters 2 to 7.

## 9. Conclusions

The official recommendations to manage COVID-19 in the outpatient setting focus on high-cost drugs, with many defects and limitations.

Therefore, one could also consider treatments meeting criteria of promising effectiveness, based on favorable RCTs of sufficient validity, safety, very favorable opportunity costs, biological plausibility, accessibility, without major commercial sponsors financially tied with the trials' principal investigators.

A small group of functional foods and/or some of their active ingredients meet all these criteria (curcuma/curcumin, quercetin, nigella sativa/black seed; and L-arginine, this one with evidence of efficacy also against Long-COVID); besides, some other substances, among which povidone-iodine (and other local antiseptics) and melatonin deserve special consideration.

## 10. Future Directions

To confirm the effectiveness and safety of the highly promising substances and functional foods discussed in this paper, larger pragmatic RCTs are needed, double blind as far as possible, and with researchers independent of commercial conflicts of interest.

For treatment of the post-acute sequelae of COVID-19 (and of COVID vaccinations) much pre-clinical and clinical research is still needed, again culminating with large pragmatic confirmative RCTs.

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**Acknowledgments:** the site c19early.org, allowing free use of all its materials (https://c19early.org/faq.html --> "**Can we use your graphs?** Yes. You can use any of our work free of charge."). Moreover, the Author is grateful to his assistant Chiara Giove, for the support in bibliographic research and the drafting of the references.

**Conflicts of Interest:** The Author declares no conflict of interest.

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