Quercetin reduces COVID-19 risk: real-time meta analysis of 12 studies

@CovidAnalysis, July 2025, Version 22 https://c19early.org/qmeta.html

Abstract

Significantly lower risk is seen for ICU admission, hospitalization, recovery, cases, and viral clearance. 11 studies from 9 independent teams in 7 countries show significant benefit.

Meta analysis using the most serious outcome reported shows 46% [20-64%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and after excluding studies using combined treatment and slightly worse for peerreviewed studies.

Results are very robust — in exclusion sensitivity analysis 9 of 12 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Studies typically use advanced formulations for greatly improved bioavailability.

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Dietary sources may be preferred. The quality of non-prescription supplements varies widely ¹⁻³. All data and sources to reproduce this analysis are in the appendix.

Other meta analyses show significant improvements with quercetin for mortality 4 , ICU admission 4,5 , and hospitalization 4,5 .

Control
Quercetin
Quercetin for COVID-19 c19early.on
Improvement, Studies, Patients Relative Risk
Ill studies 46% 12 1K -◆
Mortality 610/ 5 700
Nortality 01% 5790
e ventilation 89% 49 -◆
■ ICO admission 74% 5 790 - ◆
Hospitalization 36% 4 361
€ Recovery 35% 8 998
Zases 93% 3 346 ←
Viral clearance 56% 3 200
I RCTs 40% 11 1K -♦
I RCT mortality 61% 5 790 —
Image: State
🧝 Prophylaxis 🛛 93% 3 346 🔶—
Signed Series S
🕰 Late 35% 5 798
0 0.5 1 1.4
Favors Favors

Serious Outcome Risk





QUERCETIN FOR COVID-19 — HIGHLIGHTS

Quercetin reduces risk with very high confidence for ICU admission, recovery, cases, viral clearance, and in pooled analysis, high confidence for hospitalization, and very low confidence for mortality and ventilation.

Studies typically use advanced formulations for greatly improved bioavailability.

27th treatment shown effective in July 2021, now with p = 0.002 from 12 studies.

Real-time updates and corrections with a consistent protocol for 172 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

12 quercet	in C	OVID-19	studies				c19early.org
Di Pierro (RCT) Khan (RCT) Di Pierro (RCT) Din Ujjan (RCT)	Improv 86% 33% 67% 29%	vement, RR [Cl] 0.14 [0.01-2.72] 0.67 [0.37-1.19] 0.33 [0.01-7.99] 0.71 [0.50-1.03]	death no recov. death no recov.	Treatment 0/76 10/25 0/50 15/25	Control 3/76 15/25 1/50 21/25		Ст ¹
Early treatment	32%	0.68 [0.50-0.	93]	25/176	40/176		32% lower risk
Tau ² = 0.00, I ² = 0.0%, p = Onal (RCT) Zupanets (RCT) Shohan (RCT) Gérain (RCT) Tylishchak (RCT)	0.014 Improv -29% 29% 86% 67% 40%	vement, RR [Cl] 1.29 [0.16-10.5] 0.71 [0.32-1.58] 0.14 [0.01-2.65] 0.33 [0.01-7.70] 0.60 [0.16-2.29]	death no recov. death death no recov.	Treatment 1/49 9/99 0/30 0/25 3/30	Control 6/380 13/101 3/30 1/24 5/30		• CT ¹
Late treatment	35%	0.65 [0.35-1.	21]	13/233	28/565		35% lower risk
Tau ² = 0.00, I ² = 0.0%, p = Arslan (RCT) Margolin Rondanelli (DB RCT)	0.18 Impro 92% 94% 93%	vement, RR [Cl] 0.08 [0.01-0.79] 0.06 [0.00-0.93] 0.07 [0.01-0.91]	cases cases symp. case	Treatment 1/71 0/53 1/60	Control 9/42 9/60 4/60	•	CT ¹ CT ¹
Prophylaxis	93%	0.07 [0.02-0.	27]	2/184	22/162		93% lower risk
Tau ² = 0.00, I ² = 0.0%, p <	0.0001						
All studies	46%	0.54 [0.36-0.	80]	40/593	90/903		46% lower risk
¹ CT: study uses comb	bined tre	eatment	Effect extraction	pre-specified		0 0.25 0.5 0.75 1	1.25 1.5 1.75 2+
Tau ² = 0.08, l ² = 20.7%	%, p = 0.	002	(most serious ou	utcome, see app	endix)	ravois queicelli	Favors contro







Figure 1. A. Random effects meta-analysis. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in quercetin studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, pooled outcomes in RCTs, and one or more specific outcome in RCTs. Efficacy based on RCTs only was delayed by 6.0 months, compared to using all studies. Efficacy based on specific outcomes was delayed by 6.0 months, compared to using pooled outcomes in RCTs.

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury⁷⁻¹⁹ and cognitive deficits^{10,15}, cardiovascular complications²⁰⁻²⁴, organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits²⁵—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.





Figure 2. SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from⁶.

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors^{A,26-33}, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk³⁴, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research

In Silico studies predict inhibition of SARS-CoV-2, or minimization of side effects, with quercetin or metabolites via binding to the spike ^{B,35-48} (and specifically the receptor binding domain ^{C,49}), M^{pro D,38-41,43,44,47-65}, RNA-dependent RNA polymerase ^{E,44,47-49,66,67}, PLpro ^{F,47,52,58}, ACE2 ^{G,37,43,45,52,53,68}, TMPRSS2 ^{H,37}, nucleocapsid ^{I,47}, helicase ^{J,47,51,69}, endoribonuclease ^{K,35}, NSP16/10^{L,70}, cathepsin L^{M,71}, Wnt-3 ^{N,37}, FZD ^{O,37}, LRP6 ^{P,37}, ezrin ^{Q,72}, ADRP ^{R,41}, NRP1 ^{S,45}, EP300 ^{T,73}, PTGS2 ^{U,53}, HSP90AA1 ^{V,53,73}, matrix metalloproteinase 9 ^{W,74}, IL-6 ^{X,75,76}, IL-10 ^{Y,75}, VEGFA ^{Z,76}, and RELA ^{AA,76} proteins, and inhibition of spike-ACE2 interaction ^{AB,77}. *In Vitro* studies demonstrate inhibition of the M^{pro D,60,78-80} protein, and inhibition of spike-ACE2 interaction ^{AB,81}. *In Vitro* studies demonstrate efficacy in Calu-3 ^{AC,82}, A549 ^{AD,75}, HEK293-ACE2+^{AE,83}, Huh-7 ^{AF,42}, Caco-2 ^{AG,84}, Vero E6 ^{AH,38,84,85}, mTEC ^{AI,86}, RAW264.7 ^{AJ,86}, and HLMEC ^{AK,77} cells. Animal studies demonstrate efficacy in K18-hACE2 mice ^{AL,87}, db/db mice ^{AM,86,88}, BALB/c mice ^{AN,89}, and rats ⁸⁵. Quercetin reduced proinflammatory cytokines and protected lung and kidney tissue against LPS-induced damage in mice ⁸⁹, inhibits LPS-induced cytokine storm by modulating key inflammatory and antioxidant



pathways in macrophages⁹⁰, may block ACE2-spike interaction and NLRP3 inflammasome, limiting viral entry and inflammation⁹¹, and inhibits SARS-CoV-2 ORF3a ion channel activity, which contributes to viral pathogenicity and cytotoxicity⁹².

Analysis

We analyze all significant controlled studies of guercetin for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, peer-reviewed studies, Randomized Controlled Trials (RCTs), and higher quality studies.

Treatment timing

Figure 3 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.



or shortly thereafter



progression

Preclinical Research

or minimize infections

In Silico studies predict inhibition of SARS-CoV-2, or minimization of side effects, with quercetin or metabolites via binding to the spike B,35-48 (and specifically the receptor binding domain C,49), Mpro D,38-41,43,44,47-65, RNA-dependent RNA polymerase ^{E,44,47-49,66,67}, PLpro ^{F,47,52,58}, ACE2 ^{G,37,43,45,52,53,68}, TMPRSS2 ^{H,37}, nucleocapsid ^{I,47}, helicase ^{J,47,51,69}, endoribonuclease K,35, NSP16/10^{L,70}, cathepsin L^{M,71}, Wnt-3^{N,37}, FZD^{0,37}, LRP6^{P,37}, ezrin ^{Q,72}, ADRP^{R,41}, NRP1^{S,45}, EP300^{T,73}, PTGS2^{U,53}, HSP90AA1^{V,53,73}, matrix metalloproteinase 9^{W,74}, IL-6^{X,75,76}, IL-10^{Y,75}, VEGFA^{Z,76}, and RELA^{AA,76} proteins, and inhibition of spike-ACE2 interaction^{AB,77}. In Vitro studies demonstrate inhibition of the M^{pro D,60,78-80} protein, and inhibition of spike-ACE2 interaction ^{AB,81}. In Vitro studies demonstrate efficacy in Calu-3^{AC,82}, A549^{AD,75}, HEK293-ACE2+^{AE,83}, Huh-7^{AF,42}, Caco-2^{AG,84}, Vero E6^{AH,38,84,85}, mTEC^{AI,86}, RAW264.7^{AJ,86}, and HLMEC^{AK,77} cells. Animal studies demonstrate efficacy in K18-hACE2 mice^{AL,87}, db/db mice^{AM,86,88}, BALB/c mice^{AN,89}, and rats⁸⁵. Quercetin reduced proinflammatory cytokines and protected lung and kidney tissue against LPS-induced damage in mice⁸⁹, inhibits LPS-induced cytokine storm by modulating key inflammatory and antioxidant pathways in macrophages⁹⁰, may block ACE2-spike interaction and NLRP3 inflammasome, limiting viral entry and inflammation⁹¹, and inhibits SARS-CoV-2 ORF3a ion channel activity, which contributes to viral pathogenicity and cytotoxicity⁹².

50 In Silico studies support the efficacy of quercetin 35,37-64,66-77,85,90,91,93-98

27 In Vitro studies support the efficacy of quercetin 38,42,48,60,64,65,67,75,77-87,90,92,93,99-103

6 In Vivo animal studies support the efficacy of quercetin⁸⁵⁻⁹⁰.



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2 studies investigate novel formulations of quercetin that may be more effective for COVID-19^{100,104}.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Viral Lifecycle

SARS-CoV-2 infection and replication involves multiple steps as shown in Table 1. Each step can be disrupted by therapeutics. The timing of each step may vary significantly, and the cycle is continuous, with released virions attaching to new host cells. The efficacy of treatments depends on the delay from infection and the steps targeted. Preclinical research suggests that quercetin is most likely to interfere with early steps in the viral lifecycle, suggesting greater benefit for prophylaxis and very early treatment.

Step	Details	Approximate timing	Predicted benefit of quercetin
Viral attachment	Viral binding to specific receptors on host cell surface	Initial step	High: spike and ACE2 binding
Viral entry	Uptake of viral particle into host cell via mechanisms like endocytosis or membrane fusion	Within minutes to 1 hour	Moderate: spike binding
Viral uncoating and release	Disassembly of virion to release viral genome into host cell	1-2 hours	-
Genome replication and transcription	Production of viral mRNAs from the genome template and genome copies	2-4 hours	Moderate: RdRp binding
Translation and protein processing	Production of new viral proteins from the viral transcripts	4-8 hours	Moderate: M ^{pro} and PLpro binding
Viral assembly and budding	Self-assembly of viral components and encapsidation of viral genome to form new viral particles, often utilizing host cell membrane	8-12 hours	-
Viral release	Escape of newly formed virions from the host cell to spread infection	12-24 hours	-

Table 1. Lifecycle of SARS-CoV-2 infection and replication.

Results

Table 2 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, with different exclusions, and for specific outcomes. Table 3 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, recovery, cases, viral clearance, peer reviewed studies, and all studies excluding combined treatment studies.



	Relative Risk	Studies	Patients
All studies	0.54 [0.36-0.80] **	12	1,496
After exclusions	0.62 [0.44-0.86] **	10	1,283
Peer-reviewed	0.64 [0.48-0.84] **	11	1,383
Excluding combined treatment	0.45 [0.23-0.88] *	6	692
RCTs	0.60 [0.43-0.83] **	11	1,383
Mortality	0.39 [0.11-1.35]	5	790
ICU admission	0.26 [0.10-0.71] **	5	790
Hospitalization	0.64 [0.44-0.95] *	4	361
Recovery	0.65 [0.55-0.79] ****	8	998
Cases	0.07 [0.02-0.27] ****	3	346
Viral	0.44 [0.32-0.62] ****	3	200
RCT mortality	0.39 [0.11-1.35]	5	790
RCT hospitalization	0.64 [0.44-0.95] *	4	361

Table 2. Random effects meta-analysis for all stages combined, for
Randomized Controlled Trials, for peer-reviewed studies, with different
exclusions, and for specific outcomes. Results show the relative risk with
treatment and the 95% confidence interval. * p < 0.05 ** p < 0.01 **** p < 0.001
**** p < 0.0001.

	Early treatment	Late treatment	Prophylaxis
All studies	0.68 [0.50-0.93] *	0.65 [0.35-1.21]	0.07 [0.02-0.27] ****
After exclusions	0.69 [0.51-0.93] *	0.65 [0.35-1.21]	0.06 [0.01-0.36] **
Peer-reviewed	0.68 [0.50-0.93]*	0.65 [0.35-1.21]	0.06 [0.01-0.36] **
Excluding combined treatment	0.21 [0.02-1.83]	0.62 [0.32-1.22]	0.07 [0.01-0.91] *
RCTs	0.68 [0.50-0.93]*	0.65 [0.35-1.21]	0.08 [0.02-0.34] ***
Mortality	0.21 [0.02-1.83]	0.53 [0.12-2.38]	
ICU admission	0.13 [0.02-1.05]	0.25 [0.06-1.10]	
Hospitalization	0.32 [0.15-0.69] **	0.77 [0.57-1.03]	
Recovery	0.67 [0.53-0.84] ***	0.63 [0.46-0.86] **	
Cases			0.07 [0.02-0.27] ****
Viral	0.44 [0.32-0.62] ****		
RCT mortality	0.21 [0.02-1.83]	0.53 [0.12-2.38]	
RCT hospitalization	0.32 [0.15-0.69] **	0.77 [0.57-1.03]	

Table 3. Random effects meta-analysis results by treatment stage. Results show the relative risk with treatment and the 95% confidence interval. * *p*<0.05 ** *p*<0.01 **** *p*<0.001 **** *p*<0.0001.







12 quercetin	COVID-19	studies					c19early.org
Im Di Pierro (RCT) 86 Khan (RCT) 33 Di Pierro (RCT) 67 Din Ujjan (RCT) 29	Approvement, RR [Cl] 0.14 [0.01-2.72] 0.67 [0.37-1.19] 0.33 [0.01-7.99] 0.71 [0.50-1.03]	death no recov. death no recov.	Treatment 0/76 10/25 0/50 15/25	Control 3/76 15/25 1/50 21/25		-	ст ¹ - ст ¹
Early treatment 32	2% 0.68 [0.50-0.	93]	25/176	40/176		\bigcirc	32% lower risk
Tau ² = 0.00, l ² = 0.0%, p = 0.01 Im Onal (RCT) -29 Zupanets (RCT) 86 Gérain (RCT) 67 Tylishchak (RCT) 40	4 pprovement, RR [Cl] 9% 1.29 [0.16-10.5] 1.29 [0.16-10.5] 1.29 [0.16-10.5] 1.29 [0.16-2.5] 1.29 [0.16-2.29] 1.29 [0.16-2.29] 1.29 [0.16-2.29]	death no recov. death death no recov.	Treatment 1/49 9/99 0/30 0/25 3/30	Control 6/380 13/101 3/30 1/24 5/30		•	• CT ¹
Late treatment 35	5% 0.65 [0.35-1.	21]	13/233	28/565	<	\sim	— 35% lower risk
Tau ² = 0.00, I ² = 0.0%, p = 0.18 Im Arslan (RCT) 92 Margolin 94 Rondanelli (DB RCT) 93	3 nprovement, RR [Cl] 1% 0.08 [0.01-0.79] 1% 0.06 [0.00-0.93] 1% 0.07 [0.01-0.91]	cases cases symp. case	Treatment 1/71 0/53 1/60	Control 9/42 9/60 4/60	-		CT ¹ CT ¹
Prophylaxis 93	3% 0.07 [0.02-0.	27]	2/184	22/162	\diamond		93% lower risk
Tau ² = 0.00, I ² = 0.0%, p < 0.00	001						
All studies 46	5% 0.54 [0.36-0.	80]	40/593	90/903	<		46% lower risk
¹ CT: study uses combine Tau ² = 0.08, I^2 = 20.7%, p	d treatment = 0.002	Effect extraction (most serious ou	pre-specified Itcome, see appe	 C endix)	0.25 Favors	0.5 0.75	1 1.25 1.5 1.75 2+ Favors control

Figure 5. Random effects meta-analysis for all studies. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.



5 quercetin COVID-19 mortality results

c19early.org July 2025 Improvement, RR [CI] Treatment Control Di Pierro (RCT) 86% 0.14 [0.01-2.72] 0/76 3/76 Di Pierro (RCT) 67% 0.33 [0.01-7.99] 0/50 1/50 Early treatment 79% 0.21 [0.02-1.83] 0/126 4/126 79% lower risk Tau² = 0.00, I² = 0.0%, p = 0.16 Improvement, RR [CI] Treatment Control Onal (RCT) -29% 1.29 [0.16-10.5] 1/49 6/380 CT1 Shohan (RCT) 86% 0.14 [0.01-2.65] 0/30 3/30 Gérain (RCT) **67%** 0.33 [0.01-7.70] 0/25 1/24 CT1 Late treatment 47% 0.53 [0.12-2.38] 1/104 10/434 47% lower risk Tau² = 0.00, I² = 0.0%, p = 0.42 All studies 61% lower risk 61% 0.39 [0.11-1.35] 1/230 14/560 0.75 ¹ CT: study uses combined treatment 1 25 15 1 75 2+ Favors quercetin Favors control Tau² = 0.00, I² = 0.0%, p = 0.14

Figure 6. Random effects meta-analysis for mortality results.







Figure 8. Random effects meta-analysis for ICU admission.



c19early.org

4 quercetin COVID-19 hospitalization results c19early.org July 2025 Treatment Control Improvement, RR [CI] Di Pierro (RCT) 68% 0.32 [0.14-0.70] hosp. 7/76 22/76 Di Pierro (RCT) 67% 0.33 [0.01-7.99] hosp. 0/50 1/50 68% lower risk Early treatment 68% 0.32 [0.15-0.69] 7/126 23/126 Tau² = 0.00, I² = 0.0%, p = 0.0035 Improvement, RR [CI] Treatment Control Gérain (RCT) 38% 0.62 [0.44-0.88] hosp. time 25 (n) 24 (n) CT^1 Tylishchak (RCT) 15% 0.85 [0.81-0.89] hosp. time 30 (n) 30 (n) Late treatment 23% 0.77 [0.57-1.03] 55 (n) 54 (n) 23% lower risk Tau² = 0.03, I² = 67.6%, p = 0.073 All studies 36% 0.64 [0.44-0.95] 23/180 36% lower risk 7/181 0.25 0.5 0.75 1.25 1.5 1.75 2+ ¹ CT: study uses combined treatment Favors quercetin Favors control Tau² = 0.08, I² = 67.9%, p = 0.027

Figure 9. Random effects meta-analysis for hospitalization.

8 quercetin COVID-19 recovery results

	Impro	vement, RR [CI]		Treatment	Control					Jul	y 20	25
Khan (RCT) Di Pierro (RCT) Din Uiian (RCT)	33% 37% 29%	0.67 [0.37-1.19] 0.63 [0.46-0.88] 0 71 [0 50-1 03]	no recov. no recov. no recov	10/25 24/50 15/25	15/25 38/50 21/25						- A -	CT ¹
Early treatment	33%	0.67 [0.53-0.8	4]	49/100	74/100		<	>	33	% lov	ver ri	sk
Tau ² = 0.00, I ² = 0.0%, p = 0	0.00044											
Onal (RCT) Zupanets (RCT) Shohan (RCT) Gérain (RCT) Tylishchak (RCT)	Impro 78% 29% 32% 73% 40%	vement, RR [Cl] 0.22 [0.03-1.58] 0.71 [0.32-1.58] 0.68 [0.47-0.98] 0.27 [0.06-1.19] 0.60 [0.16-2.29]	no disch. no recov. recov. time no disch. no recov.	Treatment 1/49 9/99 30 (n) 2/25 3/30	Control 35/380 13/101 30 (n) 7/24 5/30			•			(CT ¹
Late treatment	37%	0.63 [0.46-0.8	6]	15/233	60/565		<	>	37	% lov	ver ri	sk
Tau ² = 0.00, I ² = 0.0%, p = 1	0.0042											
All studies	35%	0.65 [0.55-0.7	'9]	64/333	134/665		<	>	35	% lov	ver ri	sk
¹ CT: study uses comb	oined tre	eatment				 0 0.25	0.5	0.75	 1 1.25	1.5	1.75	2+
$Tau^2 = 0.00, I^2 = 0.0\%.$	Favors	s que	rcetir	Favor	's col	ntro						

Figure 10. Random effects meta-analysis for recovery.



3 quercetir	3 quercetin COVID-19 case results										
	Impro	ovement, RR [CI]	Treatment	Control		July 2025					
Arslan (RCT)	92%	0.08 [0.01-0.79] cases	1/71	9/42	-	CT ¹					
Margolin Rondanelli (DB RCT)	94% 93%	0.06 [0.00-0.93] cases 0.07 [0.01-0.91] symp. case	0/53 1/60	9/60 4/60	•	CT					
Prophylaxis	93%	0.07 [0.02-0.27]	2/184	22/162		93% lower risk					
Tau ² = 0.00, I ² = 0.0%, p <	0.0001										
All studies	93%	0.07 [0.02-0.27]	2/184	22/162		93% lower risk					
¹ CT: study uses com	bined tr	eatment			0 0.25 0.5 0.75	 1 1.25 1.5 1.75 2+					
0					Fours querestin	Lavora control					

Tau² = 0.00, I² = 0.0%, p < 0.0001

Favors quercetin Favors control





Figure 12. Random effects meta-analysis for viral clearance.



11 quercet	in C	OVID-19				c19 ea	rly.org			
Di Pierro (RCT)	Impro	ovement, RR [Cl] 0 14 [0 01-2 72	1 death	Treatment 0/76	Control 3/76				JU	ly 2025 ال
Khan (RCT) Di Pierro (RCT)	33% 67%	0.67 [0.37-1.19] no recov.] death	10/25 0/50	15/25 1/50				_	CT ¹
Din Ujjan (RCT)	29%	0.71 [0.50-1.03] no recov.	15/25	21/25					CT ¹
Early treatment	32%	0.68 [0.50-0	.93]	25/176	40/176		\langle		32% lo	wer risk
Tau ² = 0.00, l ² = 0.0%, p = Onal (RCT) Zupanets (RCT) Shohan (RCT) Gérain (RCT) Tylishchak (RCT)	0.014 Impro -29% 29% 86% 67% 40%	wement, RR [Cl] 1.29 [0.16-10.5 0.71 [0.32-1.58 0.14 [0.01-2.65 0.33 [0.01-7.70 0.60 [0.16-2.29] death] no recov.] death] death] no recov.	Treatment 1/49 9/99 0/30 0/25 3/30	Control 6/380 13/101 3/30 1/24 5/30		•			CT ¹
Late treatment	35%	0.65 [0.35-1	.21]	13/233	28/565	-	<		– 35% lo	ower risk
Tau ² = 0.00, I ² = 0.0%, p = Margolin Rondanelli (DB RCT)	0.18 Impro 94% 93%	ovement, RR [Cl] 0.06 [0.00-0.93 0.07 [0.01-0.91] cases] symp. case	Treatment 0/53 1/60	Control 9/60 4/60	-		_		CT ¹
Prophylaxis	94%	0.06 [0.01-0	.36]	1/113	13/120				94% lo	wer risk
Tau ² = 0.00, I ² = 0.0%, p =	0.0018									
All studies	36%	0.64 [0.48-0	.84]	39/522	81/861			>	36% lo	wer risk
¹ CT: study uses com	¹ CT: study uses combined treatment						0.5 0.7	5 1	1.25 1.5	1.75 2+
Tau ² = 0.00, I ² = 0.6%	, p = 0.0	0013	Effect extraction pre-specified (most serious outcome, see appendix)			Favors quercetin Favors control				

Figure 13. Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. Zeraatkar et al. analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. Davidson et al. also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.



Quercetin reduces COVID-19 risk: real-time meta analysis of 12 studies

6 quercetin COVID-19 studies excluding combined treatment									C19 6	arly	.org
	Impro	ovement, RR [Cl]		Treatment	Control					July .	2023
Di Pierro (RCT) Di Pierro (RCT)	86% 67%	0.14 [0.01-2.72] 0 0.33 [0.01-7.99] 0	death death	0/76 0/50	3/76 1/50						<u>n </u>
Early treatment	79%	0.21 [0.02-1.83	3]	0/126	4/126	<			79%	, lowe	r risk
Tau ² = 0.00, I ² = 0.0%, p =	0.16										
Zupanets (RCT) Shohan (RCT) Tylishchak (RCT)	Impro 29% 86% 40%	wement, RR [CI] 0.71 [0.32-1.58] r 0.14 [0.01-2.65] c 0.60 [0.16-2.29] r	no recov. death no recov.	Treatment 9/99 0/30 3/30	Control 13/101 3/30 5/30						
Late treatment	38%	0.62 [0.32-1.22	2]	12/159	21/161	<	\langle		— 38%	lowe	r risk
Tau ² = 0.00, I ² = 0.0%, p =	0.17										
	Impro	ovement, RR [Cl]		Treatment	Control						
Rondanelli (DB RCT)	93%	0.07 [0.01-0.91]	symp. case	1/60	4/60						
Prophylaxis	93%	0.07 [0.01-0.9	1]	1/60	4/60			_	93%	lowe	r risk
Tau ² = 0.00, I ² = 0.0%, p =	0.016										
All studies	55%	0.45 [0.23-0.88	8]	13/345	29/347				55%	lowe	r risk
						0 0.25	0.5 0.7	5 1	1.25 1	.5 1.7	75 2+
Tau ² = 0.06, l^2 = 6.7%, p = 0.021 Effect extraction pre-specific (most serious outcome, see					endix)	Favors	querc	etin	Favors	cont	rol

Figure 14. Random effects meta-analysis for all studies excluding combined treatment studies. Effect extraction is prespecified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Figure 15 shows a comparison of results for RCTs and observational studies. Figure 16, 17, and 18 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 2 and Table 3.



Figure 15. Results for RCTs and observational studies.

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases ¹⁰⁷, and analysis of double-blind RCTs has identified extreme levels of bias ¹⁰⁸. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.



Conflicts of interest for COVID-19 RCTs

RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example Als-Nielsen et al. analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment

High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 172 treatments we have analyzed, 67% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

RCT bias for widely available treatments

RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for quercetin are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Observational studies have been shown to be reliable

Evidence shows that observational studies can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* analyzed reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. We performed a similar analysis across

RCT vs. observational from 5,918 studies c1





Figure 19. For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments¹¹⁰.

the 172 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.98 [0.92-1.05]¹¹³. Similar results are found for all low-cost treatments, RR 1.00 [0.91-1.09]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the supplementary data. Lee et al. showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or remote survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see ^{115,116}.



Using all studies identifies efficacy 8+ months faster (9+ months for low-cost treatments)

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as \geq 10% decreased risk or >0% increased risk from \geq 3 studies. Of these, 58% have been confirmed in RCTs, with a mean delay of 7.7 months (64% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

Summary

We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.



Figure 16. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.



5 quercetin COVID-19 RCT mortality results





4 quercetin	ts	c19early.org				
	Impro	vement, RR [Cl]	Treatment	Control		July 2025
Di Pierro (RCT) Di Pierro (RCT)	68% 67%	0.32 [0.14-0.70] hosp. 0.33 [0.01-7.99] hosp.	7/76 0/50	22/76 1/50		M. W
Early treatment	68%	0.32 [0.15-0.69]	7/126	23/126		68% lower risk
Tau ² = 0.00, I ² = 0.0%, p =	0.0035					
	Impro	vement, RR [CI]	Treatment	Control		
Gérain (RCT)	38%	0.62 [0.44-0.88] hosp. time	25 (n)	24 (n)		CT ¹
Tylishchak (RCT)	15%	0.85 [0.81-0.89] hosp. time	30 (n)	30 (n)		
Late treatment	23%	0.77 [0.57-1.03]	55 (n)	54 (n)	$\langle \rangle$	23% lower risk
Tau ² = 0.03, I ² = 67.6%, p =	= 0.073					
All studies	36%	0.64 [0.44-0.95]	7/181	23/180		36% lower risk
¹ CT: study uses comb	oined tre	eatment			0 0.25 0.5 0.75 1	1.25 1.5 1.75 2+
Tau ² = 0.08, I ² = 67.9%	6, p = 0.	027		Favors quercetin	Favors control	



Exclusions

To avoid bias in the selection of studies, we analyze all non-retracted studies. Here we show the results after excluding studies with major issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on analysis of each study and identifying when there is a significant chance that limitations will substantially change the outcome of the study. We believe this can be more valuable than checklist-based approaches such as Cochrane GRADE, which can be easily influenced by potential bias, may ignore or underemphasize serious issues not captured in the checklists, and may overemphasize issues unlikely to alter outcomes in specific cases (for example certain specifics of randomization with a very large effect size and wellmatched baseline characteristics).

The studies excluded are as below. Figure 20 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Arslan, paper no longer available at the source, and the contact does not reply to queries.



Quercetin reduces COVID-19 risk: real-time meta analysis of 12 studies

Di Pierro, randomization resulted in significant baseline differences that were not adjusted for.

10 quercet	10 quercetin COVID-19 studies after exclusions								
Di Pierro (RCT) Khan (RCT) Din Ujjan (RCT)	Impro 86% 33% 29%	vement, RR [Cl] 0.14 [0.01-2.72] 0.67 [0.37-1.19] 0.71 [0.50-1.03]	death no recov. no recov.	Treatment 0/76 10/25 15/25	Control 3/76 15/25 21/25		-	July 2025	
Early treatment	31%	0.69 [0.51-0.	93]	25/126	39/126		\diamond	31% lower risk	
Tau ² = 0.00, I ² = 0.0%, p = Onal (RCT) Zupanets (RCT) Shohan (RCT) Gérain (RCT) Tylishchak (RCT)	0.017 Impro -29% 29% 86% 67% 40%	vement, RR [Cl] 1.29 [0.16-10.5] 0.71 [0.32-1.58] 0.14 [0.01-2.65] 0.33 [0.01-7.70] 0.60 [0.16-2.29]	death no recov. death death no recov.	Treatment 1/49 9/99 0/30 0/25 3/30	Control 6/380 13/101 3/30 1/24 5/30		•	• CT ¹	
Late treatment	35%	0.65 [0.35-1.	21]	13/233	28/565	<	\langle		
Tau ² = 0.00, I^2 = 0.0%, p = Margolin Rondanelli (DB RCT)	0.18 Impro 94% 93%	vement, RR [Cl] 0.06 [0.00-0.93] 0.07 [0.01-0.91]	cases symp. case	Treatment 0/53 1/60	Control 9/60 4/60			- CT ¹	
Prophylaxis	94%	0.06 [0.01-0.	36]	1/113	13/120			94% lower risk	
Tau ² = 0.00, I ² = 0.0%, p =	0.0018								
All studies	38%	0.62 [0.44-0.	86]	39/472	80/811		\bigcirc	38% lower risk	
¹ CT: study uses comb Tau ² = 0.03, $l^2 = 9.1\%$	pined tre	eatment 039	Effect extraction (most serious or	pre-specified utcome, see app	endix)	0 0.25 Favors	0.5 0.75 querceti	1 1.25 1.5 1.75 2+ n Favors control	

Figure 20. Random effects meta-analysis for all studies after exclusions. This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours^{119,120}. Baloxavir marboxil studies for influenza also show that treatment delay is critical — *Ikematsu* et *al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.



c19early.org

Treatment delay	Result
Post-exposure prophylaxis	86% fewer cases ¹²¹
<24 hours	-33 hours symptoms ¹²²
24-48 hours	-13 hours symptoms ¹²²
Inpatients	-2.5 hours to improvement ¹²³

 Table 4. Studies of baloxavir marboxil for influenza show that early treatment is more effective.

Figure 21 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.



Figure 21. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results, for example as in López-Medina et al.

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants¹²⁵, for example the Gamma variant shows significantly different characteristics¹²⁶⁻¹²⁹. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants^{130,131}.

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.



Medication quality

The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu* (*C*) et *al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer. Non-prescription supplements may show very wide variations in quality^{1,2}.

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic ¹³⁴⁻¹⁵⁰, therefore efficacy may depend strongly on combined treatments.

Effect measured

Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta analysis

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Pooled effects are no longer required to show efficacy as of January 2022

This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however pooled effects are no longer required for quercetin as of January 2022. Efficacy is now known based on specific outcomes for all studies and when restricted to RCTs. Efficacy based on specific outcomes was delayed by 6.0 months compared to using pooled outcomes. Efficacy based on specific outcomes in RCTs was delayed by 17.5 months compared to using pooled outcomes in RCTs.

Combining studies is required

For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. *"The studies reported different outcomes"* is not a good reason for disregarding results. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.



Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Ethical and practical issues limit high-risk trials

Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster and safer collection of evidence.

Validating pooled outcome analysis for COVID-19

For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Analysis of the the association between different outcomes across studies from all 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 22 shows that lower hospitalization is very strongly associated with lower mortality (p < 0.00000000001). Similarly, Figure 23 shows that improved recovery is very strongly associated with lower mortality (p < 0.00000000001). Considering the extremes, *Singh* (D) et al. show an association between viral clearance and hospitalization or death, with p = 0.003 after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 24 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh* (D) et al., with higher confidence due to the larger number of studies. As with *Singh* (D) et al., the confidence increases when excluding the outlier treatment, from p = 0.000000082 to p = 0.000000033.



Figure 22. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.





Figure 23. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.





Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as \geq 10% decreased risk or >0% increased risk from \geq 3 studies. 88% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 25 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.







Limitations

Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a nonantiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary

Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Discussion

Publication bias

Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that



value media recognition), and there are many reports of difficulty publishing positive results¹⁵²⁻¹⁵⁵. For quercetin, there is currently not enough data to evaluate publication bias with high confidence.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 26 shows a scatter plot of results for prospective and retrospective studies. 100% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 91% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 94% improvement, compared to 67% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.



Figure 26. Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.

Funnel plot analysis

Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 27 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry (p > 0.05). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, p < 0.0001, with six variants of Egger's test all showing $p < 0.05^{156-163}$. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.





Figure 27. Example funnel plot analysis for simulated perfect trials.

Conflicts of interest

Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Quercetin for COVID-19 lacks this because it is an inexpensive and widely available supplement. In contrast, most COVID-19 quercetin trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all quercetin trials represent the optimal conditions for efficacy.

Limitations

Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.



Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone ¹³⁴⁻¹⁵⁰. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes

6 of 12 studies combine treatments. The results of quercetin alone may differ. 5 of 11 RCTs use combined treatment. Other meta analyses show significant improvements with quercetin for mortality⁴, ICU admission^{4,5}, and hospitalization^{4,5}.

Reviews

Many reviews cover quercetin for COVID-19, presenting additional background on mechanisms, formulations, and related results, including ¹⁶⁴⁻¹⁸³.

Other studies

Additional preclinical or review papers suggesting potential benefits of quercetin for COVID-19 include ¹⁹⁸⁻³²⁴. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors ²⁶⁻³³, providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk ³⁴, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 28 shows an overview of the results for quercetin in the context of multiple COVID-19 treatments, and Figure 29 shows a plot of efficacy vs. cost for COVID-19 treatments.





Figure 28. Scatter plot showing results within the context of multiple COVID-19 treatments. Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy³²⁵.



Figure 29. Efficacy vs. cost for COVID-19 treatments.



Conclusion

Studies to date show that quercetin is an effective treatment for COVID-19. Significantly lower risk is seen for ICU admission, hospitalization, recovery, cases, and viral clearance. 11 studies from 9 independent teams in 7 countries show significant benefit. Meta analysis using the most serious outcome reported shows 46% [20-64%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and after excluding studies using combined treatment and slightly worse for peer-reviewed studies. Results are very robust — in exclusion sensitivity analysis 9 of 12 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Studies typically use advanced formulations for greatly improved bioavailability.

Other meta analyses show significant improvements with quercetin for mortality⁴, ICU admission^{4,5}, and hospitalization^{4,5}.

Study Notes

Arslan



Small prophylaxis RCT with 113 patients showing fewer cases with quercetin + vitamin C + bromelain prophylaxis. Note that this paper disappeared from SSRN without explanation.

Di Pierro





RCT 100 outpatients in Pakistan, 50 treated with quercetin phytosome, showing faster viral clearance and improved recovery with treatment. Patients in the treatment group were significantly younger (41 vs. 54).

Di Pierro

Quercetin Di	Pierro et al.	EARLY TRE	ATMENT RCT	-
	Improv	ement Rela	itive Risk	
İ Mortality	86%	•		
🚝 ICU admissio	n 94%	•		
Hospitalizatio	on 68%			
		0 0.5 Favors quercetin	1 1.5 2+ Favors control	
Is early treatment with quercetin beneficial for COVID-19? RCT 152 patients in Pakistan (September 2020 - March 2021) Lower ICU admission (p=0.0064) and hospitalization (p=0.0033)				
Di Pierro et al., Int	. J. General Medi	, Jun 2021	c19early.org	g

RCT 152 outpatients in Pakistan, 76 treated with quercetin phytosome, showing lower mortality, ICU admission, and hospitalization with treatment.

Din Ujjan



Small RCT with 50 outpatients, 25 treated with curcumin, quercetin, and vitamin D, showing improved recovery and viral clearance with treatment. 168mg curcumin, 260mg, 360IU vitamin D3 daily for 14 days.



Gérain



RCT 49 hospitalized COVID-19 patients, 25 treated with curcumin and quercetin, shower lower mortality/ICU admission and improved recovery with treatment. All patients received vitamin D.

336mg curcumin, 520mg quercetin, and 18µg vitamin D3 daily for 14 days. The control arm received 20µg vitamin D3 daily. Baseline fever favored treatment while vaccination favored control.

Khan



RCT 50 COVID+ outpatients in Pakistan, 25 treated with curcumin, quercetin, and vitamin D, showing significantly faster viral clearance, significantly improved CRP, and faster resolution of acute symptoms (p=0.154). 168mg curcumin, 260mg quercetin and 360IU cholecalciferol.



Margolin



Retrospective 113 outpatients, 53 (patient choice) treated with zinc, quercetin, vitamin C/D/E, I-lysine, and quina, showing lower cases with treatment. Results are subject to selection bias and limited information on the groups is provided. See ³²⁶.

Onal



RCT 447 moderate-to-severe hospitalized patients in Turkey, 52 treated with quercetin, bromelain, and vitamin C, showing no statistically significant difference in clinical outcomes.

Rondanelli



RCT 120 healthcare workers, 60 treated with quercetin phytosome, showing lower risk of cases with treatment. Quercetin phytosome 250mg twice a day.



Shohan



Small RCT with 60 severe hospitalized patients in Iran, 30 treated with quercetin, showing shorter time until discharge. All patients received remdesivir or favipiravir, and vitamin C, vitamin D, famotidine, zinc, dexamethasone, and magnesium (depending on serum levels). Quercetin 1000mg daily for 7 days. IRCT20200419047128N2.

Tylishchak



RCT 60 hospitalized COVID-19 patients with type 2 diabetes showing quercetin treatment decreased levels of inflammatory markers (interleukin-6, CRP, ferritin), reduced length of hospital stay, and improved capillaroscopy measures compared to standard care. Quercetin was administered at 0.5g intravenously once daily for 10 days. The authors hypothesize the benefits may be due to the anti-inflammatory, antioxidant and endothelium-protective effects of quercetin,

Zupanets





RCT 200 patients in Ukraine, 99 treated with IV quercetin/polyvinylirolidone followed by oral quercetin/pectin, showing improved recovery with treatment.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and metaanalyses, and submissions to the site c19early.org. Search terms are quercetin and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of quercetin for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered



Figure 30. Mid-recovery results can more accurately reflect efficacy when almost all patients recover. Mateja et al. confirm that intermediate viral load results more accurately reflect hospitalization/death.

more important than viral outcomes. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction 327. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO₂ is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to Zhang (D) et al. Reported confidence intervals and p-values are used when available, and adjusted values are used when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported p-values and confidence intervals followed Altman, Altman (B), and Fisher's exact test was used to calculate p-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1³³¹. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

Forest plots are computed using PythonMeta³³² with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I² statistic. Mixed-effects meta-regression



results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective ^{119,120}.

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

A summary of study results is below. Please submit updates and corrections at https://c19early.org/qmeta.html.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Di Pierro, 1/13/2023, Randomized Controlled Trial, Pakistan, peer-reviewed, mean age 47.6, 13 authors, study period December 2020 - September 2021, trial NCT04861298 (history), excluded in exclusion analyses: randomization resulted in significant baseline differences that were not adjusted for.	risk of death, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 50 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 50 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 50 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no recovery, 36.8% lower, RR 0.63, <i>p</i> = 0.007, treatment 24 of 50 (48.0%), control 38 of 50 (76.0%), NNT 3.6, day 7.
	risk of no viral clearance, 57.9% lower, RR 0.42, p < 0.001, treatment 16 of 50 (32.0%), control 38 of 50 (76.0%), NNT 2.3, mid-recovery, day 7.
	risk of no viral clearance, 50.0% higher, RR 1.50, $p = 1.00$, treatment 3 of 50 (6.0%), control 2 of 50 (4.0%), day 14.
	risk of no viral clearance, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 50 (0.0%), control 1 of 50 (2.0%), NNT 50, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 21.
Di Pierro (C), 6/8/2021, Randomized Controlled Trial, Pakistan, peer-reviewed, 19 authors, study period September 2020 - March 2021, trial NCT04578158 (history).	risk of death, 85.7% lower, RR 0.14, $p = 0.25$, treatment 0 of 76 (0.0%), control 3 of 76 (3.9%), NNT 25, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).



	risk of ICU admission, 94.1% lower, RR 0.06, $p = 0.006$, treatment 0 of 76 (0.0%), control 8 of 76 (10.5%), NNT 9.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 68.2% lower, RR 0.32, $p = 0.003$, treatment 7 of 76 (9.2%), control 22 of 76 (28.9%), NNT 5.1.
Din Ujjan, 1/18/2023, Randomized Controlled Trial, Pakistan, peer-reviewed, 6 authors, study period 21 September, 2021 - 21 January, 2022, this trial uses multiple treatments in the treatment arm (combined with curcumin and vitamin D) - results of individual treatments may vary, trial NCT04603690 (history).	risk of no recovery, 28.6% lower, RR 0.71, <i>p</i> = 0.11, treatment 15 of 25 (60.0%), control 21 of 25 (84.0%), NNT 4.2, no symptoms, day 7.
	risk of no recovery, 71.4% lower, RR 0.29, <i>p</i> < 0.001, treatment 6 of 25 (24.0%), control 21 of 25 (84.0%), NNT 1.7, <= 1 symptom, day 7.
	risk of no recovery, 76.9% lower, RR 0.23, <i>p</i> = 0.005, treatment 3 of 25 (12.0%), control 13 of 25 (52.0%), NNT 2.5, <= 2 symptoms, day 7.
	risk of no recovery, 85.7% lower, RR 0.14, $p = 0.23$, treatment 0 of 25 (0.0%), control 3 of 25 (12.0%), NNT 8.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), <= 3 symptoms, day 7.
	risk of no viral clearance, 90.9% lower, RR 0.09, $p = 0.05$, treatment 0 of 25 (0.0%), control 5 of 25 (20.0%), NNT 5.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of no viral clearance, 73.7% lower, RR 0.26, <i>p</i> < 0.001, treatment 5 of 25 (20.0%), control 19 of 25 (76.0%), NNT 1.8, day 7.
Khan, 5/1/2022, Randomized Controlled Trial, Pakistan, peer-reviewed, 7 authors, study period 2 September, 2021 - 28 November, 2021, this trial uses multiple treatments in the treatment arm (combined with curcumin and vitamin D) - results of individual treatments may vary, trial NCT05130671 (history).	risk of no recovery, 33.3% lower, RR 0.67, <i>p</i> = 0.15, treatment 10 of 25 (40.0%), control 15 of 25 (60.0%), NNT 5.0.
	relative CRP reduction, 39.1% better, RR 0.61, $p = 0.006$, treatment 25, control 25.
	risk of no viral clearance, 50.0% lower, RR 0.50, <i>p</i> = 0.009, treatment 10 of 25 (40.0%), control 20 of 25 (80.0%), NNT 2.5.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Gérain, 6/22/2023, Randomized Controlled Trial, Belgium, peer-reviewed, 8 authors, study period 1 April, 2021 - 29 October, 2021, this trial uses multiple treatments in the treatment arm (combined with curcumin) - results of individual treatments may vary, trial NCT04844658 (history).	risk of death, 67.1% lower, RR 0.33, $p = 0.49$, treatment 0 of 25 (0.0%), control 1 of 24 (4.2%), NNT 24, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7.
	risk of death/ICU, 91.1% lower, RR 0.09, $p = 0.02$, treatment 0 of 25 (0.0%), control 5 of 24 (20.8%), NNT 4.8, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7.



	risk of mechanical ventilation, 89.1% lower, RR 0.11, $p = 0.05$, treatment 0 of 25 (0.0%), control 4 of 24 (16.7%), NNT 6.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7.
	risk of ICU admission, 89.1% lower, RR 0.11, $p = 0.05$, treatment 0 of 25 (0.0%), control 4 of 24 (16.7%), NNT 6.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7.
	risk of no hospital discharge, 72.6% lower, RR 0.27, $p = 0.07$, treatment 2 of 25 (8.0%), control 7 of 24 (29.2%), NNT 4.7, day 14.
	risk of no hospital discharge, 58.9% lower, RR 0.41, p = 0.02, treatment 6 of 25 (24.0%), control 14 of 24 (58.3%), NNT 2.9, day 7.
	hospitalization time, 37.5% lower, relative time 0.62, $p = 0.008$, treatment median 5.0 IQR 4.0 n=25, control median 8.0 IQR 6.0 n=24.
	relative WHO score, 50.0% better, RR 0.50, <i>p</i> = 0.04, treatment 22, control 24, day 7.
<i>Onal</i> , 1/19/2021, Randomized Controlled Trial, Turkey, peer-reviewed, 10 authors, study period 7 May, 2020 - 8 July, 2020, this trial uses multiple treatments in the treatment arm (combined with bromelain and vitamin C) - results of individual treatments may vary.	risk of death, 29.3% higher, RR 1.29, <i>p</i> = 0.57, treatment 1 of 49 (2.0%), control 6 of 380 (1.6%).
	risk of ICU admission, 94.0% lower, RR 0.06, $p = 0.39$, treatment 0 of 49 (0.0%), control 14 of 380 (3.7%), NNT 27, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no hospital discharge, 77.8% lower, RR 0.22, <i>p</i> = 0.10, treatment 1 of 49 (2.0%), control 35 of 380 (9.2%), NNT 14.
Shohan, 12/2/2021, Randomized Controlled Trial, Iran, peer-reviewed, mean age 50.9 (treatment) 52.7 (control), 8 authors, study period December 2020 - January 2021, average treatment delay 7.8	risk of death, 85.7% lower, RR 0.14, $p = 0.24$, treatment 0 of 30 (0.0%), control 3 of 30 (10.0%), NNT 10.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
days.	risk of ICU admission, 40.0% lower, RR 0.60, <i>p</i> = 0.71, treatment 3 of 30 (10.0%), control 5 of 30 (16.7%), NNT 15.
	time to discharge from end of intervention, 32.4% lower, relative time 0.68, $p = 0.04$, treatment 30, control 30.
Tylishchak, 12/6/2024, Randomized Controlled Trial, Ukraine, peer-reviewed, 7 authors.	risk of no recovery, 40.0% lower, RR 0.60, <i>p</i> = 0.71, treatment 3 of 30 (10.0%), control 5 of 30 (16.7%), NNT 15, SpO2<90.
	hospitalization time, 14.6% lower, relative time 0.85, $p < 0.001$, treatment mean 13.77 (±0.75) n=30, control mean 16.13 (±0.79) n=30.
Zupanets, 9/1/2021, Randomized Controlled Trial, Ukraine, peer-reviewed, 14 authors.	risk of no recovery, 29.4% lower, RR 0.71, p = 0.50, treatment 9 of 99 (9.1%), control 13 of 101 (12.9%), NNT 26.
	recovery time, 18.2% lower, relative time 0.82, $p = 0.03$, treatment 99, control 101.



Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Arslan, 11/16/2020, Randomized Controlled Trial, Turkey, preprint, 7 authors, study period 20 March, 2020 - 31 August, 2020, this trial uses multiple treatments in the treatment arm (combined with vitamin C and bromelain) - results of individual treatments may vary, trial NCT04377789 (history), excluded in exclusion analyses: paper no longer available at the source, and the contact does not reply to queries.	risk of case, 91.7% lower, RR 0.08, <i>p</i> = 0.03, treatment 1 of 71 (1.4%), control 9 of 42 (21.4%), NNT 5.0, adjusted per study, inverted to make RR<1 favor treatment.
Margolin, 7/6/2021, retrospective, USA, peer- reviewed, 5 authors, this trial uses multiple treatments in the treatment arm (combined with zinc, vitamin C/D/E, I-lysine, and quina) - results of individual treatments may vary.	risk of case, 94.4% lower, RR 0.06, $p = 0.003$, treatment 0 of 53 (0.0%), control 9 of 60 (15.0%), NNT 6.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of COVID-19 or flu-like illness, 81.1% lower, RR 0.19, <i>p</i> = 0.01, treatment 2 of 53 (3.8%), control 12 of 60 (20.0%), NNT 6.2.
Rondanelli, 1/4/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Italy, peer- reviewed, 12 authors, study period 12 January, 2021 - 25 May, 2021, trial NCT05037240 (history).	risk of symptomatic case, 92.9% lower, HR 0.07, $p = 0.04$, treatment 1 of 60 (1.7%), control 4 of 60 (6.7%), adjusted per study, inverted to make HR<1 favor treatment, Cox proportional risk.

Supplementary Data

Supplementary Data

Footnotes

- a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.
- b. The trimeric spike (S) protein is a glycoprotein that mediates viral entry by binding to the host ACE2 receptor, is critical for SARS-CoV-2's ability to infect host cells, and is a target of neutralizing antibodies. Inhibition of the spike protein prevents viral attachment, halting infection at the earliest stage.
- c. The receptor binding domain is a specific region of the spike protein that binds ACE2 and is a major target of neutralizing antibodies. Focusing on the precise binding site allows highly specific disruption of viral attachment with reduced potential for off-target effects.
- d. The main protease or M^{pro}, also known as 3CL^{pro} or nsp5, is a cysteine protease that cleaves viral polyproteins into functional units needed for replication. Inhibiting M^{pro} disrupts the SARS-CoV-2 lifecycle within the host cell, preventing the creation of new copies.
- e. RNA-dependent RNA polymerase (RdRp), also called nsp12, is the core enzyme of the viral replicase-transcriptase complex that copies the positive-sense viral RNA genome into negative-sense templates for progeny RNA synthesis. Inhibiting RdRp blocks viral genome replication and transcription.
- f. The papain-like protease (PLpro) has multiple functions including cleaving viral polyproteins and suppressing the host immune response by deubiquitination and delSGylation of host proteins. Inhibiting PLpro may block viral replication and help restore normal immune responses.



- g. The angiotensin converting enzyme 2 (ACE2) protein is a host cell transmembrane protein that serves as the cellular receptor for the SARS-CoV-2 spike protein. ACE2 is expressed on many cell types, including epithelial cells in the lungs, and allows the virus to enter and infect host cells. Inhibition may affect ACE2's physiological function in blood pressure control.
- h. Transmembrane protease serine 2 (TMPRSS2) is a host cell protease that primes the spike protein, facilitating cellular entry. TMPRSS2 activity helps enable cleavage of the spike protein required for membrane fusion and virus entry. Inhibition may especially protect respiratory epithelial cells, buy may have physiological effects.
- i. The nucleocapsid (N) protein binds and encapsulates the viral genome by coating the viral RNA. N enables formation and release of infectious virions and plays additional roles in viral replication and pathogenesis. N is also an immunodominant antigen used in diagnostic assays.
- j. The helicase, or nsp13, protein unwinds the double-stranded viral RNA, a crucial step in replication and transcription. Inhibition may prevent viral genome replication and the creation of new virus components.
- k. The endoribonuclease, also known as NendoU or nsp15, cleaves specific sequences in viral RNA which may help the virus evade detection by the host immune system. Inhibition may hinder the virus's ability to mask itself from the immune system, facilitating a stronger immune response.
- The NSP16/10 complex consists of non-structural proteins 16 and 10, forming a 2'-O-methyltransferase that modifies the viral RNA cap structure. This modification helps the virus evade host immune detection by mimicking host mRNA, making NSP16/10 a promising antiviral target.
- m. Cathepsin L is a host lysosomal cysteine protease that can prime the spike protein through an alternative pathway when TMPRSS2 is unavailable. Dual targeting of cathepsin L and TMPRSS2 may maximize disruption of alternative pathways for virus entry.
- n. Wingless-related integration site (Wnt) ligand 3 is a host signaling molecule that activates the Wnt signaling pathway, which is important in development, cell growth, and tissue repair. Some studies suggest that SARS-CoV-2 infection may interfere with the Wnt signaling pathway, and that Wnt3a is involved in SARS-CoV-2 entry.
- The frizzled (FZD) receptor is a host transmembrane receptor that binds Wnt ligands, initiating the Wnt signaling cascade.
 FZD serves as a co-receptor, along with ACE2, in some proposed mechanisms of SARS-CoV-2 infection. The virus may take advantage of this pathway as an alternative entry route.
- p. Low-density lipoprotein receptor-related protein 6 is a cell surface co-receptor essential for Wnt signaling. LRP6 acts in tandem with FZD for signal transduction and has been discussed as a potential co-receptor for SARS-CoV-2 entry.
- q. The ezrin protein links the cell membrane to the cytoskeleton (the cell's internal support structure) and plays a role in cell shape, movement, adhesion, and signaling. Drugs that occupy the same spot on ezrin where the viral spike protein would bind may hindering viral attachment, and drug binding could further stabilize ezrin, strengthening its potential natural capacity to impede viral fusion and entry.
- r. The Adipocyte Differentiation-Related Protein (ADRP, also known as Perilipin 2 or PLIN2) is a lipid droplet protein regulating the storage and breakdown of fats in cells. SARS-CoV-2 may hijack the lipid handling machinery of host cells and ADRP may play a role in this process. Disrupting ADRP's interaction with the virus may hinder the virus's ability to use lipids for replication and assembly.
- s. Neuropilin-1 (NRP1) is a cell surface receptor with roles in blood vessel development, nerve cell guidance, and immune responses. NRP1 may function as a co-receptor for SARS-CoV-2, facilitating viral entry into cells. Blocking NRP1 may disrupt an alternative route of viral entry.
- t. EP300 (E1A Binding Protein P300) is a transcriptional coactivator involved in several cellular processes, including growth, differentiation, and apoptosis, through its acetyltransferase activity that modifies histones and non-histone proteins. EP300 facilitates viral entry into cells and upregulates inflammatory cytokine production.
- u. Prostaglandin G/H synthase 2 (PTGS2, also known as COX-2) is an enzyme crucial for the production of inflammatory molecules called prostaglandins. PTGS2 plays a role in the inflammatory response that can become severe in COVID-19 and inhibitors (like some NSAIDs) may have benefits in dampening harmful inflammation, but note that prostaglandins have diverse physiological functions.
- v. Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1) is a chaperone protein that helps other proteins fold correctly and maintains their stability. HSP90AA1 plays roles in cell signaling, survival, and immune responses. HSP90AA1 may interact with numerous viral proteins, but note that it has diverse physiological functions.
- w. Matrix metalloproteinase 9 (MMP9), also called gelatinase B, is a zinc-dependent enzyme that breaks down collagen and other components of the extracellular matrix. MMP9 levels increase in severe COVID-19. Overactive MMP9 can damage lung tissue and worsen inflammation. Inhibition of MMP9 may prevent excessive tissue damage and help regulate the inflammatory response.



- The interleukin-6 (IL-6) pro-inflammatory cytokine (signaling molecule) has a complex role in the immune response and may trigger and perpetuate inflammation. Elevated IL-6 levels are associated with severe COVID-19 cases and cytokine storm. Anti-IL-6 therapies may be beneficial in reducing excessive inflammation in severe COVID-19 cases.
- y. The interleukin-10 (IL-10) anti-inflammatory cytokine helps regulate and dampen immune responses, preventing excessive inflammation. IL-10 levels can also be elevated in severe COVID-19. IL-10 could either help control harmful inflammation or potentially contribute to immune suppression.
- z. Vascular Endothelial Growth Factor A (VEGFA) promotes the growth of new blood vessels (angiogenesis) and has roles in inflammation and immune responses. VEGFA may contribute to blood vessel leakiness and excessive inflammation associated with severe COVID-19.
- aa. RELA is a transcription factor subunit of NF-kB and is a key regulator of inflammation, driving pro-inflammatory gene expression. SARS-CoV-2 may hijack and modulate NF-kB pathways.
- ab. The interaction between the SARS-CoV-2 spike protein and the human ACE2 receptor is a primary method of viral entry, inhibiting this interaction can prevent the virus from attaching to and entering host cells, halting infection at an early stage.
- ac. Calu-3 is a human lung adenocarcinoma cell line with moderate ACE2 and TMPRSS2 expression and SARS-CoV-2 susceptibility. It provides a model of the human respiratory epithelium, but many not be ideal for modeling early stages of infection due to the moderate expression levels of ACE2 and TMPRSS2.
- ad. A549 is a human lung carcinoma cell line with low ACE2 expression and SARS-CoV-2 susceptibility. Viral entry/replication can be studied but the cells may not replicate all aspects of lung infection.
- ae. HEK293-ACE2+ is a human embryonic kidney cell line engineered for high ACE2 expression and SARS-CoV-2 susceptibility.
- af. Huh-7 cells were derived from a liver tumor (hepatoma).
- ag. Caco-2 cells come from a colorectal adenocarcinoma (cancer). They are valued for their ability to form a polarized cell layer with properties similar to the intestinal lining.
- ah. Vero E6 is an African green monkey kidney cell line with low/no ACE2 expression and high SARS-CoV-2 susceptibility. The cell line is easy to maintain and supports robust viral replication, however the monkey origin may not accurately represent human responses.
- ai. mTEC is a mouse tubular epithelial cell line.
- aj. RAW264.7 is a mouse macrophage cell line.
- ak. HLMEC (Human Lung Microvascular Endothelial Cells) are primary endothelial cells derived from the lung microvasculature. They are used to study endothelial function, inflammation, and viral interactions, particularly in the context of lung infections such as SARS-CoV-2. HLMEC express ACE2 and are susceptible to SARS-CoV-2 infection, making them a relevant model for studying viral entry and endothelial responses in the lung.
- al. A mouse model expressing the human ACE2 receptor under the control of the K18 promoter.
- am. A mouse model of obesity and severe insulin resistance leading to type 2 diabetes due to a mutation in the leptin receptor gene that impairs satiety signaling.
- an. A mouse model commonly used in infectious disease and cancer research due to higher immune response and susceptibility to infection.

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