Propolis for COVID-19: real-time meta analysis of 3 studies

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https://c19early.org/ppmeta.html

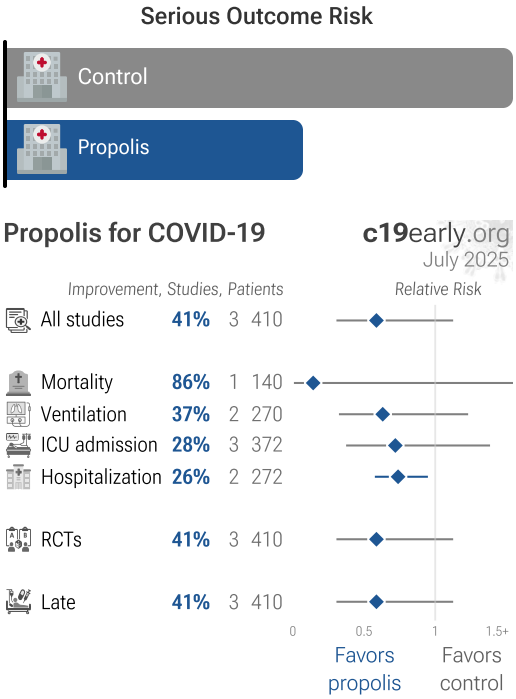
Abstract

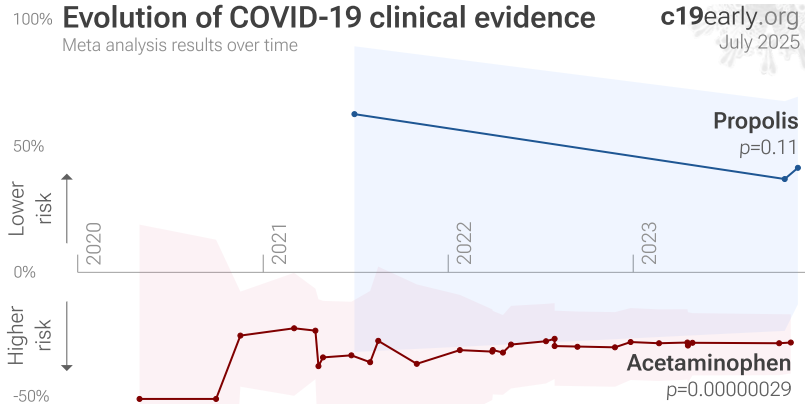
Significantly lower risk is seen for hospitalization and recovery. 3 studies from 2 independent teams in 2 countries show significant benefit.

Meta analysis using the most serious outcome reported shows 41% [-13-69%] lower risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 410 patients and only 23 control events for the most serious outcome in trials to date. Studies to date are from only 2 different groups.

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Propolis currently has no early treatment studies. All data and sources to reproduce this analysis are in the appendix.





PROPOLIS FOR COVID-19 — HIGHLIGHTS

Propolis reduces risk with low confidence for hospitalization, recovery, and in pooled analysis, and very low confidence for mortality and ventilation.

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.

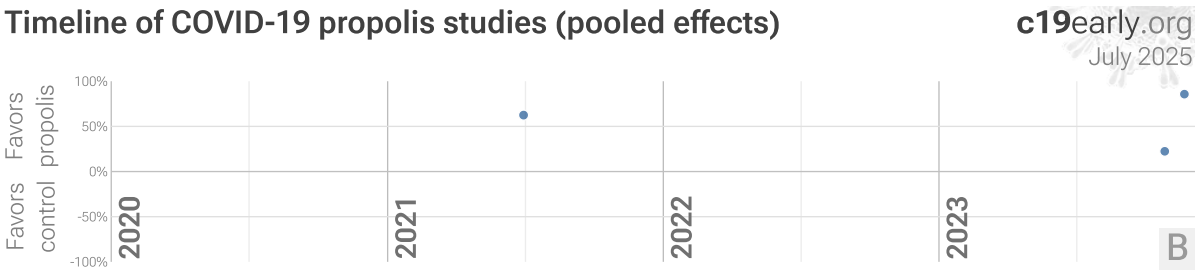


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in propolis studies.**

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 injury[2-14] and cognitive deficits[5,10], cardiovascular complications[15-19], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[20]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

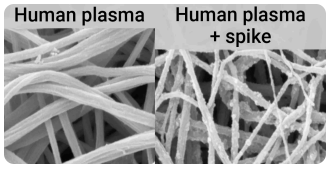


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[1].**

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,21-28], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[29], 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 with propolis or metabolites via binding to the spike[B,30], M^{pro}[C,30], and RNA-dependent RNA polymerase[D,30] proteins. Propolis may inhibit spike protein and ACE2 interaction[31], may inhibit SARS-CoV-2 through interactions with MAPK1[32], inhibited SARS-CoV-2 in Vero E6 cells at a concentration comparable to a combination of four antiviral components[33], may mitigate hyperinflammation via STAT1, NOS2, and BTK targeting[34], and may suppress Epstein-Barr Virus reactivation[34].

Analysis

We analyze all significant controlled studies of propolis 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, individual outcomes, and Randomized Controlled Trials (RCTs).

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. Currently all propolis studies use late treatment.

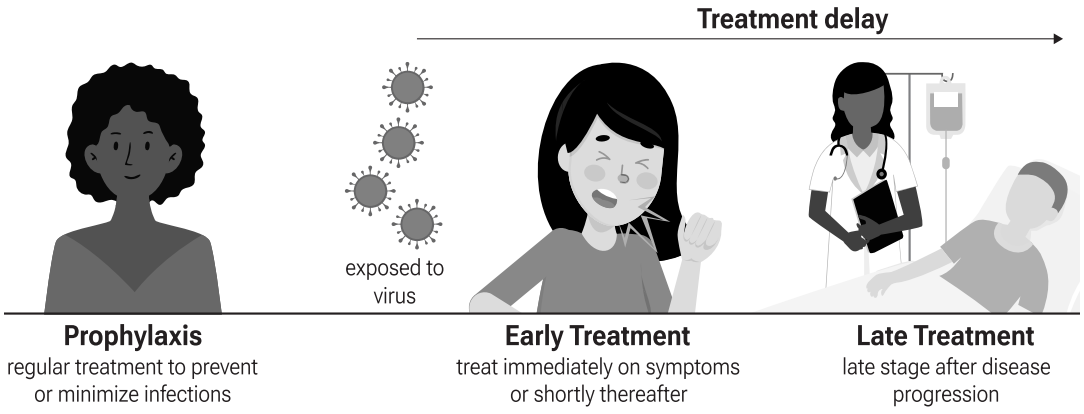


Figure 3. Treatment stages.

Preclinical Research

In Silico studies predict inhibition of SARS-CoV-2 with propolis or metabolites via binding to the spike [B,30], M^{pro} [C,30], and RNA-dependent RNA polymerase [D,30] proteins. Propolis may inhibit spike protein and ACE2 interaction [31], may inhibit SARS-CoV-2 through interactions with MAPK1 [32], inhibited SARS-CoV-2 in Vero E6 cells at a concentration comparable to a combination of four antiviral components [33], may mitigate hyperinflammation via STAT1, NOS2, and BTK targeting [34], and may suppress Epstein-Barr Virus reactivation [34].

4 *In Silico* studies support the efficacy of propolis [30,32,34,35].

4 *In Vitro* studies support the efficacy of propolis [30,31,33,35].

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.

Results

Table 1 summarizes the results for all studies, for Randomized Controlled Trials, and for specific outcomes. Figure 4, 5, 6, 7, 8, and 9 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, and recovery.

	Relative Risk	Studies	Patients
All studies	0.59 [0.31-1.13]	3	410
RCTs	0.59 [0.31-1.13]	3	410
Ventilation	0.63 [0.32-1.23]	2	270
ICU admission	0.72 [0.37-1.39]	3	372
Hospitalization	0.74 [0.58-0.95] *	2	272

Table 1. **Random effects meta-analysis for all studies, for Randomized Controlled Trials, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$.

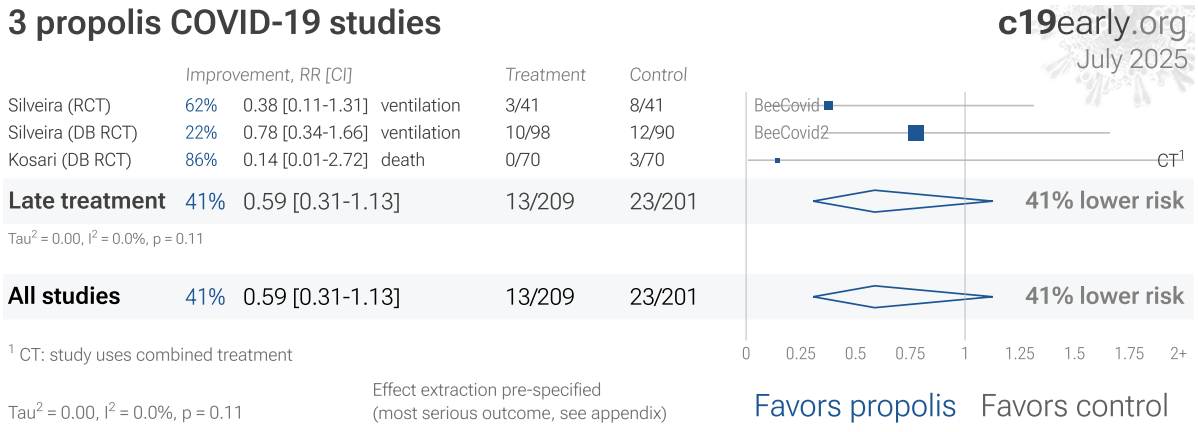


Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

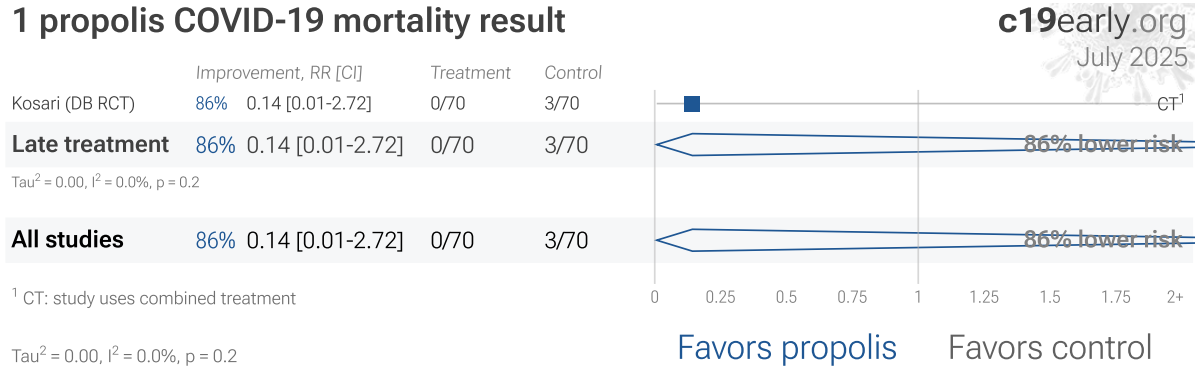


Figure 5. **Random effects meta-analysis for mortality results.**

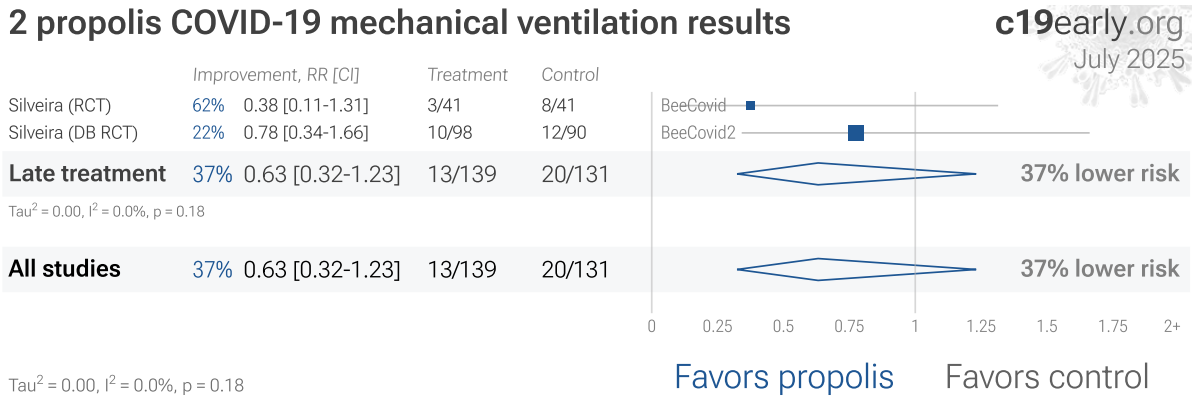


Figure 6. Random effects meta-analysis for ventilation.

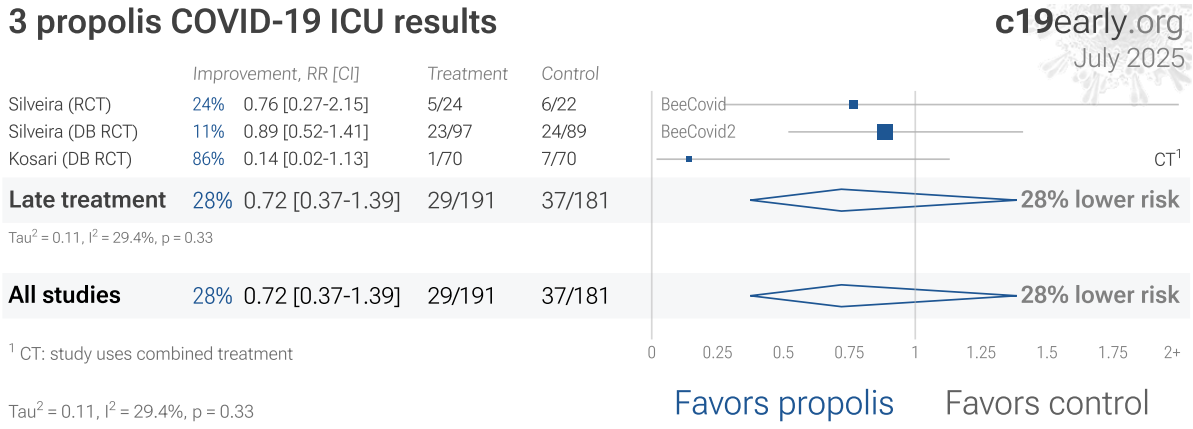


Figure 7. Random effects meta-analysis for ICU admission.

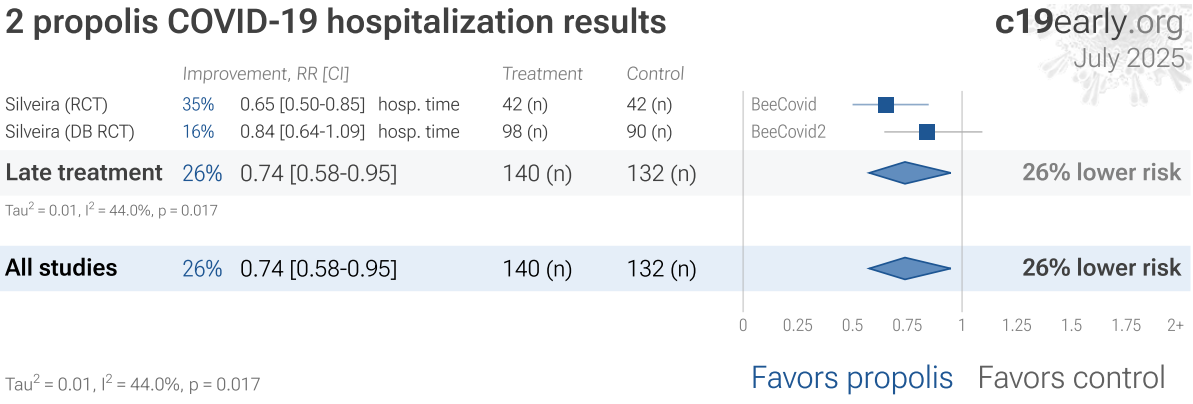


Figure 8. Random effects meta-analysis for hospitalization.

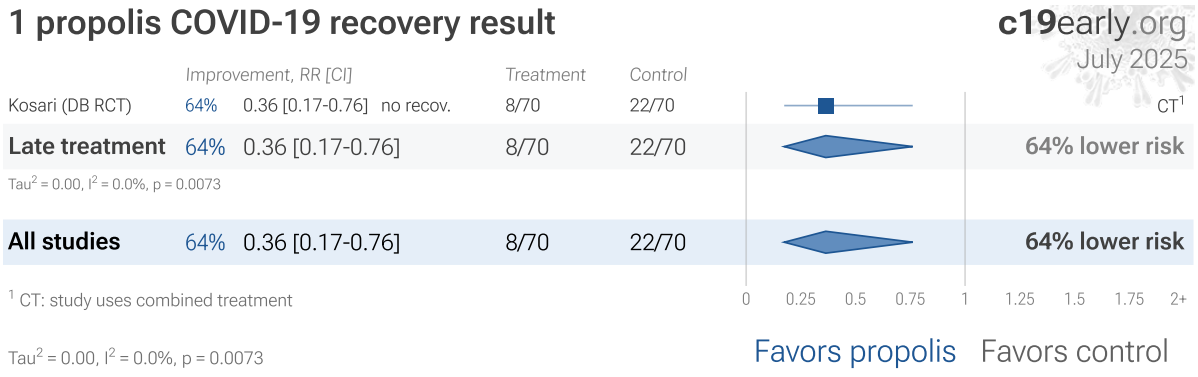


Figure 9. **Random effects meta-analysis for recovery.**

Randomized Controlled Trials (RCTs)

Currently all studies are RCTs.

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[36,37]. 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.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases[38]
<24 hours	-33 hours symptoms[39]
24-48 hours	-13 hours symptoms[39]
Inpatients	-2.5 hours to improvement[40]

Table 2. **Studies of baloxavir marboxil for influenza show that early treatment is more effective.**

Figure 10 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.

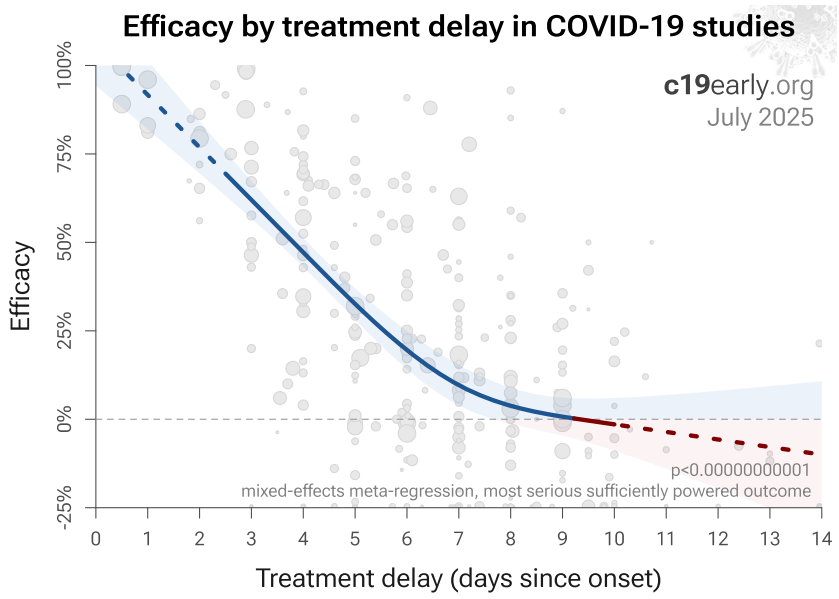


Figure 10. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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 variants [42], for example the Gamma variant shows significantly different characteristics [43-46]. 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 [47,48].

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 et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

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 [51-67], 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

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 11 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 12 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh 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 13 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.000000082$ to $p = 0.0000000033$.

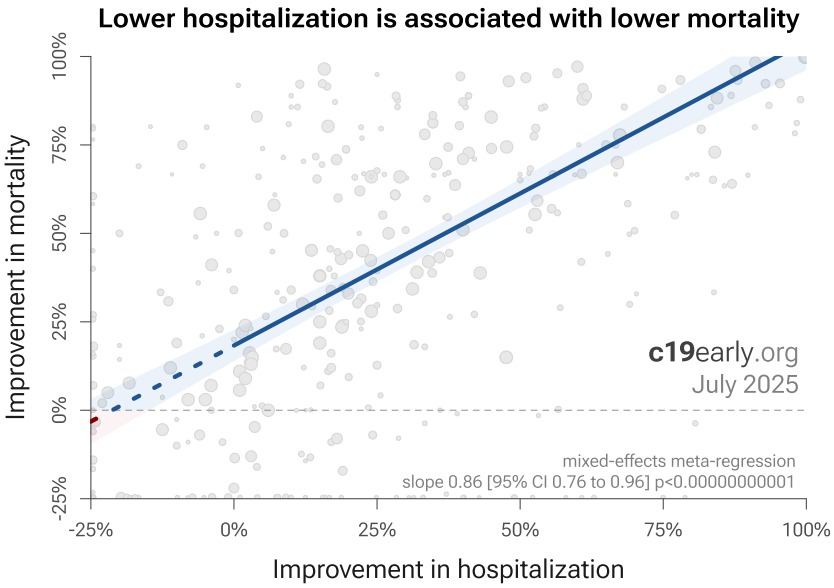


Figure 11. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

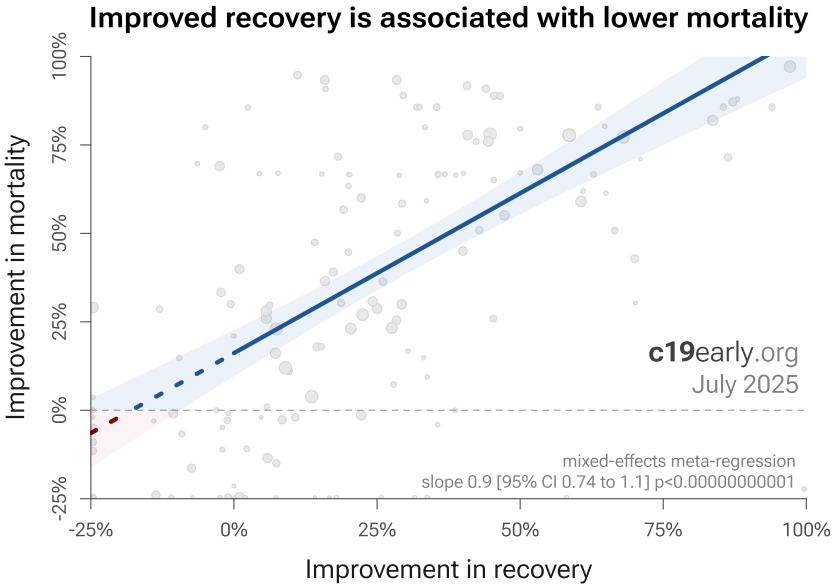


Figure 12. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

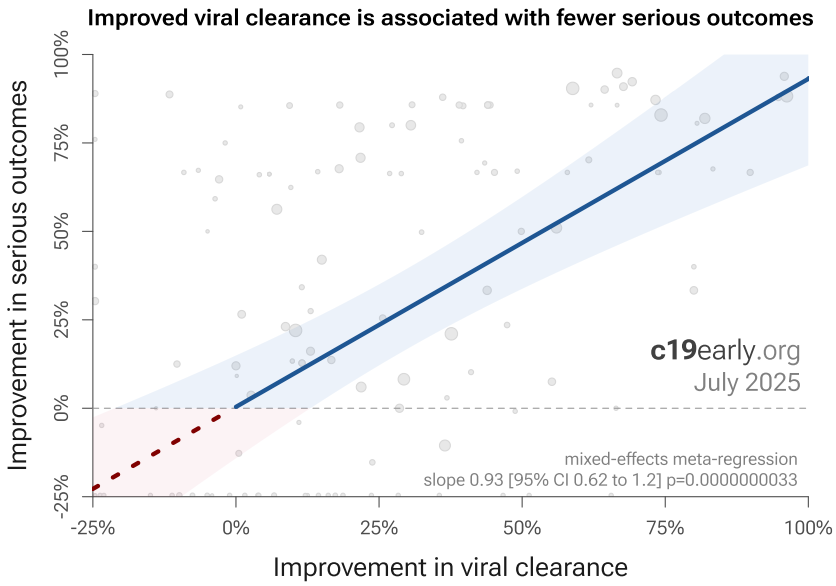


Figure 11. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

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 ≥10% decreased risk or >0% increased risk from ≥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 14 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

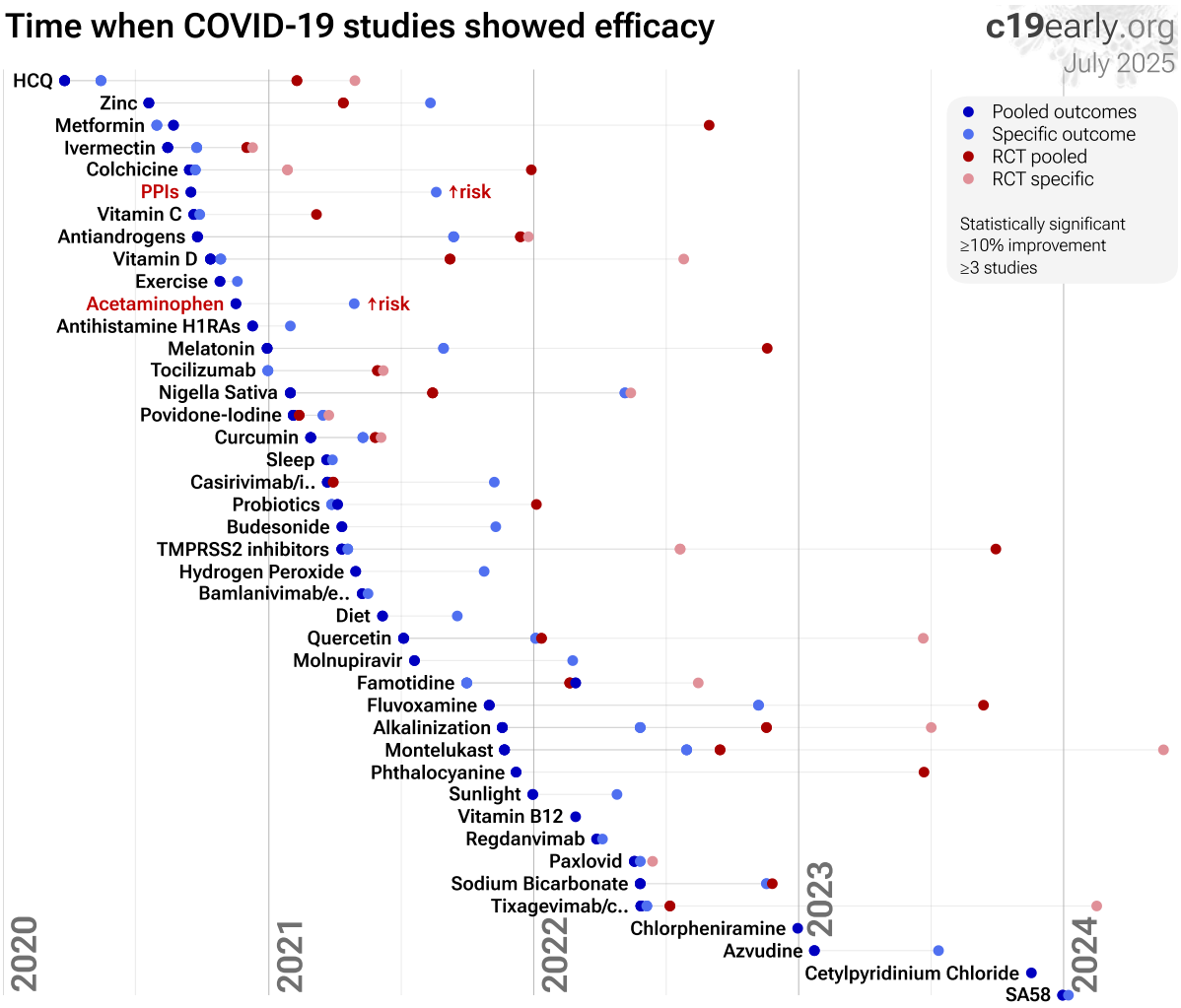


Figure 14. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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 non-antiviral 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 results[69-72]. For propolis, there is currently not enough data to evaluate publication bias with high confidence.

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. Propolis for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 propolis 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 propolis 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[51-67]. 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

1 of 3 studies combine treatments. The results of propolis alone may differ. 1 of 3 RCTs use combined treatment. Currently all studies are peer-reviewed.

Reviews

Multiple reviews cover propolis for COVID-19, presenting additional background on mechanisms and related results, including [73-77].

Other studies

Additional preclinical or review papers suggesting potential benefits of propolis for COVID-19 include [81-87]. 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 [21-28], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [29], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 15 shows an overview of the results for propolis in the context of multiple COVID-19 treatments, and Figure 16 shows a plot of efficacy vs. cost for COVID-19 treatments.

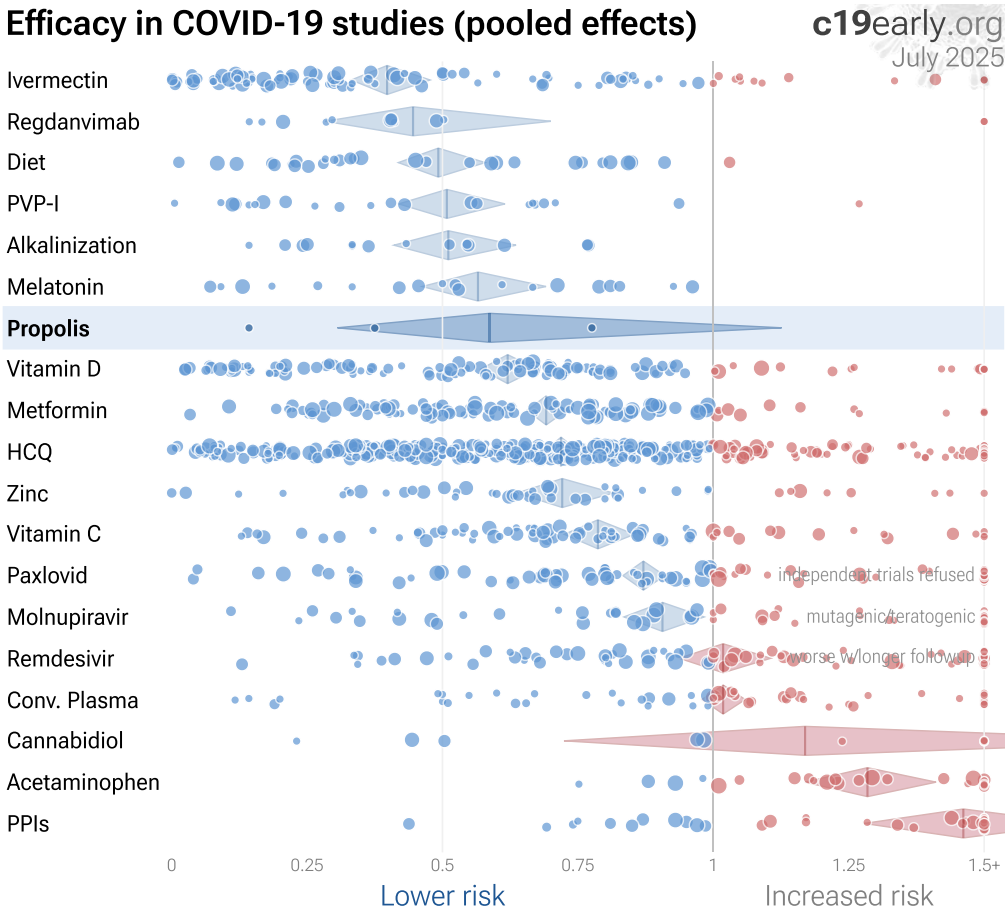


Figure 15. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [88].

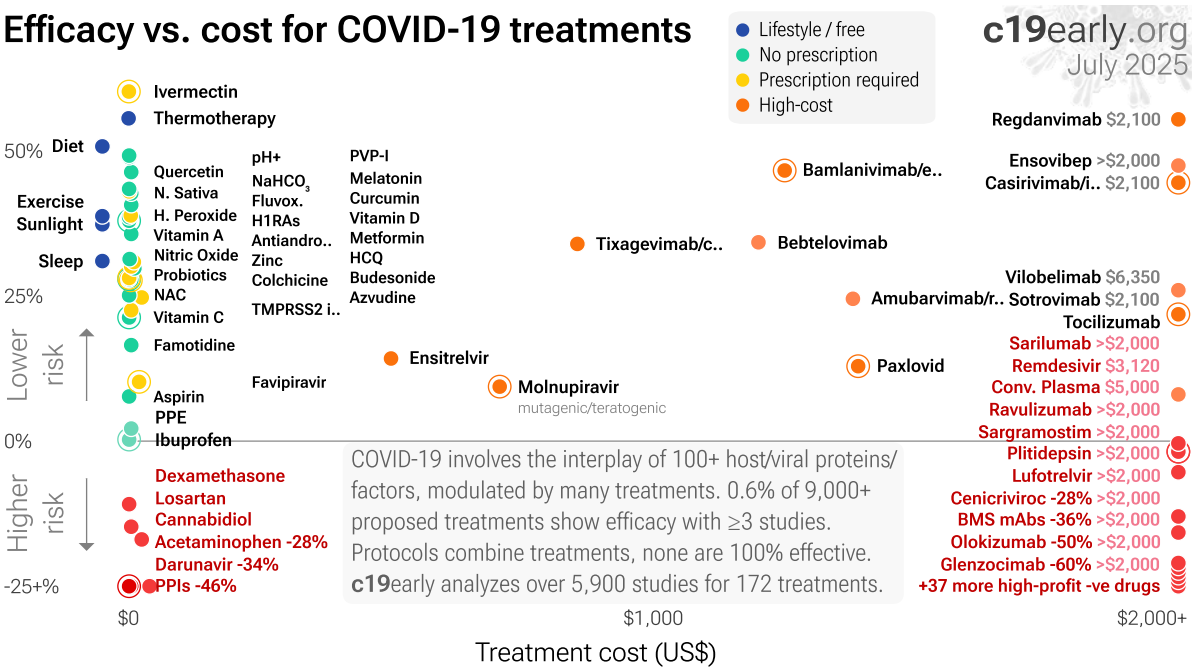


Figure 16. Efficacy vs. cost for COVID-19 treatments.

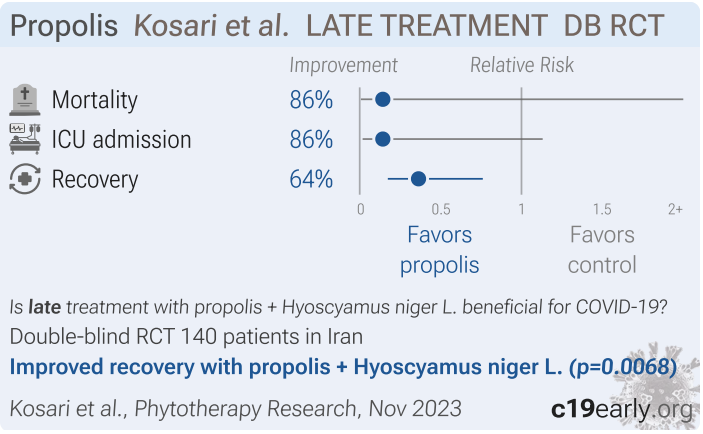
Conclusion

Significantly lower risk is seen for hospitalization and recovery. 3 studies from 2 independent teams in 2 countries show significant benefit. Meta analysis using the most serious outcome reported shows 41% [-13-69%] lower risk, without reaching statistical significance. Currently all studies are RCTs.

Currently there is limited data, with only 410 patients and only 23 control events for the most serious outcome in trials to date. Studies to date are from only 2 different groups.

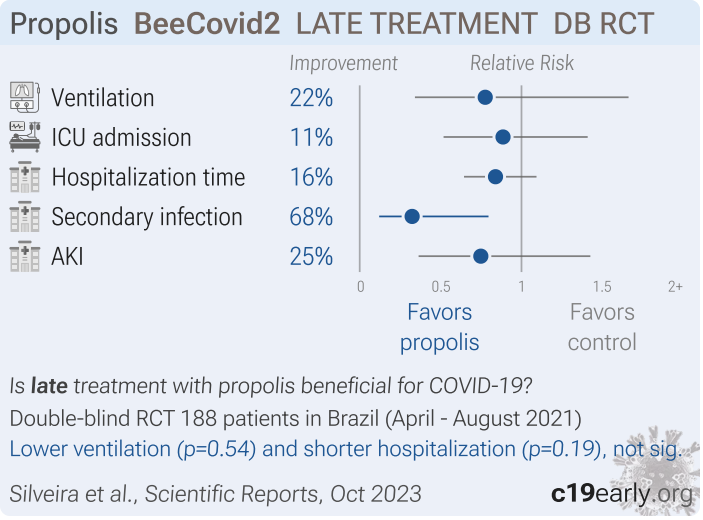
Study Notes

Kosari



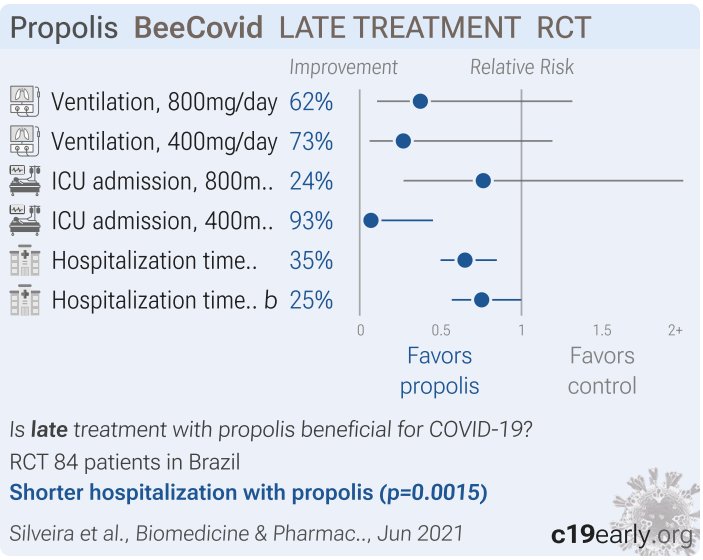
RCT 140 patients showing lower progression and improved recovery with propolis plus Hyoscyamus niger L.syrup.

Silveira



RCT 188 patients in Brazil, showing shorter hospitalization and improved outcomes with propolis, but without statistical significance. The incidence of secondary infections was significantly lower in the treatment group.

Silveira



RCT 124 hospitalized COVID-19 patients in Brazil. The treatment groups received standardized green propolis extract (EPP-AF) at doses of 400mg/day or 800mg/day for 7 days, in addition to standard care. The EPP-AF groups had significantly shorter hospital stays post-intervention. The high dose EPP-AF group also had lower rates of acute kidney injury. No significant differences were seen for other outcomes like oxygen therapy duration or need for mechanical ventilation. The propolis adjunct treatment appeared safe with no discontinuations due to side effects.

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 meta-analyses, and submissions to the site c19early.org. Search terms are propolis 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 propolis for COVID-19 that report a comparison with a control group are included in the main analysis. 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.

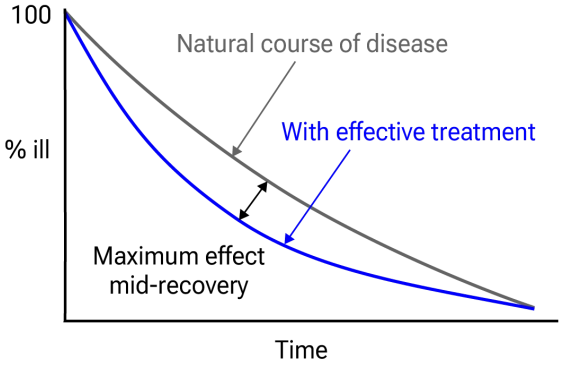


Figure 17. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 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 [89]. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 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 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 1 [93]. 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 PythonMeta [94] 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 I^2 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 [36,37].

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/ppmeta.html.

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.

Kosari, 11/22/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 15 authors, this trial uses multiple treatments in the treatment arm (combined with Hyoscyamus niger L.) - results of individual treatments may vary, trial IRCT20200516047462N1.	**risk of death, 85.7% lower, RR 0.14, *p* = 0.24**, treatment 0 of 70 (0.0%), control 3 of 70 (4.3%), NNT 23, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 6.
	risk of ICU admission, 85.7% lower, RR 0.14, *p* = 0.06, treatment 1 of 70 (1.4%), control 7 of 70 (10.0%), NNT 12.
	risk of no recovery, 63.6% lower, RR 0.36, *p* = 0.007, treatment 8 of 70 (11.4%), control 22 of 70 (31.4%), NNT 5.0, day 6.
Silveira, 10/27/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Brazil, peer-reviewed, 24 authors, study period April 2021 - August 2021, trial NCT04800224 (history) (BeeCovid2).	**risk of mechanical ventilation, 22.4% lower, RR 0.78, *p* = 0.54**, treatment 10 of 98 (10.2%), control 12 of 90 (13.3%), NNT 32, adjusted per study, odds ratio converted to relative risk.
	risk of ICU admission, 11.4% lower, RR 0.89, *p* = 0.65, treatment 23 of 97 (23.7%), control 24 of 89 (27.0%), NNT 31, adjusted per study, odds ratio converted to relative risk.
	hospitalization time, 16.1% lower, relative time 0.84, *p* = 0.19, treatment mean 6.48 (±5.99) n=98, control mean 7.72 (±7.06) n=90.
	secondary infection, 67.6% lower, RR 0.32, *p* = 0.02, treatment 6 of 98 (6.1%), control 17 of 90 (18.9%), NNT 7.8, adjusted per study, odds ratio converted to relative risk.
	AKI, 25.1% lower, RR 0.75, *p* = 0.41, treatment 13 of 98 (13.3%), control 16 of 90 (17.8%), NNT 22, adjusted per study, odds ratio converted to relative risk.
Silveira (B), 6/30/2021, Randomized Controlled Trial, Brazil, peer-reviewed, 25 authors, trial NCT04480593 (history) (BeeCovid).	**risk of mechanical ventilation, 62.5% lower, RR 0.37, *p* = 0.19**, treatment 3 of 41 (7.3%), control 8 of 41 (19.5%), NNT 8.2, 800mg/day.
	risk of mechanical ventilation, 73.0% lower, RR 0.27, *p* = 0.09, treatment 2 of 38 (5.3%), control 8 of 41 (19.5%), NNT 7.0, 400mg/day.
	risk of ICU admission, 23.6% lower, RR 0.76, *p* = 0.73, treatment 5 of 24 (20.8%), control 6 of 22 (27.3%), NNT 16, 800mg/day.
	risk of ICU admission, 93.0% lower, RR 0.07, *p* = 0.005, treatment 0 of 27 (0.0%), control 6 of 22 (27.3%), NNT 3.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), 400mg/day.
	hospitalization time, 34.9% lower, relative time 0.65, *p* = 0.001, treatment mean 8.2 (±5.62) n=42, control mean 12.6 (±6.61) n=42, 800mg/day.
	hospitalization time, 24.6% lower, relative time 0.75, *p* = 0.049, treatment mean 9.5 (±7.42) n=40, control mean 12.6 (±6.61) n=42, 400mg/day.

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 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.

d. 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.

References

1. **Ryu** et al., *Fibrin drives thromboinflammation and neuropathology in COVID-19*, Nature, doi:10.1038/s41586-024-07873-4.
2. **Rong** et al., *Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19*, Cell Host & Microbe, doi:10.1016/j.chom.2024.11.007.
3. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.
4. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.
5. **Hampshire** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.
6. **Duloquin** et al., *Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2*, Journal of Clinical Medicine, doi:10.3390/jcm13051397.
7. **Sodagar** et al., *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, Biomolecules, doi:10.3390/biom12070971.
8. **Sagar** et al., *COVID-19-associated cerebral microbleeds in the general population*, Brain Communications, doi:10.1093/braincomms/fcae127.
9. **Verma** et al., *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, bioRxiv, doi:10.1101/2024.06.02.596989.
10. **Panagea** et al., *Neurocognitive Impairment in Long COVID: A Systematic Review*, Archives of Clinical Neuropsychology, doi:10.1093/arclin/acae042.
11. **Ariza** et al., *COVID-19: Unveiling the Neuropsychiatric Maze—From Acute to Long-Term Manifestations*, Biomedicines, doi:10.3390/biomedicines12061147.
12. **Vashisht** et al., *Neurological Complications of COVID-19: Unraveling the Pathophysiological Underpinnings and Therapeutic Implications*, Viruses, doi:10.3390/v16081183.
13. **Ahmad** et al., *Neurological Complications and Outcomes in Critically Ill Patients With COVID-19: Results From International Neurological Study Group From the COVID-19 Critical Care Consortium*, The Neurohospitalist, doi:10.1177/19418744241292487.
14. **Wang** et al., *SARS-CoV-2 membrane protein induces neurodegeneration via affecting Golgi-mitochondria interaction*, Translational Neurodegeneration, doi:10.1186/s40035-024-00458-1.
15. **Eberhardt** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.
16. **Van Tin** et al., *Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF-κB Signaling*, Cells, doi:10.3390/cells13161331.
17. **Borka Balas** et al., *COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice*, Reviews in Cardiovascular Medicine, doi:10.31083/j.rcm2405125.
18. **AlTaweel** et al., *An In-Depth Insight into Clinical, Cellular and Molecular Factors in COVID19-Associated Cardiovascular Ailments for Identifying Novel Disease Biomarkers, Drug Targets and Clinical Management Strategies*, Archives of Microbiology & Immunology, doi:10.26502/ami.936500177.

19. **Saha** et al., *COVID-19 beyond the lungs: Unraveling its vascular impact and cardiovascular complications—mechanisms and therapeutic implications*, Science Progress, doi:10.1177/00368504251322069.

20. **Trender** et al., *Changes in memory and cognition during the SARS-CoV-2 human challenge study*, eClinicalMedicine, doi:10.1016/j.eclinm.2024.102842.

21. **Dugied** et al., *Multimodal SARS-CoV-2 interactome sketches the virus-host spatial organization*, Communications Biology, doi:10.1038/s42003-025-07933-z.

22. **Malone** et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, Nature Reviews Molecular Cell Biology, doi:10.1038/s41580-021-00432-z.

23. **Murigneux** et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.

24. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.

25. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.

26. **Niarakis** et al., *Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches*, Frontiers in Immunology, doi:10.3389/fimmu.2023.1282859.

27. **Katiyar** et al., *SARS-CoV-2 Assembly: Gaining Infectivity and Beyond*, Viruses, doi:10.3390/v16111648.

28. **Wu** et al., *Decoding the genome of SARS-CoV-2: a pathway to drug development through translation inhibition*, RNA Biology, doi:10.1080/15476286.2024.2433830.

29. **c19early.org**, c19early.org/treatments.html.

30. **Al balawi** et al., *Assessing multi-target antiviral and antioxidant activities of natural compounds against SARS-CoV-2: an integrated in vitro and in silico study*, Bioresources and Bioprocessing, doi:10.1186/s40643-024-00822-z.

31. **dos Santos** et al., *Countercurrent chromatography isolation of green propolis biomarkers: potential blockers of SARS-CoV-2 RBD and ACE2 interaction*, Journal of Chromatography A, doi:10.1016/j.chroma.2024.465265.

32. **Siregar** et al., *Exploring Therapeutic Potential of Nutraceutical Compounds from Propolis on MAPK1 Protein Using Bioinformatics Approaches as Anti-Coronavirus Disease 2019 (COVID-19)*, BIO Web of Conferences, doi:10.1051/bioconf/20248800007.

33. **Karaoğlu** et al., *Chewable tablet with herbal extracts and propolis arrests Wuhan and Omicron variants of SARS-CoV-2 virus*, Journal of Functional Foods, doi:10.1016/j.jff.2023.105544.

34. **Anshori** et al., *Uncovering the Therapeutic Potential of Propolis Extract in Managing Hyperinflammation and Long COVID-19: A Comprehensive Bioinformatics Study*, Chemistry & Biodiversity, doi:10.1002/cbdv.202401947.

35. **Ay** et al., *Investigation of The Inhibition of SARS-CoV-2 Spike RBD and ACE-2 Interaction by Phenolics of Propolis Extracts*, Journal of Apitherapy and Nature, doi:10.35206/jan.1471090.

36. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.

37. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.

38. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.

39. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.

40. **Kumar** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, The Lancet Infectious Diseases, doi:10.1016/S1473-3099(21)00469-2.

41. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.3071.

42. **Korves** et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, medRxiv, doi:10.1101/2024.03.08.24303818.

43. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.

44. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.

45. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, medRxiv, doi:10.1101/2021.08.27.21262754.

46. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, Research Square, doi:10.21203/rs.3.rs-910467/v1.

47. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.

48. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.

49. **Williams**, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.

50. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, Rapid Communications in Mass Spectrometry, doi:10.1002/rcm.9358.

51. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.

52. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.

53. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.

54. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.

55. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.

56. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.

57. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.

58. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.

59. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.

60. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.

61. **Xing** et al., *Published anti-SARS-CoV-2 in vitro hits share common mechanisms of action that synergize with antivirals*, Briefings in Bioinformatics, doi:10.1093/bib/bbab249.

62. **Chen** et al., *Synergistic Inhibition of SARS-CoV-2 Replication Using Disulfiram/Ebselen and Remdesivir*, ACS Pharmacology & Translational Science, doi:10.1021/acsptsci.1c00022.

63. **Hempel** et al., *Synergistic inhibition of SARS-CoV-2 cell entry by otamixaban and covalent protease inhibitors: pre-clinical assessment of pharmacological and molecular properties*, Chemical Science, doi:10.1039/D1SC01494C.

64. **Schultz** et al., *Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2*, Nature, doi:10.1038/s41586-022-04482-x.

65. **Ohashi** et al., *Potential anti-COVID-19 agents, cepharanthine and nelfinavir, and their usage for combination treatment*, iScience, doi:10.1016/j.isci.2021.102367.

66. **Al Krad** et al., *The protease inhibitor Nirmatrelvir synergizes with inhibitors of GRP78 to suppress SARS-CoV-2 replication*, bioRxiv, doi:10.1101/2025.03.09.642200.

67. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.

68. **Singh** et al., *The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis*, Journal of Antimicrobial Chemotherapy, doi:10.1093/jac/dkae045.

69. **Meneguesso**, A., *Médica defende tratamento precoce da Covid-19*, www.youtube.com/watch?v=X5FCrIm_19U.

70. **Boulware**, D., *Comments regarding paper rejection*, twitter.com/boulware_dr/status/1311331372884205570.

71. **Meeus**, G., *Online Comment*, twitter.com/gertmeeus_MD/status/1386636373889781761.

72. **twitter.com**, twitter.com/KashPrime/status/1768487878454124914.

73. **Kustiawan** et al., *New insights of propolis nanoformulation and its therapeutic potential in human diseases*, ADMET and DMPK, doi:10.5599/admet.2128.

74. **Ożarowski** et al., *The Effects of Propolis on Viral Respiratory Diseases*, Molecules, doi:10.3390/molecules28010359.

75. **Zullkiflee** et al., *Propolis: Its Role and Efficacy in Human Health and Diseases*, Molecules, doi:10.3390/molecules27186120.

76. **Dilokthornsakul** et al., *Potential effects of propolis and honey in COVID-19 prevention and treatment: A systematic review of in silico and clinical studies*, Journal of Integrative Medicine, doi:10.1016/j.joim.2022.01.008.

77. **Zulhendri** et al., *The Potential Use of Propolis as a Primary or an Adjunctive Therapy in Respiratory Tract-Related Diseases and Disorders: A Systematic Scoping Review*, Biomedicine & Pharmacotherapy, doi:10.1016/j.biopha.2021.112595.

78. **Kosari** et al., *The influence of propolis plus Hyoscyamus niger L. against COVID-19: A phase II, multicenter, placebo-controlled, randomized trial*, Phytotherapy Research, doi:10.1002/ptr.8047.

79. **Silveira** et al., *Standardized Brazilian green propolis extract (EPP-AF®) in COVID-19 outcomes: a randomized double-blind placebo-controlled trial*, Scientific Reports, doi:10.1038/s41598-023-43764-w.

80. **Silveira (B)** et al., *Efficacy of Brazilian green propolis (EPP-AF®) as an adjunct treatment for hospitalized COVID-19 patients: A randomized, controlled clinical trial*, Biomedicine & Pharmacotherapy, doi:10.1016/j.biopha.2021.111526.

81. **Duarte Silveira** et al., *Efficacy of propolis as an adjunct treatment for hospitalized COVID-19 patients: a randomized, controlled clinical trial*, medRxiv, doi:10.1101/2021.01.08.20248932.

82. **Bilir** et al., *Evaluation of the Effect of Anatolian Propolis on Covid-19 in Healthcare Professionals*, ScienceOpen, doi:10.14293/S2199-1006.1.SOR-.PPZR1OD.v1.

83. **Abedini** et al., *N-Chromosome Royal Jelly, Propolis and Bee Pollen Supplementation Improve the Clinical Conditions of COVID-19 Patients: A Randomized Controlled Trial*, Traditional and Integrative Medicine, doi:10.18502/tim.v6i4.8269.

84. **Shaibani** et al., *Antiviral Activity of Natural Compounds Immuno Formula Shiban2/5 against SARS-CoV-2*, Advances in Bioscience and Biotechnology, doi:10.4236/abb.2025.163005.

85. **Hidayat** et al., *Molecular docking study of East Java propolis compounds as ACE-2 inhibitors for Covid-19*, THE 3RD INTERNATIONAL CONFERENCE ON NATURAL SCIENCES, MATHEMATICS, APPLICATIONS, RESEARCH, AND TECHNOLOGY (ICON-SMART2022): Mathematical Physics and Biotechnology for Education, Energy Efficiency, and Marine Industries, doi:10.1063/5.0212825.

86. **Chavda** et al., *SARS-CoV-2 Variants and Global Population Vulnerability*, Apple Academic Press, doi:10.1201/9781003467939.

87. **Low** et al., *COVID-19 Therapeutic Potential of Natural Products*, International Journal of Molecular Sciences, doi:10.3390/ijms24119589.

88. **c19early.org (B)**, c19early.org/timeline.html.

89. **Mateja** et al., *The choice of viral load endpoint in early phase trials of COVID-19 treatments aiming to reduce 28-day hospitalization and/or death*, The Journal of Infectious Diseases, doi:10.1093/infdis/jiaf282.

90. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.

91. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.

92. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.

93. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.

94. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.