Andrographolide for COVID-19: real-time meta analysis of 7 studies

@CovidAnalysis, July 2025, Version 8
https://c19early.org/apmeta.html

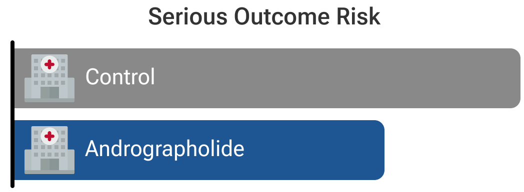
Abstract

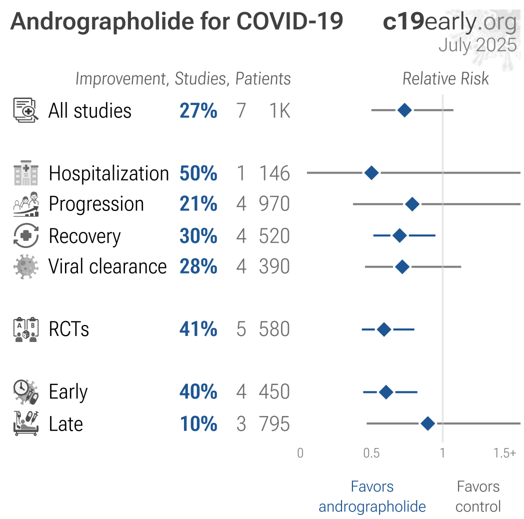
Significantly lower risk is seen for recovery. 2 studies from 2 independent teams in 2 countries show significant benefit.

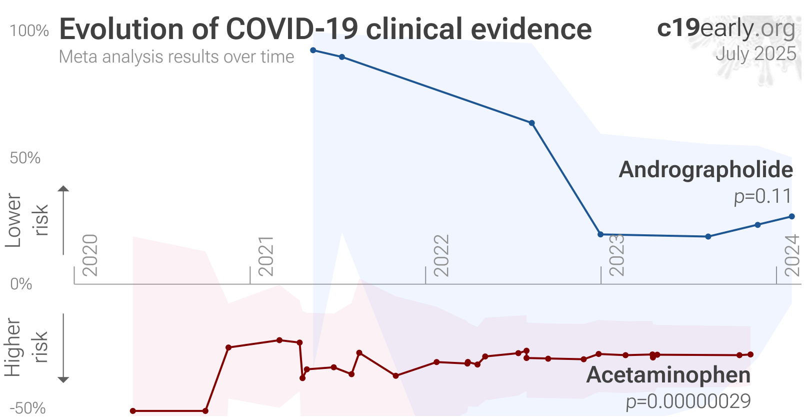
Meta analysis using the most serious outcome reported shows 27% [-8-50%] lower risk, without reaching statistical significance. Results are similar for Randomized Controlled Trials. Early treatment is more effective than late treatment.

1 RCT with 3,060 patients has not reported results (3 years late) [1].

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. All data and sources to reproduce this analysis are in the appendix.







ANDROGRAPHOLIDE FOR COVID-19 — HIGHLIGHTS

Andrographolide reduces risk with high confidence for recovery, low confidence for pooled analysis, and very low confidence for viral clearance.

Early treatment is more effective than late treatment.

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.

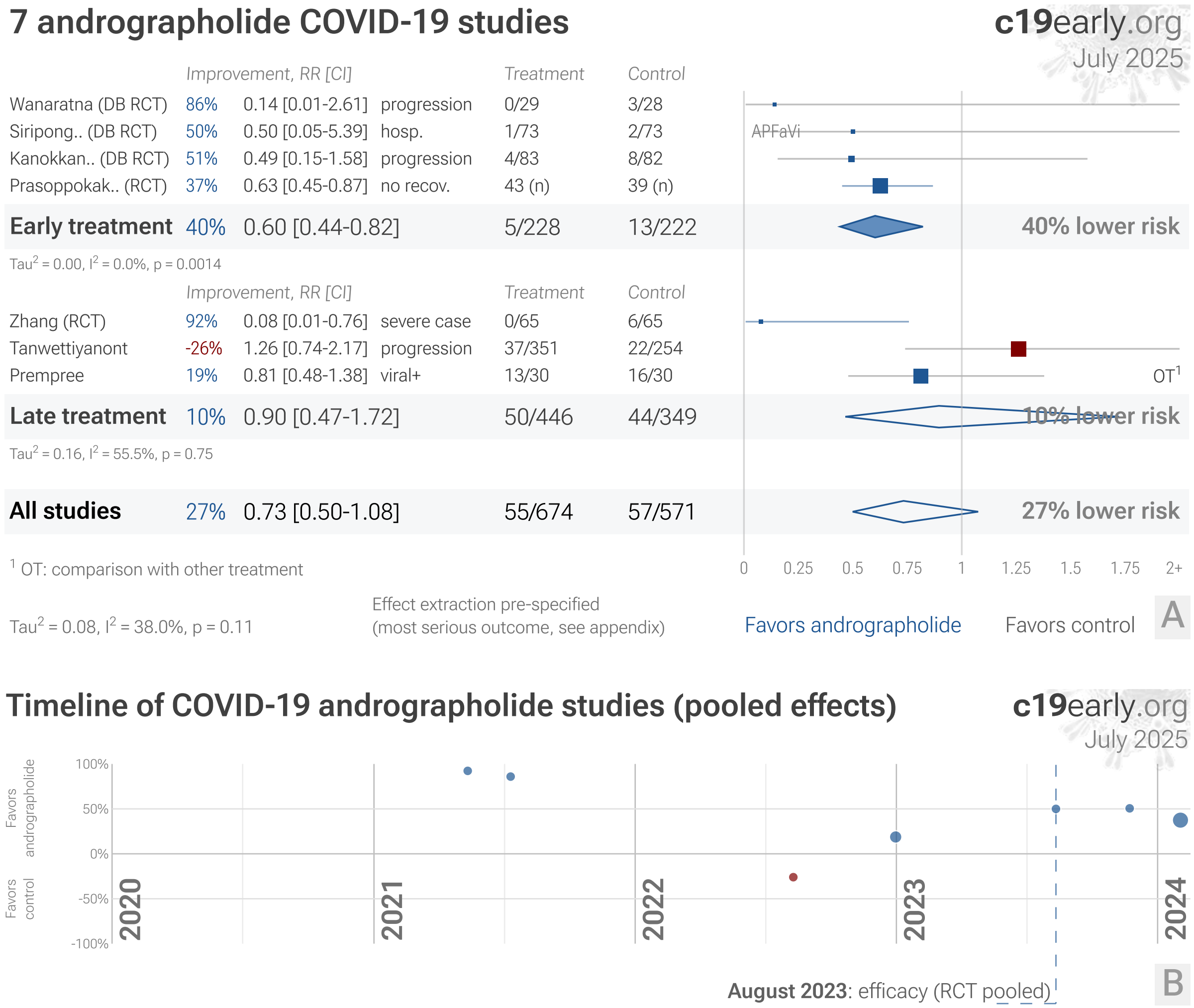


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in andrographolide studies.** The marked date indicates the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for 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 injury [3-15] and cognitive deficits [6,11], cardiovascular complications [16-20], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits [21]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

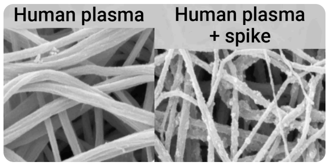


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from [2].**

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,22-29], 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 [30], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research

In Vitro studies demonstrate inhibition of the M^{pro} [B,31] protein. *In Vitro* studies demonstrate efficacy in Calu-3 [C,31], A549 [D,32], and HUVEC [E,31] cells. Animal studies demonstrate efficacy in Sprague Dawley mice [F,31] and Golden Syrian hamsters [G,32]. Andrographolide inhibits M^{pro} in a dose-dependent manner [31], reduces ACE2 levels in the lung tissue of mice in combination with baicalein [31], inhibits binding between the SARS-CoV-2 spike protein and ACE2 [31], alleviates lung inflammation and cytokine storm in mice [31], and improves survival and reduces lung inflammation via anti-inflammatory effects in Syrian hamsters [32].

Analysis

We analyze all significant controlled studies of andrographolide 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, 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.

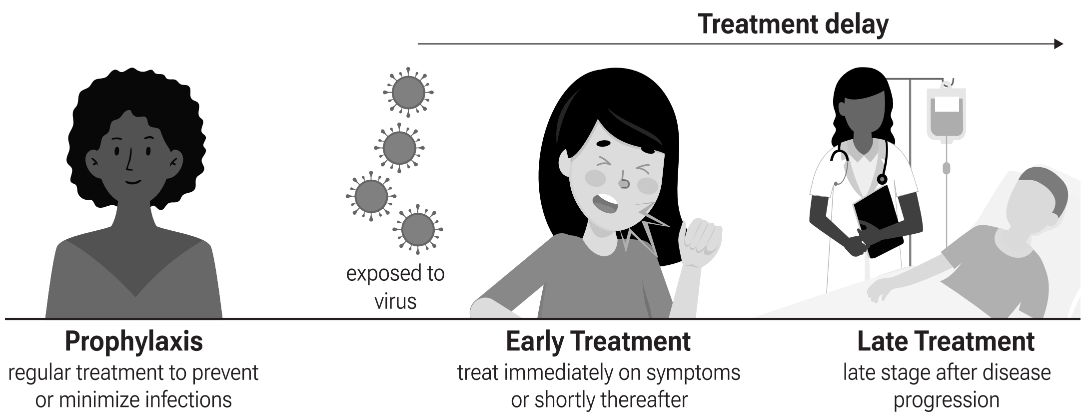


Figure 3. Treatment stages.

Preclinical Research

In Vitro studies demonstrate inhibition of the M^{pro} [B,31] protein. *In Vitro* studies demonstrate efficacy in Calu-3 [C,31], A549 [D,32], and HUVEC [E,31] cells. Animal studies demonstrate efficacy in Sprague Dawley mice [F,31] and Golden Syrian hamsters [G,32]. Andrographolide inhibits M^{pro} in a dose-dependent manner [31], reduces ACE2 levels in the lung tissue of mice in combination with baicalein [31], inhibits binding between the SARS-CoV-2 spike protein and ACE2 [31], alleviates lung inflammation and cytokine storm in mice [31], and improves survival and reduces lung inflammation via anti-inflammatory effects in Syrian hamsters [32].

12 *In Silico* studies support the efficacy of andrographolide [33-44].

9 *In Vitro* studies support the efficacy of andrographolide [31-33,45-50].

3 *In Vivo* animal studies support the efficacy of andrographolide [31,32,50].

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 stages combined, for Randomized Controlled Trials, and for specific outcomes. Table 2 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, and 9 show forest plots for random effects meta-analysis of all studies with pooled effects, hospitalization, progression, recovery, and viral clearance.

	Relative Risk	Studies	Patients
All studies	0.73 [0.50-1.08]	7	1,245
RCTs	0.59 [0.43-0.80] ***	5	580
Recovery	0.70 [0.51-0.95] *	4	520
Viral	0.72 [0.45-1.13]	4	390

***Table 1.* Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$.

	Early treatment	Late treatment
All studies	0.60 [0.44-0.82] **	0.90 [0.47-1.72]
RCTs	0.60 [0.44-0.82] **	0.08 [0.01-0.76] *
Recovery	0.76 [0.56-1.03]	0.52 [0.32-0.85] **
Viral	0.86 [0.51-1.45]	0.60 [0.35-1.03]

***Table 2.* Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$.

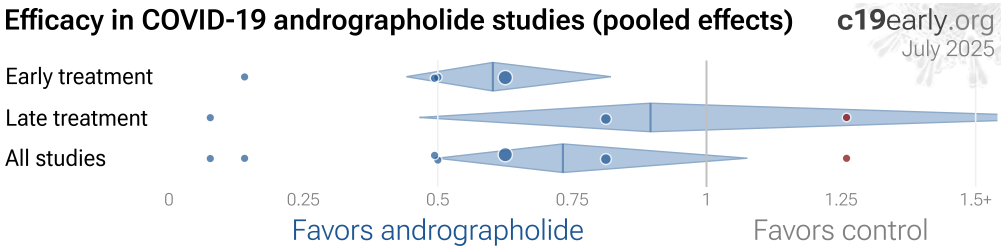


***Figure 4.* Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

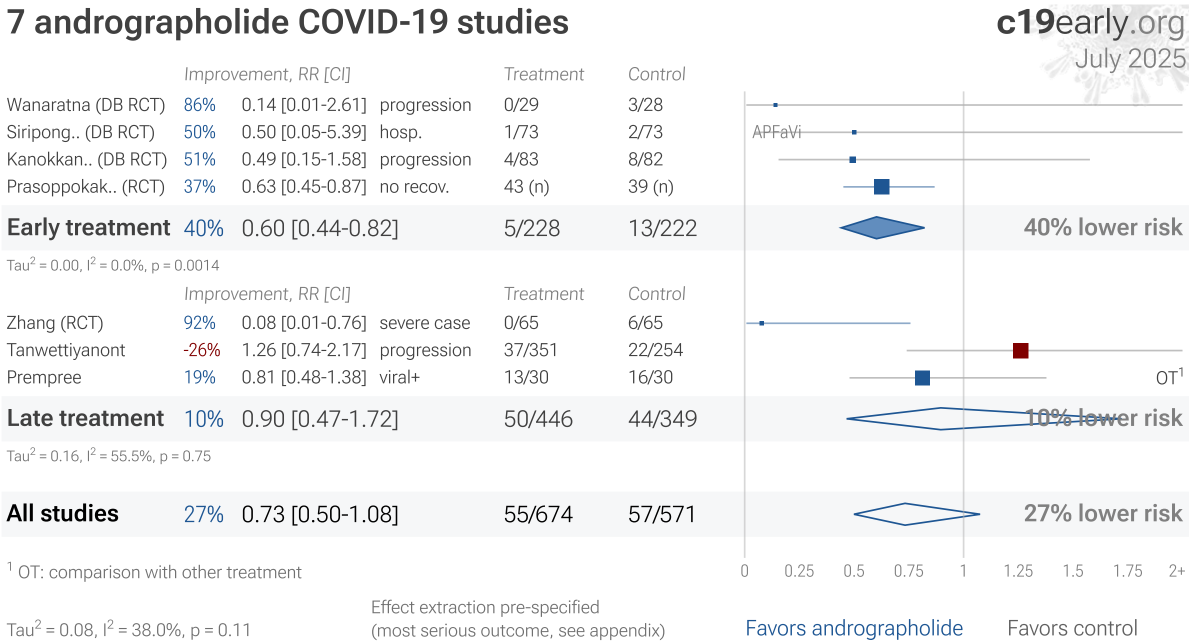


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

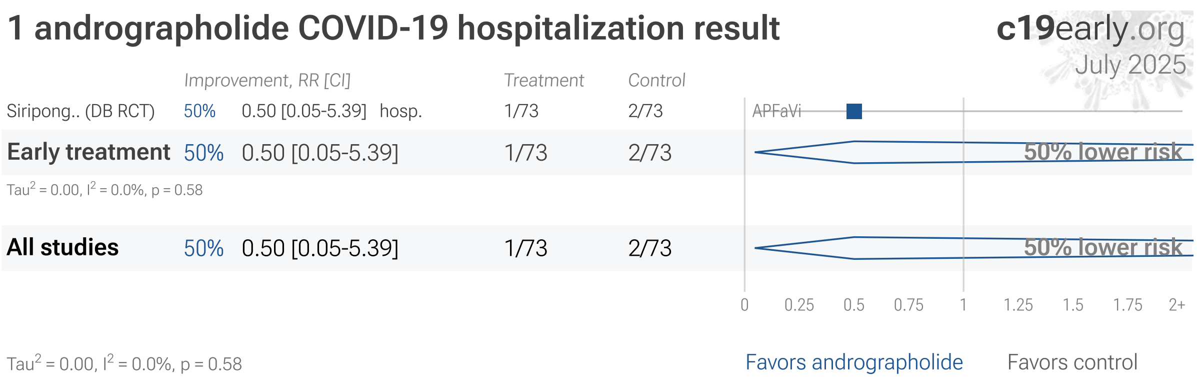


Figure 6. **Random effects meta-analysis for hospitalization.**

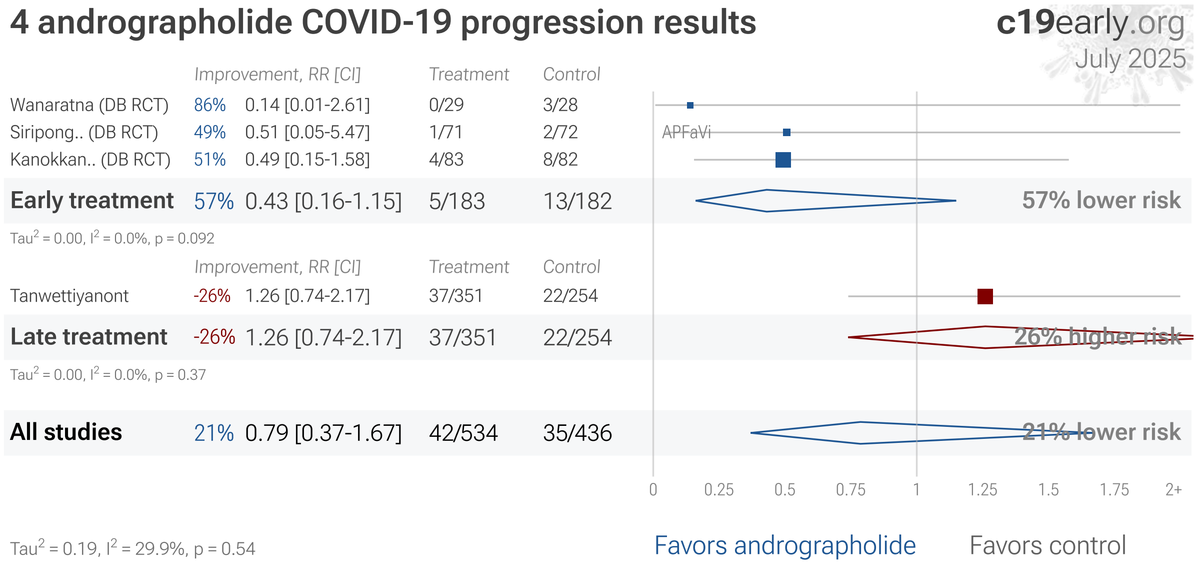


Figure 7. Random effects meta-analysis for progression.

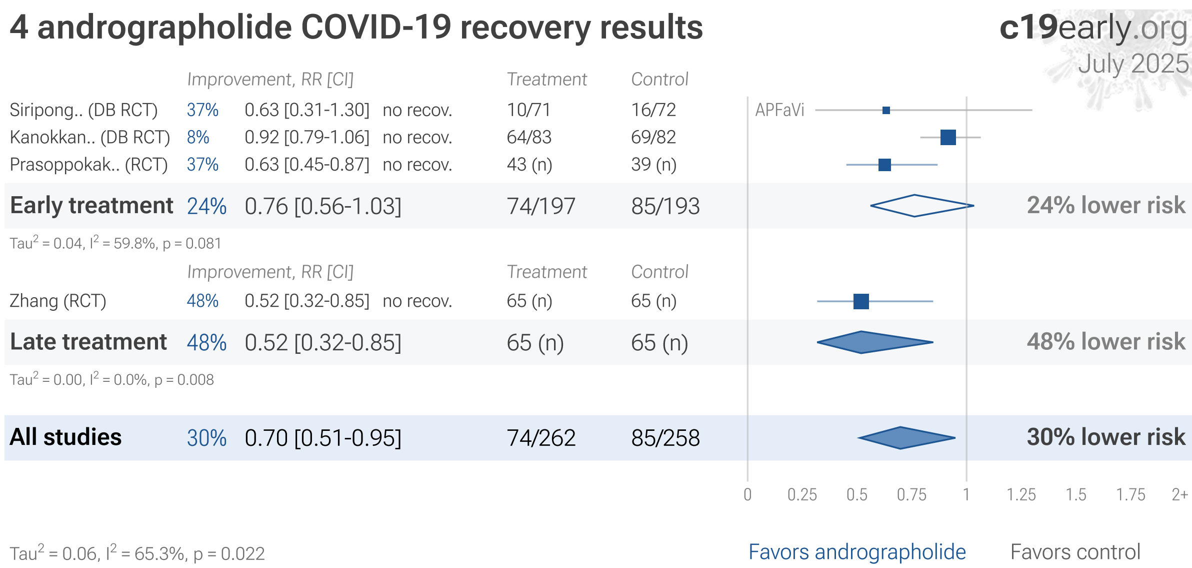


Figure 8. Random effects meta-analysis for recovery.

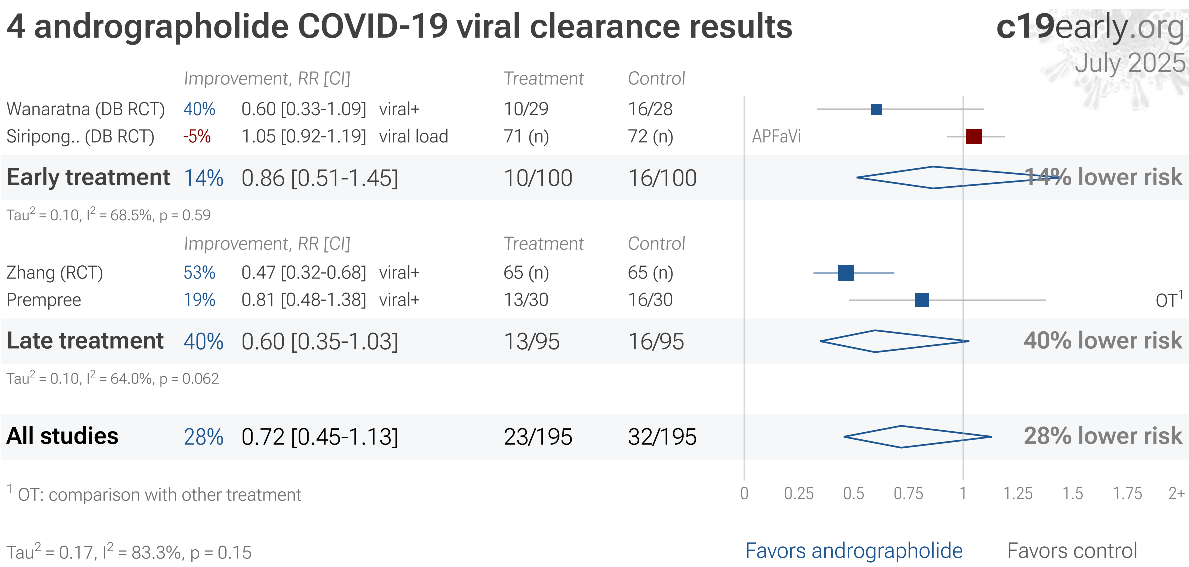


Figure 9. Random effects meta-analysis for viral clearance.

Randomized Controlled Trials (RCTs)

Figure 10 shows a comparison of results for RCTs and observational studies. Figure 11 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1 and Table 2.

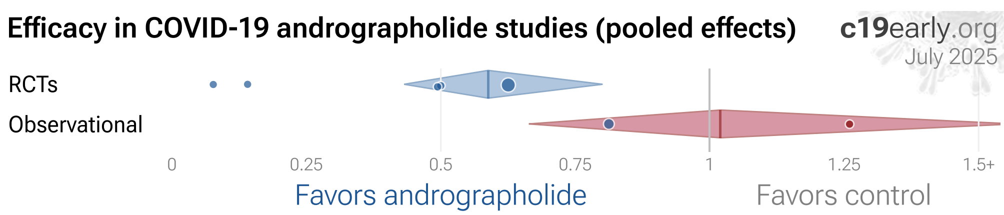


Figure 10. Results for RCTs and observational studies.

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 [51], and analysis of double-blind RCTs has identified extreme levels of bias [52]. 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.

Observational studies have been shown to be reliable

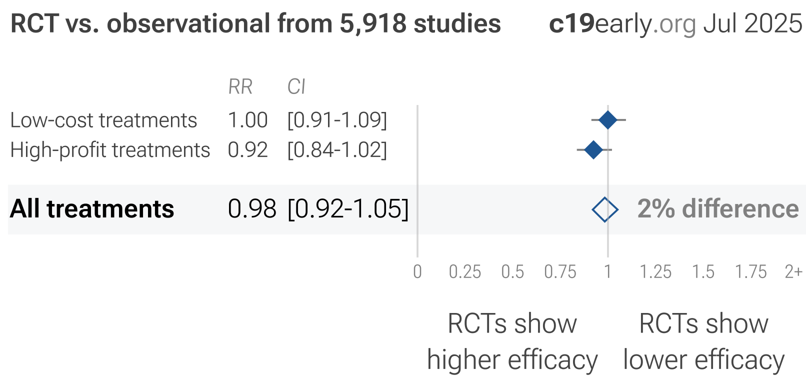


Figure 12. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[54].**

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 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][57]. 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[59,60].

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 ≥10% decreased risk or >0% increased risk from ≥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.

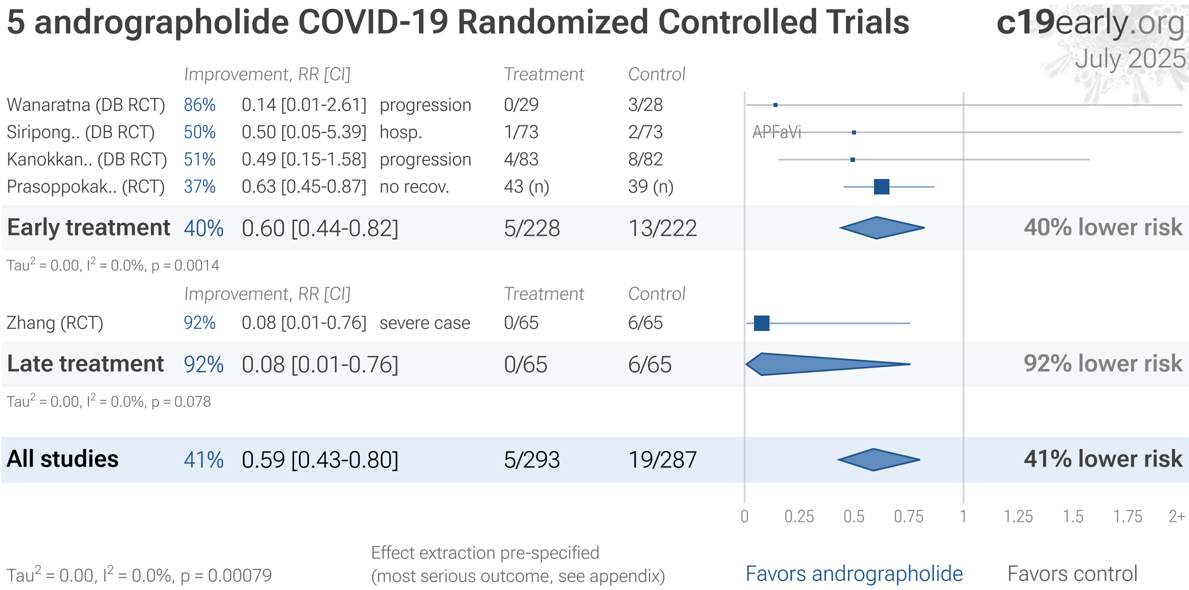


Figure 11. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Unreported RCTs

1 andrographolide RCT has not reported results [1]. The trial reports report an estimated total of 3,060 patients. The result is delayed over 3 years.

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 [61,62]. 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 [63]
<24 hours	-33 hours symptoms [64]
24-48 hours	-13 hours symptoms [64]
Inpatients	-2.5 hours to improvement [65]

Table 3. **Studies of baloxavir marboxil for influenza show that early treatment is more effective.**

Figure 13 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.

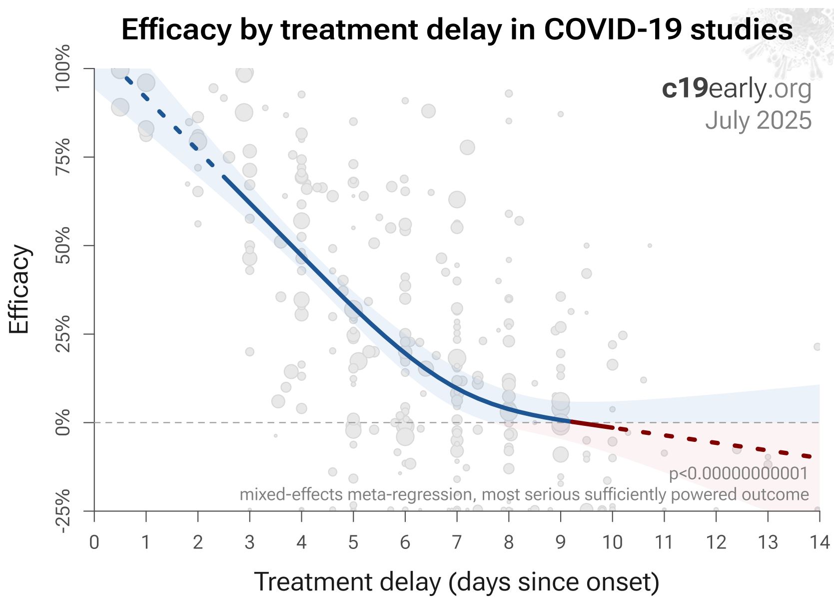


Figure 13. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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[67], for example the Gamma variant shows significantly different characteristics[68-71]. 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[72,73].

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[31,76-91], 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 14 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 15 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 16 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*.

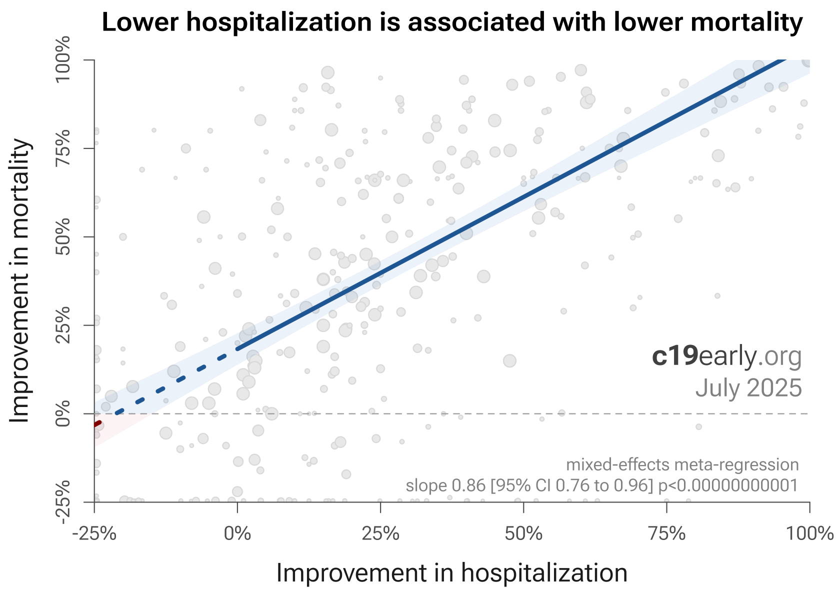


Figure 14. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

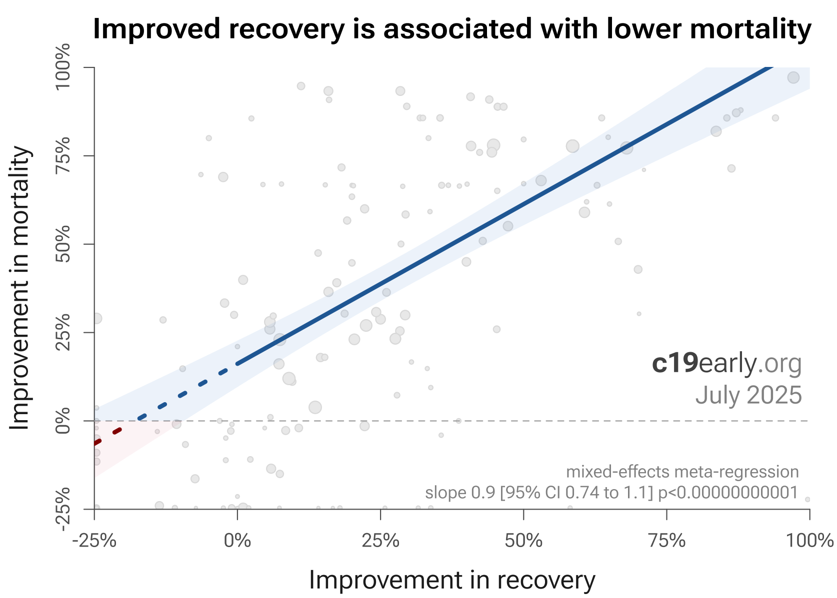


Figure 15. **Improved recovery is associated with lower mortality, supporting pooled outcome analysis.**

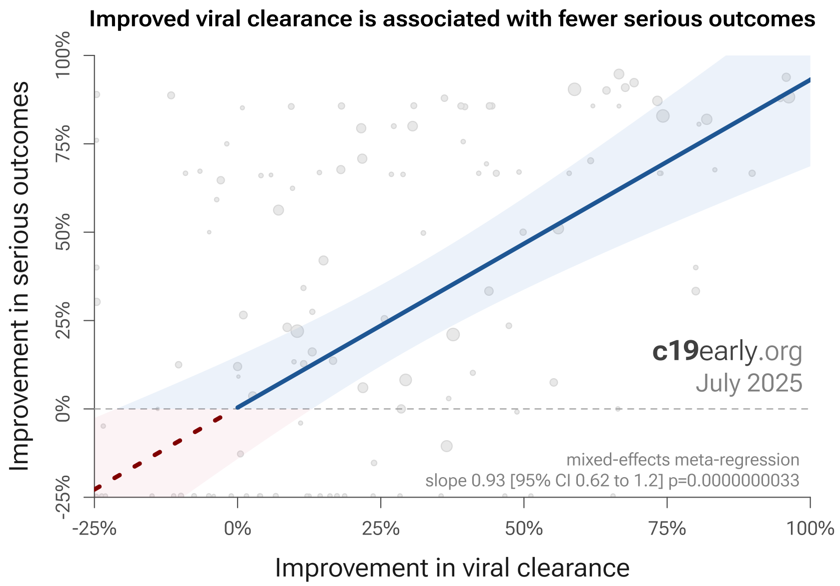


Figure 14. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

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 17 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

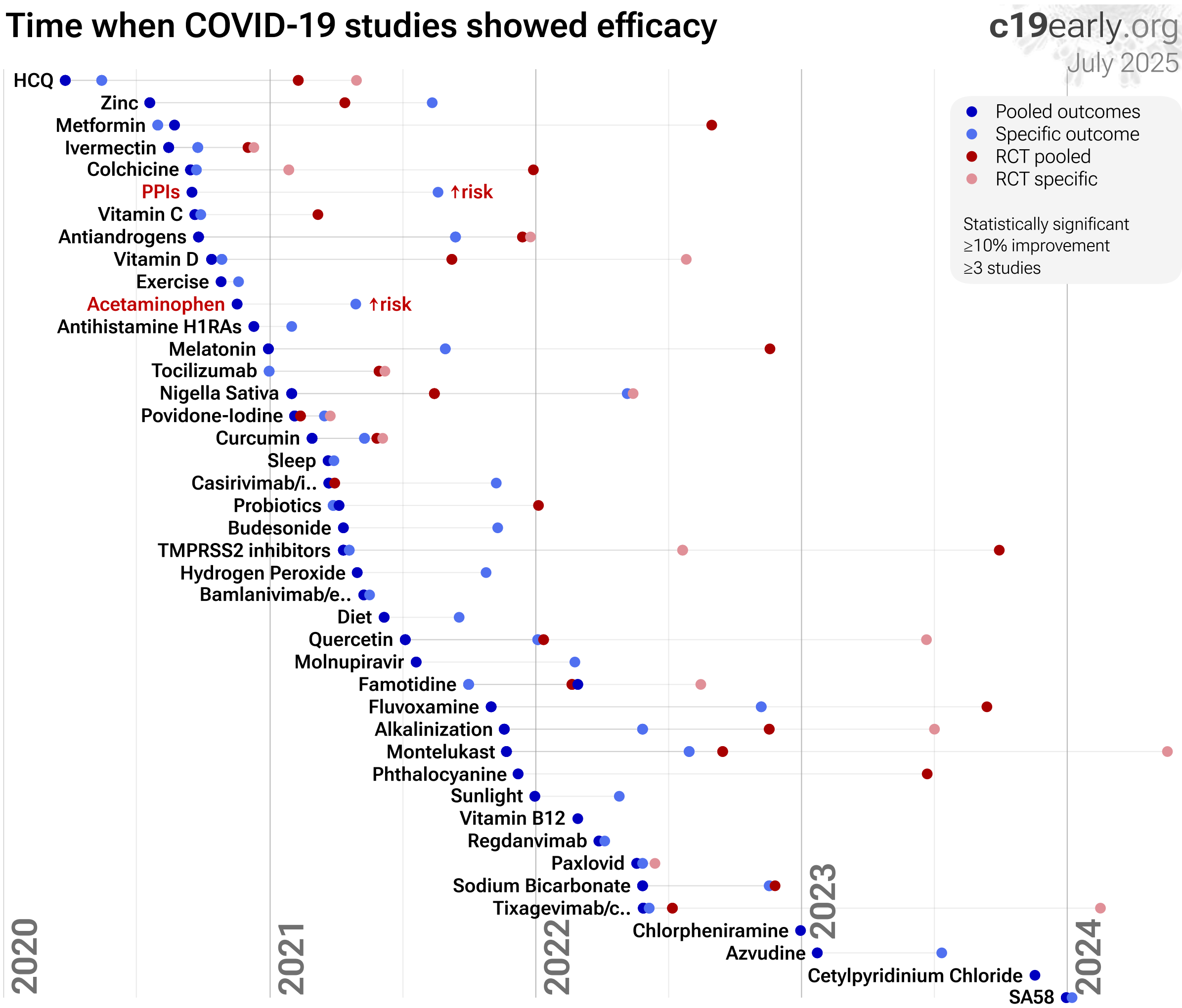


Figure 17. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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[93-96]. For andrographolide, there is currently not enough data to evaluate publication bias with high confidence.

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 18 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 $p < 0.05$[97-104]. 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.

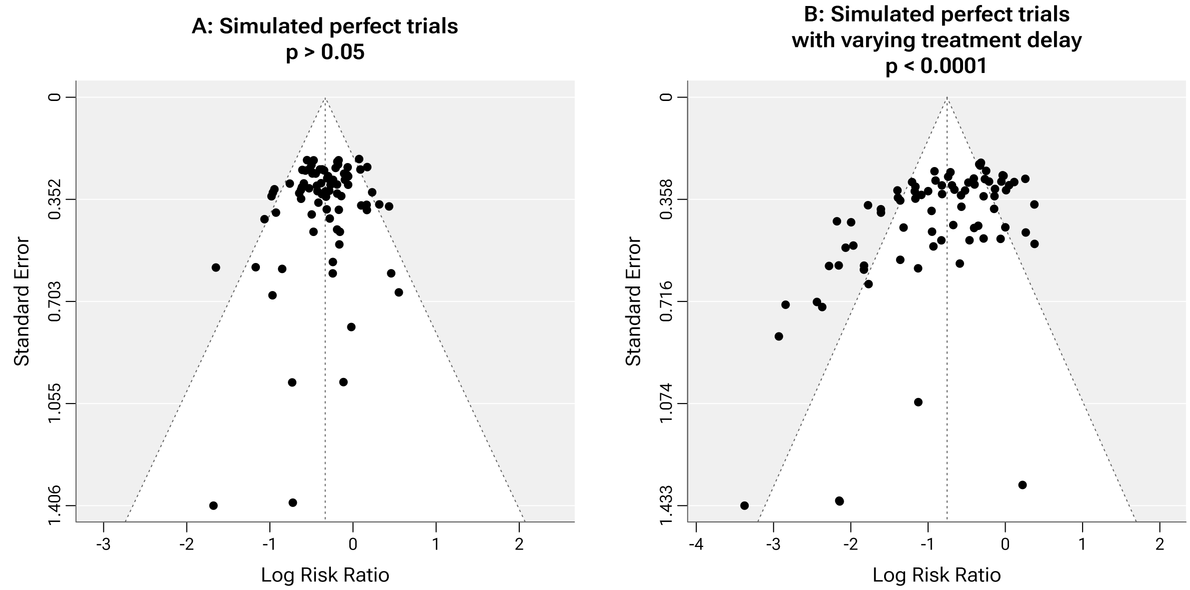


Figure 18. **Example funnel plot analysis for simulated perfect trials.**

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. Andrographolide for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 andrographolide 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 andrographolide 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[31,76-91]. 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 the 7 studies compare against other treatments, which may reduce the effect seen. Currently all studies are peer-reviewed.

Reviews

Multiple reviews cover andrographolide for COVID-19, presenting additional background on mechanisms and related results, including[105,106].

Other studies

Additional preclinical or review papers suggesting potential benefits of andrographolide for COVID-19 include[117-141]. 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[22-29], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk[30], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 19 shows an overview of the results for andrographolide in the context of multiple COVID-19 treatments, and Figure 20 shows a plot of efficacy vs. cost for COVID-19 treatments.

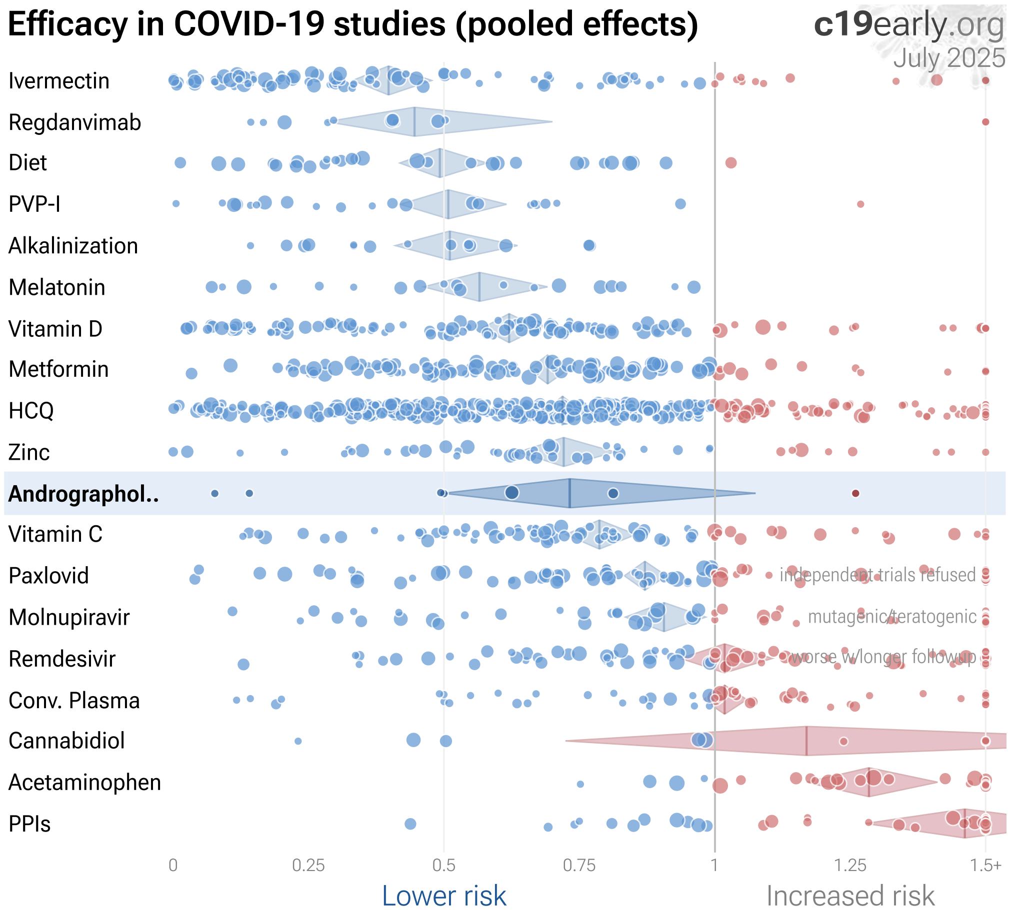


Figure 19. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [142].

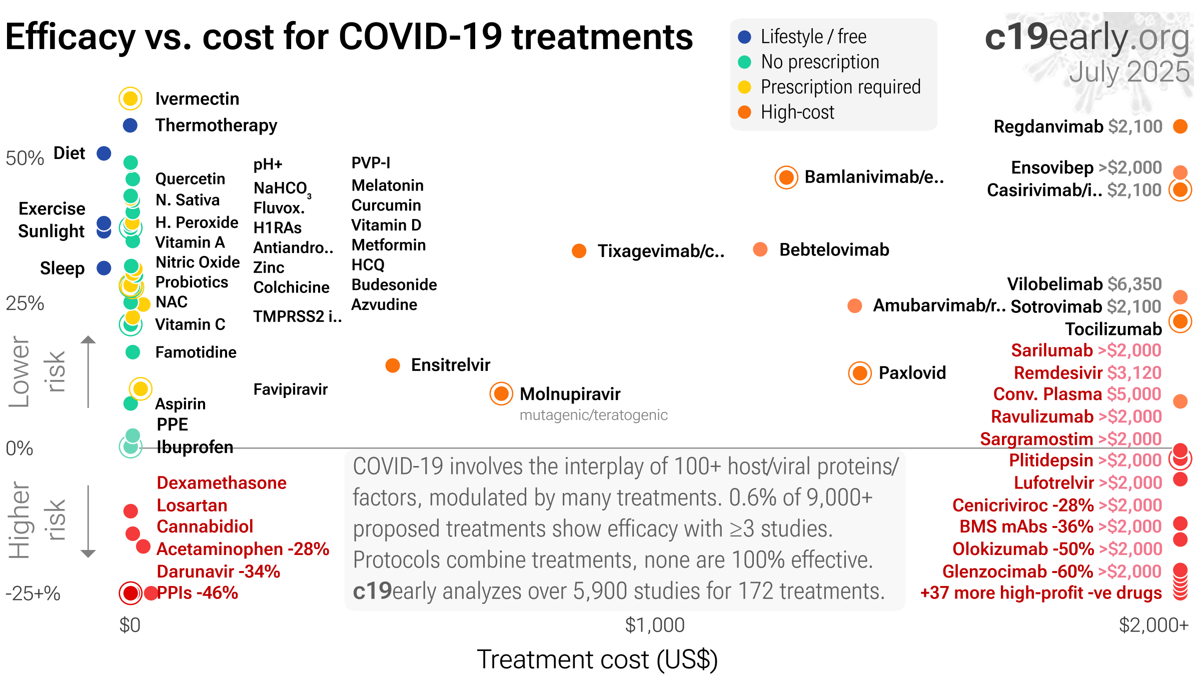


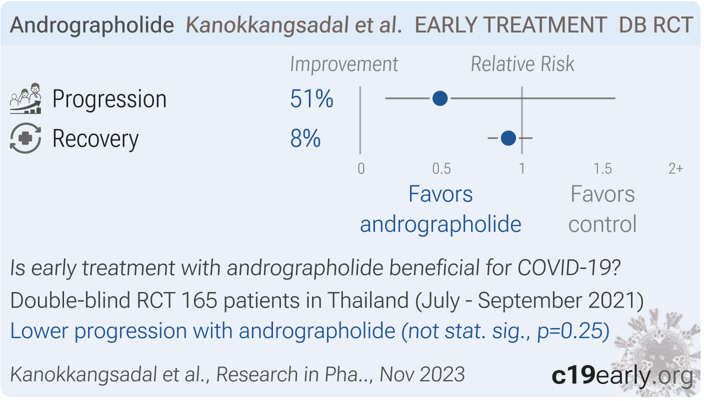
Figure 20. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Significantly lower risk is seen for recovery. 2 studies from 2 independent teams in 2 countries show significant benefit. Meta analysis using the most serious outcome reported shows 27% [-8-50%] lower risk, without reaching statistical significance. Results are similar for Randomized Controlled Trials. Early treatment is more effective than late treatment.

Study Notes

Kanokkangsadal

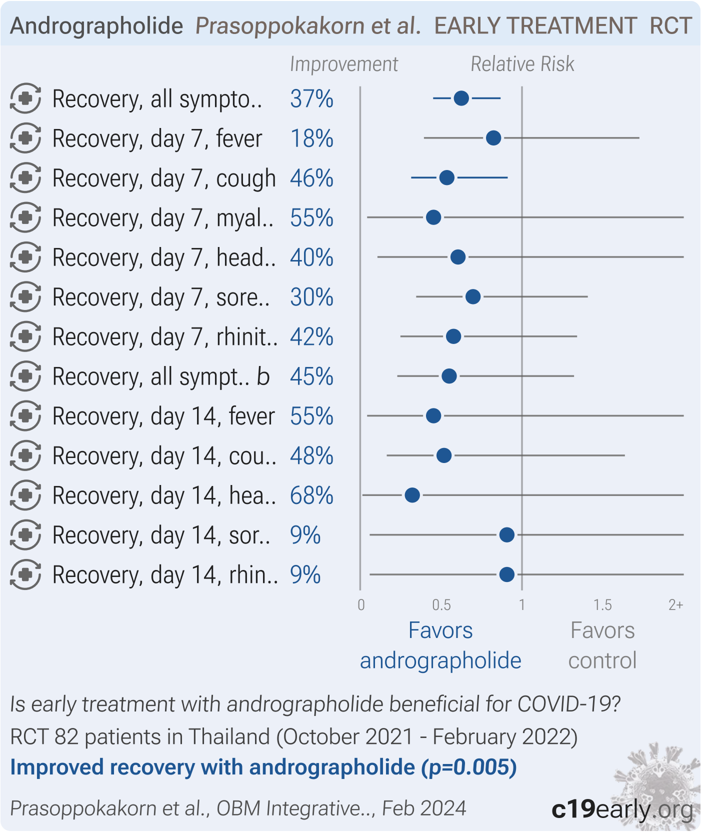


RCT 165 low-risk mild COVID-19 patients in Thailand receiving either 180mg/day of Andrographis paniculata extract or placebo for 5 days. No significant difference was found between groups for disease progression, though A. paniculata showed lower progression. Most symptoms improved similarly between groups, though A. paniculata provided faster relief for headaches and loss of smell. All patients recovered with 14 days. The main side effect was mild diarrhea.

Numthavaj

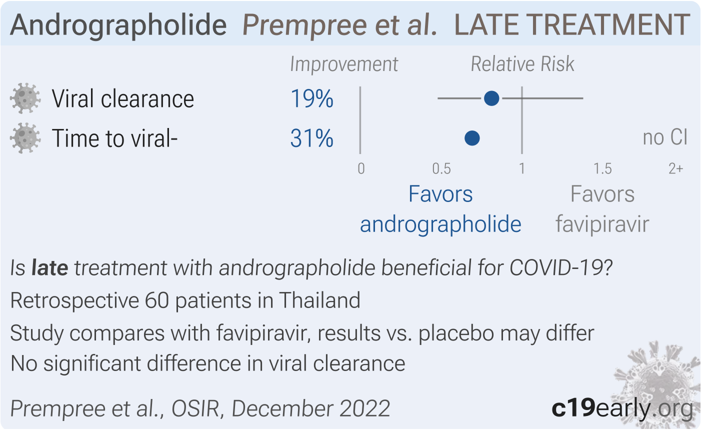
Estimated 3,060 patient andrographolide early treatment RCT with results not reported over 3 years after estimated completion.

Prasoppokakorn



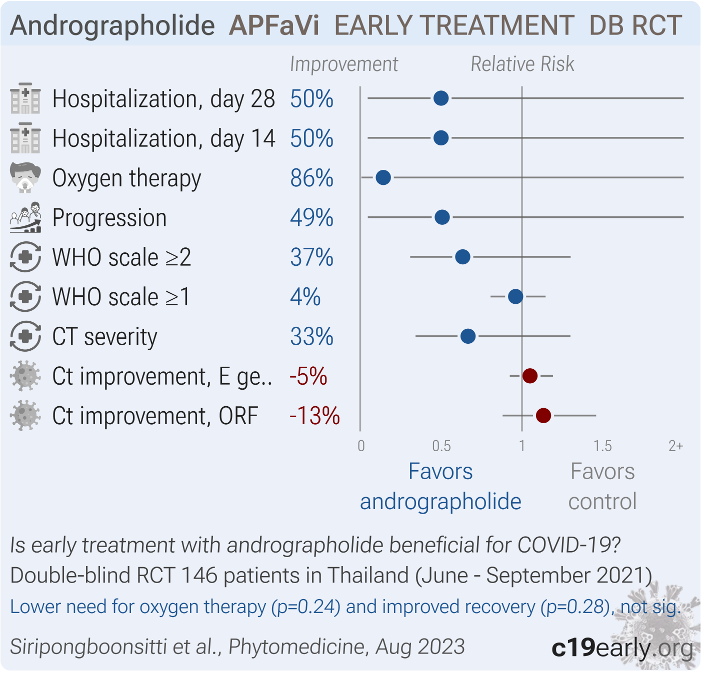
Randomized controlled trial of 82 mild COVID-19 outpatients showing significantly greater reduction in cough and lower inflammatory markers at day 7. Symptomatic improvement was significant at day 7 when combining all symptoms reported, but not for other symptoms individually. There was no progression to severe pneumonia in either group.

Prempree



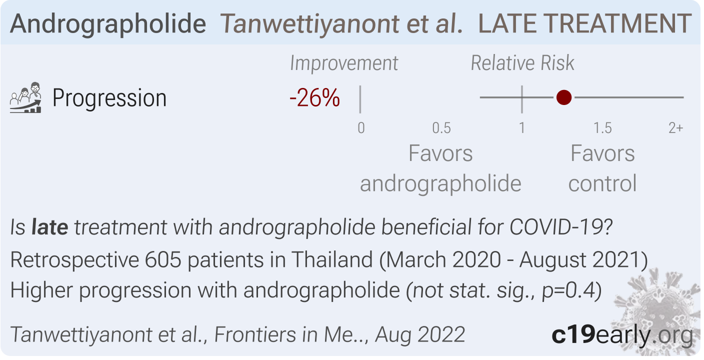
Retrospective 120 patients in Thailand, showing improved viral clearance with andrographis compared with favipiravir.

Siripongboonsitti



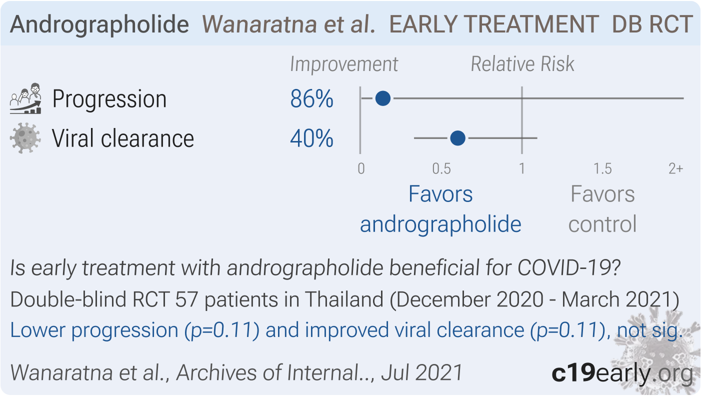
RCT 146 mild/moderate COVID-19 patients in Thailand, showing no significant difference in clinical outcomes. There were very few serious outcomes.

Tanwettiyanont



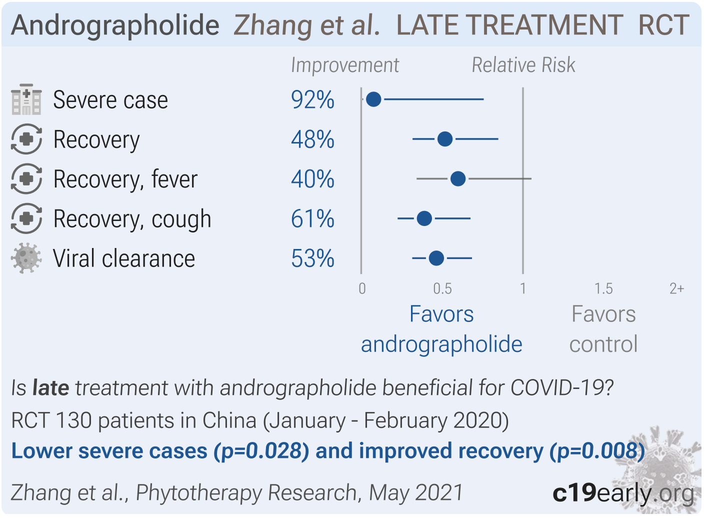
Retrospective 605 hospitalized patients in Thailand, showing higher progression with andrographis, without statistical significance.

Wanaratna



RCT 63 mild COVID-19 patients showing lower progression and improved viral clearance with andrographis, without statistical significance.

Zhang



RCT 130 hospitalized COVID-19 patients in China, showing lower progression and improved recovery with Xiyanping injection (9-dehydro-17-hydro-andrographolide and sodium 9-dehydro-17-hydro-andrographolide-19-yl sulfate, which are derived from andrographis).

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 andrographolide 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 andrographolide 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.

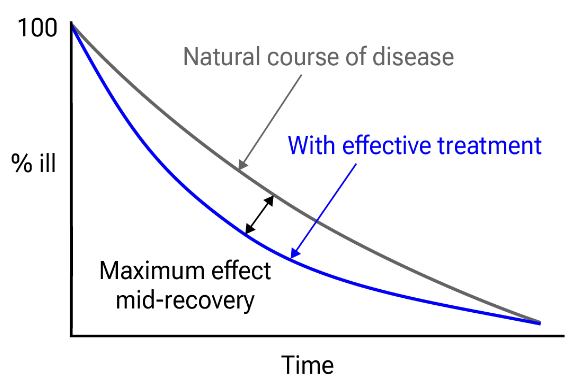


Figure 21. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 [143]. 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 (C) 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 [147]. 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 [148] 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 [61,62].

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/apmeta.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.

Kanokkangsadal, 11/23/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Thailand, peer-reviewed, 9 authors, study period July 2021 - September 2021, trial TCTR20210809004.	risk of progression, 50.6% lower, RR 0.49, *p* = 0.25, treatment 4 of 83 (4.8%), control 8 of 82 (9.8%), NNT 20.
	risk of no recovery, 8.4% lower, RR 0.92, *p* = 0.33, treatment 64 of 83 (77.1%), control 69 of 82 (84.1%), NNT 14, total recovery, day 5.
Numthavaj, 5/30/2022, Single Blind Randomized Controlled Trial, Thailand, trial NCT05019326 (history).	Estimated 3,060 patient RCT with results unknown and over 3 years late.
Prasoppokakorn, 2/2/2024, Randomized Controlled Trial, Thailand, peer-reviewed, 7 authors, study period October 2021 - February 2022, trial TCTR20210906002.	risk of no recovery, 37.5% lower, RR 0.63, *p* = 0.005, treatment 43, control 39, all symptoms combined.

	risk of no recovery, 17.5% lower, RR 0.82, *p* = 0.62, treatment 10 of 43 (23.3%), control 11 of 39 (28.2%), NNT 20, day 7, fever.
	risk of no recovery, 46.4% lower, RR 0.54, *p* = 0.03, treatment 13 of 43 (30.2%), control 22 of 39 (56.4%), NNT 3.8, day 7, cough.
	risk of no recovery, 54.7% lower, RR 0.45, *p* = 0.60, treatment 1 of 43 (2.3%), control 2 of 39 (5.1%), NNT 36, day 7, myalgia.
	risk of no recovery, 39.5% lower, RR 0.60, *p* = 0.66, treatment 2 of 43 (4.7%), control 3 of 39 (7.7%), NNT 33, day 7, headache.
	risk of no recovery, 30.2% lower, RR 0.70, *p* = 0.34, treatment 10 of 43 (23.3%), control 13 of 39 (33.3%), NNT 9.9, day 7, sore throat.
	risk of no recovery, 42.3% lower, RR 0.58, *p* = 0.29, treatment 7 of 43 (16.3%), control 11 of 39 (28.2%), NNT 8.4, day 7, rhinitis.
	risk of no recovery, 45.0% lower, RR 0.55, *p* = 0.18, treatment 43, control 39, all symptoms combined.
	risk of no recovery, 54.7% lower, RR 0.45, *p* = 0.60, treatment 1 of 43 (2.3%), control 2 of 39 (5.1%), NNT 36, day 14, fever.
	risk of no recovery, 48.2% lower, RR 0.52, *p* = 0.34, treatment 4 of 43 (9.3%), control 7 of 39 (17.9%), NNT 12, day 14, cough.
	risk of no recovery, 67.8% lower, RR 0.32, *p* = 0.48, treatment 0 of 43 (0.0%), control 1 of 39 (2.6%), NNT 39, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14, headache.
	risk of no recovery, 9.3% lower, RR 0.91, *p* = 1.00, treatment 1 of 43 (2.3%), control 1 of 39 (2.6%), NNT 419, day 14, sore throat.
	risk of no recovery, 9.3% lower, RR 0.91, *p* = 1.00, treatment 1 of 43 (2.3%), control 1 of 39 (2.6%), NNT 419, day 14, rhinitis.
Siripongboonsitti, 8/12/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Thailand, peer-reviewed, 10 authors, study period 11 June, 2021 - 15 September, 2021, trial TCTR20210609001 (APFaVi).	**risk of hospitalization, 50.0% lower, RR 0.50, *p* = 1.00,** treatment 1 of 73 (1.4%), control 2 of 73 (2.7%), NNT 73, day 28.
	risk of hospitalization, 50.0% lower, RR 0.50, *p* = 1.00, treatment 1 of 73 (1.4%), control 2 of 73 (2.7%), NNT 73, day 14.
	risk of oxygen therapy, 85.7% lower, RR 0.14, *p* = 0.24, treatment 0 of 73 (0.0%), control 3 of 73 (4.1%), NNT 24, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of progression, 49.3% lower, RR 0.51, *p* = 1.00, treatment 1 of 71 (1.4%), control 2 of 72 (2.8%), NNT 73, day 4.
	WHO scale ≥2, 36.6% lower, RR 0.63, *p* = 0.28, treatment 10 of 71 (14.1%), control 16 of 72 (22.2%), NNT 12, day 14.
	WHO scale ≥1, 3.9% lower, RR 0.96, *p* = 0.69, treatment 54 of 71 (76.1%), control 57 of 72 (79.2%), NNT 32, day 14.
	CT severity, 33.3% lower, RR 0.67, *p* = 0.24, treatment 71, control 72, day 5.

	relative Ct improvement, 5.0% worse, RR 1.05, *p* = 0.46, treatment 71, control 72, E gene, day 5.
	relative Ct improvement, 13.3% worse, RR 1.13, *p* = 0.34, treatment 71, control 72, ORF, day 5.
Wanaratna, 7/11/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Thailand, peer-reviewed, 7 authors, study period December 2020 - March 2021, trial TCTR20210708001.	**risk of progression, 85.9% lower, RR 0.14, *p* = 0.11**, treatment 0 of 29 (0.0%), control 3 of 28 (10.7%), NNT 9.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no viral clearance, 39.7% lower, RR 0.60, *p* = 0.11, treatment 10 of 29 (34.5%), control 16 of 28 (57.1%), NNT 4.4, day 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.

Prempree, 12/31/2022, retrospective, Thailand, peer-reviewed, 9 authors, this trial compares with another treatment - results may be better when compared to placebo.	**risk of no viral clearance, 18.8% lower, RR 0.81, *p* = 0.61**, treatment 13 of 30 (43.3%), control 16 of 30 (53.3%), NNT 10, day 14.
Tanwettiyanont, 8/10/2022, retrospective, Thailand, peer-reviewed, mean age 35.4, 8 authors, study period 1 March, 2020 - 31 August, 2021.	**risk of progression, 26.0% higher, HR 1.26, *p* = 0.40**, treatment 37 of 351 (10.5%), control 22 of 254 (8.7%), Cox proportional hazards.
Zhang (B), 5/12/2021, Randomized Controlled Trial, China, peer-reviewed, mean age 46.3, 12 authors, study period 27 January, 2020 - 20 February, 2020, trial NCT04295551 (history).	**risk of severe case, 92.3% lower, RR 0.08, *p* = 0.03**, treatment 0 of 65 (0.0%), control 6 of 65 (9.2%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no recovery, 48.2% lower, HR 0.52, *p* = 0.008, treatment 65, control 65, inverted to make HR<1 favor treatment.
	risk of no recovery, 40.1% lower, HR 0.60, *p* = 0.07, treatment 65, control 65, inverted to make HR<1 favor treatment, fever.
	risk of no recovery, 60.9% lower, HR 0.39, *p* = 0.001, treatment 65, control 65, inverted to make HR<1 favor treatment, cough.
	risk of no viral clearance, 53.5% lower, HR 0.47, *p* < 0.001, treatment 65, control 65, inverted to make HR<1 favor treatment.

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 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.

c. 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.

d. 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.

e. HUVEC (Human Umbilical Vein Endothelial Cells) are primary endothelial cells derived from the vein of the umbilical cord. They are used to study vascular biology, including inflammation, angiogenesis, and viral interactions with endothelial cells.

f. An outbred multipurpose breed of albino mouse used extensively in medical research.

g. A rodent model widely used in infectious disease research due to their susceptibility to viral infections and similar disease progression to humans.

References

1. ***Numthavaj*** et al., *Andrographis Paniculata vs Boesenbergia Rotunda vs Control in Asymptomatic COVID-19*, NCT05178173, clinicaltrials.gov/study/NCT05019326.
2. ***Ryu*** et al., *Fibrin drives thromboinflammation and neuropathology in COVID-19*, Nature, doi:10.1038/s41586-024-07873-4.
3. ***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.
4. ***Yang*** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.
5. ***Scardua-Silva*** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.
6. ***Hampshire*** et al., *Cognition and Memory after Covid-19 in a Large Community Sample*, New England Journal of Medicine, doi:10.1056/NEJMoa2311330.
7. ***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.
8. ***Sodagar*** et al., *Pathological Features and Neuroinflammatory Mechanisms of SARS-CoV-2 in the Brain and Potential Therapeutic Approaches*, Biomolecules, doi:10.3390/biom12070971.
9. ***Sagar*** et al., *COVID-19-associated cerebral microbleeds in the general population*, Brain Communications, doi:10.1093/braincomms/fcae127.
10. ***Verma*** et al., *Persistent Neurological Deficits in Mouse PASC Reveal Antiviral Drug Limitations*, bioRxiv, doi:10.1101/2024.06.02.596989.
11. ***Panagea*** et al., *Neurocognitive Impairment in Long COVID: A Systematic Review*, Archives of Clinical Neuropsychology, doi:10.1093/arclin/acae042.
12. ***Ariza*** et al., *COVID-19: Unveiling the Neuropsychiatric Maze—From Acute to Long-Term Manifestations*, Biomedicines, doi:10.3390/biomedicines12061147.
13. ***Vashisht*** et al., *Neurological Complications of COVID-19: Unraveling the Pathophysiological Underpinnings and Therapeutic Implications*, Viruses, doi:10.3390/v16081183.
14. ***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.
15. ***Wang*** et al., *SARS-CoV-2 membrane protein induces neurodegeneration via affecting Golgi-mitochondria interaction*, Translational Neurodegeneration, doi:10.1186/s40035-024-00458-1.
16. ***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.
17. ***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.
18. ***Borka Balas*** et al., *COVID-19 and Cardiac Implications—Still a Mystery in Clinical Practice*, Reviews in Cardiovascular Medicine, doi:10.31083/j.rcm2405125.
19. ***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.

20. **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.
21. **Trender** et al., *Changes in memory and cognition during the SARS-CoV-2 human challenge study*, eClinicalMedicine, doi:10.1016/j.eclinm.2024.102842.
22. **Dugied** et al., *Multimodal SARS-CoV-2 interactome sketches the virus-host spatial organization*, Communications Biology, doi:10.1038/s42003-025-07933-z.
23. **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.
24. **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.
25. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.
26. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.
27. **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.
28. **Katiyar** et al., *SARS-CoV-2 Assembly: Gaining Infectivity and Beyond*, Viruses, doi:10.3390/v16111648.
29. **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.
30. **c19early.org**, c19early.org/treatments.html.
31. **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.
32. **Kongsomros** et al., *In vivo evaluation of Andrographis paniculata and Boesenbergia rotunda extract activity against SARS-CoV-2 Delta variant in Golden Syrian hamsters: Potential herbal alternative for COVID-19 treatment*, Journal of Traditional and Complementary Medicine, doi:10.1016/j.jtcme.2024.05.004.
33. **Zhang** et al., *Effects and Mechanisms of Andrographolide for COVID-19: A Network Pharmacology-Based and Experimentally Validated Study*, Natural Product Communications, doi:10.1177/1934578X241288428.
34. **Thomas** et al., *Cheminformatics approach to identify andrographolide derivatives as dual inhibitors of methyltransferases (nsp14 and nsp16) of SARS-CoV-2*, Scientific Reports, doi:10.1038/s41598-024-58532-7.
35. **Bhattarai** et al., *Investigating the binding affinity of andrographolide against human SARS-CoV-2 spike receptor-binding domain through docking and molecular dynamics simulations*, Journal of Biomolecular Structure and Dynamics, doi:10.1080/07391102.2023.2174596.
36. **Nguyen** et al., *The Potential of Ameliorating COVID-19 and Sequelae From Andrographis paniculata via Bioinformatics*, Bioinformatics and Biology Insights, doi:10.1177/11779322221149622.
37. **Dassanayake** et al., *Molecular Docking and In-Silico Analysis of Natural Biomolecules against Dengue, Ebola, Zika, SARS-CoV-2 Variants of Concern and Monkeypox Virus*, International Journal of Molecular Sciences, doi:10.3390/ijms231911131.
38. **Ningrum** et al., *Potency Of Andrographolide, L-Mimosine And Asiaticoside Compound As Antiviral For Covid-19 Based On In Silico Method*, Proceedings Universitas Muhammadiyah Yogyakarta Undergraduate Conference, doi:10.18196/umygrace.v2i2.418.
39. **Ravichandran** et al., *Identification of Potential Semisynthetic Andrographolide Derivatives to Combat COVID-19 by Targeting the SARS-COV-2 Spike Protein and Human ACE2 Receptor– An In-silico Approach*, Biointerface Research in Applied Chemistry, doi:10.33263/BRIAC132.155.
40. **Saeheng** et al., *In Silico Prediction of Andrographolide Dosage Regimens for COVID-19 Treatment*, The American Journal of Chinese Medicine, doi:10.1142/S0192415X22500732.
41. **Khanal** et al., *Combination of system biology to probe the anti-viral activity of andrographolide and its derivative against COVID-19*, RSC Advances, doi:10.1039/D0RA10529E.
42. **Rehan** et al., *A Computational Approach Identified Andrographolide as a Potential Drug for Suppressing COVID-19-Induced Cytokine Storm*, Frontiers in Immunology, doi:10.3389/fimmu.2021.648250.
43. **Rajagopal** et al., *Activity of phytochemical constituents of Curcuma longa (turmeric) and Andrographis paniculata against coronavirus (COVID-19): an in silico approach*, Future Journal of Pharmaceutical Sciences, doi:10.1186/s43094-020-00126-x.
44. **Dey** et al., *The role of andrographolide and its derivative in COVID-19 associated proteins and immune system*, Research Square, doi:10.21203/rs.3.rs-35800/v1.
45. **Chaopreecha** et al., *Andrographolide attenuates SARS-CoV-2 infection via an up-regulation of glutamate-cysteine ligase catalytic subunit (GCLC)*, Phytomedicine, doi:10.1016/j.phymed.2024.156279.
46. **Li** et al., *Andrographolide suppresses SARS-CoV-2 infection by downregulating ACE2 expression: A mechanistic study*, Antiviral Therapy, doi:10.1177/13596535241259952.
47. **Low** et al., *The wide spectrum anti-inflammatory activity of andrographolide in comparison to NSAIDs: a promising therapeutic compound against the cytokine storm*, bioRxiv, doi:10.1101/2024.02.21.581396.
48. **Siridechakorn** et al., *Inhibitory efficiency of Andrographis paniculata extract on viral multiplication and nitric oxide production*, Scientific Reports, doi:10.1038/s41598-023-46249-y.
49. **Mohd Abd Razak** et al., *In Vitro Anti-SARS-CoV-2 Activities of Curcumin and Selected Phenolic Compounds*, Natural Product Communications, doi:10.1177/1934578X231188861.

50. **Pu** et al., *The effects and mechanisms of the anti-COVID-19 traditional Chinese medicine, Dehydroandrographolide from Andrographis paniculata (Burm.f.) Wall, on acute lung injury by the inhibition of NLRP3-mediated pyroptosis*, Phytomedicine, doi:10.1016/j.phymed.2023.154753.
51. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings, Second Edition*, doi:10.1002/9780470691922.
52. **Gøtzsche**, P., *Bias in double-blind trials*, Doctoral Thesis, University of Copenhagen, www.scientificfreedom.dk/2023/05/16/bias-in-double-blind-trials-doctoral-thesis/.
53. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.
54. **c19early.org (B)**, c19early.org/apsupp.html#fig_rctobs.
55. **Concato** et al., NEJM, 342:1887-1892, doi:10.1056/NEJM200006223422507.
56. **Anglemyer** et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews 2014, Issue 4, doi:10.1002/14651858.MR000034.pub2.
57. **c19early.org (C)**, c19early.org/rctobs.html.
58. **Lee** et al., *Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines*, Arch Intern Med., 2011, 171:1, 18-22, doi:10.1001/archinternmed.2010.482.
59. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.
60. **Nichol** et al., *Challenging issues in randomised controlled trials*, Injury, 2010, doi: 10.1016/j.injury.2010.03.033, www.injuryjournal.com/article/S0020-1383(10)00233-0/fulltext.
61. **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.
62. **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.
63. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.
64. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.
65. **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.
66. **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.
67. **Korves** et al., *SARS-CoV-2 Genetic Variants and Patient Factors Associated with Hospitalization Risk*, medRxiv, doi:10.1101/2024.03.08.24303818.
68. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.
69. **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.
70. **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.
71. **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.
72. **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.
73. **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.
74. **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.
75. **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.
76. **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.
77. **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.
78. **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.
79. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.
80. **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.
81. **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.

82. ***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.

83. ***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.

84. ***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.

85. ***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.

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

87. ***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.

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

89. ***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.

90. ***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.

91. ***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.

92. ***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.

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

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

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

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

97. ***Rothstein***, H., *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*, www.wiley.com/en-ae/Publication+Bias+in+Meta+Analysis:+Prevention,+Assessment+and+Adjustments-p-9780470870143.

98. ***Stanley*** et al., *Meta-regression approximations to reduce publication selection bias*, Research Synthesis Methods, doi:10.1002/jrsm.1095.

99. ***Rücker*** et al., *Arcsine test for publication bias in meta-analyses with binary outcomes*, Statistics in Medicine, doi:10.1002/sim.2971.

100. ***Peters***, J., *Comparison of Two Methods to Detect Publication Bias in Meta-analysis*, JAMA, doi:10.1001/jama.295.6.676.

101. ***Moreno*** et al., *Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study*, BMC Medical Research Methodology, doi:10.1186/1471-2288-9-2.

102. ***Macaskill*** et al., *A comparison of methods to detect publication bias in meta-analysis*, Statistics in Medicine, doi:10.1002/sim.698.

103. ***Egger*** et al., *Bias in meta-analysis detected by a simple, graphical test*, BMJ, doi:10.1136/bmj.315.7109.629.

104. ***Harbord*** et al., *A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints*, Statistics in Medicine, doi:10.1002/sim.2380.

105. ***Chidambaram***, K., *Antiviral efficacy of Andrographis paniculata and andrographolides: A narrative review*, Asian Pacific Journal of Tropical Biomedicine, doi:10.4103/apjtb.apjtb_751_23.

106. ***Intharuksa*** et al., *A Comprehensive Review of Andrographis paniculata (Burm. f.) Nees and Its Constituents as Potential Lead Compounds for COVID-19 Drug Discovery*, Molecules, doi:10.3390/molecules27144479.

107. ***Prasoppokakorn*** et al., *Efficacy and Safety of Andrographolide and Favipiravir Versus Favipiravir Monotherapy in Patients with Mild COVID-19 Infection: A Multicenter Randomized Controlled Trial*, OBM Integrative and Complementary Medicine, doi:10.21926/obm.icm.2401013.

108. ***Kanokkangsadal*** et al., *Andrographis paniculata extract versus placebo in the treatment of COVID-19: a double-blinded randomized control trial*, Research in Pharmaceutical Sciences, doi:10.4103/1735-5362.389947.

109. ***Bhardwaj*** et al., *Effectiveness of ayurvedic formulation, NAOQ19 along with standard care in the treatment of mild-moderate COVID-19 patients: A double blind, randomized, placebo-controlled, multicentric trial*, Journal of Ayurveda and Integrative Medicine, doi:10.1016/j.jaim.2023.100778.

110. ***Siripongboonsitti*** et al., *Efficacy of Andrographis paniculata extract treatment in mild to moderate COVID-19 patients being treated with favipiravir: A double-blind, randomized, placebo-controlled study (APFaVi trial)*, Phytomedicine, doi:10.1016/j.phymed.2023.155018.

111. ***Shanker*** et al., *A randomized controlled pilot study of add-on therapy of CIM-MEG19 (standardized Andrographis paniculata formulation) in mild to moderate COVID-19*, Phytomedicine Plus, doi:10.1016/j.phyplu.2022.100398.

112. ***Bhardwaja*** et al., *An integrative approach to clinical recovery for COVID-19 patients using an Ayurvedic formulation: A multicentric double-blind randomized control trial*, Research Square, doi:10.21203/rs.3.rs-1165680/v1.

113. ***Wanaratna*** et al., *Efficacy and Safety of Andrographis Paniculata Extract in Patients with Mild COVID-19: A Randomized Controlled Trial*, Archives of Internal Medicine

Research, doi:10.26502/aimr.0125.

114. **Prempree** et al., *SARS-CoV-2 Clearance from Andrographis paniculata, Boesenbergia rotunda, and Favipiravir among Mild COVID-19 Cases in Klong Prem Central Prison during Mid-2021: a Retrospective Study*, OSIR, 15:4, www.osirjournal.net/index.php/osir/article/download/311/251.

115. **Tanwettiyanont** et al., *Use of Andrographis paniculata (Burm.f.) Wall. ex Nees and risk of pneumonia in hospitalised patients with mild coronavirus disease 2019: A retrospective cohort study*, Frontiers in Medicine, doi:10.3389/fmed.2022.947373.

116. **Zhang (B)** et al., *Efficacy and safety of Xiyanping injection in the treatment of COVID-19: A multicenter, prospective, open-label and randomized controlled trial*, Phytotherapy Research, doi:10.1002/ptr.7141.

117. **Sa-ngiamsuntorn** et al., *Anti-SARS-CoV-2 Activity of Andrographis paniculata Extract and Its Major Component Andrographolide in Human Lung Epithelial Cells and Cytotoxicity Evaluation in Major Organ Cell Representatives*, Journal of Natural Products, doi:10.1021/acs.jnatprod.0c01324.

118. **Wanaratna (B)** et al., *Efficacy and safety of Andrographis paniculata extract in patients with mild COVID-19: A randomized controlled trial*, medRxiv, doi:10.1101/2021.07.08.21259912.

119. **Zhu** et al., *Efficient discovery of potential inhibitors for SARS-CoV-2 3C-like protease from herbal extracts using a native MS-based affinity-selection method*, Journal of Pharmaceutical and Biomedical Analysis, doi:10.1016/j.jpba.2021.114538.

120. **Baby** et al., *Exploring TMPRSS2 Drug Target to Combat Influenza and Coronavirus Infection*, Scientifica, doi:10.1155/sci5/3687892.

121. **He** et al., *Coinfection of COVID-19 and malaria: clinical profiles, interactions, and strategies for effective control*, Malaria Journal, doi:10.1186/s12936-025-05315-8.

122. **Adha** et al., *Herbal Medicines as Complementary Therapy for Managing Complications in COVID-19 Patients with Diabetes Mellitus*, Diabetes, Metabolic Syndrome and Obesity, doi:10.2147/dmso.s498774.

123. **Jabeen** et al., *Insights for Future Pharmacology: Exploring Phytochemicals as Potential Inhibitors Targeting SARS-CoV-2 Papain-like Protease*, Future Pharmacology, doi:10.3390/futurepharmacol4030029.

124. **Lei** et al., *Small molecules in the treatment of COVID-19*, Signal Transduction and Targeted Therapy, doi:10.1038/s41392-022-01249-8.

125. **Masoudi-Sobhanzadeh** et al., *Structure-based drug repurposing against COVID-19 and emerging infectious diseases: methods, resources and discoveries*, Briefings in Bioinformatics, doi:10.1093/bib/bbab113.

126. **Sharun** et al., *A comprehensive review on pharmacologic agents, immunotherapies and supportive therapeutics for COVID-19*, Narra J, doi:10.52225/narra.v2i3.92.

127. **Ramezani** et al., *Effect of herbal compounds on inhibition of coronavirus; A systematic review and meta-analysis*, Authorea, Inc., doi:10.22541/au.170668000.04030360/v1.

128. **Liu** et al., *Plant-derived compounds as potential leads for new drug development targeting COVID-19*, Phytotherapy Research, doi:10.1002/ptr.8105.

129. **He (B)** et al., *Recent advances towards natural plants as potential inhibitors of SARS-Cov-2 targets*, Pharmaceutical Biology, doi:10.1080/13880209.2023.2241518.

130. **Akter** et al., *Plausibility of natural immunomodulators in the treatment of COVID-19–A comprehensive analysis and future recommendations*, Heliyon, doi:10.1016/j.heliyon.2023.e17478.

131. **Rafiq** et al., *A Comprehensive Update of Various Attempts by Medicinal Chemists to Combat COVID-19 through Natural Products*, Molecules, doi:10.3390/molecules28124860.

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

133. **Abou Baker** et al., *An overview on medicinal plants used for combating coronavirus: Current potentials and challenges*, Journal of Agriculture and Food Research, doi:10.1016/j.jafr.2023.100632.

134. **Xue** et al., *Repurposing clinically available drugs and therapies for pathogenic targets to combat SARS-CoV-2*, MedComm, doi:10.1002/mco2.254.

135. **Srivastava** et al., *A Brief Review on Medicinal Plants-At-Arms against COVID-19*, Interdisciplinary Perspectives on Infectious Diseases, doi:10.1155/2023/7598307.

136. **Nasirzadeh** et al., *Inhibiting IL-6 During Cytokine Storm in COVID-19: Potential Role of Natural Products*, MDPI AG, doi:10.20944/preprints202106.0131.v1.

137. **Guerra** et al., *Critical Review of Plant-Derived Compounds as Possible Inhibitors of SARS-CoV-2 Proteases: A Comparison with Experimentally Validated Molecules*, ACS Omega, doi:10.1021/acsomega.2c05766.

138. **Jamalipour Soufi** et al., *Potential inhibitors of SARS-CoV-2: recent advances*, Journal of Drug Targeting, doi:10.1080/1061186X.2020.1853736.

139. **Uma Reddy** et al., *Multifaceted role of plant derived small molecule inhibitors on replication cycle of sars-cov-2*, Microbial Pathogenesis, doi:10.1016/j.micpath.2022.105512.

140. **Mukherjee** et al., *Role of medicinal plants in inhibiting SARS-CoV-2 and in the management of post-COVID-19 complications*, Phytomedicine, doi:10.1016/j.phymed.2022.153930.

141. **Ma** et al., *Screening S protein – ACE2 blockers from natural products: Strategies and advances in the discovery of potential inhibitors of COVID-19*, European Journal of Medicinal Chemistry, doi:10.1016/j.ejmech.2021.113857.

142. **c19early.org (D)**, c19early.org/timeline.html.

143. **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.

144. **Zhang (C)** 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.

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

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

147. **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.

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