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# Folic acid as placebo in controlled clinical trials of hydroxychloroquine prophylaxis in COVID-19: Is it scientifically justifiable?

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ABSTRACT

Using folic acid (FA) as placebo complicates the interpretation of the findings of few RCTs evaluating safety and efficacy of hydroxychloroquine prophylaxis in COVID-19. FA is found to bind to furin-protease and spike: ACE2 interface of SARS-CoV-2. In clinical studies, FA level was lowest among severe patients compared to mild and moderate disease. A single controlled study reported the benefit of combination of folic acid with Pyridoxine & cyanocobalamin in terms of clinical and laboratory cure parameters. One hypothesis associates the differences in geographical variation of disease severity with prevalence of methyl tertahydrofolic acid reductase (MTHFR) C677T polymorphism. Other possible domains, where FA is hypothesized to be beneficial are COVID-19 associated pulmonary hypertension and hyper-homocystinemia. So, scientific justification of using folic acid as placebo in COVID-19 trials seems scientifically not credible and this may be one of the major factors for failure of many agents. We need to be more careful in choosing our placebo especially when conducting a placebo controlled trial.

Folic acid is being used as placebo in few RTCs of evaluating safety and efficacy of hydroxychloroquine prophylaxis in COVID-19 [1]. However, one issue complicates the interpretation of the findings of these trials. Folic acid is gradually coming up an anti-COVID-19 agent. in a multimodal network-biology based study on SARS-CoV-2 human interactome, folic acid was predicted as a top candidate for drug repurposition (16th rank) [2] as agent for re-purposing against COVID-19. In in-silico studies, folic acid is found to bind to NSP-13 [3], furin [4], spike:ACE2 interface [5,6], PLPro [5], MPro [5] and NSP15 [5] of SARS-CoV-2, which are important targets from drug design perspective.

5,10 methyltetrahydrofolate is converted to 5-methyl-tetrahydrofolate by the enzyme methyl tertahydrofolic acid reductase (MTHFR) and thus helps in providing methyl groups for recycling of homocysteine to methionine. A single study hypothesized that the differences in geographical variation of COVID-19 disease severity may be related to the prevalence of (MTHFR) C677T popymorphism [7]. High dose folic acid is again hypothesized as a potential treatment of pulmonary hypertension (even when associated with COVID-19) and folic acid may help in the same by reversing uncoupling of eNOS and restoring NO production [8].

NSP14 of SARS-CoV is a guanine N7-methyl-transferase and is crucial for viral transmission and replication of SARS-CoV-2 and thus SARS-CoV-2 may use host S-adenosyl methionine (SAM) for viral RNA capping [9], utilization of which results in production of homocysteine, which enhance ACE-2 activation [10] and SARS-CoV-2 may take help of this enhanced activated ACE2 system to get entry to host cell [9]. High homocysteine is reported in the context of severe COVID-19 also or patients with progression of disease [11]. In clinical studies, folic acid is known to lower the level of homocysteine. In COVID-19 also, in a single controlled study, patients treated with Angiovit (Pyridoxine:4mg, folic acid;5mg & cyanocobalamin:6μg) showed reduced duration of fever and hospital stay, and normalized the level of homocysteine, D-Dimer and CRP [12]. In clinical studies, with 162 Israeli patients, Itelman et al found that folic acid level was lowest among severe patients compared to mild and moderate severity category [13].

So, scientific justification of using folic acid as placebo in COVID-19 trials seems scientifically not credible and this may be one of the major factors for failure of an anti COVID-19 agent.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

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*Abbreviations:* NSP, Non structural protein; MPro, main protease; PL Pro, Papaine-like protease; NO, Nitric oxide; HCQ, Hydroxychloroquine; RCT, Randomized controlled trial; ACE2, Angiotensin converting enzyme 2; eNOS, endothelial nitric acid synthase.

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Hardeep Kaur[a], Phulen Sarma[a], Anusuya Bhattacharyya[b], Manisha Prajapat[a], Subodh Kumar[a], Ajay Prakash[a], Bikash Medhi[a,*]
[a] *Department of Pharmacology, PGIMER, Chandigarh, India*
[b] *Department of Ophthalmology, GMCH-32 Chandigarh, India*

[*] Corresponding author at: Dept. of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
*E-mail address:* drbikashus@yahoo.com (B. Medhi).