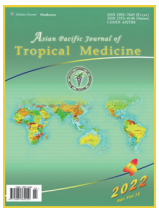

Letter to Editor

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# A hypothetical mechanism whereby malaria infection protects against COVID−19

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I would like to add new findings in support of a novel hypothesis stating that malaria infection may protect against COVID-19[1–3]. As this might facilitate understanding the underlying mechanism behind this association, the discovery of better preventive measures and therapeutic agents for the management of this terrible pandemic.

Just very recently, Huang *et al*.[4] provided the first experimental data to investigate the capacity of SARS-CoV-2 to infect and the virus is likely to be transmitted by mosquitoes. They showed that even under extreme conditions, SARS-CoV-2 is unable to replicate in most widely distributed mosquitoes namely *Aedes (Ae.) aegypti*, *Ae. albopictus* and *Culex quinquefasciatus*; therefore, the virus cannot be transmitted to people even in the unlikely event that a mosquito feeds upon a viremic host. Interestingly, in endemic areas where individuals experience repeated *Plasmodium falciparum* infections over many years, it is shown that monocytes of malaria-infected adults produce more IL-10 and express higher levels of the regulatory molecules CD163, CD206, Arginase-1 and TGM2, suggesting that past malaria exposure most possibly mitigated monocyte-associated immunopathology induced by other pathogens such as SARS-CoV-2[5].

Furthermore, Foo *et al*. recently showed that AEG12, a type of mosquito protein, is up-regulated in response to blood meals and flavivirus infection. AEG12 displays cytolytic and hemolytic activity by selectively delivering unsaturated fatty acid cargoes into phosphatidylcholine-rich lipid bilayers. Meanwhile, this property enables AEG12 to inhibit replication of coronaviruses. This novel finding unveils the mechanistic understanding of AEG12 function and provides the necessary implications for AEG12 possible application as a broad-spectrum therapeutic against cellular and viral targets[6].

Saliva of anopheline mosquitoes carries several antihemostatic compounds such as anophelins which are regarded as small protein thrombin inhibitors[7]. Another similar in-depth structural and functional analyses yielded detailed novel insights into the mechanism of thrombin inhibition by the antihemostatic salivary protein cE5 from mosquitoes such as *Anopheles gambiae*[8]. There are numerous studies reporting anti-thrombin property from other mosquitoes such as *Anopheles albimanus* saliva[9].

Figure 1 illustrates a consolidated update of the hypothetical pathways by which repeated malaria-infection might protect against COVID-19.

If this hypothesis[3] proves to be true, it will have deep environmental implications. For example, extensive mosquito control/elimination programs might have theoretically resulted in rapid rise in incidence and prevalence of COVID-19 in malaria-endemic areas. China implemented an extensive malaria elimination program in Hubei Province between 2005 and 2016[10], with Wuhan as the central outbreak point and capital city, I question whether mosquito elimination programs in China can meanwhile causally predispose the population to COVID-19 corollary to being malaria-naïve? Though this seems to be implausible-because besides Wuhan, many other provinces also implemented extensive mosquito control/elimination programs-this question may merit further research both retrospectively (by data analysis) and prospectively (by proper designs) and may be insightful for researchers.

## Conflict of interest statement

The author declares that there is no conflict of interest.

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The author is an independent researcher who is a member of Advisory Board of the Nutrition Society, London, UK and also a member of the American Physical Society, USA.



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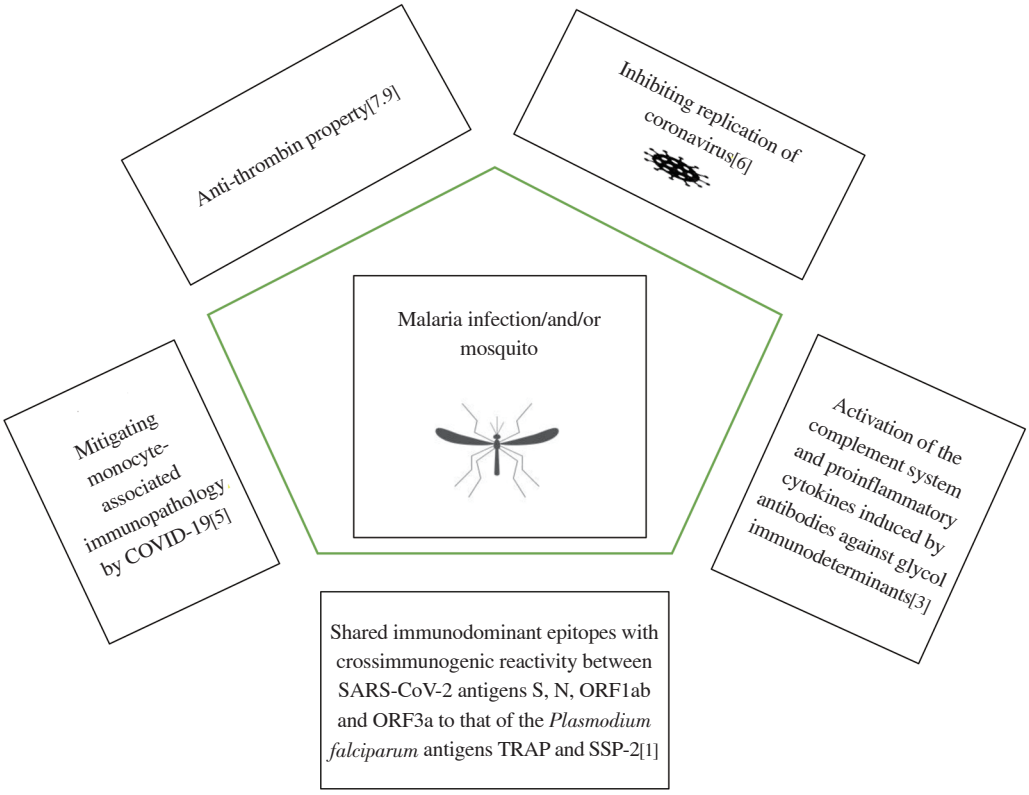


**Figure 1.** Hypothetical pathways whereby repeated malaria-infection might protect against COVID-19.

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## Author's contributions

R.R. developed the theoretical formalism and fully contributed to the writing of the letter.

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