This study focus on repurposed drugs against SARS-CoV-2. The authors found two drugs quinacrine and suramin could inhibit SARS-CoV-2 $3CL^{pro}$ activity competitive and non-competitive, respectively. Different biomedical experiments were carried out to prove the binding between the drugs with SARS-CoV-2 $3CL^{pro}$. And the two drugs were further proved to work synergistically by inhibiting SARS-CoV-2 $3CL^{pro}$ activity. Recent study from other groups indicate that suramin inhibits SARS-CoV-2 by targeting its RdRp, and quinacrine may target ACE2 and furin to inhibit SARS-CoV-2. So it's kind of interest that the authors here declare that quinacrine and suramin could also bind to SARS-CoV-2 $3CL^{pro}$ and inhibit its activity.

Recommendations and suggestions

1. The experiments were well designed and fully supported the conclusion that quinacrine and suramin could bind SARS-CoV-2 $3CL^{pro}$ and inhibit its activity. However, the study lack of validation in in vitro cell models. Although, there are published data show that quinacrine and suramin could inhibit SARS-CoV-2 replication in cell models, the inhibiting effects were due to the drugs binding to RdRp and ACE2/furin, respectively, rather than $3CL^{pro}$. Thus, I am wondering how the authors could prove that quinacrine and suramin can inhibit SARS-CoV-2 replication in cell models by impairing $3CL^{pro}$ activity.

2. The two drugs have already been reported to inhibit SARS-CoV-2 replication by targeting RdRp and ACE2/furin, respectively. So I'm curious about how the authors could come up with the idea to test their effects on $3CL^{pro}$.

3. The authors predicted the possible binding mode of the two drugs against $3CL^{pro}$, and also the key residues involved in the binding. However, these results are speculative, and I would recommend further mutagenesis study which will make the conclusion more convincing.

4. Line21. Johnson & Johnson vaccine are not included.

5. Line 76. Same as above.

6. Line 336. $3CLp^{ro}$ should be replaced by $3CL^{pro}$.