



REVIEW ARTICLE

Potential role of flavonoids against SARS-CoV-2 induced diarrhea

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ABSTRACT

COVID-19, caused by the SARS-CoV-2 virus, can lead to massive inflammation in the gastrointestinal tract causing severe clinical symptoms. SARS-CoV-2 infects lungs after binding its spike proteins with alveolar angiotensin-converting enzyme 2 (ACE2), and it also triggers inflammation in the gastrointestinal tract. SARS-CoV-2 invades the gastrointestinal tract by interacting with Toll-like receptor-4 (TLR4) that induces the expression of ACE2. The influx of ACE2 facilitates cellular binding of more SARS-CoV-2 and causes massive gastrointestinal inflammation leading to diarrhea. Diarrhea prior to COVID-19 infection or COVID-19-induced diarrhea reportedly ends up in a poor prognosis for the patient. Flavonoids are part of traditional remedies for gastrointestinal disorders. Preclinical studies show that flavonoids can prevent infectious diarrhea. Recent studies show flavonoids can inhibit the multiplication of SARS-CoV-2. In combination with vitamin D, flavonoids possibly activate nuclear factor erythroid-derived-2-related factor 2 that downregulates ACE2 expression in cells. We suggest that flavonoids have the potential to prevent SARS-CoV-2 induced diarrhea.

Keywords: SARS-CoV-2; diarrhea; flavonoids; quercetin

INTRODUCTION

Two severe coronavirus incidences emerged before the present pandemic. The first SARS-CoV or Severe Acute Respiratory Syndrome coronavirus was reported from Guangdong Province in China in mid-November 2002 (Wang & Eaton, 2007). The second, known as Middle East Respiratory Syndrome coronavirus or MERS-CoV was reported from the Middle East in 2012 (Sharif-Yakan & Kanj, 2014). The third coronavirus, SARS-CoV-2, which is the cause of the present pandemic, was reported from Wuhan, China at the tail end of December 2019 (da Costa *et al.*, 2020). Four other coronaviruses are known to affect humans, namely HCoV-229E, HCoV-NL63, HCoV-OC43 and HKU1, but they cause mild upper respiratory tract diseases, which rarely progress to any serious conditions and fatalities (Liu *et al.*, 2021a).

COVID-19, caused by the severe acute respiratory syndrome (SARS)-CoV-2 has led to the largest pandemic of the 21st century. As of July 25, 2021, the recorded COVID-19 cases are 194,583,817 that caused 4,171,749 deaths globally (<https://www.worldometers.info/coronavirus/>). To date, at least six vaccines have received emergency approval, but there is significant concern on the safety, efficacy, and

feasibility of vaccinating twice approximately 7.8 billion people worldwide. There is also concern about the acceptability of new vaccines, as recent limited surveys showed that not all people wished to vaccinate themselves against SARS-CoV-2 (Dodd *et al.*, 2021). Moreover, COVID-19 vaccines will provide preventative measures against SARS-CoV-2 for a limited time.

COVID-19 and diarrhea

Diarrhea appears to be a common feature in a certain percentage of infected patients, and this has been observed in SARS, MERS, and SARS-CoV-2 infections. Around 10.6 percent of patients reportedly had diarrhea during SARS infection; the percentage rose to 30% during MERS infection, the latter being much more deadly than SARS (D'Amico *et al.*, 2020).

The COVID-19 induced gastrointestinal manifestations share similar viral or bacterial infection pathways in humans. Briefly, the virus or viral RNAs triggers the body's immune system that activates rapidly to prevent viral antigens and their multiplications inside the body. SARS-CoV-2 infects human lungs after binding its spike proteins with alveolar angiotensin-converting enzyme 2 (ACE2) and causes an increase of angiotensin II in the bloodstream that triggers

the release of chemokines and activates both cytotoxic (CD8+) and helper (CD4+) T-cell lymphocytes and activity of macrophages and NK cells (Ye *et al.*, 2020). Cytotoxic T-cells produce IL-2 and IFN γ , and helper T-cells release proinflammatory cytokines such as IL-4, IL-17, IL-21, and IFN γ . It causes massive mucus release and severe acute respiratory distress syndrome. The increased cytokines in the bloodstream and SARS-CoV-2 invasion in the gastrointestinal tract by interacting with gut ACE2 receptors cause gastrointestinal dysbiosis. SARS-CoV-2 also binds with Toll-like receptors (TLR) (especially with TLR4). A healthy gut contains reduced TLR4, but increased expression of TLR4 has been reported under inflammatory conditions (Dheer *et al.*, 2016; Hug *et al.*, 2018). SARS-CoV-2 Spike protein binding with TLR4 may cause increased expression of ACE-II receptors in alveoli's cellular surfaces and thus increase the intensity of infection (Aboudounya & Heads, 2021). Increased inflammation causes significant damage in the single-cell layers of intestinal mucosa and activations of macrophages, NK-cell, and T-cell lymphocytes to release a massive amount of proinflammatory cytokines and chemokines. The imbalance in the gut microbiota and damage of mucosal cellular barriers facilitate multiplications of SARS-CoV-2 and translocation into other tissues. This dysbiosis triggers diarrhea, bloody diarrhea, mucus secretions, and gastrointestinal pain (Figure 1).

Interestingly, an analysis of COVID-19 severity found a more significant percentage of diarrheal occurrence in severe patients than in less severe patients (5.8% versus 3.5%, respectively) (Guan *et al.*, 2020). The opposite also holds true; patients with diarrhea followed by infection with the SARS-CoV-2 virus were more likely to develop acute respiratory distress and require mechanical ventilation than COVID-19 non-diarrheal patients (6.76% versus 2.08%, respectively) (Jin *et al.*, 2020). This would suggest a gut-lung axis where changes in the gut biome because of COVID-19 would trigger a systemic cytokine release, which may exacerbate COVID-19 induced lung distress. On the other hand, COVID-19 does cause changes in the gut microbiota with a decrease in beneficial microorganisms and an increase in opportunistic pathogens, which can be discerned in the fecal samples of COVID-19 patients (Zuo *et al.*, 2020).

Age, mode of delivery (normal or Caesarian), consumption of nutrients, antioxidants, natural antimicrobial compounds, and probiotics, along with mental well-being, can contribute to gastrointestinal microbiota (Thursby & Juge, 2017), preventing diarrhea and increase immunity against common viral and bacterial infections. Flavonoids are secondary metabolites of plants. Flavonoids such as quercetin, hesperetin, baicalin, luteolin, gallicocatechin and epigallocatechin gallate are antioxidants, anti-inflammatory, and antimicrobial agents. These compounds can boost the immunity of people against viruses as they inhibit some enzymes (e.g. Papain Like protease (PLpro), RNA-dependent RNA polymerase (RdRp), Chymotrypsin-Like Protease (3CLpro), and NTPase/helicase), which are essential for the replication and transcription of SARS-CoV-2 (Russo *et al.*, 2020; Mouffouk *et al.*, 2021). Flavonoids like epigallocatechin-3-gallate (from green tea) along with vitamin D3 consumption are believed to activate the nuclear factor erythroid-derived 2-related factor 2 (Nrf2 transcription factor) that down-regulates ACE2 expression from the cellular surfaces and may protect cells against SARS-CoV-2 infection (Mendonca & Soliman, 2020). This interaction would help develop immunity against infections, reduce oxidative stress, and release proinflammatory cytokines caused by the virus (Figure 1).

Role of flavonoids against COVID-19 induced diarrhea

Flavonoids can act against COVID-19 induced diarrhea in three ways. It can alleviate COVID-19, it can alleviate diarrhea, or it can alleviate both COVID-19 and diarrhea. Amelioration of acute and chronic diarrhea by flavonoids has been attributed to reducing intestinal motility and reducing chronic gut intestinal inflammatory injury (Gálvez *et al.*, 2001). It has been shown repeatedly that various flavonoids can ameliorate diarrhea through a number of mechanisms. For instance, *Psidium guajava* has been traditionally used to prevent gastrointestinal disorders in many countries, and flavonoids like quercetin (from *Psidium guajava*) prevent *Shigella* and *Escherichia coli*-induced diarrhea (Hirudkar *et al.*, 2020). Incidentally, quercetin may also inhibit viral entry into host cells and *in silico* studies have shown that the flavonoid can inhibit Mpro of SARS-CoV-2 (Brito *et al.*, 2021). A similar observation is applicable also for baicalein, a flavonoid present in *Scutellaria baicalensis*. Baicalein has been shown to inhibit SARS-CoV-2 and its 3C-like protease replication *in vitro* (Liu *et al.*, 2021b), and suppress colonic motility (Kim *et al.*, 2019). In senna extract-induced acute diarrhea in BALB/c mice, flavonoids from *Malus pumila* leaves lowered diarrhea index and decreased the levels of inflammatory cytokines like interleukin 6 (IL-6), interleukin 12 (IL-12), and tumor necrosis factor- α (TNF- α). This ameliorating effect was reported to be caused by ten flavonoids, namely rutin, hyperoside, isoquercitrin, taxifolin, quercitrin, hesperidin, myricetin, baicalin, neohesperidin dihydrochalcone and quercetin (Yi *et al.*, 2020). Incidentally most of these flavonoids have been variously reported to be able to bind and inhibit various integral proteins of SARS-CoV-2 necessary for viral entry and replication in human cells (Alzaabi *et al.*, 2021). Thus, flavonoids can have a dual effect of alleviating diarrhea through inhibitory effects on causative agents (like SARS-CoV-2) as well as contractile inhibitions (Zhang *et al.*, 2003).

Quercetin, Luteolin and Quercetin 7-rhamnoside showed efficacy against porcine epidemic diarrhea virus (Choi *et al.*, 2009), as these compounds interfere the viral replication at initial stage and thus similarly it can work against SARS-CoV-2 induced diarrhoea. *In silico* studies exhibit that quercetin interacts firmly with SARS-CoV-2 spike proteins (Colunga Biancatelli *et al.*, 2020; Derosa *et al.*, 2021), and the compound showed potent inhibition against 3CLpro and PLpro enzymes of SARS-CoV-2 (Derosa *et al.*, 2021). Noticeably, its efficacy after oral consumption is limited by its poor solubility and bioavailability, which can be improved by developing a complex with phospholipids like lecithin as it was done in a randomized clinical trial (Di Pierro *et al.*, 2021). In this clinical study, daily oral intake of 1 g quercetin improved symptoms, reduced fatigue, improved appetite and overall health conditions of non-critical COVID-19 patients (Di Pierro *et al.*, 2021). Flavonoids such as quercetin can inhibit interleukin (IL)-6, IL-17, tumor necrosis factor (TNF)- α and other proinflammatory markers from inflamed GI lumen or other organs (especially lung and other parts of the respiratory system) affected by viral or bacterial infections, which are major symptoms of COVID-19 (Huang *et al.*, 2020; Bastaminejad *et al.*, 2021). The compound (quercetin) also displayed efficacy against lung infections (Heinz *et al.*, 2010; Wang *et al.*, 2018).

Nigella sativa oil or extract (key flavonoids: Quercetin, kaempferol and quercitrin) showed efficacy against diarrhea and protective effects on rodents' gastric and cecal tissues (Eida *et al.*, 2015; Toma *et al.*, 2015). Another clinical study showed (ID: NCT04401202 in ClinicalTrials.gov) that oral treatment of essential oil of *Nigella sativa* (500 mg/capsule,

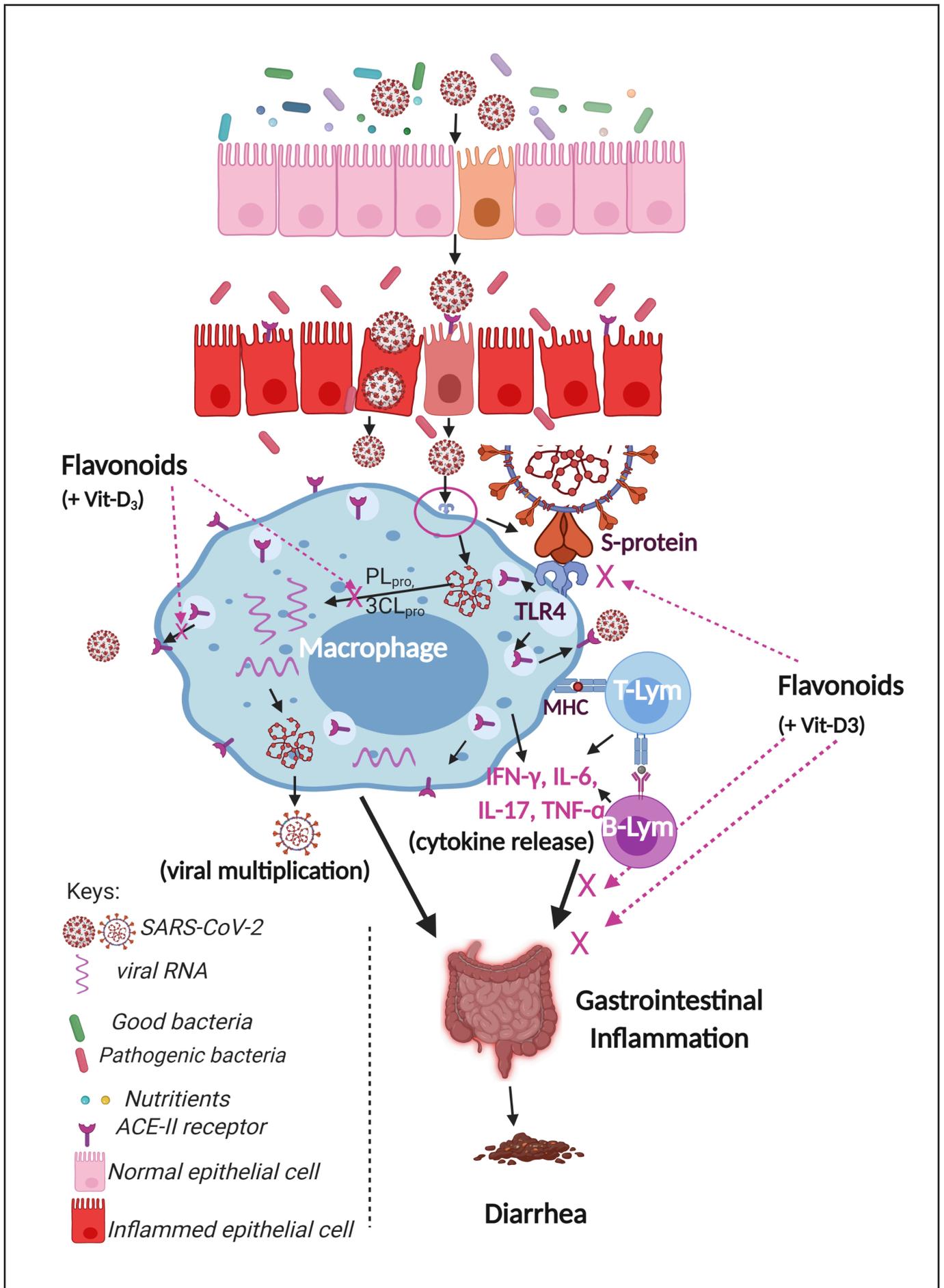


Figure 1. Role of flavonoids against SARS-CoV-2 induced diarrhea (made with biorender.com).

Table 1. Role of flavonoids against SARS-CoV-2 associated infections

Names of flavonoids	Role against SARS-CoV-2	Reference
(-)-Epigallocatechin-3-O-gallate (EGCG)	Inhibited SARS-CoV-2 spike protein interaction with ACE2 receptor (<i>in silico</i>)	(Wang <i>et al.</i> , 2021)
(-)-Gallocatechin gallate (GCG)	Inhibited 3CL _{pro} and PL _{pro} proteins (<i>in silico</i>)	(Swargiary <i>et al.</i> , 2020)
Kaempferol	Inhibited COVID-19 enzymes 3CL _{pro} and PL _{pro} (<i>in silico</i>)	(He <i>et al.</i> , 2020; Khan <i>et al.</i> , 2021)
Luteolin	1. Reduced proinflammatory cytokines (e.g. TNF- α , IL-1 β , IL-6, and so on) 2. Prevented Toll-like receptor 4 (TLR4)/TNF receptor-associated factor 6/nuclear transcription factor- κ B (NF- κ B) signaling pathway of inflammation	(Yang <i>et al.</i> , 2020)
Puerarin	1. Inhibited SARS-CoV-2 spike protein interaction with ACE2 receptor (<i>in silico</i>) 2. It suppressed inflammatory markers (e.g. TNF- α , IL-2, IL-17, mitogen-activated protein kinase (MAPK), peroxisome-proliferator activator receptor γ (PPAR γ) and nitric oxide synthase 3 (NOS3))	(Qin <i>et al.</i> , 2021)
Quercetin	Inhibited SARS-CoV-2 spike protein interactions with ACE2 receptor (<i>in silico</i>)	(Di Pierro <i>et al.</i> , 2021)
Quercetin	Inhibited COVID-19 enzymes 3CL _{pro} and PL _{pro} (<i>in silico</i>)	(Derosa <i>et al.</i> , 2021)
Quercetin	Reduced proinflammatory cytokines (e.g. IL-6, IL-17, TNF- α)	(Bastaminejad & Bakhtiyari, 2020; Huang <i>et al.</i> , 2020)
Luteolin	Improved smell or taste disorders of patients with post-COVID-19 infections (clinical study)	(D'Ascanio <i>et al.</i> , 2021)
Quercetin	Quercetin reduced the length of hospital stay and severity of infections in SARS-CoV-2 infected patients with mild and moderate symptoms (clinical study)	(Di Pierro <i>et al.</i> , 2021)

twice daily) for ten days moderately improved symptoms of COVID-19 in non-critical patients against patients treated with the standard form of care (Koshak *et al.*, 2020). COVID-19 patients treated with quercetin-rich traditional Chinese herbs reportedly experienced improved immunity against SARS-CoV-2 and less hospitalization (Luo *et al.*, 2020). Various other flavonoids like (-)-Gallocatechin gallate (GCG), (-)-Epigallocatechin-3-O-gallate (EGCG), Kaempferol, Luteolin, and Puerarin showed promising effects against COVID-19 infections (Table 1). These flavonoids act against the SARS-CoV-2 by three major ways: (1) inhibition of interactions between ACE-2 of host cells and SARS-CoV-2 spike proteins, (ii) inhibition of SARS-CoV-2 protease enzymes like 3CL_{pro} and PL_{pro} and its replication process, and (iii) inhibition of proinflammatory cytokines (e.g. IL-6, IL-17, TNF- α) caused by SARS-CoV-2 infection (Figure 1, Table 1). SARS-CoV-2 produces inflammation in gastrointestinal tract, lungs and other organs. Flavonoids have antidiarrheal, anti-inflammatory and antiviral properties, as shown in preclinical, preliminary clinical and *in silico* studies (Colunga Biancatelli *et al.*, 2020; Hirudkar *et al.*, 2020; D'Ascanio *et al.*, 2021; Derosa *et al.*, 2021; Di Pierro *et al.*, 2021). Flavonoids can not only alleviate inflammation through down-regulation of pro-inflammatory cytokines (Ginwala *et al.*, 2019) but also disrupt the lipid raft and inhibit TLR4 signaling (Pei *et al.*, 2020). Thus, flavonoid compounds may provide good therapeutic or supplementary reliefs against SARS-CoV-2 induced diarrhea (Figure 1).

To date, any evidence of the role of flavonoids against SARS-CoV-2 induced diarrhea is preliminary, and more importantly, *in vitro* preclinical and clinical studies are essential to explore the full potential of these compounds against SARS-CoV-2-induced diarrhea. On the other hand,

a number of flavonoids have anti-diarrheal effects, as demonstrated in non-COVID-19 patients (Chen *et al.*, 2014). It has been suggested that "flavonoids may ameliorate acute and chronic diarrhea by inhibition of intestinal motility and secretion and may also be helpful in reducing chronic inflammatory injury in the gut by protecting it from oxidative stress and preserving mucosal function" (Galvez *et al.*, 2001). Flavonoids have been used in traditional medicines over the centuries, and these compounds have antimicrobial, antiviral, and gastro-entero-protective effects and may be potential therapeutics for SARS-CoV-2-induced diarrhea. From that viewpoint, flavonoids deserve a closer examination for their potentially beneficial effects in improving COVID-19 prognosis when diarrhea is a comorbidity.

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Conflicts of interest

The authors declare that there are no conflicts of interest and the work has not been submitted elsewhere.

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