# GALLIUM MALTOLATE AS A POTENTIAL TREATMENT FOR COVID-19

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GALLIUM (Ga) is a metallic element that has demonstrated antiviral and anti-inflammatory activity. Gallium formulated as gallium nitrate for injection has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of hypercalcemia of malignancy. Gallium nitrate is not, however, absorbed orally. Gallium maltolate (GaM), a small molecule that has been studied in several FDA-approved Phase 1 clinical trials in the U.S., is absorbed orally and may also be administered via inhalation into the lungs. Based on its known therapeutic activities, oral GaM is hypothesized to prevent disease progression in COVID-19 patients, therefore obviating ICU admission, shortening the duration of hospitalization, and improving survival rates. Because GaM has been shown safe and well tolerated in clinical trials, can be manufactured at low cost in large quantities, and is administered orally once per day, it is well suited to large-scale distribution and use.

An *in vitro* assay found GaM effective at inhibiting the replication of SARS-CoV-2 in Vero E6 cells. The results, shown in Figure 1, indicate that the GaM concentration needed to inhibit viral replication by 50% ($EC_{50}$) is about 14 μM, a level attainable with orally administered GaM. No cytotoxicity was observed up to at least 200 μM.

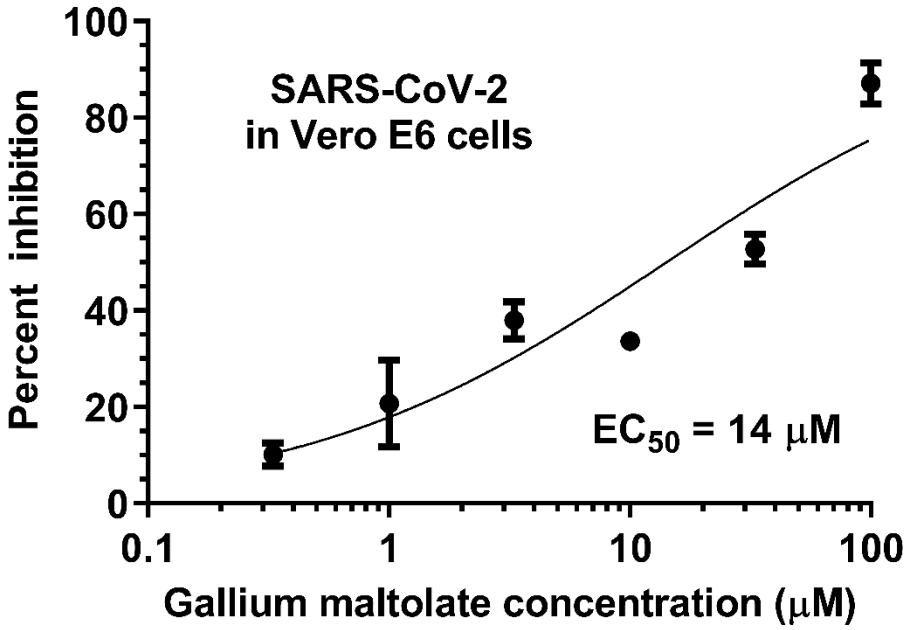


Figure 1. Inhibition of SARS-CoV-2 replication in Vero E6 cells by gallium maltolate at several concentrations. The infected cells were exposed to the gallium maltolate for 24 hours, then the cell media were assayed for viral RNA using quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) methods.

Antiviral activity of Ga has also been demonstrated in cell cultures infected with influenza A virus (Enkirch et al., 2019), and HIV (Stapleton et al., 1999). The mechanisms for the antiviral activity can be hypothesized based on Ga and zinc (Zn) being adjacent elements in the periodic table, so they have many similar properties. Zinc has efficacy against some RNA viruses, including coronaviruses and hepatitis E virus, possibly in part by acting against the RNA-dependent RNA polymerase (e.g., te Velthuis et al., 2010; Kaushik et al., 2017). SARS-CoV-2 is dependent on the host enzyme furin, which can be inhibited by Zn (Podsiadlo et al., 2004). On the other hand, Zn is essential for entry into cells by RNA viruses, including coronaviruses (Phillips et al., 2017; York et al., 2007), and it is probable that Ga would interfere with Zn-dependent cell entry.

Iron deprivation has been proposed as an effective means to inhibit the replication of SARS-CoV-2 (Liu et al., 2020). Because Ga is a potent competitor of ferric iron (Bernstein, 1998; Chitambar, 2016), this is another mechanism by which GaM may act against the virus.

The selective anti-inflammatory activity of Ga may also be highly beneficial for COVID-19 patients. Ga potently attenuates excessive pro-inflammatory macrophage activity, but does not suppress beneficial immune reactions (Bernstein, 1998; de Albuquerque Wanderley Sales, 2020). In addition, Ga inhibits proliferation and activation of pro-inflammatory T helper type 1 (Th-1) cells, but not of pro-antibody Th-2 cells (Bernstein, 1998). In a murine model of septic shock, which is an often-lethal inflammatory condition that has many similarities to severe late-stage COVID-19, Ga provided clear ameliorating effects (Krecic-Shepard et al., 1999). Ga is, therefore, expected to prevent or mitigate the dangerous hyperinflammatory reactions associated with severe COVID-19.

A large, randomized, controlled clinical trial found that dexamethasone, a potent anti-inflammatory steroid, significantly decreased the death rate in patients with severe COVID-19 (RECOVERY Collaborative Group, 2020). A small study in rats with adjuvant-induced arthritis, a generally lethal inflammatory condition, found orally administered GaM to be at least as effective at dexamethasone at inhibiting inflammation (Figure 2).

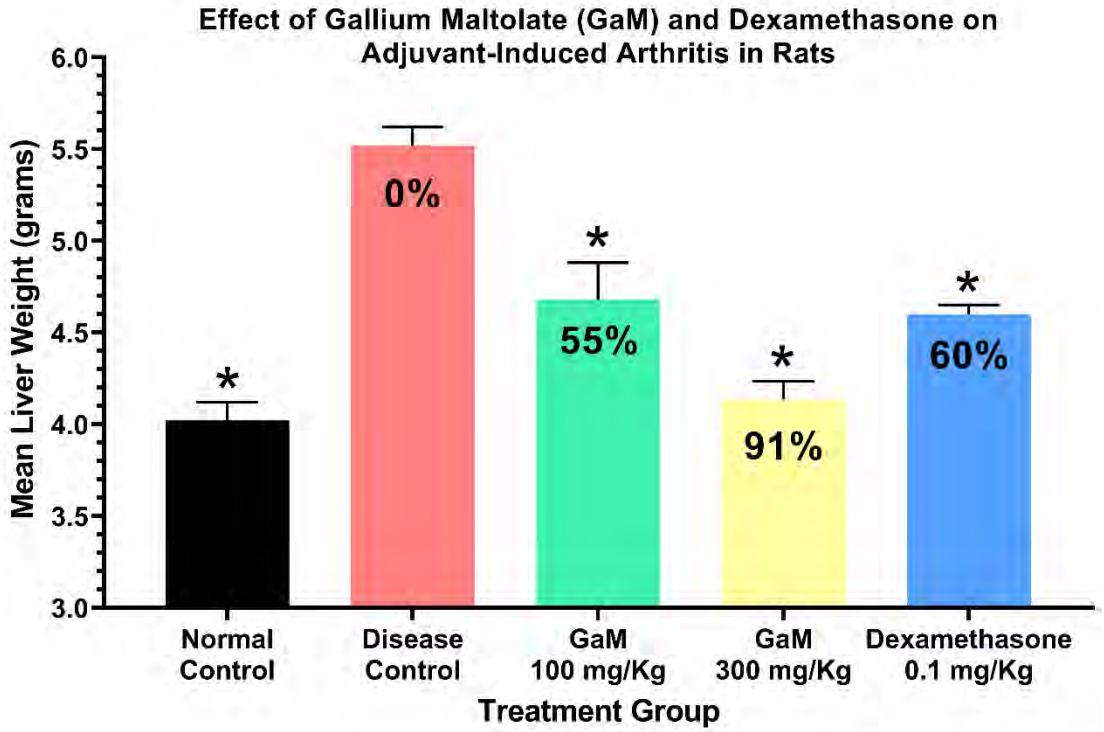


Figure 2. Effects of oral gallium maltolate at 100 and 300 mg/Kg/day and of oral dexamethasone at 0.1 mg/Kg/day for 21 days on liver enlargement in rats with adjuvant-induced arthritis. Percent inhibition of liver weight increase is indicated. Asterisks indicate statistically significant differences ($p < 0.05$) from disease control. Experiments carried out under the supervision of Dr. Alison Bendele at the University of Colorado, Boulder.

Gallium maltolate has shown no dose-limiting or other significant toxicity in clinical trials, even when administered at very high oral doses for many weeks at a time (Bernstein, 2013).

Substantial amounts of GaM are available, which have been manufactured in accordance with current Good Manufacturing Practice (cGMP) regulations. Clinical trials in COVID-19 patients could thus begin soon. Upon request, a synopsis can be provided regarding a proposed clinical trial to investigate the efficacy of GaM in hospitalized patients with confirmed COVID-19, using 2 g/day x 10 days of orally administered GaM versus placebo.

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