

# The Potential Role of Xanthohumol in SARS-CoV-2 Treatment—Globally Accessible and Economically Viable

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**Abstract:** Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in significant global morbidity and mortality and there are a lack of effective therapies. There is a need for treatment which could be available for all in the global community, as well as within hospital, which is efficacious, affordable and safe. Xanthohumol from hop extract has been shown in vitro and in vivo to have antiviral properties against RNA and DNA viruses but also importantly anti-inflammatory properties against severe respiratory syndrome via inhibition of NFκB dependent pathways. We review the evidence for xanthohumol to be considered as a treatment for SARS-CoV-2 infection. We need an economic and globally available therapy and thinking beyond the traditional is important; thus, studies are warranted to assess efficacy of xanthohumol against SARS-CoV-2.

**Keywords:** COVID-19, SARS-CoV-2, xanthohumol, hops

## Plain Language Summary

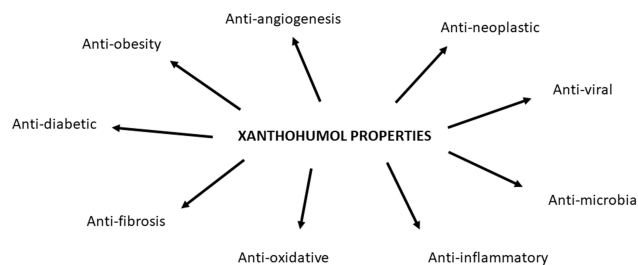
Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in significant global illness and death and there are a lack of effective therapies. There is a need for treatment which could be available for all in the global community, as well as within hospital, which is not only effective, but also affordable and safe. Xanthohumol is a hop extract which has been shown in experiments to have antiviral properties against different viruses and importantly, anti-inflammatory properties. We review the evidence for xanthohumol to be considered as a globally available and cheap treatment for SARS-CoV-2 infection. Thinking beyond the traditional is important and studies are warranted to assess treatment benefit of xanthohumol against SARS-CoV-2.

## Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in significant global morbidity and mortality with subsequent major economic and social consequences, however there is a dire lack of effective therapies.<sup>1</sup> We need to consider all potential therapeutic options assessing their efficacy and safety but also availability and cost so that the global community could utilize a cheap and effective therapy.

Xanthohumol is a natural substance isolated from *Humulus lupulus* (Hops). Its molecular formula is C<sub>21</sub>H<sub>22</sub>O<sub>5</sub>. Increasing studies suggested benefits of

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**Figure 1** Xanthohumol properties.

xanthohumol in a variety of conditions, including antineoplastic, antiviral, anti-inflammatory and anti-oxidative properties<sup>2</sup> (Figure 1). We review the potential of xanthohumol not only as a candidate for antiviral therapy, but also to prevent excessive activation of inflammation as well as protect organs when disease progresses.

## Methods

A PubMed search was performed for publications from 1990 through 2020, using the following key words, including both medical subject heading (MeSH) terms and free language words/phrases: “COVID-19”, “SARS-COV-2”, “hop extract”, “xanthohumol”, “antiviral” and “alternative medicine”. Articles that were relevant to antiviral effects of hop extract were assessed for eligibility as full-text articles. No language restriction was applied. Reference lists from studies selected by the electronic search were manually searched to identify further relevant reports. The quality and strength of the results were considered.

## Antiviral Effect of Xanthohumol

Xanthohumol has been shown to have a wide range of antiviral effects in many *in vitro* and *in vivo* studies against both DNA and RNA viruses such as bovine viral diarrhea virus (BDDV), cytomegalovirus (CMV), herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), porcine reproductive and respiratory syndrome virus (PRRSV).<sup>3–5</sup> Infection with PRRSV was first identified in the 1980s in North America and in China in 2006 resulting in a devastating epidemic in pigs.<sup>4,5</sup> This single-stranded RNA virus infection shares similarities with SARS-CoV-2 with high fever, significant morbidity and severe respiratory disease resulting in high mortality. In view of these similar clinical features with SARS-COV-2, we present a rationale related to antiviral activity, anticytokine effect and general metabolic interactions predominantly related to PRRSV infection with potentially translatable mechanisms to SARS-COV-2. A previous study using

high-throughput screening method in 386 natural compounds found that xanthohumol was the most effective in inhibiting PRRSV.<sup>5</sup>

*In vitro* studies showed that xanthohumol could effectively inhibit replication of a BVDV, CMV, HSV-1, HSV-2 and PRRSV with a low inhibitory concentration required to reduce viral replication by 50% ranging from 1.7–7.0  $\mu$ M and a high toxic concentration suggestive of potentially good therapeutic efficacy.<sup>3–5</sup> *In vivo* study also showed that xanthohumol was effective in reducing virus level in PRRSV infected pigs in a dose-dependent manner.<sup>4</sup>

## Anti-inflammatory Effect of Xanthohumol

The cytokine storm of SARS-CoV-2 infection maybe one of the major causes leading to severe respiratory syndrome. Severe COVID-19 is found associated with increased levels of several cytokines, such as interleukin-6 (IL-6).<sup>6</sup> A recent study found IL-6 blockade could reduce the requirement for ICU admission and mechanical ventilation in patients with COVID-19.<sup>7</sup> This promising result demonstrates the importance of abrogating inflammation or at least, anti-IL-6 in COVID-19. In addition, an earlier study on SARS-CoV in 2014 found that inhibiting inflammation could significantly prolong the survival of mice infected with SARS-CoV and that activation of NF- $\kappa$ B, upstream of IL-6, played a major role in SARS-CoV-induced inflammation.<sup>8</sup>

Increasing numbers of studies indicate that xanthohumol can inhibit NF- $\kappa$ B pathway and also inhibit the NF- $\kappa$ B-dependent pro-inflammatory gene expressions, such as IL-6, IL-1, IL8 and TNF- $\alpha$ .<sup>4,5,9</sup> There was also a dose-dependent inhibition of lung inflammatory infiltrate by xanthohumol in PRRSV infection in pigs and significant improvement in postmortem pathology in xanthohumol-treated pigs.<sup>4</sup> There may be a paradigm with SARS-CoV-2-induced lung “ARDS”-type inflammation and ability for xanthohumol to potentially inhibit NF- $\kappa$ B-dependent inflammation in severe COVID-19 patients.

## Other Biological Effects

Patients with COVID-19 usually manifest dysfunction of multiple organs such as impairment of liver function and aberrant blood glucose. Fasting blood glucose level was recently found to be significantly associated with poor outcome of patients with COVID-19.<sup>10</sup> The efficacy of xanthohumol to protect against cell injury, and normalize blood glucose was investigated and validated by a number

of studies.<sup>2,11–13</sup> Xanthohumol could inhibit activation of the transcription factor NF- $\kappa$ B and expression of NF- $\kappa$ B dependent proinflammatory genes in hepatocyte and hepatic stellate cells.<sup>14</sup>

## Safety and Pharmacokinetics of Xanthohumol in Humans

Xanthohumol is in essence a widely used natural food supplement. No adverse effects were reported in a previous clinical trial which studied the safety and pharmacokinetics of xanthohumol in 24 men and 24 women.<sup>15</sup> Xanthohumol can be converted into 8-prenylnaringenin (8-PN) which is one of the most potent phytoestrogens and a study further investigated the potential adverse effect of hop extract including xanthohumol on sex hormones and found that xanthohumol did not affect sex hormones or blood clotting.<sup>16</sup>

## Scalability and Accessibility of Xanthohumol

Xanthohumol is currently available from hop extract and there are commercially available, over the counter, high concentration capsules of xanthohumol. The potential is that xanthohumol could be manufactured generically from hop extract and could be available cheaply and globally for treatment of SARS-CoV-2. Higher concentrations can be achieved from production of synthetic xanthohumol but this may be a more expensive process although equally available. As yet unexplored, in vitro studies on SARS-CoV-2 infected cells are planned to assess antiviral and anti-cytokine effects and appropriately powered clinical trials are needed.

## Conclusion

There is an urgent need for a treatment for SARS-CoV-2 which would be available within the global community, as well as within hospital, which is efficacious, affordable and safe. Xanthohumol has been shown to have antiviral efficacy in other DNA and RNA virus infections and also anti-inflammatory properties, in addition to having other beneficial metabolic effects. Thinking beyond the traditional is important and studies are warranted to assess the efficacy of xanthohumol against SARS-CoV-2, similarly other “alternative” therapies need to be explored.

## Disclosure

Martyn Caplin reports acting as a medical advisor to a dietary supplements company, ProfBiotics AltruVita and

has received honoraria for academic advisory boards and meeting from Novartis, Ipsen and Pfizer. The authors report no other potential conflicts of interest in this work.

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