

# Randomised clinical trial to determine the safety of quercetin supplementation in patients with chronic obstructive pulmonary disease

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## ABSTRACT

**Introduction** Quercetin is a plant flavonoid and has potent antioxidant and anti-inflammatory properties. In a preclinical model of chronic obstructive pulmonary disease (COPD), quercetin reduced markers of both oxidative stress and lung inflammation and also reduced rhinovirus-induced progression of lung disease. Although quercetin appears to be an attractive natural alternative to manage COPD, the safety of quercetin supplementation in this population is unknown.

**Methods** We recruited COPD patients with mild-to-severe lung disease with FVE1 ranging between >35% and <80% and supplemented with either placebo or quercetin at 500, 1000 or 2000 mg/day in a dose-escalation manner. The duration of quercetin supplementation was 1 week.

**Results** Patients had no study drug-related severe adverse events based on blood tests, which included both complete blood counts and evaluation of comprehensive metabolic panel. One of the patients reported mild adverse events included gastro-oesophageal reflux disease, which was observed in both placebo and quercetin groups.

**Conclusions** Quercetin was safely tolerated up to 2000 mg/day as assessed by lung function, blood profile and COPD assessment test questionnaire.

**Trial registration number** NCT01708278

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the major cause of mortality and morbidity in the USA and growing cause of chronic disease globally. The current pharmacological therapies for COPD, such as corticosteroids and  $\beta$ 2 agonists, may provide symptom relief, reduce the rate of exacerbations, hospitalisations and possibly mortality, but despite this, many patients still experience symptoms, exacerbations and disease progression. Although the exact cellular mechanisms underlying COPD pathogenesis are not completely understood, the consensus is that oxidative stress and inflammation induced by exposure to cigarette smoke or other environmental or occupational hazards

are responsible for development of COPD.<sup>1</sup> Therefore, a nutraceutical with potent antioxidant and anti-inflammatory properties and relatively few side effects could be an attractive treatment option for COPD.

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a dietary flavonoid and has potent antioxidant and anti-inflammatory properties. We have demonstrated that oral treatment with a low dose of quercetin decreases inflammation, oxidative stress and matrix metalloproteinase production in a mouse model of COPD.<sup>2</sup> Quercetin supplemented diet also alleviates rhinovirus-induced lung inflammation in mice with COPD phenotype.<sup>3</sup> Recent studies have also demonstrated amelioration of hyperglycaemia, reduction of blood pressure and improvement of cardiovascular health by inhibiting platelet aggregation in experimental models.

Accumulating epidemiological evidence suggests that quercetin-rich diets are associated with lower incidence of asthma<sup>4</sup> and reduce disease severity in subjects with COPD.<sup>5</sup> Treatment with quercetin decreased markers of oxidative stress and inflammation in plasma of patients with pulmonary sarcoidosis, another chronic lung inflammatory disease driven by oxidative stress.<sup>6,7</sup> In another study, quercetin was shown to reduce blood pressure and plasma lipids in overweight or obese subjects with a high cardiovascular disease risk.<sup>8</sup> Daily intake of quercetin-rich onion peel extract (equivalent to 100 mg of quercetin/day) for 10 weeks decreased blood pressure, serum lipids and blood glucose levels in male smokers.<sup>9</sup> Additionally, treatment with quercetin for 12 weeks reduced the risk of acquiring upper respiratory infection in a large population of healthy adults.<sup>10</sup> The latter study also suggests that quercetin treatment in healthy volunteers has no adverse



effects. Furthermore, a meta-analysis of randomised controlled trials indicated treatment with quercetin reduces plasma C reactive protein<sup>11</sup> and blood pressure in hypertensive subjects.<sup>12</sup> Despite these epidemiological and experimental pieces of evidence, there have been no clinical trials examining the therapeutic effects of quercetin in COPD. An objective of this study was to determine the safety of quercetin supplementation in patients with COPD, because it is the first step towards using quercetin as a therapeutic agent in these patients.

## MATERIALS AND METHODS

### Clinical trial registration

This safety study was a randomised, double-blind, placebo-controlled, single-centre dose-escalation phase I clinical trial registered with ClinicalTrials.gov. It is a single-centre study conducted at the University of Michigan.

### Study drug

Quercetin and placebo were supplied by Quercegen Pharmaceuticals (Sudbury, Massachusetts, USA) as orange-flavoured soft chews. Quercetin chews consisted 500 mg of quercetin, 325 mg of vitamin C and 10 mg vitamin B<sub>3</sub>. Placebo formulation contained vitamin C and vitamin B<sub>3</sub> in the same proportion as quercetin chews.

### Patient enrolment and study design

All subjects were recruited from the University of Michigan Pulmonary Clinic. Patients with COPD with mild-to-moderate lung disease with forced expiratory volume in one second (FEV<sub>1</sub>):forced vital capacity ratio of <0.7 and a per cent predicted FEV<sub>1</sub> of >35% and <80% as determined by postbronchodilator spirometry were recruited for the study. All subjects had a smoking history of 10 pack-years or more and ceased to smoke for at least 2 months at the time of recruitment. Out of 12 recruited subjects with COPD, 10 eligible subjects between the ages of 40 and 80 years were enrolled (table 1). One subject

dropped out because he was unable to come to study visits after being determined to be eligible and therefore was not randomised.

Enrolled subjects were divided into three cohorts, with three subjects in each cohort. In each cohort, one subject was allocated to placebo and the other two subjects to one of the three doses of quercetin (500, 1000 or 2000 mg/day) as per the randomisation codes that were generated by a biostatistician prior to subject enrolment. The study design involved dose escalation in separate cohorts. Subjects in cohort 1 were treated with 500 mg quercetin; those in cohort 2 were treated with 1000 mg; and those in cohort 3 were treated with 2000 mg/day. The safety of quercetin treatment was assessed at low dose prior to treating subjects in another cohort with the next higher dose. All subjects avoided quercetin-rich diets for 7 days prior to (run-in period) and during quercetin therapy. Subjects in each cohort were treated with placebo or quercetin orally for 7 days. The study subjects took the study drug twice a day, along with food, and maintained a study drug log. Study drugs were provided for three extra days, and therefore, the remaining study drugs were collected from the subjects at the end of the study period. Compliance was determined on the basis of the study drug log and by counting the remaining study drug chews. Blood was collected and spirometry was performed at the run-in period and at the end of 1-week treatment with the study drug. Safety was determined by assessing postbronchodilator FEV<sub>1</sub>, blood profile (complete blood count and comprehensive metabolic panel) and patient-reported adverse events. Due to small number of subjects in each arm, we were not able to perform statistical analysis.

### Patient and public involvement

This study involved participation of a COPD population. Informed consent with study details was obtained from patients, and the written consent was obtained from each enrolled subject. Patients recorded symptoms daily in 'COPD Assessment Test', a standardised questionnaire.

**Table 1** Patient cohort and treatment

Patient number	Race	Age	Sex	% FEV <sub>1</sub>	FEV <sub>1</sub> /FVC	Treatment
1	Caucasian	76	F	79.9	80.6	500
2	Caucasian and Alaska Native/American Indian	60	M	55.5	67.6	500
3	Caucasian	63	F	37.0	63.0	Placebo
4	Caucasian	58	M	51.2	86.3	1000
5	Caucasian	77	F	38.4	63.6	Placebo
6	Caucasian	78	M	50.2	49.9	1000
7	Caucasian	67	F	57.1	64.2	2000
8	Caucasian	62	M	45.4	68.8	Placebo
9	Caucasian	72	M	48.8	52.9	2000

F, female; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; M, male.

**Table 2** Effect of quercetin on lung function and blood counts and blood glucose levels

Treatment	FEV <sub>1</sub>		FEV <sub>1</sub> /FVC		WBC (K/mL)		Platelets (K/mL)		Fasting glucose (mg/dL)	
	At run-in (%)	Post-treatment (%)	At run-in (%)	Post-treatment (%)	At run-in	Post-treatment	At run-in	Post-treatment	At run-in	Post-treatment
Quercetin dose (mg/day)										
Placebo	38.8	35.0	51.0	63.6	5.4	6.4	236	223	90	99
Placebo	40.9	40.3	63.6	63.3	5.5	4.6	170	167	89	126
Placebo	53.3	50.7	70.6	74.6	5.6	5.8	135	130	111	84
500 mg/day	75.7	79.3	79.8	82.4	5	5	259	266	89	98
500 mg/day	46.7	43.2	66.8	63.9	10.6	11.1	236	268	138	89
1000 mg/day	53.0	47.3	89.0	92.5	6.2	5.5	144	153	122	125
1000 mg/day	49.5	50.5	53.1	49.9	5.5	4.6	164	178	234	139
2000 mg/day	53.9	55.5	67.1	66.0	8.3	8.3	280	298	143	140
2000 mg/day	50.0	47.3	52.0	56.4	5.7	5.3	271	277	150	91

FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; WBC, white blood cell.

Abnormal laboratory results and the patient-reported symptoms were reviewed by the clinical principal investigator to determine the severity of the abnormality and the causality of the study participation. The clinical investigator informed the participants if the abnormalities were clinically significant.

## RESULTS AND DISCUSSION

Subjects showed 100% compliance. There were no serious adverse events or substantial changes in complete blood count and lung function in any of the groups (table 2). All the patients showed parameters of liver and kidney functions within the range at run-in and post-treatment (data not shown). Interestingly, five out of six patients assigned to quercetin group had higher than normal fasting blood glucose levels at run-in. Three out of five subjects showed reduced blood sugar levels after quercetin treatment, irrespective of the quercetin dose. Unfortunately, none of the subjects in the placebo group had higher than normal fasting blood glucose levels, and therefore it is not possible to predict whether this effect is due to quercetin. Since we did not expect any changes to occur in blood sugar levels following quercetin treatment, we did not consider distribution of subjects with high blood glucose levels in both the placebo and quercetin groups during randomisation. Patient-reported adverse events were gastro-oesophageal reflux disease (GERD), stomach upset, breathlessness, chest congestion, headache and nausea. None of these events were determined to be study drug-related except in two subjects, one in the placebo group and the other one in the 500 mg quercetin dosing group. Both subjects reported symptoms of GERD, and the subject in the placebo group needed treatment to reduce the GERD symptoms. Taken together, these results indicate that subjects with COPD safely tolerated up to 2000 mg/day quercetin. However, the limitations of this trial are the small sample size and the short duration of treatment period with the study drug. Therefore, the

safety of quercetin should be confirmed in a large cohort of patients and after prolonged treatment with quercetin, that is, for at least 6 months.

**Contributors** MH, clinical investigator, designed and conducted the study and finalised the manuscript. TAB compiled the data and prepared the tables for the manuscript. FJM designed the study. ATC developed the database and entered the data. US conceived and designed the study and prepared the manuscript.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study was conducted according to modified Declaration of Helsinki under the approval of the institutional review board of University of Michigan, Ann Arbor (IRB#HUM00061735).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

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