Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The effect of quercetin on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review

Monique Aucoin[a,*], Kieran Cooley[a,b,c], Paul Richard Saunders[a], Valentina Cardozo[a], Daniella Remy[a], Holger Cramer[b,d], Carlos Neyre Abad[e], Nicole Hannan[f]

[a] Canadian College of Naturopathic Medicine, Toronto, Ontario, Canada
[b] Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, New South Wales, Australia
[c] Pacific College of Health Sciences, San Diego, California, United States
[d] Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany
[e] University of California, Los Angeles, Los Angeles, California, United States
[f] School of Pharmacy and Pharmacology, Griffith University, Gold Coast, Queensland, Australia

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ABSTRACT

Brief overview: There is currently insufficient evidence to recommend quercetin supplementation as a therapy for the treatment or prevention of COVID-19. Three human clinical trials with low risk of bias suggest that oral quercetin may have a beneficial effect on the incidence and duration of respiratory tract infections in certain populations; however, further research is needed.

Verdict: Current evidence on the efficacy of quercetin supplementation in the treatment and prevention of COVID-19 is insufficient for its clinical recommendation at this time. Quercetin exhibits both immunomodulatory and antimicrobial effects in preclinical studies; however, only three human clinical trials, each with a low risk of bias rating, were identified in this rapid review. One study reported a decrease in incidence of upper respiratory tract infections following a competitive athletic event. A larger community clinical trial reported a benefit in older, athletic adults only.

1. Background

Quercetin is a polyphenolic compound, a type of flavonoid which is found in a variety of plants consumed by humans and available as a dietary supplement. Its physiologic effects include antioxidant, anti-inflammatory, immunomodulatory and anti-pathogenic properties [1–3]. Animal and *in vitro* studies have demonstrated effects of quercetin on immune activity including increased neutrophil chemotaxis, macrophage phagocytosis, NK cell lytic activity and mitogen-stimulated lymphocyte proliferation. Quercetin regulates the expression of some genes related to cytokine production [2]. When added to cell cultures, quercetin exerts antiviral and antibacterial properties, including inhibition of influenza A strains H1N1, H3N2 and inhibition of H5N1 entry [4]. Quercetin supplements are used by some naturopathic doctors to support healthy immune function and response to inflammation. Research has been undertaken using quercetin supplementation in the general population and in competitive athletes as it is established that intense and prolonged exercise is responsible for a transient decrease in immune function and increase in risk of infection [2].

2. Search strategy

2.1. Research question

What is the role of quercetin in the treatment and recovery of COVID-19 and other respiratory tract infections?

2.2. Inclusion/exclusion criteria

Studies were included if reporting human prospective intervention studies sampling adults (aged 18 and over), which assessed

* Corresponding author.
E-mail address: maucoin@ccnm.edu (M. Aucoin).

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the effect of quercetin supplementation on the incidence or treatment of respiratory tract infections. Studies including pediatric populations were excluded.

2.3. Databases

Medline (Ovid), AMED (Ovid), CINAHL (EBSCO), EMBASE (Ovid)

2.4. Search terms (example)

[Medline (Ovid)]

((Randomized Controlled Trials as Topic/ OR randomized controlled trial/ OR Random Allocation/ OR Double Blind Method/ OR Single Blind Method/ OR clinical trial/ OR clinical trial, phase i.pt. OR clinical trial, phase ii.pt. OR clinical trial, phase iii.pt. OR clinical trial, phase iv.pt. OR controlled clinical trial.pt. OR randomized controlled trial.pt. OR multicenter study.pt. OR clinical trial.pt. OR exp Clinical Trials as topic/ OR (clinical adj trial$).tw. OR ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. OR PLACEBOS/ OR placebo$.tw. OR randomly allocated.tw. OR allocated adj2 random$).tw.) NOT (letter/ OR historical article/)) AND ((Quercetin or Quercetol or 3,3′,4′,5,7-pentahydroxylavone. af) AND ("avian influenza (H5N1)"/ or "influenza A (H1N1)"/ or Influenza A virus/ or influenza C/ or exp influenza/ or highly pathogenic avian influenza/ or Influenza B virus/ or highly pathogenic avian influenza virus/ or avian influenza virus/ or seasonal influenza/ or "Influenza A virus (H1N1)"/ or Asian influenza/ or swine influenza/ or influenza A/ or pandemic influenza/ or Influenza C virus/ or influenza B/ or avian influenza/ or Influenza virus or SARS or MERS or respir$ or Middle East Respiratory Syndrome Coronavirus or severe acute respiratory syndrome/)

2.5. Screening

Titles and abstract screening and full text screening were completed by one reviewer and checked for accuracy by a second reviewer. Similarly, data extraction was completed by a single reviewer and checked for accuracy by a second reviewer. Any discrepancies were resolved by consensus.

2.6. Critical appraisal

The risk of bias (RoB) of study findings was assessed using the revised Cochrane RoB tool for randomised trials (RoB 2) https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2?authuser=0.

3. Results

The search identified 138 results, including 22 duplicates. 116 citations were screened. The citations were screened by title and abstract against the inclusion and exclusion criteria, and 112 citations were excluded. The full text of the remaining four articles were assessed for eligibility and one was excluded due to an incorrect intervention. The remaining three studies underwent extraction.

All three studies were double-blind, placebo-controlled randomized clinical trials and were conducted in outpatient settings in the World Health Organization (WHO) region of the Americas. Two of the studies involved participants who were trained athletes [1,2] (n = 40 and n = 39 respectively), while the third involved a diverse range of 1023 healthy and unhealthy individuals from the community [3]. The studies involving athlete participants delivered the intervention for 3 weeks before and 2 weeks after a competitive athletic event in order to assess for the prevention of immune disturbance (blood and salivary immune markers) and respiratory tract infection (questionnaire).

The two studies assessing the impact on athletic-event-related immune perturbation assessed blood levels of immune components [1,2]. All 3 studies assessed the incidence and duration of respiratory tract infections using a symptom survey or checklist.

Two studies used a soft chew containing a combination of quercetin, vitamin C and nicotinamide [2,3]; one study used a total daily dose of 1000 mg quercetin [2], while the other compared doses of 500 mg and 1000 mg of quercetin to placebo [3]. The third study used a daily dose of 1000 mg quercetin powder [1].

Risk of bias, as assessed by the Cochrane Risk of Bias 2.0 tool, was low in all three studies.

4. Summary of findings

The two studies involving athletes assessed for the potential of quercetin to counter the immune perturbations that occurred as a result of participation in the competitive athletic event; however, no statistically significant difference was observed between the treatment and control groups with respect to natural killer cells, granulocyte respiratory burst activity, monocyte cell counts or salivary IgA output [1,2].

In one post-athletic event study, no statistically significant difference was found in the duration of illness, as measured by total post-race illness days [2]. In the other, a statistically significant decrease in the incidence of upper respiratory tract infection symptoms in the two-week period following the event was reported [3].

In the study that included a large community sample, no statistically significant difference was observed in the incidence, severity or duration of respiratory tract infection between the intervention and control group [3]. However, *a priori* sub-group analysis revealed two statistically significant differences favouring oral quercetin. Subjects older than 40 years of age who self-rated in the top half of the population for fitness level experienced a 36 % reduction in Upper Respiratory Tract Infection (URTI) severity and 31 % reduction in total URTI sick days compared to placebo when taking the 1000 mg per day dose. Of the two studies reporting statistically significant benefits, one used quercetin as a monotherapy and the other used it in combination with vitamin C and nicotinamide.

5. Clinical significance

Based on the evidence identified in this rapid review, quercetin may be an effective intervention to decrease the frequency and duration of respiratory tract infections; however, more research is needed. At this time, there is insufficient evidence to recommend the use of this supplement in the treatment or prevention of COVID-19.

6. Disclaimer

This article should not replace individual clinical judgement. The views expressed in this rapid review are the views of the authors and not necessarily from the host institutions. The views are not a substitute for professional medical advice.

Summary of studies examining quercetin and respiratory tract infections in humans

Identification			Methods									Outcomes	
Author	Country and WHO Region	Sponsorship source/ association	Design	Statistical method (s)	Study Population	Quercetin form and Dose	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total N, N in intervention and placebo	Measure of Outcome	Outcome
Henson D et al. [2]	USA, Region of the Americas	Defense Advanced Research Projects Agency and Army Research Office. Product supplied by Quercegen Pharma	DBPC RCT	2 (groups) x 2 (time points) repeated measures ANOVA, Student's t-tests, comparison of incidence rates between groups using a Kaplan-Meier analysis	Ultra marathoners who completed 160 km race	Soft chews containing total of 1000 mg quercetin, 1000 mg vitamin C, 40 mg niacin, 80 kilocalories of sugar, carnauba wax, soy lecithin, corn starch, glycerin, palm oil, colour; 2 soft chews, BID; 1000 mg/day Quercetin	3 weeks before and 2 weeks after race	1. qualified for the Western States Endurance Run (completed a 160-km trail race or three 80-km races within the cutoff times, or raced 80 km in less than 11 hours or 100 km in less than 14 hours)	1. enrolled in the study but did not complete the 140 km race	placebo soft chews (sugars in a carnauba wax, soy lecithin, corn starch, glycerine, and palm oil base colored with FD&C yellow #5 and #6)	63 randomized but only those who completed race included (39) quercetin N = 18, placebo N = 21	Heparin-derived plasma quercetin	Quercetin: Increased plasma concentration of quercetin (6.6-fold increase (pre-race) compared to placebo group and 3.1-fold higher (post-race) ($p < 0.001$)
												Pre and post -race Immune markers: leukocyte subset counts (neutrophils, lymphocytes, monocytes, T-cells, NK cells, B cells), granulocyte oxidative burst activity, hemoglobin, hematocrit, plasma cortisol, myeloperoxidase and salivary IgA.	No difference between placebo and quercetin
												Post-race URTI illness incidence (measured *via* symptom-checklist illness logs).	No statistically significant effect on post-race URTI illness rates.
												Total days of illness post-race (measured *via* symptom-checklist illness logs).	No statistically significant difference
Nieman DC et al. [1]	USA, Region of the Americas	Defense Advanced Research Projects Agency (DARPA) and the Army Research Office (ARO). D. C. Nieman holds a position on the science advisory board	DBPC RCT	Student's t-tests on interaction effects, 2 (groups) x 6 (time points) repeated-measures ANOVA. When Box's M violated assumptions for univariate approach, a multivariate approach to	trained male cyclists	500 mg pure quercetin powder, tang powder and food colouring. Subjects mixed power with 8oz water BID before meals; 1000 mg/day quercetin	3 weeks before, during 3-day intense exercise, and 2 weeks after	Male, trained cyclists (note: study does not define what "trained" entails)		placebo supplements (form not specified)	N = 40 quercetin N = 20, placebo N = 20	Plasma quercetin	Plasma quercetin levels for the intervention group were 9.2-fold higher than those in the placebo group. ($p < 0.001$)
												Pre- and post-exercise changes in Blood: Complete	No difference

(*Continued*)

Summary of studies examining quercetin and respiratory tract infections in humans

Identification			Methods									Outcomes	
Author	Country and WHO Region	Sponsorship source/ association	Design	Statistical method (s)	Study Population	Quercetin form and Dose	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total N, N in intervention and placebo	Measure of Outcome	Outcome
		for Quercegen Pharma.		repeated-measures ANOVA was used (Pillaris trace). Comparison of incidence rates between groups using Kaplan–Meier analysis								blood count including leukocyte subset counts, hemoglobin, and hematocrit, NK-cell activity, PHA-stimulated lymphocyte proliferation and polymorphonuclear (PMN) oxidative-burst activity; plasma epinephrine and norepinephrine; plasma quercetin (quercetin and its primary conjugates); plasma myeloperoxidase. Saliva: Salivary IgA. Total days of URTI illness 2 weeks post-exercise program	Quercetin: 1/20 Placebo: 9/20 Kaplan–Meier analysis statistic = 8.31, P = 0.004
Heinz SA et al [3]	USA, Region of the Americas	Coca-Cola and Querce- gen Pharma. D. C. provided funding and were involved in designing the study. Nieman holds a position on the science advisory board for Quercegen Pharma	DBPC RCT	One-way ANOVA, with a Tukey post hoc analysis; Stepwise linear regression; 3 (group) × 2 (time) repeated measures ANOVA with Bonferroni adjusted independent t-tests	Adults from the general population	Soft chew tablets of either 125 or 250 mg quercetin, 125 or 250 mg vitamin C (ascorbic acid and sodium ascorbate), 5 or 10 mg niacin (nicotinamide), and 20 kcal of sugars, r, carnauba wax, soy lecithin, corn starch, glycerin, palm oil, colour. 2 chews, BID 500 mg/day (Q-500) *vs* 1000 mg/day (Q-1000) quercetin	12 weeks	1. 18–85 years of age 2. Male or female 3. age 18–85 4. diseased and non-diseased subjects	1. institutionalized 2. pregnant or lactating	placebo soft chews (20 kcal of sugars in a carnauba wax, soy lecithin, corn starch, glycerine, and palm oil base colored with FD&C yellow #5 and #6)	1023 recruited, 1002 completed the trial Q-500 N = 334, Q-1000 N = 333, Placebo N = 335	Total plasma quercetin The Wisconsin Upper Respiratory Symptom Survey (WURSS) to assess URTI incidence and symptomatology	Q-500 and Q-1000: increase from baseline ($p < 0.001$) All quercetin: No difference in URTI incidence, duration, severity compared to placebo *Subgroup analysis:* Q-1000 group: >40 years old with higher (top 50 %) self-rated fitness showed lower URTI severity (36% reduction p=;.020), and

D= two times per day.

DBPC RCT = double blind, placebo-controlled randomized clinical trial.

URTI = upper respiratory tract infection.

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