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About curcumin again (and the gut microbiota)

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In 2017, I wrote an editorial on the possible inefficacy of curcumin [1]. Recently, the possible effect of curcumin on the gut microbiota has been discussed. Curcumin is a polyphenolic compound with a long history of use as a dietary spice, food-colouring agent and herbal remedy. Curcumin exhibits anti-inflammatory, antioxidant, anticancer, antiviral and neurotrophic activity and therefore holds promise as a therapeutic agent to prevent and treat several disorders. However, a major barrier to curcumin's clinical efficacy is its poor bioavailability. Efforts have therefore been made to develop curcumin formulations that have greater bioavailability and systemic tissue distribution. Nevertheless, curcumin's potential as a therapeutic agent may not solely rely on its bioavailability but also on its positive influence on gastrointestinal health, function and structure.

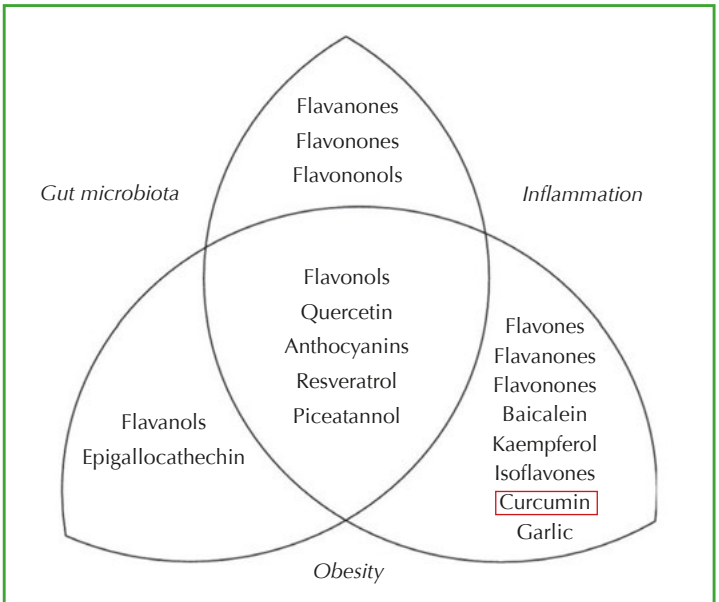

Figure 1 - Relationships between polyphenols (including curcumin), the gut microbiota, inflammation and obesity. Modified from Carrera-Quintanar *et al* (2018) Gut microbiota as prophylactics and for the treatment of obesity and inflammatory diseases. Mediators Inflamm 2018:9734845

Recent in vitro animal and human studies investigating the effects of curcumin on the intestinal microbiota, in addition to intestinal permeability and gut inflammation, have indicated new mechanisms behind curcumin's therapeutic efficacy [2]. Bidirectional interaction between curcumin and the gut microbiota is suggested: (1) gut microbiota regulation by curcumin and (2) curcumin biotransformation by the gut microbiota. This has pharmacological implications calling for: (1) the identification of metabolites which are more active and bioavailable than curcumin; (2) assessment of the contribution of gut microbiota regulation of curcumin to its pharmacological effects; and (3) the development of a gut microbiota regulation-based disease prevention/treatment strategy for curcumin in view of its clinical safety. Resolution of these issues could improve our understanding of the mechanisms of action of curcumin and provide future direction on the use of this natural compound to combat human disease [3].

In a new review of curcumin [4], Carrera-Quintanar *et al* describe how curcumin is metabolized by the gut microbiota and show how the biotransformation of turmeric curcuminoids by the human gut microbiota is reminiscent of equol production from the soybean isoflavone daidzein [5]. In particular, they describe curcumin as a modulator of the gut microbiota during colitis and colon cancer [6] and improver of intestinal barrier function [5]. Curcumin's efficacy as a potent anti-inflammatory and neuroprotective agent as well as a treatment for obesity [7] could be related to its possible direct impact on the gut microbiota (Fig. 1). Although there is extensive research on curcumin, there are still too few papers dealing with the relationship between curcumin and the gut microbiota. It is likely new

insights will reveal its close relationship with the gut microbiota in the near future.

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ORIGINAL RESEARCH

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New dietary proteins for cholesterol control: lupin and hempseed

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ABSTRACT

The consumption of dietary proteins from vegetable sources can be very helpful in the dietary management of hypercholesterolemia. While it is well established that soy proteins can reduce LDL-cholesterol, particularly in patients with high cholesterolemia, novel protein sources have lately attracted much interest. Recent studies have clearly established the nutraceutical properties of eggs and egg peptides, which have significant effects on both cholesterolemia and blood pressure. In the last few years, extensive studies have shown that lupin and hempseed proteins have good cholesterol-lowering properties. Lupin, particularly *Lupinus angustifolius*, is characterized by peptides that can significantly raise LDL-receptor activity and also reduce PCSK9 levels, thus providing very effective treatment for hypercholesterolemic patients when used as substitutes or additives for standard drugs. More recently, hempseed, a protein source rarely evaluated clinically, has been shown to reduce cholesterolemia in animal models, by inhibiting HMG-CoA reductase activity, upregulating LDL receptors and, surprisingly, also increasing PCSK9 levels, with an overall profile similar to that of statins. These novel additions to the nutraceutical armamentarium for treating raised cholesterol may lead to exciting progress in the management of hypercholesterolemic patients.

Keywords

Nutraceutical proteins
Soy
Lupin
Hempseed
Cholesterolemia
LDL receptors
PCK9 activity
Atherosclerosis
Peptides

Introduction

Changes in the types of dietary protein consumed have significantly influenced the treatment of hypercholesterolemia over the last 40 years. In the earliest study [1], it was shown that in severely hypercholesterolemic in-patients (mean cholesterol 322 mg/dl), total substitution of animal proteins with a soy protein-based diet over a period of 6 weeks (3-week crossover from animal to soy proteins and vice versa) lowered total cholesterol by a mean of 21% and LDL-cholesterol by a mean of 23% compared with an animal protein diet. The study was appropriately designed, since compliance was 100% guaranteed, and also evaluated the addition of cholesterol (given as 500 mg/day in lyophilized egg yolk) which was found to not modify the cholesterol-lowering effect of soy proteins.

At that time, soy proteins were the best available means for reducing cholesterolemia, as drug alternatives consisted of anion exchange resins (cholestyramine, colestipol) with poor palatability and very low compliance. In this earliest study, there was clear evidence of a correlation between the severity of hypercholesterolemia and plasma cholesterol reduction by soy. A later meta-analysis by Anderson *et al* [2] showed that a mean daily intake of 48 g of soy proteins was associated with a mean total cholesterol reduction of –13 to –32.9 mg/dl (–9.3%) and an LDL-cholesterol reduction of 12.9% with modest changes in triglycerides and HDL.

The Anderson meta-analysis was performed when statins were starting to be prescribed in daily practice. This dramatic change in drug approach made it increasingly difficult to evaluate the cholesterol-lowering activity of soy or other proteins in severe hypercholesterolemia as determined in the earlier studies. However, the Anderson study [2] provided a nomogram based on quartiles of initial cholesterol and

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