Clinical Nutrition Experimental 3 (2015) 8–14

Contents lists available at ScienceDirect

Clinical Nutrition Experimental

journal homepage: http://www.clinicalnutritionexperimental.com

The value of flavonoids for the human nutrition: Short review and perspectives

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ARTICLE INFO

Article history:
Received 10 March 2015
Accepted 4 September 2015
Available online 25 September 2015

Keywords:
Flavonoids
Human nutrition
Inflammation
Nutritional value
Inflammatory factors

SUMMARY

Flavonoids are phytochemicals and belong to the polyphenols. A wide variety of beneficial factors has been attributed to their mode of action. Some of their activities concerns the inhibition of inflammatory pathways and the down regulation of genes involved in chronic inflammatory disease states. These genes enhance the inflammatory signaling pathways leading to expression of inflammatory cytokines and chemokines. Flavonoids from fruits, vegetable and tea compounds can block many proinflammatory proteins and thus function as natural inhibitors of inflammation. Instead of using nonsteroidal anti-inflammatory drugs natural inhibitors could possibly be used to suppress the intensity of the inflammation in the chronically inflamed mucosa in patients with chronic inflammatory bowel disease. Natural inhibitors like flavonoids are xenobiotics which are metabolized by the cytochrome P-450 enzymes and conjugating protective enzymes. Flavonoids can induce these protective enzymes by upregulation and thereby could act as protective metabolic barrier within the intestinal mucosa. The nutritional value of flavonoids is probably related to their anti-inflammatory activity and through this mechanism responsible for prevention of neoplasia. The evidence for their clinical efficacy as essential compounds is still preliminary at best and limited but suggestive.

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http://dx.doi.org/10.1016/j.yclnex.2015.09.001

Contents

1. Introduction 9
2. Physiology 9
3. Function 9
4. Anti-inflammatory activities by natural inhibitors 10
5. Natural inducers 11
6. Microbiota 11
7. Challenges and opportunities 11
Conflict of interest 13
References 13

1. Introduction

Vitamins are essential for the human nutrition. They cannot be synthesized in the body, they need to be taken up from exogenous sources in our nutrition and are essential for the health and the function of our body. Flavonoids are similar in that they cannot be synthesized, they are foreign compounds and are contained in our nutrition, but are they really essential for the human health? Could these phytochemicals play a role comparable to that of vitamins? To find out about this we have to explore their fate when they interact with the biology of the organism. Plant derived phytochemicals play an important role as protective factors against free radicals, reactive oxygen species and toxic chemical compounds. The concept of their role as natural inhibitors of inflammation has evolved recently [1,2] and their metabolism was clarified [3] .

Flavonoids belong to the polyphenols and are widely distributed within the plant kingdom and are mainly contained in fruits, vegetables and teas [4]. There are more than 4000 flavonoid species and there are 6 major groups according to their chemical structure: Flavones, flavonols, flavanols, flavanones, anthocyanidins and isoflavonoids [5].

2. Physiology

The uptake and the absorption takes place in the small intestinal mucosa but only small amounts enter the central compartment of the body from where they reach the liver and the kidney. Phase 1 metabolism by cytochrome P-450 enzymes and phase 2 metabolism by conjugating enzymes are performed in the liver and the gut and the water-soluble products are excreted by the kidney and into the bile [3]. The mucosa is exposed to a much higher concentration than the other tissues and therefore here the biological activity is concentrated. A great fraction remains within the lumen of the gut and reaches the colon where the flavonoids are metabolized by the microbiota to small breakdown products among them butyrate and acetate which are the metabolic fuel of the mucosa.

3. Function

Flavonoids use the same xenobiotic metabolizing enzyme system which is used for the distribution and disposition of drugs but do they exercise drug related effects?

There is a wealth of clinical and laboratory studies and data that suggest that flavonoids have beneficial effects in a wide variety of clinical fields such as cardiovascular disorders [6], neurology, urology, immunology and last but not least gastroenterology (Table 1). It is difficult to find a common functional denominator that can explain all these findings. The most convincing factor which could explain the beneficial findings is that flavonoids act best in preventing medicine. Flavonoids need to be given before the pathophysiological event occurs. That could mean that a protective wall should be induced before the noxious factor comes into play. The mechanism which is used to build up the

Table 1
Beneficial effects of flavonoids in disease states [7].

Anticarcinogenic activities	Colorectal cancer, cancer of liver, esophagus, breast, non-Hodgkin lymphoma [17]
Cardiovascular improvement	Rate of stroke reduced, lower blood pressure [18]
Metabolic control improved	Diabetes mellitus improved [19]
Neuroprotection	Cognitive enhancement [20]
Antisecretory action	Diarrheal disease treatment [21]
Restoration of intestinal microflora	Improvement of microbiota [8]
Prevention of metabolic disease	Treatment of obesity [22]
Intestinal barrier protection	Prevention of colitis [23]

protective enzymes is by enzyme induction. This involves activation of the related genes via cytosolic transcription factors using the xenobiotic response element which is transferred into the nucleus of the exposed cells [7]. Flavonoids can bind to the Toll like receptors [8] of the plasma membrane and thus initiate the process of enzyme induction. Many of the protective enzymes have antioxidative functions and can trap oxygen radicals and other free radicals.

4. Anti-inflammatory activities by natural inhibitors

Inflammatory states are common in clinical medicine [1] and it is now believed that chronic inflammation is the base for many degenerative disorders such as cardiovascular diseases, atherosclerosis, rheumatic disorders and osteoarthritis. In the past infectious agents were held responsible for many chronic ailments such as chronic inflammatory bowel disease but it now becomes clear that a persistently activated inflammatory cascade is the cause for many of these disorders [9]. The signaling pathways for inflammation are chronically activated and the inflammatory genes are overexpressed (Fig. 1). The components of this pathway have been delineated and could serve as targets for therapy with drugs and biological agents. Specific immunologic proteins such as cytokines and chemokines were discovered and their role in chronic inflammation has been clarified [10]. Flavonoids such as tea

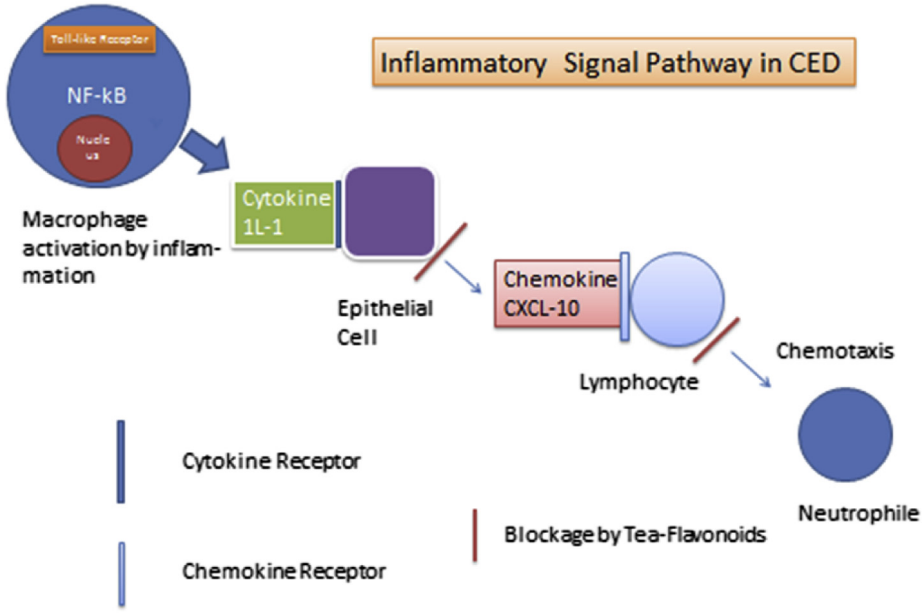

Fig. 1. Blockage of inflammatory signal pathway by tea flavonoids in patients with chronic inflammatory bowel disease.

flavonoids (epigallocatechin gallate and apigenin) inhibit certain steps within the pathway (Table 2) and their efficacy in clinical models is being tested. Figures 2 and 3 illustrate the inhibitory action of flavonoids at the level of cytokine and chemokine production [11].

5. Natural inducers

Flavonoids can induce protective enzymes such as certain cytochrome P-450 enzymes (CYP 3A4) and conjugating enzymes such as glucuronosyl transferases and glutathione transferases. These enzymes metabolize carcinogenic environmental compounds and thereby detoxify these chemicals [5]. By way of natural induction the intestinal mucosa builds up a metabolic barrier which prevents the intrusion of noxious compounds into the body. A diet which lacks flavonoids is devoid of this capacity and cannot maintain this metabolic barrier. The clinical consequences of a failing metabolic barrier are unfavorable genetic mutation with development of hyperplasia, aberrant crypt foci and dysplasia as well as adenomas and carcinomas in the intestinal mucosa. Some years ago we have published, that an artificial enteric diet which lacks natural inducers depresses the xenobiotic P-450 enzyme system of the small intestinal mucosa in patients [12]. Recently we found that the conjugating phase 2 enzymes of the colonic mucosa are diminished in patients with colon cancer compared to adenoma patients [13]. This could mean that there is a progressive loss of protective enzymes activities during the neoplastic development. Flavonoids might play a role as natural inducers and thus prevent neoplasia. However this notion is still hypothetical since some P-450 enzymes can toxify foreign compounds into carcinogenic products.

6. Microbiota

Flavonoids influence the composition of the microbial flora within the colon lumen both quantitatively and qualitatively. Thereby they act as prebiotics and support the growth of bifidum and lactobacilli bacteria [14]. Lack of certain phytochemicals in the diet could lead to an inflammatory status and flavonoids could stimulate the anti-inflammatory aryl hydrocarbon Ah receptor [15].

7. Challenges and opportunities

Our nutrition seems to promote an inflammatory status in the body especially in the gut and in the liver. Inflammatory genes are upregulated, cytokines and chemokines are overexpressed. The balance between protective and toxifying enzymes is disturbed especially at their portal of entry in the mucosa of the gut. There is an increase of dietary toxins due to the modern modes of food processing and production. At the same time the protective factors are reduced due to a lack of plant derived polyphenols such as flavonoids. These compounds could provide a metabolic barrier and could act much like anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAID's) but without their unwanted side effects [1]. There is a chance that dietary supplements on flavonoid bases could replace drugs in chronic inflammatory bowel diseases. However, their safety, efficacy, tolerability and their pharmacology need to be examined in valid clinical studies. Flavonoid sources as nutritional

Table 2
Anti-inflammatory efficacy of flavonoids from green tea (EGCG) and from chamomile (Apigenin).

	EGCG	Apigenin
Cytokine	MCP-1 ↓↓ RANTES ↓↓ MIP-1 ↓↓ JAK ↓	COX-2 ↓ NO ↓ NF-kB ↓
Cellular Targets	T-cells ↓ APC-cells ↓	Monocytes ↓ Makrophages ↓ Neutrophiles ↓

MIP: makrophage inhibitory protein MCP: monocytes chemoattractant protein RANTES: chemokine CCL-5 APC: adenomatosis polyposis coli cells ↓ inhibition.

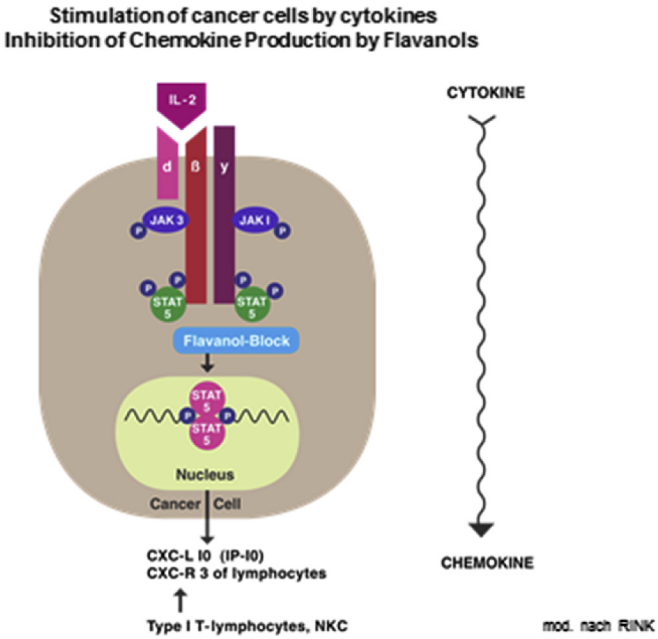

Fig. 2. Stimulation of cancer cells by cytokine IL-2 and its inhibition by flavanols.

supplements for therapeutic use were developed such as flavonoid capsules which reduced the recurrence of neoplasia in patients with colorectal cancer [16]. These flavonoid capsules consist of a flavonoid mixture [7] (mainly apigenin-10 mg- and epigallocatechin gallate-10 mg per capsule),

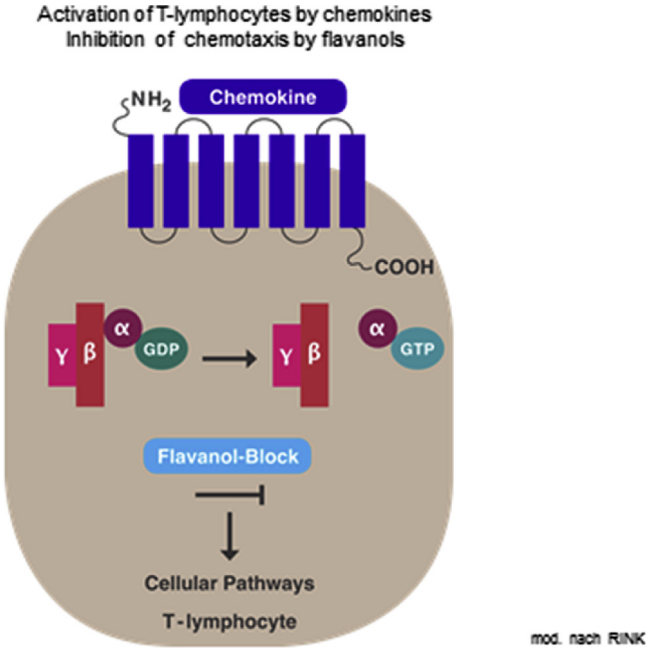

Fig. 3. Inhibition of chemotaxis by flavanols.

400 mg inulin and a vitamin mixture (110 mg vitamin C, 2.6 mg vitamin B 6, 220 μg folic acid and 4 μg vitamin B 12).

The nutritional value of flavonoids in vivo and in vitro is quite convincing but it is still unclear whether they are essential and which specific species are most efficacious for which clinical indication. For the clinical application the evidence is limited but suggestive. To prove causality clinical intervention studies with defined amounts of flavonoids and valid clinical endpoints and outcomes are required. Furthermore it would be interesting to look at the pathophysiology of animals on flavonoid deficient diet. However, so far no flavonoid deficiency disease has been identified [4]. Patients on Flavonoid-depleted nutrition like the one on oral elemental and total parenteral nutrition could suffer from chronic persistent inflammation [12]. They could be a model for a flavonoid deficiency syndrome.

Conflict of interest

Harald Hoensch holds a patent for a flavonoid combination.
Reinhard Oertel: None.

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