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RESEARCH ARTICLE

EFFECTS OF DIETARY POLIPHENOLS ON INTESTINAL INFLAMMATION

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ABSTRACT

Polyphenols are natural, ubiquitous compounds abundant in food and beverages derived from plants, vegetables and fruits. Diets rich in polyphenols have a well-known association with reduction of several disease owing to their anti-oxidant, anti-inflammatory and vasculoprotective properties. Phenolic compounds exerts their action on different pro-inflammatory pathways, like the acid arachidonic pathway, the NF-κB pathway and MAPK pathway just to mention some. Since inflammatory bowel disease share similar signaling basis with other inflammatory processes, an increasing number of studies start to focus on possible role of polyphenols in the prevention and treatment of these pathological conditions. Inflammatory bowel diseases (IBD) are chronic disorders whose real etiopathogenesis is still not completely understood. This paper focus on the potential of polyphenols for treating IBD, with an emphasis on cellular mechanisms and pharmacological aspects.

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INTRODUCTION

Polyphenols are natural, organic compounds, which derive from plant metabolism. As the world itself suggests, at least one phenol unit characterizes their chemical structure. Phenolic compounds exert a wide range of biological activities. They have well-known, anti-inflammatory, antioxidants, antimicrobial, immunomodulatory, anticancer, antidiabetic, cardio-protective, neuro-protective, and gastro-protective properties (1). Polyphenols are ubiquitous in nature, especially fruits, vegetables, dry legumes, cereals, olives, cocoa, tea, coffee and wine (2). Polyphenols can be divided into two main structural classes, flavonoids and non-flavonoids, according to the number of phenolic rings and their type of linkages, as well as the main dietary sources. The flavonoid group is further subdivided intoanthocyanins, flavonols, flavanones, isoflavones, and flavan-3-ols. The non-flavonoid group includes phenolic acids, stilbenes, and lignans (3). The health benefits of phenolic compounds are immense, so much so that they can be called "lifespan essentials" (4). The beneficial effects of polyphenols depend on several factors: dietary amounts in usual diet, absorption, metabolism and food processing methods. In fact, during food storage, phenolic compounds are lost, for example because of high temperatures (boiled onions and tomatoes lose up to 80% of their flavonoid quercetin content) (5). Also removing peels or outer layers from fruits or cereals can provoke significant losses (6, 7).

The average daily intake in Western populations is approximately of 1g/day (8). Bioavailability of polyphenols is generally low, since they are poorly absorbed and rapidly catabolized. Maintenance of their high concentration in blood and tissues requires repeated ingestion of significant amounts of food containing these compounds over time (9). The gut and its microbiota strictly modulate the metabolism of polyphenols. Only a minimal part of ingested polyphenols is absorbed in the upper digestive system so that 90-95% of these compounds interacts with microbiota, resulting in the production of phenyl propionic, phenylacetic, and benzoic acids. Flavonoids and their metabolites influence the composition of gut microbiota by inhibiting the growth of some pathogens and promoting the growth of beneficial genera such as Lactobacillus and Bifidobacterium (10). Since original research articles and reviews on phenolic compounds are numerous in the literature, the purpose of this article is not to describe them all but we want to focus our attention on their anti-inflammatory effects, in particular their potential benefits on intestinal inflammation.

INFLAMMATION: molecular basis

Inflammation is a type of nonspecific response that the immune systemcarries out against potentially harmful stimuli, such as damaged cells, pathogen organisms, toxic compounds or irradiation (11). Therefore, inflammation is protective and necessary to safeguard the host (12).

The inflammatory response is mediated by the activation of signaling pathways that regulate the concentration of inflammatory mediators in resident tissue cells and inflammatory cells recruited from the blood (13). The latters are leukocytes (neutrophils, eosinophils and macrophages) from the blood to the extra-vascular tissue. Furthermore, the most known molecules involved in inflammatory process can be divided in (14, 15):

- **Cytokines:** tumour necrosis factor α (TNFα), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10) and chemokines: interleukin-8 (IL-8), monocyte-chemoattractant protein-1 (MCP1), macrophage inflammatory molecule 1α (MIP1α)
- **Vasoactive amines:** histamine and 5-hydroxytryptamin (5-HT)
- **Adhesion molecules:** intercellular adhesion molecule 1 (ICAM 1), vascular adhesion molecule 1 (VCAM 1), selectins
- **Lipid-derived eicosanoids:** prostaglandin E2 (PGE2), prostaglandin I2 (PGI2), leukotriene B4 (LTB4), leukotriene C4 (LTC4)

Mediators activate the inflammatory progress, binding their corresponding receptors. This connection starts several intracellular signaling pathways, such the mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways.
Other molecules also involved are the inflammatory proteins in blood - i.e. C-reactive protein (CRP), haptoglobin, serum amyloid A, fibrinogen, and alpha 1-acid glycoprotein (16), and certain enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), NADPH oxidase (NOX), inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 (17). The inflammatory response involves many cell types: macrophages, monocytes, neutrophils lymphocytes (natural killer cells, T cells, and B cells), and mast cells (18), platelets (19). Under normal circumstances, inflammation is self-limiting, since the production of chemokines is spatially- and temporally-controlled. Conversely, an imbalance of pro-inflammatory and anti-inflammatory mediators can disrupt homeostasis and can lead to uncontrolled chronic inflammation (20). When chronic, uncontrolled flogosis affects the intestinal tract, alternating recurrent inflammatory injury and repair, we can talk of Inflammatory Bowel Disease (IBD). IBD include a group of idiopathic chronic inflammatory conditions, which Crohn's Disease (CD), Ulcerative Colitis (UC), collagenous colitis and lymphocytic colitis. The aetiology of these disease is not fully understood yet but factors like genetic predisposition and environmental factors are called forth (21).

Until a few years ago, it was thought that IBD were disease of the Western countries, but nowadays the incidence and prevalence has increased in Eastern Europe and Asia (22). The common onset of CD is 30-40 years, although recently an increasing trend of incidence in childhood-onset has been observed (23). UC usually has a bimodal distribution of disease onset with an initial peak in the third decade and a second peak between the ages of 50 and 80 (24). Histologically, CD's main feature is the patchytransmural inflammation, which could potentially involve the whole tract of the intestinal mucosa, whereas the inflammation in UC is limited to the superficial layers of thecolonic mucosa (25). IBD can also have extraintestinal complications (26). IBD is typically considered to be a chronic intermittent disease, with alternation of episodes of activerelapses and remissions. The treatment of these focuses (rather than a complete cure) mainly on reducing disease progression, its symptoms and complications, maintaining remission and improving quality of life(27) and entails anti-inflammatory agents, such as aminosalicylates andcorticosteroids. More recently, as recommended by the World Gastroenterology Organization immunomodulators (thiopurines,cyclosporine, methotrexate) and anti-TNF-αantibodies (infliximab, adalimumab, and certolizumab) have been approved for patients with inadequate response to the standard treatment (28). Unfortunately, a high percentage of IBD patients require surgical resection of the gastrointestinal tract, whose extent may lead to changes in intestinal absorption and metabolic function.
In IBD, a dysregulation of mucosal barrier, microbiota, innate and adaptative immunity is well documented (29).

The abnormal tissue infiltration by cells involved in the host defence like lymphocytes, macrophages and granulocytes results lead to the release of a great amount of proinflammatory cytokines, chemokines and reactive oxygen species (ROS), determining further inflammation and damage to the mucosa. Due to the physiological and biochemical actions of ROS, many of the clinical and pathophysiological features of Crohn's disease might be explained by an imbalance ratio of ROS and antioxidant molecules (30).

In light of the above mentioned, polyphenols – given their anti-inflammatory potential - could be useful in mitigate the intestinal inflammation. Below, we will describe the evidence so far about polyphenols and intestinal inflammation.

POLYPHENOLSTO FIGHT

…INFLAMMATION

Polyphenols may modulate inflammation, influencing the:

- Acid arachidonic pathway
- Nitric oxide synthase pathway
- Cytokine system
- NF-κB pathway
- MAPK pathway

Acid arachidonic pathway:
Acid arachidonic belongs to the omega-6 polyunsaturated fatty acids and has multiple functions, both directly and through its metabolites, prostaglandins (PG), namely PGF2a, PGE2, and PGI2. Arachidonic acid promotes inflammation so that the inhibition of the corresponding generating enzymes (phospholipase A2, cyclooxygenase (COX), lipoxygenase) can be considered an important anti-inflammatory strategy. Dietary polyphenols are able to inhibit phospholipase A2, cyclooxygenase, lipoxygenase, without the side effects of the anti-inflammatory drugs, which similarly act on these enzymes. Phenolic compounds from red wine and black tea turned out to be able to inhibit cyclooxygenase in different cell types, both in mice and humans: quercetin (31), epigallocatechin, gallocatechin epicatechingallate, catechin gallate, epigallocatechin gallate (32, 33, 34). Likewise, kaempferol reduces flogosis through the reduction of PGE2 levels (35), as well as oleuropein, hydroxytyrosol, tyrosol and other phenolic compounds in extra virgin olive oil (36). These molecules seem to influence different enzymes and mechanisms involved in inflammation (reduction of lipoxygenase activity, ROS-induced arachidonic acid (37), thromboxane production (38), reduction of cyclooxygenase activity) (39).

Nitric oxide synthase pathway: Nitric oxide is involved in maintaining homeostasis but, if synthetized in great amounts by inducible nitric oxide synthase (iNOS), is responsible of inflammatory process and acts synergistically with other inflammatory molecules (40). Catechin, fisetin, naringenin (41), curcumin, gallic acid, resveratrol, main polyphenols of extra virgin olive oil and ferulic acid down-regulate nitric oxide production and/or iNOS enzyme (42) through different mechanisms. Even procyanidin from wine and polyphenols from extravirgin olive oil modulate the nitric oxide production (43), the resistance to oxidative stress and the cytotoxicity induced by nitric oxide (44).

Cytokine system: Polyphenols exert their anti-inflammatory activity in multiple ways according to their specific chemical structure. For example, quercetin and catechins both inhibit TNF-α and IL-1β and promote IL-10 release (45, 46). Phenolic oleuropein and caffeic acid decrease the production of IL-1β (47) and kaempferol decreased the production of IFNγ, both in humans and murine models (48, 49).

NF-κB pathway: NF-κB has a pivotal role in immune, inflammatory, stress, proliferative and apoptotic responses, influencing the induction of genes producing pro-inflammatory cytokines, chemokines, acute-phase protein, adhesion molecules and other molecules involved in flogosis (50).

Polyphenols have been shown to modulate NF-κB activation at various steps of its activation process (51, 52). The most studied phenolic compounds have been epigallocathechingallate (53, 54, 55), quercetin, tyrosol, lycopene. In particular, the latter three molecules are interestingly linked to a potential protective effect against gliadin toxicity and intestinal inflammation in coeliac disease (56).

MAPK pathway: Mitogen-activated protein kinases (MAPK) are a family of Serine/Threonine kinases that regulate, among others, cell growth, proliferation, differentiation and death (57). An increase in their activity brings to the synthesis of inflammation mediators (58, 59, 60) so that they could became a therapeutic target for anti-inflammatory therapies. Many polyphenols can modulate MAPK pathway: kaempferol, chrysin, apigenin, luteolin (61), quercetin (62, 63), cyanidin (64), cathechins (65).

…INTESTINAL INFLAMMATION

There is evidence to suggest polyphenol supplementation could be helpful in managing intestinal inflammation, modulating different inflammation pathways. For example, their predominant anti-inflammatory mechanism is attributed to the inhibition on TLR4/NF-κB-mediated signaling pathways (66, 67). Polyphenols modulate the cascade reactions via Toll-like receptors (TLRs), nucleotide-binding oligomerization domain proteins (NOD), which are highly expressed in intestinal epithelial and immune cells. TLRs is involved in activation of (NF-κB) and IRF (IFN regulatory factor), in the subsequent production of pro-inflammatory cytokines and in generation of ROS (68).

Many polyphenols inhibit the pro-inflammatory stimuli in multiple ways: curcumin and isothiocyanate inhibit TLR4 dimerization, blocking its activation, while resveratrol interferes with TLR4 signal with subsequent reduction in cytokine production (69).

Various bioactive polyphenols such as curcumin, apigenin, resveratrol, epigallocatechin gallate, kaempferol, quercetin, iberin, naringin, luteolin, phloretin etc., has the property to interfere with TLR/ NF-κB mediated inflammatory reactions (70, 71, 72). Another crucial, anti-inflammatory effect is the modulation on cyclooxygenase-2 and the inflammatory cytokines. Resveratrol can reduce the synthesis and release of pro-inflammatory cytokines and COX-2 expression, while modulating the release of ROS production and inhibiting neutrophil infiltration (73, 74). Luteolin displayed significant inhibition of infiltration of IFN-γ and reduction of the expression of mRNA for pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β (75). Others phenolic compounds, which showed effects on pro-inflammatory cytokines,were quercetin, rutin, polyphenols in mango (68). As previously mentioned, iNOS is responsible of inflammation. Polyphenols may exert protective effects on intestinal damage, modulating the iNOS pathway, too. More specifically, ellagic acid has been shown to downregulate the release of pro-inflammatory cytokine, reducing COX-2 and iNOS enzyme activity in murin models of Ulcerative Colitis (76). Also, luteolin, scopoletin, resveratrol possess inhibitory effects on iNOS (68). Flavonoids also regulate the activity of T-reg cells in the intestine, downregulating the expression of inflammatory cytokines, and consequently suppressing inflammation. Mileo et al underlined the role of resveratrol and its derivatives, curcumin, chlorogenic acid and cocoa polyphenols in reducing the colonic infiltration of immune cells (77). Finally, yet importantly, polyphenols can also act as probiotic, influencing positively the gut microbiota. Green tea polyphenols promote the growth of beneficial microbiota like Christensenellaceae, Bifidobacterium, and Bacteroides and inhibited pathogenic bacteria such as Bilophila, Enterobacteriaceae (78). All the above findings suggest that polyphenols could effectively reduce the intestinal inflammation and could actually be an important therapeutic strategy for the treatment and prevention of IBD.

POTENTIAL THERAPEUTIC ROLE OF POLYPHENOLS ON IBD: the evidence so far

For example, Wanget al showed the potential of grape seed polyphenols to prevent or delay the progression of IBD (79), as well as green tea phenolic compounds (80). In these studies, plant compounds were able to reduce inflammatory and oxidant patterns in IBD resulting in improvement of the disease scores and of weight loss, mucosal damage and intestinal symptoms. Those results were previously reported by many authors, mainly in animal models. The epigallocathechingallate of green tea reduced macro and microscopic damage of colon after 8 days of treatment, reducing inflammation, TNF-α and IFN-γ (doses 0.1%). However, doses higher than therapeutic shown negative effects on bleeding, weight loss, inflammation (doses in murine models of 0.5% epigallocathechingallate). The 0.1% EGCG diet is equivalent to approximately 0.5 g EGC/day for humans. It is unlikely to reach this quantity in humans if we think that the EGCG content of green tea brewed at 80 °C for 3 minutes ranged from 100 to 350 mg/l (81). Tomatoes, rich in anthocyanins, flavonols, and stilbenoids, alleviate the symptoms in animal models of IBD (82). In humans, polyphenols present in mangoes (200–400 g/day of mango pulp) ameliorated the symptoms in 10 IBD patients, during the 8-week treatment period (83).

Furthermore, in murine models of colitis, anthocyanins in blueberry extract protected dose-dependently from weight loss, diarrhea and mortality. Especially, the 20 and 40 mg/kg doses reduced colon shortening, macroscopic and histological damage. All dosages decreased colonic IL-12, TNF-α, interferon (IFN)-γ mRNA and increased colonic IL-10 mRNA (81). Studies on models of IBD have several limitations related to the difficulty of translating from animal models to human the effective equivalent dose of polyphenols. A phenolic compound may be effective in rodents but if the dose is not reachable in humans, the findings are not translatable. For example, 30 mg/day of resveratrol improved induced colitis in mice. Most red wine have only 2–5 mg resveratrol/land other food sources negligible quantities, so that in this case a supplementation is needed, bearing in mind that over-supplementation of polyphenols could exacerbate intestinal inflammation and damage (81). Furthermore, polyphenols are catabolized by gut microbiota and are generally poorly absorbed, so that what researchers find in vitro or in animals does not always reflects the complex metabolism in cells or tissues (84). Clinical studies of polyphenols in humans are limited. However, there are some encouraging data, although on small samples and of short duration. 22 patients with Chron's Disease with a semivegetarian diet (high in polyphenols)led to maintenance of remission over 2 years compared to an omnivorous diet (94% vs 33%) (86). Other authors suggested that pycnogenol, a polyphenol from Pine Bark Extract, at doses of 2 mg/kg body weight led to better antioxidant profile, while markers of inflammation were unchanged (86).

Biedermann et al administered anthocyanin-rich bilberries at a dose of 160 g/day (840 mg anthocyanins per day) for six weeks to patients with ulcerative colitis with mild to moderate symptoms. A significant reduction in the clinical disease activity index was found after only one week, summed to a decrease of fecal calprotectin level (after two weeks), a reduction of IFN-γ and IFN-γ R2 expression in colon biopsy and an increase of anti-inflammatory IL-10 (after six weeks) (87). One study analysed the effect of enema with Curcuma longa extra (72% curcumin, 18% dimethoxy curcumin and 9.4% bis-demethoxy curcumin) in patients with distal ulcerative colitis compared to placebo. Both groups were also treated with oral 5-aminosalicylates. Patients treated with curcuma showed better clinical response, remission and improvement in endoscopic findings (88). In another placebo-controlled double-blind work, 3 g of curcumin with conventional therapy showed the potential to induce remission in patients with mild to moderate ulcerative colitis (89). Lower dose (1.5 g/die) were also effective in reducing inflammatory serum biomarkers such as C-reactive protein and erythrocyte sedimentation rate, but with no effect on TNF-a levels. Curcumin also reduced Simple Clinical Colitis Activity Index (SCCAI) and Inflammatory Bowel Disease Questionnaire 9 (90). Resveratrol decreased inflammatory markers (91), the disease activity and improved the quality of life and the total antioxidant capacity in patients with ulcerative colitis (92).

In other two studies, self-reported data from patients' record showed a link between the proanthocyanidins and daidzein and improvement of IBD symptoms, especially abdominal pain, diarrhea and intestinal mucus (mucus reflects the intestinal healing) (93, 94).

CONCLUSION

Polyphenols are complex and ubiquitous compounds abundant in food and beverages derived from plants, vegetables and fruits. Diets rich in polyphenols have a well-known association with reduction of several disease in virtue of their anti-inflammatory and vasculoprotective properties. Crohn's disease and ulcerative colitis, the two most common forms of IBD, are multifactorial disorders resulting from a dysfunctional epithelial, innate and adaptive immune response to externa stimuli. Since inflammatory bowel diseases share with other pathological conditions an inflammatory pathogenesis, some authors have begun to investigate the possible benefits of phenolic compounds. As a matter of fact, a lot of polyphenols have shown anti-inflammatory effects, acting on the same pathways and mechanisms that perpetuate intestinal inflammation, especially the inhibition of TLR4/NF-κB-mediated signaling pathways. Phenolic compounds can also modulate the production of cytokines, ROS, the activity of enzymes involved in inflammation and can positively affect gut microbiota. They can earn a chance to become a full-fledged therapeutic tool in treating IBD. In fact results in vitro, in vivo and in humans are encouraging. However, while consciousness about polyphenol-intestinal inflammation relationship is now know, there is still a long way to go. Evident shortcomings and limitations of the interactions between polyphenols and the GI tract exist, mainly due to the low bioavailability of phenolic compounds, their metabolism primarily subject to gut microbiota's health, the real translatability of results from laboratory to reality. The animal studies suggest that phenolic compounds have a wide therapeutic window, and that potentially several combinations/dosages would be beneficial but in some cases excessive dosages could be harmful. Safety studies in both healthy and IBD volunteers are desirable but ethical and practical limitations are obvious. Another issue to investigate is the food–drug interactions: how does polyphenols potentiate or reduce the absorption/metabolism of the conventional therapies?. While some questions remained unanswered, it is undoubted that diet is the key to maintain or restore health for several pathological condition and natural compound such as polyphenols could have the potential to modulate the clinical course of disabling diseases like IBD, maybe without the side effects of common drugs.

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