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Review Article

Multifunctions of dietary polyphenols in the regulation of intestinal inflammation

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ABSTRACT

Food for specified health use is a type of functional food approved by the Japanese government, with more than 1250 products in 10 health-claim categories being approved as of April 2016. Polyphenols are currently used as functional ingredients in seven of the 10 categories. Although they have not yet been used for the food-for-specified-health-use category of "gut health promotion," polyphenols are expected to contribute to the future development of gut-modulating food. Intestinal functions include digestion/absorption, acting as a barrier, recognition of external factors, and signal transduction. Owing to incessant exposure to external stress factors including food substances, bacteria, and environmental chemicals, intestines are always inflammatory to some extent, which may cause damage to and dysfunction of intestinal tissues depending on the situation. We identified food factors that could suppress immoderate inflammation in the intestines. In addition to certain amino acids and peptides, polyphenols such as chlorogenic acid and isoflavones were found to suppress inflammation in intestinal cells. Intestinal inflammation is caused by various factors in diverse mechanisms. Recent studies revealed that activation of pattern recognition receptors, such as Toll-like receptors and nucleotide-binding oligomerization domain proteins, in epithelial cells triggers intestinal inflammation. Intracellular receptors or signaling molecules controlling the intestinal detoxification system are also involved in the regulation of inflammation. Differentiation of regulatory T cells by activating a transcription factor Foxp-3 is known to suppress intestinal inflammation. A variety of phytochemicals including polyphenols modulate these receptors and signaling molecules, and are thus anti-inflammatory. Polyphenols affect epigenetic changes occurring in intestinal tissues by interacting with the enzymes responsible for DNA methylation and histone acetylation. New types of anti-inflammatory food factors may be discovered by examining dietary substances that interact with the abovementioned target molecules.

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1. Food for specified health uses and polyphenols

Food for specified health use (FoSHU) is a functional food approved by the Consumer Affairs Agency of the Government of Japan [1]. The FoSHU system started in 1991, and over 1250 FoSHU products are currently approved. Major health-promoting functions of the current products include gut health promotion, regulation of intestinal absorption of nutrients, and metabolic regulation such as that of lipid and bone metabolism [2]. Major functional food substances used for these purposes include carbohydrates, proteins/peptides, lipids, minerals, vitamins, and polyphenols. Polyphenols have increasingly been used as a FoSHU ingredient in recent years. In particular, multifunctional properties of polyphenols are receiving increasing attention. As of the end of April 2016, polyphenols are used as functional ingredients in seven of 10 FoSHU categories (Table 1). This means that polyphenols are recognized as essential ingredients with enormous potential for the development of functional food products. It is well known that the intestines play crucial roles in health maintenance and disease prevention [3]. The promising future of dietary polyphenols as intestine-modulating substances is discussed in this review.

2. Functions of the intestines

Small and large intestines are important organs with a variety of functions (Figure 1), with food digestion and nutrient absorption being the most fundamental functions. Digestive enzymes secreted by pancreatic and gastrointestinal tissues as well as brush-border enzymes expressed at the surface of the intestinal epithelium are involved in gastrointestinal digestion of dietary substances. Food-derived low-molecular-weight digests, such as monosaccharides, amino acids, dipeptides, and fatty acids, are then absorbed by respective transporters or via other mechanisms present in the intestinal epithelium [4].

The intestinal epithelium also acts as a barrier against harmful substances such as pathogenic bacteria and food allergens. Epithelial cell monolayers stabilized by tight junctions provide a physical barrier, but the epithelium also has chemical and biological barrier systems [4]. The chemical barrier includes the detoxification system that metabolizes and detoxifies xenobiotic compounds such as environmental chemicals. Detoxified compounds will further be excreted from epithelial cells to the intestinal tract via efflux transporters. Below the epithelial cell monolayers, many immune cells, including T lymphocytes, monocytes, and dendritic cells, are present and form a unique immune system called the gut mucosal immune system [5]. This biological system recognizes pathogenic microorganisms invading from the apical side of the epithelium and prevents their invasion by secreting specific immunoglobulin A antibodies against them.

Table 1 – Food for specified health use categories using functional polyphenol ingredients.

Health claim category (function)	Examples of functional polyphenol ingredients used
1. Reduces blood glucose level	Guava tea polyphenol
2. Reduces blood cholesterol level	Green tea polyphenol (catechin)
3. Reduces blood neutral lipid level and body fat	Green tea polyphenol (catechin) Black tea polyphenol (theaflavin) Oolong tea polymerized polyphenol Apple polyphenol (procyanidin) Monoglucosylhesperidine Isoquercitrin Chlorogenic acid Tectorigenin
4. Lowers blood pressure	Monoglucosylhesperidine Isoquercitrin Chlorogenic acid
5. Promotes gut health	None
6. Promotes tooth health	Green tea polyphenol (catechin)
7. Promotes dental gum health	Macrocarpal Soybean isoflavone
8. Promotes bone health	Soybean isoflavone
9. Enhances mineral absorption	None
10. Improves skin condition	None

3. Inflammation in the intestines

Intestinal epithelial cells are always exposed to a variety of external stresses, including food-derived stimulants, environmental chemicals, and intestinal bacteria. Generating a proper response to these stimulants is one of the major roles of the epithelial cells. Immune cells present in the lamina propria, which is the space beneath the epithelial cell monolayer, also recognize external substances, including pathogens and allergens. To respond to these external stimulants, intestinal epithelial and immune cells are cooperatively activated, thereby producing cytokines and other bioactive compounds that reinforce and restore the intestinal barrier. These protective responses may, however, simultaneously induce inflammation. In other words, the intestinal epithelium is an inflammatory tissue by nature, always maintaining a moderate inflammatory state. This type of inflammation in normal intestines is mild and controllable, and is, therefore, called “controlled inflammation” [6]. However, if inflammatory reactions immoderately proceed because of excessive stress or the formation of a vicious reaction cycle, disruption of the epithelial tissues and dysfunction of the intestines will occur. A typical and severe example of such uncontrollable inflammation is inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis [7]. In Japan, The number of Crohn's disease and ulcerative colitis patients were estimated to be approximately 40,000 and 180,000, respectively, in 2014. Treatment of inflammatory bowel disease with drugs such as aminosalicylate and anti-tumor necrosis factor-alpha antibody (infliximab) is now available; although these drugs effective, development of other treatments, including nutritional or food therapeutics, are also expected [8].

Although the molecular mechanism for inflammatory bowel disease is not fully understood, inflammatory reactions