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Regulation of the Notch signaling pathway by functional foods for intestinal homeostasis: from mechanistic insights to targeted therapies

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ABSTRACT: The Notch signaling pathway, an evolutionarily conserved mechanism, plays a critical role in regulating the fate of intestinal epithelial cells by modulating processes including proliferation, differentiation, and apoptosis. Dysregulation of this pathway has been linked to a range of intestinal disorders and colorectal cancer. Recent research indicates that functional foods, which encompass polyphenols, dietary fibers, unsaturated fatty acids, and probiotics, may have the capacity to modulate the Notch signaling pathway. These compounds exert their effects by regulating receptor expression, modulating signal transduction, altering target gene expression, and interacting with gut microbiota, thereby indirectly influencing Notch activity. This review examines the critical role of the Notch signaling pathway in maintaining intestinal health and explores the potential of functional foods to enhance this pathway, thereby promoting gut health and preventing intestinal diseases. It highlights the therapeutic potential of functional foods by integrating insights from molecular, cellular, and microbiota research. Future research should explore the effects of bioactive compounds, personalized nutrition based on genetic and microbial profiles, and omics interdisciplinary methods to optimize functional foods for gut health. These advancements could lead to precision nutrition strategies for preventing and treating intestinal diseases.

Keywords: Notch signaling pathway, gut homeostasis, functional foods

1. Introduction

The Notch signaling pathway is critical for maintaining the integrity of intestinal epithelial cells (IECs), which serve as the first line of defense against a wide range of microorganisms in the gut. Dysregulation of this pathway is associated with an increased susceptibility to inflammatory disorders, as demonstrated by studies in which IEC-specific deletion of *Rbpj* in mice leads to chronic colitis due to compromised epithelial integrity and heightened intestinal permeability. Furthermore, the interaction between gut microbiota and the Notch signaling pathway plays a pivotal role, as the microbiota can modulate Notch activation and regulation, thereby influencing gut health. Functional foods, such as prebiotics and probiotics, have been shown to positively affect the diversity of the gut microbiota and may enhance Notch pathway modulation. These foods,

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rich in bioactive compounds, support immune function and promote a balanced microbiome, both of which are essential for maintaining gut homeostasis and preventing inflammatory conditions.

The gut is frequently termed the "second brain" of the human body, functioning as an essential locus for digestion and immune defense while accommodating a complex ecosystem of symbiotic microorganisms. The maintenance of gut homeostasis is imperative for overall health; however, its intricate and sensitive nature renders it vulnerable to both internal and external influences [1]. The intestinal epithelium, comprising a cellular layer lining the gastrointestinal tract, functions as a critical barrier that impedes the entry of pathogenic microorganisms and toxins, while simultaneously facilitating nutrient absorption and mediating communication of immune molecules [2]. To maintain gut homeostasis, intestinal epithelial cells continuously renew and differentiate to meet the body's nutrient absorption needs, microbial balance, and immune defense requirements [3]. The Notch signaling pathway, a conserved signaling system, plays a central role in regulating cell differentiation, proliferation, and self-renewal [4]. It also plays an indispensable role in maintaining gut homeostasis.

The Notch signaling pathway is a highly conserved signal transduction system, extensively studied for its role in regulating the fate determination of intestinal epithelial cells. Notch signaling is mediated through intercellular interactions, primarily involving the binding of Notch receptors to ligands, such as those in the Delta-like and Jagged families [5]. Upon activation, the Notch receptor undergoes proteolytic cleavage, resulting in the release of the Notch intracellular domain (NICD). Subsequently, the NICD translocates to the nucleus, where it interacts with various transcription factors to initiate the transcription of target genes. This signaling cascade influences critical cellular processes, including proliferation, differentiation, and apoptosis [6]. In the intestinal epithelium, Notch signaling regulates the differentiation of intestinal epithelial cells, ensuring that various cell types—absorptive cells, goblet cells, enteroendocrine cells, and Paneth cells—are generated in the correct proportions to maintain normal gut function [7]. Specifically, activation of Notch signaling helps inhibit goblet cell differentiation while promoting absorptive cell differentiation, which is crucial for the formation of the intestinal barrier [8].

Notch signaling in the gut plays a role that extends beyond mere homeostasis. Disruption of this pathway has been strongly linked to the development of various gastrointestinal disorders. Both excessive activation and inhibition of Notch signaling are thought to contribute significantly to the progression of diseases such as inflammatory bowel disease (IBD) and colon cancer [9]. For example, excessive activation of Notch signaling can promote abnormal proliferation of intestinal cells, leading to impaired differentiation and an increased risk of tumor formation [10]. Conversely, the suppression of Notch signaling may impair intestinal regeneration and repair, increasing the susceptibility of the gut to damage and chronic inflammation. Previous studies suggest that Notch signaling interacts with other key pathways, such as the Wnt and Hedgehog pathways, which collectively influence the cell fate determination, proliferation, and self-renewal of intestinal cells [11, 12].

Research is increasingly focused on modulating Notch signaling to protect gut health. Traditional drugs can regulate this signaling but often come with side effects and dependency issues. Recently, natural functional foods have gained attention for their potential to naturally influence Notch signaling through their components [13]. A variety of natural bioactive compounds, such as polyphenols, dietary fibers, unsaturated fatty acids, probiotics, and their metabolites, have exhibited significant potential in regulating Notch signaling [14]. Specifically, polyphenolic compounds, including tea polyphenols and resveratrol, have been shown to inhibit the overactivation of Notch signaling, thereby facilitating the normal differentiation and repair of intestinal epithelial cells [15, 16]. Short-chain fatty acids (SCFAs), such as butyrate and acetate, produced by the metabolism of dietary fibers by the gut microbiota also influence Notch signaling activation through epigenetic modifications and contribute to immune balance regulation [17]. Furthermore, probiotics and their metabolites have been shown to enhance intestinal barrier function and combat inflammation via the Notch signaling pathway both *in vitro* and *in vivo* [18].

The biological effects and underlying mechanisms of functional food components are attracting growing interest. These foods' ability to influence Notch signaling pathways holds promise not only for preventing and treating gut-related disorders but also for advancing personalized nutrition and targeted therapeutic strategies. For instance, in addressing gut inflammation and colon cancer, the targeted consumption of specific functional foods can modulate Notch signaling in a way that complements conventional drug treatments, potentially minimizing side effects and reducing reliance on medication [19]. Moreover, the "nutraceutical" approach, which is based on functional food components, can help tailor nutritional interventions for individuals on the basis of their Notch signaling status and gut health needs, enabling precision nutrition and personalized health management.

Although substantial evidence supports the role of functional foods in regulating Notch signaling, their effects are still limited by factors such as bioavailability, metabolic pathways, and individual differences [20]. Many natural bioactive compounds demonstrate promising regulatory effects *in vitro*, yet their clinical potential is often limited due to challenges in achieving effective concentrations *in vivo*, owing to factors such as digestion, absorption, and metabolism [15-18]. Therefore, improving the bioavailability of these active compounds and gaining a more comprehensive understanding of their metabolic pathways are essential challenges that need to be addressed. Future research should prioritize the investigation of the specific mechanisms through which functional foods influence Notch signaling, as well as examine their interactions with other cellular pathways. This approach will provide deeper insights into their broader role in maintaining gut homeostasis.

In summary, functional foods that influence Notch signaling pathways present significant promise for sustaining gut homeostasis and preventing intestinal diseases. This review explores the fundamental role of Notch signaling in gut health, evaluates the molecular mechanisms through which functional foods modulate Notch signaling, and discusses their potential in the prevention and treatment of intestinal diseases. The

objective is to offer both theoretical and practical insights for future personalized nutrition interventions and targeted therapeutic strategies.

2. The role of the Notch signaling pathway in gut homeostasis

The Notch signaling pathway is a highly conserved intercellular communication system prevalent across multicellular organisms, playing a crucial role in cell fate determination across various tissues. Within the gastrointestinal tract, Notch signaling is integral to maintaining epithelial cell homeostasis and orchestrating vital physiological processes, including cell proliferation, self-renewal, and differentiation. Consequently, it is essential for the normal development of intestinal epithelial cells, the maintenance of barrier integrity, and the facilitation of repair mechanisms following tissue injury [21]. Intestinal epithelial cells, as the frontline defenders of gut homeostasis, directly influence the health of the entire digestive system and even the whole body. As a central control mechanism for this dynamic balance, the impact of Notch signaling on gut homeostasis is highly important.

2.1 Basic mechanism of the Notch signaling pathway

The core of the Notch signaling pathway consists of Notch receptors, ligands, and downstream target genes. In mammals, the Notch signaling system includes four receptors (Notch1–4) and multiple ligands (including the Delta-like and Jagged families) [22, 23]. Notch signaling is typically activated through direct cell-to-cell interactions, where a Notch receptor on the surface of one cell binds to a ligand on an adjacent cell, triggering a cascade of molecular events. This interaction leads to the proteolytic cleavage of the Notch receptor, releasing the Notch intracellular domain (NICD), which then translocates to the nucleus. Once in the nucleus, the NICD interacts with transcriptional complexes to regulate the expression of downstream target genes [24]. The activation of the receptor and subsequent transcriptional regulation profoundly impact cellular processes such as differentiation, proliferation, and self-renewal.

Within the gut, the activation of Notch signaling is crucial for preserving the equilibrium of epithelial cell differentiation. The intestinal epithelium comprises a diverse array of cell types, including enterocytes, goblet cells, Paneth cells, and endocrine cells. These cells perform vital functions such as nutrient absorption, mucus secretion, immune defense, and hormone production. The relative proportions of these cell types are meticulously regulated by Notch signaling pathways [25, 26]. During the differentiation process of intestinal stem cells, the activation of Notch signaling facilitates their differentiation into enterocytes while inhibiting the formation of goblet cells [27]. This regulatory mechanism ensures the proper distribution of cell types within the gut, thereby maintaining its barrier function and fulfilling essential nutrient absorption requirements.

2.2 Role of Notch signaling in intestinal cell fate determination

Notch signaling plays a crucial role in the development of both the small and large intestines by controlling the self-renewal and differentiation of intestinal epithelial cells, essential for maintaining gut balance. This pathway acts as a key determinant of epithelial stem cell fate, driving their differentiation into

enterocytes while preventing the formation of goblet cells, thereby reinforcing the gut's barrier function [28]. Upon activation of Notch signaling, the accumulation of the Notch intracellular domain (NICD) suppresses the expression of transcription factors like Atoh1, thereby inhibiting the formation of secretory cells, including goblet and Paneth cells, while promoting the differentiation of enterocytes [29]. This differentiation process is essential for preserving the structural integrity and functional capacity of the gut barrier. Disruption of Notch signaling can disturb this differentiation equilibrium, potentially resulting in a compromised gut barrier or aberrant cell proliferation.

2.3 Interaction of Notch signaling with other signaling pathways

Notch signaling does not act in isolation but interacts closely with other signaling pathways, such as the Wnt, Hedgehog, and TGF- β pathways, to regulate intestinal cell fate [22]. These pathways influence the proliferation and differentiation of intestinal epithelial cells through various mechanisms and cascades. For example, Wnt signaling is another key regulator of intestinal stem cell maintenance, providing signals from regions near Paneth cells at the base of the crypts to support stem cell self-renewal [30]. When Wnt and Notch signals act together, intestinal stem cells receive multilevel regulation to balance their self-renewal and differentiation needs [31]. Hedgehog signaling, on the other hand, participates in cross-layer regulation between the epithelial layer and the underlying stroma, working in tandem with Notch signaling to determine the differentiation direction and proliferation of epithelial cells [32]. These interactions increase the complexity of the signaling network, allowing the intestinal epithelium to adapt to environmental changes with remarkable flexibility and resilience.

2.4 Dysregulation of Notch signaling and its association with gut diseases

Dysregulation of Notch signaling has been implicated in various gut diseases, including inflammatory bowel disease (IBD), colorectal cancer, and intestinal infections. In IBD (such as Crohn's disease and ulcerative colitis), both the aberrant activation and inhibition of Notch signaling can contribute to the initiation and chronicity of inflammatory responses [33]. For example, inhibition of Notch signaling may lead to abnormal differentiation of intestinal epithelial cells, with an increased proportion of goblet and endocrine cells, which weakens the stability of the intestinal barrier, making it easier for pathogenic microbes to cross into the body [34]. Additionally, excessive activation of Notch signaling may lead to the overproliferation of intestinal cells, increasing the risk of cancer. Research has demonstrated that in patients with colorectal cancer, Notch signaling is frequently hyperactivated. This hyperactivation may contribute to abnormal cell proliferation and differentiation, thereby facilitating carcinogenesis [35]. Therefore, dysregulated Notch signaling is a potential pathological mechanism underlying gut diseases.

2.5 Dynamic regulation of Notch signaling in tissue regeneration

The self-renewal capacity of the intestinal epithelium depends on the sustained activity of stem cells, and Notch signaling also plays an important role in tissue regeneration after injury [36]. In gut injury and tissue repair, Notch signaling is regulated to maintain cell regeneration at the site of damage [37]. During the repair

phase, the dynamic regulation of Notch signaling precisely governs the proliferation and differentiation of stem cells at the injury site, thereby ensuring the restoration of the intestinal barrier [30, 35]. When the gut is subjected to physical damage or pathogen invasion, the rapid modulation of Notch signaling can initiate the proliferation and differentiation of intestinal epithelial cells, facilitating the repair process [38]. This ability allows the gut to respond quickly to environmental changes and tissue damage, making it one of the critical mechanisms in maintaining gut homeostasis.

2.6 Interaction between Notch signaling and the microbiota

Recent evidence has increasingly highlighted the close relationship between the gut microbiota and Notch signaling. Metabolites produced by the gut microbiota, such as short-chain fatty acids, can regulate Notch signaling activity, affecting the differentiation of intestinal epithelial cells [39]. For example, short-chain fatty acids such as butyrate can regulate Notch signaling through epigenetic modifications, thereby inhibiting inflammation and promoting gut homeostasis [40]. This finding indicates that Notch signaling is not only regulated by host factors but also directly or indirectly influenced by the gut microbiota, further enhancing our understanding of the mechanisms underlying the regulation of gut homeostasis.

The Notch signaling pathway plays a role in gut homeostasis not only as a structural safeguard but also as a dynamic regulator. By regulating the differentiation of intestinal epithelial cells, maintaining the integrity of the epithelial barrier, and playing a critical role in injury repair, inflammatory responses, and microbial balance, Notch signaling is a central factor in the regulation of gut homeostasis [41]. Dysregulation of Notch signaling can lead to various gut diseases, and understanding its mechanisms in maintaining gut homeostasis and disease pathogenesis will provide new therapeutic targets for the treatment and prevention of gut diseases.

3. Functional foods and their regulation of the Notch Signaling pathway

As our understanding of the relationship between nutrition and health continues to deepen, functional foods have emerged as potential natural interventions, increasingly gaining focus in modern nutritional science and food research [42]. Functional foods refer to food components with specific biological activities that positively influence health. These foods not only fulfill the basic nutritional needs of the body but also regulate various physiological functions to prevent and improve a range of chronic diseases [43]. In recent years, functional foods have attracted significant attention for their role in gut health, inflammation regulation, immune support, and cancer prevention [44].

3.1 Definition and classification of functional Foods

Functional foods are a category of foods that provide health benefits beyond basic nutrition. These foods are characterized by their ability to promote health and reduce the risk of disease, thanks to the presence of bioactive compounds. The concept of functional foods is closely tied to the idea of food as medicine, where certain foods are consumed not only for their nutritional value but also for their potential to improve health outcomes. The classification of functional foods can be complex due to the diverse nature of the foods and the bioactive compounds they contain (Table 1). One approach to classifying functional foods is based on the

source of the bioactive ingredients. For instance, functional foods can be derived from plants, animals, or microorganisms [45]. Plant-based functional foods frequently contain phytochemicals, including flavonoids and carotenoids, which have demonstrated antioxidant and anti-inflammatory properties [40, 43]. Animal-based functional foods might include dairy products enriched with probiotics or omega-3 fatty acids, which are known to support gut health and cardiovascular function, respectively [46].

Another classification system for functional foods is based on the type of health benefit they provide. Some functional foods are designed to enhance specific physiological functions, such as improving digestive health, boosting immune function, or reducing the risk of chronic diseases like heart disease and diabetes [47]. For example, foods fortified with dietary fiber can aid in digestion and help maintain healthy blood sugar levels [48]. Functional foods can also be categorized by their level of processing. This classification considers whether the foods are minimally processed, processed, or ultra-processed, with the understanding that the degree of processing can affect the bioavailability and efficacy of the bioactive compounds [49]. Minimally processed functional foods, such as fresh fruits and vegetables, tend to retain more of their natural nutrients and bioactive compounds compared to highly processed foods [50]. The development and consumption of functional foods are influenced by various factors, including consumer perceptions, regulatory frameworks, and scientific research. Consumers often view functional foods as a way to compensate for unhealthy lifestyle choices, although there is some skepticism about their efficacy and safety [51]. Regulatory bodies play a crucial role in defining and approving health claims associated with functional foods, ensuring that these claims are supported by scientific evidence [52]. In summary, functional foods are an important component of modern diets, offering potential health benefits that extend beyond basic nutrition. Their classification can be based on the source of bioactive ingredients, the health benefits they provide, and their level of processing. As research continues to uncover the health-promoting properties of various foods, the definition and classification of functional foods will likely evolve, providing consumers with more options to support their health and well-being.

Table 1. Functional food categories

Category	Definition	Examples
Probiotics	Live microorganisms that confer health benefits when consumed in adequate amounts	Yogurt, Kefir, Kimchi, Sauerkraut, Miso
Prebiotics	Non-digestible food ingredients that promote the growth of beneficial gut bacteria	Chicory root, Garlic, Onions, Bananas, Asparagus
Antioxidant-Rich Foods	Foods containing compounds that neutralize free radicals and reduce oxidative stress	Blueberries, Green tea, Dark chocolate, Spinach, Walnuts
Unsaturated fatty acids	Essential fatty acids that support heart, brain, and immune health	Fatty fish (salmon, mackerel), Flaxseeds, Chia seeds, Walnuts, Algal oil
Fiber-Rich Foods	Foods high in dietary fiber that support digestion and gut health	Whole grains (oats, barley), Legumes (beans, lentils), Fruits (apples, pears), Vegetables (broccoli, carrots)
Plant-Based Proteins	Protein sources derived from plants, supporting muscle health and sustainability	Soy products (tofu, tempeh), Lentils, Chickpeas, Quinoa, Nuts and seeds

Fortified Foods	Foods enhanced with additional nutrients to address dietary deficiencies	Fortified cereals (iron, vitamin B12), Fortified milk (vitamin D), Fortified orange juice (calcium)
Low-Glycemic Index Foods	Foods that cause a slower, more gradual rise in blood sugar levels	Whole grains, Legumes, Non-starchy vegetables (leafy greens, broccoli), Nuts and seeds

3.2 Regulation of the Notch signaling pathway by functional foods

This review provides an overview of diverse functional foods and their constituents, emphasizing their effects on the Notch signaling pathway concerning various diseases or conditions. The components discussed include probiotics, prebiotics, tea polyphenols, resveratrol, and anthocyanins, each associated with distinct health benefits and their role in modulating Notch signaling within the context of various intestinal disorders (as shown in Table 2).

Table 2. The Role of Functional food in Modulating the Notch Signaling Pathway

Component	Disease or Condition	Study Overview	Findings	References
Probiotics (<i>Lactobacillus</i> , <i>Bifidobacterium</i>)	Inflammatory bowel disease (IBD), intestinal epithelial repair	Examined probiotics' modulation of Notch signaling via SCFAs and HDAC inhibition, targeting Hes1/Hey1.	Reduced pro-inflammatory cytokines (TNF- α), enhanced goblet cell differentiation, promoted intestinal stem cell (ISC) differentiation.	[53]–[58]
Prebiotics (inulin, oligosaccharides)	Ulcerative colitis, colorectal cancer (CRC)	Studied fermentation of prebiotics to SCFAs, focusing on butyrate's role in HDAC inhibition and Notch regulation.	Butyrate suppressed oncogenic Notch1 in CRC, improved gut barrier integrity, and reduced systemic inflammation.	[60]–[63]
Tea polyphenols	Intestinal carcinogenesis, differentiation disorders	Investigated suppression of Notch receptors and NICD accumulation in intestinal epithelial cells.	Inhibited excessive Notch activation, promoted normal differentiation/proliferation of intestinal cells.	[66]–[68]
Resveratrol	Intestinal tumors	Explored resveratrol's interaction with Notch receptors to inhibit pathway overactivation.	Reduced tumor incidence by modulating Notch-mediated cell differentiation.	[69]
Anthocyanins	Intestinal cell renewal	Analyzed anthocyanins' upregulation of Notch target genes (Hes family).	Enhanced self-renewal and differentiation of intestinal cells, maintaining homeostasis.	[70]

3.2.1. Probiotics

Probiotics, classified as functional foods, have increasingly demonstrated their distinct benefits in modulating the gut microbiota and the host immune system [53]. These probiotics are live microorganisms that, when ingested in adequate amounts, confer health benefits to the host. They are predominantly found in a variety of fermented foods and nutritional supplements (Fig. 1). Fermented dairy products, such as yogurt and kefir, are among the most common sources of probiotics. These products commonly contain strains of *Lactobacillus* and *Bifidobacterium*, which are well-recognized for their positive effects on gastrointestinal health and digestive function. Specifically, probiotics like *Lactobacillus* and *Bifidobacterium* influence the Notch signaling pathway by promoting gut microbiota equilibrium and generating metabolites such as short-chain fatty acids (SCFAs). SCFAs, notably butyrate, inhibit histone deacetylases (HDACs), which

epigenetically regulate Notch target genes (Hes1 and Hey1), thereby enhancing intestinal stem cell differentiation and facilitating epithelial repair [37, 54]. The Notch signaling pathway is a crucial regulator of intestinal stem cell (ISC) differentiation and epithelial repair. Within this pathway, target genes such as Hes1 and Hey1 play significant roles in maintaining the balance between proliferation and differentiation of ISCs. Hes1, a transcription factor, is known to promote the proliferation of intestinal epithelial cells by enhancing STAT3-dependent transcription, which is crucial for the antimicrobial response and tissue regeneration, particularly in conditions such as ulcerative colitis [54]. Similarly, Hey1, another Notch target gene, is involved in the regulation of ISC differentiation, contributing to the maintenance of intestinal homeostasis [55]. The modulation of Notch signaling and its target genes can significantly impact ISC behavior. For instance, the inhibition of Notch signaling through various mechanisms, such as the use of γ -secretase inhibitors, has been shown to induce the differentiation of ISCs into secretory cell types, including goblet cells, which are essential for maintaining the mucosal barrier and facilitating epithelial repair [56]. Additionally, the role of Notch signaling in the proliferation and differentiation of ISCs is further highlighted by studies demonstrating that the pathway's activation is necessary for maintaining stem cell activity and preventing premature differentiation [57]. Overall, the regulation of Notch target genes like Hes1 and Hey1 is integral to the processes of ISC differentiation and epithelial repair, underscoring the importance of this signaling pathway in intestinal health and disease management. In inflammatory bowel disease (IBD), probiotics reduce pro-inflammatory cytokines (e.g., TNF- α) that aberrantly activate Notch signaling, thereby restoring gut homeostasis. Studies also show that probiotics enhance Notch1-dependent goblet cell differentiation, critical for mucosal immunity and barrier function [58].



Fig. 1. Schematic illustration for applications of probiotics

3.2.2. Dietary Fibers, Prebiotics, and Their Microbial Metabolites

Dietary fiber and its metabolites are integral to the maintenance of human health and the prevention of various diseases. Predominantly located in fruits, vegetables, whole grains, and legumes, dietary fibers are resistant to digestion by human enzymes [59]. Instead, they undergo fermentation by gut microbiota, resulting in the production of advantageous metabolites, such as SCFAs and other microbial derivatives (Fig. 4). Prebiotics, including inulin and oligosaccharides, are a type of nondigestible fermentable carbohydrate that are selectively fermented by beneficial bacteria in the gut. This process alters the composition and metabolic potential of the gastrointestinal microbiome, leading to increased SCFA production [60]. The SCFAs produced, such as acetate, propionate, and butyrate, are known to have various health benefits, including the regulation of metabolic processes and immune responses. One of the mechanisms through which SCFAs exert their effects is by inhibiting histone deacetylases (HDACs).

Butyrate, a crucial SCFA, enhances histone acetylation, promoting transcriptional activation of Notch targets involved in intestinal cell differentiation [40]. The Notch signaling pathway is crucial for maintaining intestinal homeostasis and regulating cell differentiation and proliferation. Butyrate has been shown to affect the expression of genes associated with the Notch pathway, which promotes the differentiation of intestinal epithelial cells and enhances their barrier function [61, 62]. This interaction is especially noteworthy, as it facilitates the differentiation and function of intestinal epithelial cells, thereby promoting barrier integrity and reducing permeability. In colorectal cancer models, prebiotic-derived butyrate suppresses oncogenic Notch1 signaling by downregulating the Notch intracellular domain (NICD) and inducing apoptosis. Prebiotics also improve gut barrier integrity, reducing systemic inflammation that dysregulates Notch pathways [63].

The fermentation of prebiotics into SCFAs has been extensively studied for its potential to improve metabolic health. For instance, inulin, a type of fructan, has been shown to enhance fat oxidation and promote SCFA production in overweight and obese individuals, suggesting its role in improving substrate metabolism [64]. Additionally, inulin-type fructans have been found to improve conditions such as ulcerative colitis by increasing SCFA levels, particularly butyrate, which is associated with reduced inflammation and improved gut health [65]. These metabolites have been demonstrated to confer numerous health benefits, including anti-inflammatory properties, modulation of gut microbiota composition, and enhancement of metabolic health [66]. In conclusion, the fermentation of dietary fibers and prebiotics into SCFAs and their subsequent role in HDAC inhibition and Notch signaling regulation highlights the importance of these dietary components in maintaining gut health and preventing disease. Aberrations in the Notch pathway are implicated in a range of gastrointestinal disorders, such as inflammatory bowel disease (IBD) and colorectal cancer. Further research into the specific mechanisms and clinical applications could provide valuable insights into their potential as therapeutic agents [59, 62, 67].

3.2.3. Antioxidant-Rich Foods

Antioxidant-rich foods, which are abundant in natural bioactive compounds, have been shown to modulate the Notch signaling pathway, offering potential therapeutic benefits. One of the key ways

antioxidant-rich foods influence the Notch signaling pathway is through the modulation of oxidative stress, which is known to affect Notch signaling. For instance, melatonin, a potent antioxidant, has been shown to attenuate oxidative stress injury and apoptosis in diabetic conditions by activating the Notch1/Hes1 signaling pathway. This activation helps in reducing oxidative damage and promoting cell survival, highlighting the protective role of antioxidants in managing oxidative stress-related diseases [68]. Furthermore, natural products such as curcumin, found in turmeric, have demonstrated the ability to inhibit cancer cell survival and metastasis through the Notch-1 signaling pathway. Curcumin's interaction with the Notch pathway suggests its potential as a chemopreventive agent, particularly in cancers where Notch signaling is aberrantly activated [69]. This indicates that dietary agents rich in antioxidants can modulate Notch signaling, thereby influencing cancer progression and offering a complementary approach to conventional therapies. Additionally, the modulation of Notch signaling by dietary lipids, which are often rich in antioxidants, has been observed in various models. For example, dietary cholesterol has been shown to influence Notch signaling in *Drosophila*, affecting intestinal development and metabolism. This suggests that dietary components can have a lasting impact on tissue structure and function through their interaction with the Notch pathway [65].

Fig. 2 illustrates the chemical structures and dietary sources of tea polyphenols, resveratrol, and anthocyanins. For example, tea polyphenols, especially catechins, have been found to suppress the expression of Notch receptors, reducing the accumulation of NICD and thus inhibiting excessive activation of the Notch signaling pathway [66]. In intestinal epithelial cells, excessive activation of Notch signaling is often associated with uncontrolled cell proliferation, differentiation disorders, and intestinal carcinogenesis [67]. Tea polyphenols, by modulating Notch signaling, promote the normal differentiation and proliferation of intestinal epithelial cells, thereby enhancing gut barrier function [68]. Similarly, resveratrol interacts with Notch receptors to inhibit the overactivation of Notch signaling and reduce the incidence of intestinal tumors [69]. Anthocyanins primarily regulate the self-renewal and differentiation of intestinal cells by upregulating the expression of Notch signaling target genes, such as Hes family genes [70].

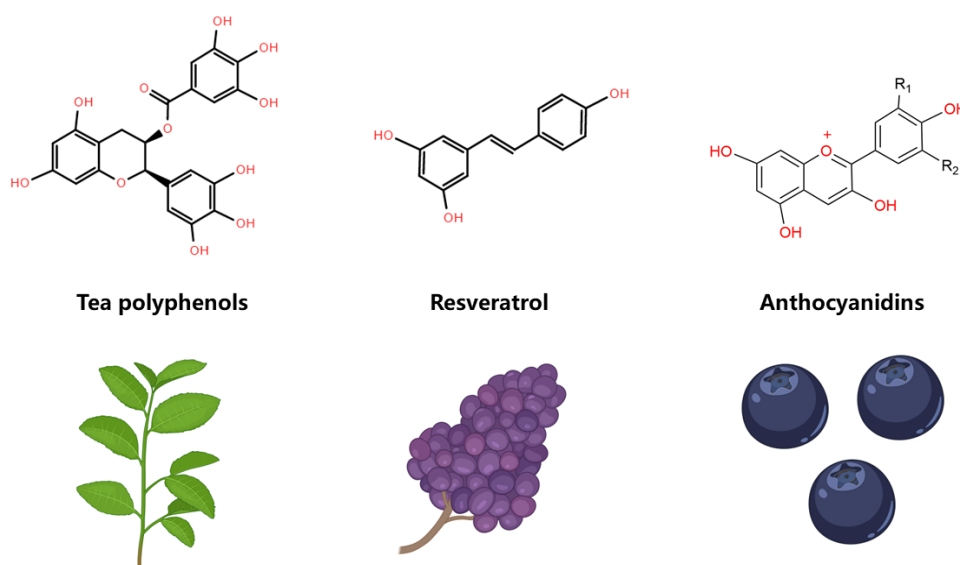


Fig. 2. Chemical structure, examples, and food sources of some polyphenolic compounds (Tea polyphenols, resveratrol, and anthocyanins)

3.2.4. Unsaturated Fatty Acids

Unsaturated fatty acids, especially omega-3 fatty acids (such as eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), are widely regarded as anti-inflammatory nutrients (as shown in Fig. 3) [71]. These fatty acids play a crucial role in modulating inflammatory processes and have been linked to various health benefits, particularly in the context of chronic diseases. Omega-3 fatty acids are known to influence the production of lipid mediators that can either promote or resolve inflammation. For instance, EPA and DHA are precursors to specialized pro-resolving mediators, which actively participate in the resolution of inflammation and have been shown to reduce the levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) in various studies [72]. Moreover, the anti-inflammatory effects of omega-3 fatty acids extend to their ability to alter membrane fluidity and signaling pathways within cells. This modulation can lead to changes in gene expression related to inflammation and lipid metabolism, thereby contributing to their protective effects against conditions such as cardiovascular disease, obesity, and metabolic syndrome. Additionally, recent research has highlighted the importance of the balance between omega-3 and omega-6 fatty acids in the diet, as an excess of omega-6 fatty acids can promote inflammatory processes, while adequate intake of omega-3 fatty acids can counteract these effects [71]. Studies have shown that omega-3 fatty acids regulate the Notch signaling pathway and play a crucial role in the regulation of gut inflammation. Omega-3 fatty acids can reduce the secretion of proinflammatory factors, inhibit excessive proliferation and abnormal differentiation of intestinal epithelial cells, and thus help maintain intestinal homeostasis [72]. Omega-3 fatty acids facilitate a moderate activation of Notch signaling pathways, attenuate deleterious immune responses, mitigate intestinal inflammation, and enhance gastrointestinal health [73].

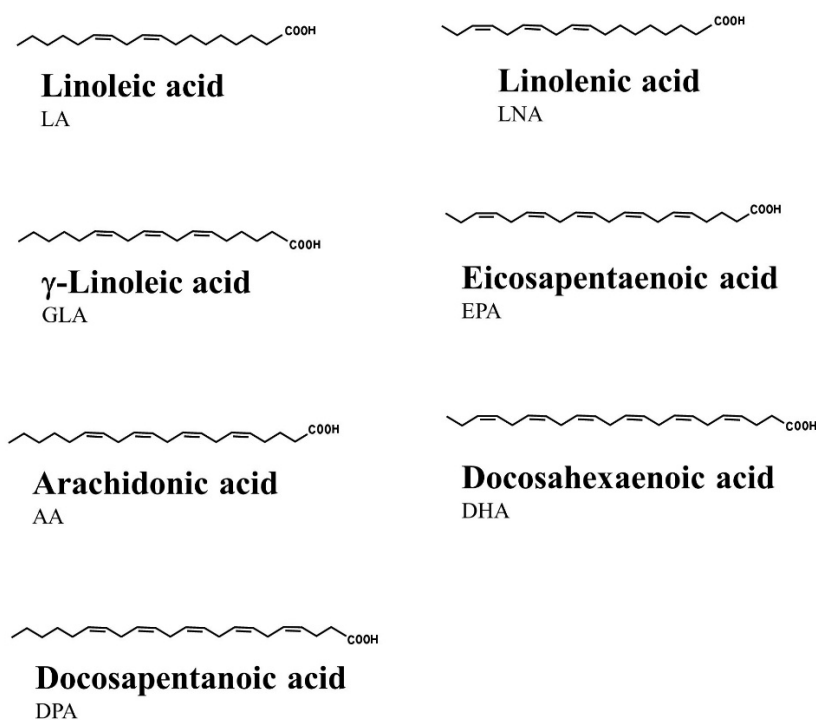


Fig. 3. Chemical structure of Omega-3 and Omega-6 polyunsaturated fatty acids

3.2.5. Plant-Derived Bioactive Compounds and Proteins

Soy isoflavones have been studied for their potential role in cancer prevention and treatment, particularly in hormone-dependent cancers such as breast cancer. One of the mechanisms by which soy isoflavones exert their effects is through the modulation of the Notch signaling pathway. The Notch pathway is crucial for cell differentiation, proliferation, and apoptosis, and its dysregulation has been implicated in various cancers, including breast cancer. Research indicates that soy isoflavones can inhibit the cleavage of Notch1, a critical step in the activation of the Notch signaling pathway. This inhibition leads to a reduction in the expression of Hes1, a downstream target of Notch signaling, which is known to play a role in maintaining the cancer stem cell population and promoting tumor growth. By reducing Hes1 expression, soy isoflavones may decrease the proliferation of cancer cells and enhance their sensitivity to other therapeutic agents.

Moreover, the interplay between glutathione and other cellular pathways, such as the Nrf2-ARE pathway, is also significant. The activation of the Nrf2-ARE pathway by compounds like l-methionine has been shown to stimulate endogenous antioxidant activity, which includes the upregulation of glutathione synthesis. This process helps in reducing ROS-derived oxidative stress, thereby protecting cells from damage [79]. Such findings suggest that enhancing glutathione synthesis through dietary or genetic means could be a potential strategy for improving oxidative stress resistance in plants and possibly influencing pathways like Notch signaling.

3.2.6. Fortified Foods

Furthermore, the interaction between Vitamin D and Notch signaling is not limited to prostate cancer. Studies have shown that Vitamin D can modulate Notch signaling in other cancer types as well, such as breast cancer, where it affects the expression of Notch target genes and influences cancer stem cell properties [81]. Folate plays a crucial role in maintaining DNA methylation, which is a key mechanism in the silencing of Notch-related oncogenes. Aberrant methylation of promoter regions is a significant mechanism underlying the inactivation of tumor suppressor genes during carcinogenesis. Studies have shown that methylated DNA from tumor cells can be released into circulation, serving as a potential marker for non-invasive tumor detection. The catalytic activities of folate metabolism-related enzymes and the synthesis of methyl donors are vital for cellular methylation reactions (Fig. 5).

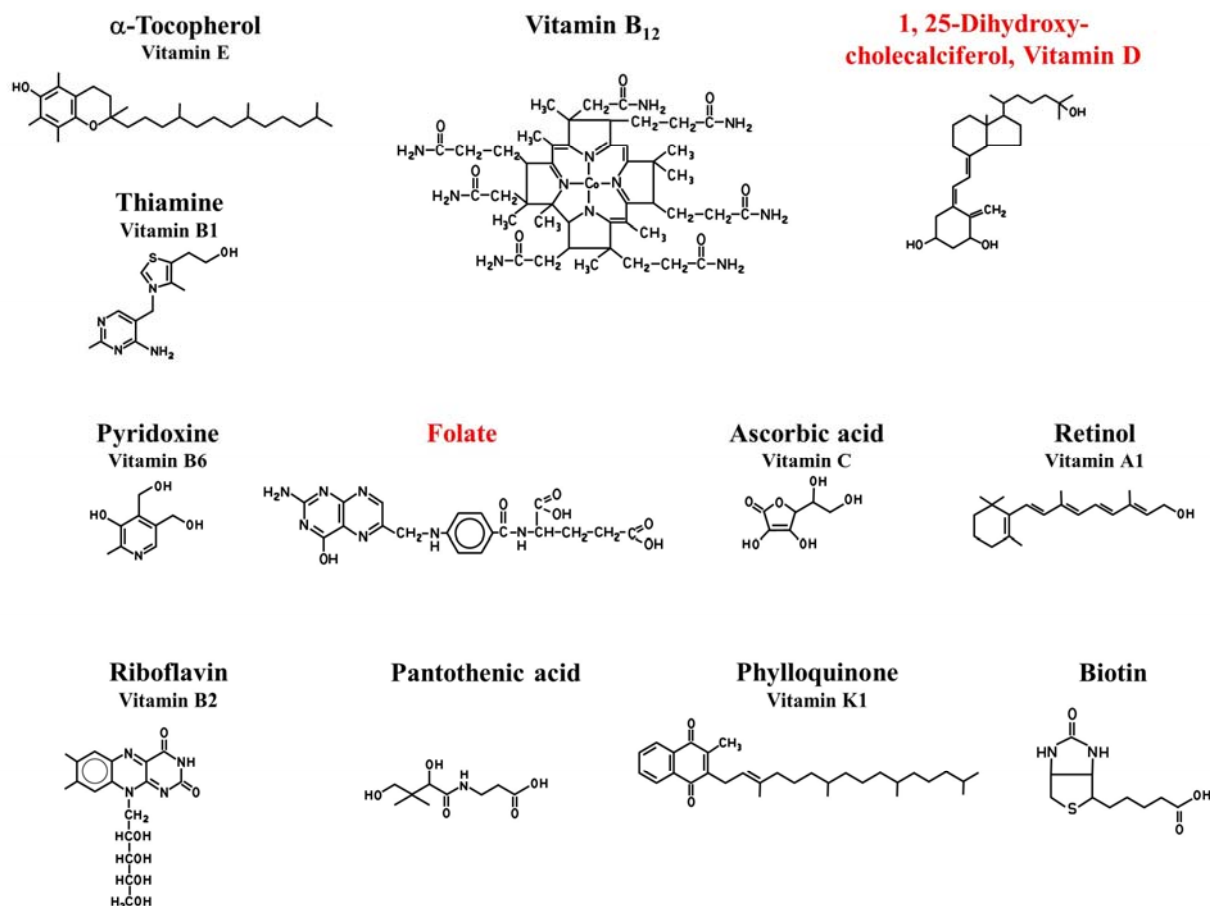


Fig. 5. Chemical structures of vitamins

3.2.7. Low-Glycemic Index Foods

High-sugar diet in the initiation and exacerbation of inflammatory bowel diseases. Prior studies have demonstrated that a two-day exposure to a high-sugar diet swiftly modifies gut microbial composition, leading to a reduction in short-chain fatty acids and an increased susceptibility to chemically induced colitis [82]. Low-glycemic diets have been shown to play a significant role in stabilizing insulin and insulin-like growth factor 1 (IGF-1) levels, which in turn can reduce the activity of the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway. This pathway is crucial in cellular growth, proliferation, and survival, and its dysregulation is often implicated in cancer progression. By stabilizing insulin/IGF-1 levels, low-glycemic diets may help mitigate the hyperactivation of the PI3K/Akt/mTOR pathway, which is known to amplify Notch signaling in various cancers. Notch signaling is a fundamental pathway that regulates cell differentiation, proliferation, and apoptosis, and its aberrant activation is associated with tumorigenesis. Research has demonstrated that dietary interventions, such as calorie restriction or glucose restriction, can inhibit energy-dependent pathways, including IGF-1/PI3K/Akt/mTOR, in cancer cells. For instance, a study on curcumin treatment combined with glucose restriction in hepatoma cells showed that this combination inhibited intracellular alkalinization and tumor growth by affecting the mTOR complex and reducing the phosphorylation of downstream targets like 4EBP1, ultimately inhibiting cell migration and proliferation [83].

Moreover, the suppression of insulin feedback has been found to enhance the efficacy of PI3K inhibitors in cancer treatment. Inhibition of PI3K can lead to transient hyperglycemia due to disrupted glucose metabolism, which is usually counteracted by compensatory insulin release. However, this insulin feedback can reactivate the PI3K/mTOR signaling axis in tumors, potentially compromising treatment effectiveness. Preventing this feedback through dietary or pharmaceutical approaches has been shown to enhance the efficacy of PI3K inhibitors, providing a promising strategy for improving cancer treatment outcomes [84]. Additionally, the crosstalk between different signaling pathways, such as the Hedgehog and Wnt pathways, with the PI3K/Akt/mTOR pathway, highlights the complexity of cellular signaling in cancer. These pathways are traditionally associated with cellular growth and differentiation but are also involved in regulating cellular homeostasis and energy balance [85].

The findings indicate that functional foods, owing to their bioactive constituents, possess therapeutic potential in modulating the Notch signaling pathway. This presents promising strategies for the prevention and treatment of various intestinal diseases, the promotion of epithelial repair, and the enhancement of gut health. Further investigation into their specific mechanisms and interactions is necessary to optimize the clinical application of these foods.

4. Mechanistic research: regulation of the Notch signaling pathway by functional foods

The Notch signaling pathway is a highly conserved intercellular communication mechanism that plays a crucial role in maintaining various physiological processes, including cell proliferation, differentiation, fate determination, and tissue homeostasis. Notch signaling, a critical pathway governing cell fate and development, is essential for maintaining gut health. Recent research has increasingly demonstrated that functional foods and their bioactive components have the capacity to modulate Notch signaling. This modulation suggests a potential for these foods to influence intestinal homeostasis, enhance gut barrier function, and prevent or treat intestinal diseases. This section examines the mechanisms by which functional foods regulate the Notch signaling pathway and their prospective roles in sustaining intestinal homeostasis.

4.1 Regulation of the expression of genes downstream of Notch

The final effect of Notch signaling is mediated through the regulation of its downstream target genes. Common Notch target genes include *Hes*, *Hey*, and *p21*, which play significant roles in regulating cell fate, inhibiting excessive proliferation, and maintaining intestinal homeostasis [86]. Functional foods regulate Notch signaling by influencing the expression of these target genes. For example, short-chain fatty acids such as butyrate can upregulate the expression of *Hes1* and *Hey1*, promoting the differentiation and self-renewal of intestinal epithelial cells and thus enhancing gut barrier function [58, 87]. Butyrate functions not only through altering the transcriptional activity of Notch signaling but also by regulating the immune microenvironment of the gut, suppressing the release of inflammatory factors and maintaining intestinal homeostasis. Moreover, bioactive components in functional foods, such as selenium compounds, can activate genes such as *p21* that inhibit the cell cycle, suppressing excessive proliferation of intestinal epithelial cells and reducing the risk of

intestinal carcinogenesis [88]. Selenium regulates Notch signaling downstream effects, maintaining the normal differentiation of intestinal epithelial cells and preventing intestinal inflammation.

4.2 Regulation of the gut microbiota and their metabolites

The gut microbiota plays a crucial role in regulating Notch signaling [89]. An increasing number of studies have shown that functional foods can indirectly regulate Notch signaling by affecting the structure and metabolism of the gut microbiota [90]. Dietary fibers, probiotics, and other functional food components can promote the growth of beneficial microbes, regulate the production of short-chain fatty acids, and thereby influence Notch signaling. For example, dietary fibers and probiotics in the diet can regulate Notch signaling activity through their metabolites, particularly short-chain fatty acids [91]. SCFAs modulate Notch signaling by affecting the expression of target genes, enhancing the differentiation and repair of intestinal epithelial cells and promoting the restoration of gut barrier function (as shown in Fig. 4) [92]. Additionally, probiotics produce metabolites such as lactic acid, which affects the immune microenvironment in the gut and modulates Notch signaling activation, effectively preventing intestinal inflammation [93].

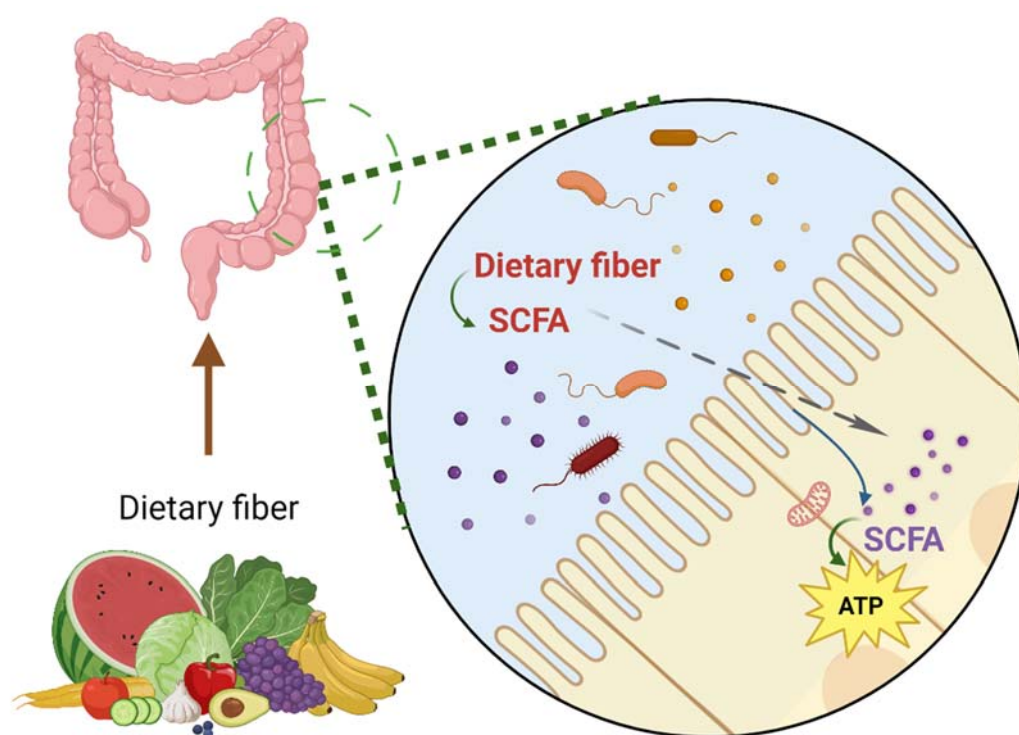


Fig. 4. A diagrammatic representation of the synthesis of SCFAs via the fermentation of dietary fibre by gut microbial species

The gut microbiota and Notch signaling have a complex and bidirectional interaction that is essential for maintaining intestinal homeostasis. The gut microbiota can influence Notch signaling through various mechanisms. For example, certain bacteria in the gut can produce metabolites that directly or indirectly affect the expression and activity of Notch pathway components (Fig. 6). On the other hand, Notch signaling can also impact the composition and function of the gut microbiota. In *Drosophila*, it has been shown that Notch signaling in the intestinal epithelium can regulate the production of antimicrobial peptides, which can in turn affect the gut microbiota composition. In mammals, dysregulation of Notch signaling has been associated with

changes in the gut microbiota, leading to an imbalance in the microbial community. Understanding this interaction may provide new insights into the pathogenesis of intestinal diseases and potential therapeutic targets.

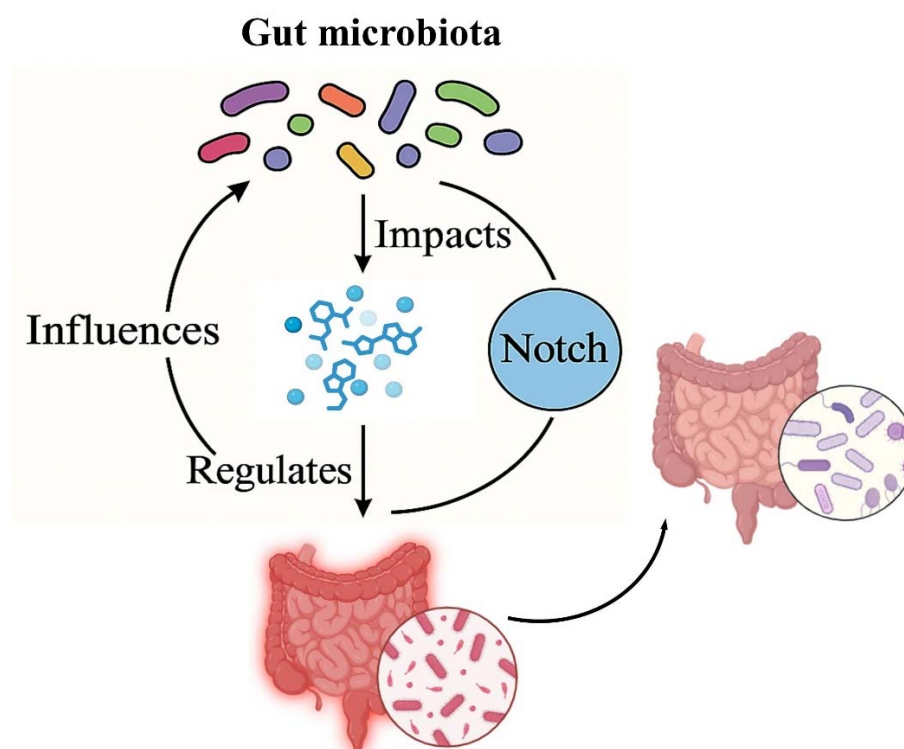


Fig. 6. Gut microbes and Notch signaling pathway

5. Functional foods and the regulation of the Notch signaling pathway: clinical and therapeutic implications

The modulatory impact of functional foods on the Notch signaling pathway has been substantiated through a multitude of preclinical and clinical investigations. Preclinical studies have demonstrated that constituents such as polyphenols, dietary fibers, and SCFAs derived from functional foods can modulate various stages of the Notch signaling pathway. This modulation enhances intestinal homeostasis and mitigates the progression of intestinal diseases [45]. Nonetheless, notwithstanding these significant findings, the clinical efficacy of functional foods in modulating Notch signaling necessitates further validation. Future clinical studies should focus on evaluating the efficacy and safety of functional foods in patients with different intestinal diseases, such as ulcerative colitis, Crohn's disease, and intestinal cancer, and further explore the potential of functional foods in promoting gut health.

5.1 Regulation of the Notch signaling pathway by functional foods

The importance of Notch signaling in intestinal homeostasis, particularly in regulating the proliferation and differentiation of intestinal epithelial cells, has been widely studied. The precise regulation of Notch signaling ensures the normal renewal of intestinal epithelial cells and the maintenance of gut barrier function. Functional foods can regulate intestinal homeostasis by modulating multiple stages of Notch signaling, including receptor expression, signal transduction, and downstream target gene regulation. Components such

as short-chain fatty acids, plant polyphenols, dietary fibers, and probiotics have been shown to modulate Notch signaling activation and inhibition, thereby improving gut health and holding potential in the prevention and treatment of intestinal diseases [94, 95].

For example, SCFAs promote the differentiation of intestinal epithelial cells and enhance barrier function, thereby improving the intestinal microenvironment and effectively preventing inflammatory bowel diseases and other intestinal disorders. Plant polyphenols such as tea polyphenols and resveratrol exert their effects by inhibiting the expression of Notch receptors or by regulating γ -secretase activity, altering Notch signal transduction, and increasing the stability of the intestinal epithelium, thereby reducing the risk of intestinal carcinogenesis [96]. The effects of probiotics are related to regulating the intestinal microecological balance and improving immune responses, indirectly influencing Notch signaling. These studies not only confirm the role of functional foods in intestinal homeostasis but also demonstrate their potential for clinical application as interventions in gut-related diseases.

5.2 Functional foods in the prevention and treatment of intestinal diseases

Notch signaling plays a key role in a variety of intestinal diseases, including inflammatory bowel disease (IBD), intestinal cancer, and gut infections [97]. Abnormal activation or suppression of Notch signaling is closely associated with pathological changes in these diseases [98]. By modulating Notch signaling, functional foods can play important roles in the prevention and treatment of intestinal diseases.

Notch signaling plays a significant role in the immune response within the gut, particularly in T-cell activation and differentiation, as well as in the proliferation and differentiation of intestinal epithelial cells [99]. Research indicates that functional foods such as SCFAs and dietary fibers can regulate Notch signaling activation, promote the self-repair of intestinal epithelial cells, enhance gut barrier function, and reduce intestinal inflammation [100]. As a result, functional foods may serve as important complementary therapeutic agents in the prevention and treatment of IBD.

Intestinal cancers, particularly colorectal cancer, are also closely linked to dysregulation of Notch signaling. Overactivation of Notch signaling leads to abnormal proliferation of intestinal epithelial cells and the formation of undifferentiated tumor cells [101]. Certain bioactive components in functional foods, such as polyphenols and selenium compounds, may help slow the progression of intestinal cancers by inhibiting excessive Notch signaling activation [102, 103]. By further optimizing functional food components and developing interventions targeting the Notch signaling pathway, new strategies for the prevention and treatment of intestinal cancer may emerge.

5.3 Clinical application and future prospects of functional foods

Although existing research has demonstrated the regulatory effects of functional foods on Notch signaling, their clinical application faces several challenges. First, the bioavailability, mechanisms of action, and metabolic processes of different food components in humans are not yet fully understood, which could impact their clinical efficacy. Second, although functional foods have shown efficacy in animal models, their effects in humans still require further validation. Therefore, future research should focus on the design of

clinical trials to evaluate the regulatory effects of functional foods on Notch signaling and their practical applications in gut health management.

Furthermore, with the increasing diversification of functional foods, the rational selection and combination of different functional food components to achieve the maximum therapeutic effect is an important area for future research. By conducting in-depth studies on the components of functional foods and exploring their mechanisms of action in gut health, personalized and precise nutritional intervention strategies may be developed. These strategies could significantly increase the clinical effectiveness of functional foods in the treatment of intestinal diseases.

6. Conclusion

With the escalation of global health challenges, there is a growing recognition of the critical role gut health plays in modulating systemic immunity, metabolism, and neurological function. The preservation of gut homeostasis is contingent upon various physiological regulatory mechanisms, among which the Notch signaling pathway is a crucial cell communication system. This pathway is instrumental in processes such as the proliferation, differentiation, fate determination, and tissue repair of intestinal epithelial cells. Recent research has demonstrated that functional foods significantly contribute to the maintenance of gut homeostasis, the prevention of intestinal diseases, and the enhancement of gut barrier function by modulating various components of the Notch signaling pathway. This review has synthesized current knowledge on the role of Notch signaling in intestinal homeostasis and examined the influence of functional foods on this process. As our understanding of Notch signaling deepens, the targeted application of functional foods to regulate this pathway has emerged as a key area of interest for future research endeavors. Variability in gut microbiome composition, immune responses, and genomic backgrounds can result in substantial differences in the regulation of Notch signaling. Consequently, future research should investigate the impact of functional foods on Notch signaling within the context of personalized medicine and precision nutrition. The objective of personalized nutrition is to formulate targeted nutritional intervention strategies based on an individual's genotype, phenotype, and environmental factors.

By systematically identifying and analyzing individual variations in Notch signaling and integrating these findings with specific components of functional foods, personalized intervention pathways can be elucidated. For instance, certain dietary components, such as SCFAs and plant polyphenols, may prove more efficacious for individuals predisposed to specific intestinal diseases, whereas other populations might derive greater benefit from alternative functional foods. With the advancement of precision nutrition, it is anticipated that the integration of data from genomics, metabolomics, and gut microbiota will enhance the development of tailored nutritional strategies. Research on the regulation of Notch signaling by functional foods is anticipated to expand, particularly within the domains of personalized nutrition, precision medicine, and interdisciplinary studies. Future investigations should focus on elucidating the specific mechanisms by which functional foods modulate Notch signaling, examining their potential applications in a range of intestinal diseases, and advancing their transition from laboratory research to clinical practice. Furthermore,

with the advent of novel nutritional interventions, the precise modulation of Notch signaling holds promise for innovative therapeutic strategies. In summary, the capacity of functional foods to modulate Notch signaling and sustain intestinal homeostasis, along with their potential in the prevention and treatment of gastrointestinal diseases, establishes them as essential elements in the future management of gut health. As scientific research advances, it is anticipated that functional foods will assume an increasingly significant role in personalized nutrition and the management of intestinal disorders.

Declaration of competing interest

The authors declare that they have no known competing of interest with respect to the work described in this manuscript.

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