Research interest in free fatty acid-binding receptors has been growing during the past decade, with an aim to better understand the modulation of host physiology in response to nutrition. G-protein-coupled receptor 43 (GPR43), also called free fatty acid receptor 2 (FFA2/FFAR2), binds short-chain fatty acids (SCFAs) produced by the microbial fermentation of carbohydrates and has shown promising therapeutic potential. This review presents current knowledge regarding the pharmacological properties of GPR43 and addresses its functions in selected organs (adipose tissue, intestine and immune cells). Furthermore, the demonstration of GPR43 involvement in several pathological conditions such as obesity, inflammatory disease, and cancer suggests new fields of interest related to this receptor. Finally, GPR43 could be a key player in gut microbiota-host crosstalk, although further research is needed to clearly evaluate its role in the management of host health by nutrients or treatments targeting the gut microbiota.

GPR43 and GPR41 as key receptors for short-chain fatty acids

G-protein-coupled receptors (GPCRs) are seven-transmembrane (7TM) receptors that mediate cellular responses to the majority of hormones and neurotransmitters, and are therefore attractive targets for drug discovery [1]. Free fatty acids (FFAs) have long been considered as key signaling molecules in numerous physiological and pathological processes. The recent identification of a family of GPCRs that bind FFAs has highlighted new potential mechanisms of action for FFAs in health and disease [2].

Among these FFAs receptors, GPR43 is present in a large variety of tissues, including adipose tissue, inflammatory cells, and gastrointestinal (GI) tract and is activated by SCFAs [3–6]. SCFAs are the major anions present in the large intestine of non-ruminant mammals. They are produced by the gut microbiota through the fermentation of undigested carbohydrates and dietary fibers (Box 1) [7]. The identification of these endogenous ligands of GPR43 has led the scientific community to propose a new appellation for GPR43, namely FFA2 or FFAR2 [2,5]. SCFAs bind GPR43 in the following rank order of potency: propionate ≥ acetate > butyrate > valerate > formate (Figure 1, panel 1) [3–5]. Importantly, SCFAs also activate another receptor of the same family, GPR41, with propionate and butyrate being the most potent agonists [3,4]. Both receptors can couple to Goq, resulting in inhibition of the adenylate cyclase pathway, but only GPR43 is also able to couple to Goq, thus leading to activation of the phospholipase C (PLC) pathway and increased intracellular calcium levels [3,4].

GPR41 and GPR43 bind the same family of ligands (SCFAs), exhibit some overlapping expression, and partially share signaling pathways (Goq). Furthermore, both receptors represent potentially interesting targets for drug discovery. The pathophysiological roles of GPR41 have been largely described in several recent reviews and will not be discussed here [8–10]. We will focus solely on GPR43 in order to address in detail all aspects related to this receptor. In this review, we briefly present the pharmacological tools currently available to study GPR43. We also evaluate the relevance of GPR43 in the symbiotic relationship between the gut microbiota and its host in adipose tissue, GI tract, and immune cells. Finally, we examine the therapeutic potential of GPR43 for treating diseases such as obesity, diabetes, inflammatory disorders, and cancer.

Evaluation of GPR43 as a target: a pharmacological challenge

SCFAs exert variable actions through several pathways [11–13]. Therefore, the development of selective agonists and antagonists of GPR43 is required to decipher which beneficial effects of the SCFAs may be dependent on their binding to GPR43 and to investigate the therapeutic potential of modulating GPR43 activity. Two other arguments are in favor of the development of pharmacological tools specific for GPR43: firstly, SCFA potency is low, ranging from high micromolar to low millimolar concentrations; secondly, GPR43 knockout (KO) mice could not be an ideal model to investigate GPR43 function because of an altered expression of GPR41 in these mice, which could interfere with the interpretation of the data related to SCFAs [11,14].

Designing selective GPR43 modulators requires characterization of its orthosteric and allosteric binding pockets, including the identification of the requirements for selective activation of GPR43 versus GPR41. Two arginine and one histidine have been established as crucial for recognition of SCFAs by human orthologs of both receptors (R180, R255, H242 for hGPR43 and R185, R258, H245 for hGPR41) [8,15,16]. The difference in selectivity at the

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Box 1. Introducing the gut microbiota and prebiotics

The microbiota consists of 100 trillion microorganisms, which outnumber human cells in the body by at least tenfold. The majority of the microbes reside in the gut, where they exert diverse and crucial functions (e.g., energy extraction from undigested food, bile acid metabolism, regulation of mucosal immunity and gut barrier function, production of metabolic regulators) [7,43]. Gut microbiota composition is influenced by various factors coming from the host and the environment, such as diet, age, genetic background, or immunity [43].

The whole gut bacterial gene set, defined as the microbiome, is around 150 times larger than the human genome. This extensive gene set confers to the gut microbes a huge metabolic capacity [56]. Accordingly, the diversity of the produced metabolites, including SCFAs, could explain why these gut microbes are involved in a symbiotic relationship with the host [43]. SCFAs are rapidly absorbed by the colonic mucosa and contribute towards energy requirements of the host. Butyrate is mostly consumed by the intestinal cells, propionate is cleared by the liver, whereas acetate is mainly metabolized in human muscle, kidney, heart, and brain [7].

The prebiotic concept is defined as the selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host [7]. For instance, inulin-type fructans (ITF) are nondigestible carbohydrates fermented in the colon that exhibit prebiotic properties. ITF administration increases bifidobacteria levels – but also modifies other bacteria – and improves health in different pathophysiological conditions [50,51,57,58]. Of note, SCFA levels in cecal content and serum are increased in rodents and humans after administration of prebiotics or fermentable carbohydrates owing to bacterial fermentation [22,59,60].

**Figure 1.** Structure of physiological and synthetic ligands of G-protein-coupled receptor 43 (GPR43). The pEC50 value is the negative logarithm of the half-maximal effective concentration, whereas the pIC50 is the negative logarithm of the half-maximal inhibitory concentration. All the cell lines used overexpressed human GPR43.

- **Physiologic agonists**
  - Acetate
    - pEC50 = 3.36
  - Propionate
    - pEC50 = 3.54
  - Butyrate
    - pEC50 = 3.43
- **Orthosteric agonist**
  - 2-methylacrylic acid
    - pEC50 = 3.79
- **Allosteric agonist**
  - Compound 58
    - pIC50 = 6.15
- **Agonist**
  - Compound 34
    - pEC50 = 7.68
- **Inverse agonist**
  - Compound 4/CATPB
    - pIC50 = 7.70

Orthosteric site between hGPR41 and hGPR43 has been explored using structure–activity relationship analysis of small carboxylic acids, and three amino acids (E166, L183, C184) have been identified as critical for selective orthosteric activation of hGPR43 versus hGPR41 [17]. In addition, residues (e.g., L173) and extracellular loop 2 are also important for positive allosteric effects on hGPR43 [18,19].

Schmidt et al. explored the orthosteric activation potential of an expanded set of small carboxylic acids including carboxylic acids with additional branched, unsaturated, and cyclic tails. The authors proposed that compounds with an sp- or sp2-hybridized α-carbon preferentially activate hGPR43, whereas hGPR41-selective ligands contained a substituted sp3-hybridized α-carbon. They showed that the development of small molecules with a higher selectivity for GPR43 versus GPR41 than propionate and acetate was feasible (Figure 1, panel 2), but a gain of potency remains to be achieved [17].

Two allosteric modulators with agonist activity, derived from phenylacetamide, have been described in 2008. Lee et al. highlighted the existence of nonoverlapping binding sites for the synthetic and endogenous ligands [20]. Two years later, the same team reported a full series of GPR43 agonists based on these two lead molecules, with optimization of pharmacokinetic properties (Figure 1, panel 3) [21]. Importantly, the synthetic and endogenous ligands seem to activate the intracellular pathways in a different way [17,20,22]. Phenylacetamide derivatives are equally...
potent on \( \alpha_{i} \)-cAMP and \( \alpha_{q} \)-PLC pathways, whereas propionate and acetate are more potent on \( \alpha_{i} \)-cAMP than on \( \alpha_{q} \)-PLC pathways [20]. More recently, Euroscreen has patented several series of GPR43 agonists, with some of them exhibiting interesting potency (Figure 1, panel 4) [8,23].

Two series of GPR43 antagonists have also been protected by Euroscreen [24] and Galapagos [25], with both patents including pharmacological and functional assays. Their claims are supported by Hudson et al. who described one of these compounds (Figure 1, panel 5) as a full ‘inverse agonist’ at the human GPR43 ortholog with very little, if any, activity at the mouse ortholog [26].

Finally, a chemically engineered receptor activated solely by synthetic ligands (RASSL) is a useful alternative for probing receptor function and was provided in an elegant study based on pharmacological variation between species orthologs. Knock-in transgenesis of this RASSL will allow investigating GPR43 function in vivo [27].

For therapeutic prospects, the potency, affinity, and pharmacokinetics properties of GPR43 modulators must be improved. The safety of a chronic administration of an agonist or antagonist is not known yet and must be investigated before ruling on the ‘druggability’ of GPR43. The pharmacological challenges related to FFA receptors, including careful description of crucial residues and recent patents, have been discussed in two well-written recent reviews [8,28].

**GPR43 and lipid metabolism**

In 2005, Hong et al. demonstrated that GPR43 was expressed in mouse white adipose tissue (WAT), to a higher extent in adipocytes than in stromal vascular cells, and overexpressed in the adipose tissue of mice fed a high-fat (HF) diet [29]. GPR43 expression was increased during the differentiation of 3T3-L1 preadipocytes and an agonist of the peroxisome proliferator-activated receptor \( \gamma \) (PPAR\( \gamma \)), a master regulator of the differentiation process, reinforced this overexpression. Furthermore, acetate and propionate increased lipid accumulation in differentiating cells and propionate induced GPR43 and PPAR\( \gamma \) overexpression during differentiation. 3T3-L1 cells transfected with a small interfering RNA (siRNA) to reduce GPR43 expression exhibited lower mRNA levels of PPAR\( \gamma \) and aP2 – a PPAR\( \gamma \) target gene, marker of adipocyte differentiation – and accumulated less fat during differentiation. The authors thus suggested that GPR43 and SCFAs play an important role in adipogenesis (Figure 2) [29].

Moreover, acetate and propionate were shown to inhibit the lipolytic activity in 3T3-L1 differentiated adipocytes. Interestingly, GPR43 siRNA-transfected cells and adipocytes isolated from GPR43 KO mice did not respond to propionate and acetate, suggesting that GPR43 activation can result in lipolysis inhibition [29,30]. Moreover, an intraperitoneal injection of acetate led to reduced plasma FFAs in wild type mice but not in GPR43 KO animals, thus highlighting that the antilipolytic activity of acetate through GPR43 activation also occurred in vivo [30].

The hypothesis that GPR43 may be implicated in adipogenesis has been recently reinforced by our own results [31]. We confirmed that GPR43 is overexpressed in subcutaneous adipose tissue (SAT) of mice fed a HF diet. This effect was associated with fat mass accumulation, increased adipocyte size, and decreased basal lipolysis. We also observed an overexpression of several PPAR\( \gamma \) target genes in SAT, thus reflecting HF diet-induced PPAR\( \gamma \) activation. Interestingly, a supplementation with inulin-type fructans (ITF) prebiotics (Box 1) reduced fat mass, adipocyte size, and SAT expression of GPR43 and PPAR\( \gamma \) target genes. We hypothesized that the inhibitory effect of ITF prebiotics on PPAR\( \gamma \) activity, potentially through modulation of gut microbiota, may contribute to their anti-obesity properties. Importantly, GPR43 expression was positively correlated with expression of PPAR\( \gamma \) target genes [31]. To confirm this potential link between PPAR\( \gamma \) activity and GPR43 expression, we performed ex vivo experiments on mouse SAT explants incubated with different modulators of PPAR\( \gamma \) activity. Interestingly, a

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**Figure 2.** Location and physiological functions of G-protein-coupled receptor 43 (GPR43). Studies in rodents have highlighted that short-chain fatty acids (SCFAs) bind to GPR43 to exert several physiological actions. GPR43 activation on intestinal enteroendocrine cells (in pink) induces the production of peptide YY (PYY) and glucagon-like peptide 1 (GLP-1). PYY inhibits intestinal transit and appetite, whereas GLP-1 is anorexigenic and stimulates insulin secretion. In mice, GPR43 expression increases during adipogenesis and SCFAs stimulate adipocyte differentiation (fibroblast in orange). Through their binding to GPR43, SCFAs also inhibit lipolysis in mature adipocytes (in yellow). Finally, SCFAs induce chemotaxis of neutrophils (in blue) through GPR43 activation. Abbreviations: TG, triglycerides; FFAs, free fatty acids.
PPARγ agonist led to an overexpression of GPR43 and aP2, whereas the addition of a PPARγ antagonist completely blunted these effects [31]. Consequently, PPARγ appears to be a driver of GPR43 mRNA levels in mouse adipose tissue. However, we have recently demonstrated that this phenomenon does not occur in humans. Indeed, a PPARγ agonist did not impact GPR43 expression in human preadipocytes, whereas it markedly increased the expression of aP2. Furthermore, GPR43 agonists (acetate, propionate, and one phenylacetamide derivative) were not able to induce differentiation of these preadipocytes, unlike what was observed in mice [32].

To further understand GPR43 involvement in obesity and related metabolic disorders, the effects of a HF diet on energy, glucose, and lipid metabolism were studied in GPR43 KO mice [14]. Interestingly, after 25 to 30 weeks of a HF diet, GPR43-deficient mice exhibited lower body weight, decreased fat mass, and increased food intake associated with increased fecal energy content and higher energy expenditure. GPR43 deficiency also led to improved glucose control, lower plasma lipids and hepatic triglycerides content, and lower macrophage content in WAT of HF diet-fed mice [14]. Altogether, these data reinforced the hypothesis that GPR43 is involved in metabolic control (Table 1).

Finally, SCFAs were shown to stimulate production of leptin, an anorexigenic hormone, in mouse white adipocytes, and GPR41 was proposed as the molecular mediator of this effect [33]. However, other authors suggested that GPR43, not GPR41, may be responsible for SCFA-induced leptin secretion [34].

These observations further highlight the need to develop selective pharmacological tools to solely modulate GPR43 activity, without impacting GPR41.

**GPR43 and GI tract functions**

SCFAs produced by bacterial fermentation of nondigested carbohydrates are not only absorbed and used as nutrients in the intestine (butyrate) or in distant organs but they also regulate key functions of the GI tract [35]. Because GPR43 is largely expressed throughout the gut, several authors have suggested that some effects of SCFAs could be GPR43-dependent. In 2006, Karaki et al. demonstrated that GPR43 was expressed in rat distal ileum and colon. Interestingly, peptide YY (PYY)-containing enteroendocrine L cells were immunoreactive for GPR43, whereas 5-hydroxytryptamine (5-HT) immunoreactive mast cells coexpressed GPR43 [36]. PYY is a satiogenic peptide that inhibits upper GI motility and SCFAs have been shown to induce its release in the blood [37]. Therefore, SCFAs might stimulate L cells to release PYY via GPR43 activation, thus slowing intestinal transit (Figure 2). GPR43 expression in these enteroendocrine L cells was observed likewise in the human colon [38]. SCFAs also exert physiological effects on colonic motility and secretion via 5-HT release [35] and Karaki et al. proposed this might be attributable to the activation of GPR43 on 5-HT-containing mast cells [36]. The presence of GPR43 throughout the rat gut, with the lowest mRNA levels observed in the esophagus and stomach and the highest levels detected in the colon, was confirmed in another study [39].

Glucagon-like peptide 1 (GLP-1) is another gut hormone released by enteroendocrine L cells that is involved in the control of intestinal function and glucose metabolism [40]. SCFA infusion was shown to induce plasma GLP-1 release in animals and humans [41]. Interestingly, colocalization of GPR43 and GLP-1 in enteroendocrine L cells was demonstrated in both rat and human colon and terminal ileum [42]. In rodents, supplementation with fermentable carbohydrates increased GLP-1 production and the density of GPR43/GLP-1-positive enteroendocrine L cells in the proximal colon [42,43]. Therefore, a higher colonic production of SCFAs following dietary fiber fermentation may, via GPR43 activation in enteroendocrine L cells, increase GLP-1 secretion.

This hypothesis has been recently confirmed by Tolhurst et al. [11]. The SCFA-triggered secretion of GLP-1 was almost completely abolished in primary colonic cultures from GPR43 KO mice but was also reduced, to a lesser extent, in mice lacking GPR41. GPR43-deficient mice had significantly reduced colonic GLP-1 protein content. Moreover, basal and glucose-stimulated levels of active GLP-1 were reduced in both GPR43 and GPR41 KO mice. These effects were associated with impaired glucose tolerance. Even if mice lacking GPR43 also exhibited decreased colonic expression of GPR41, a dominant role for GPR43 in SCFA-induced L cell activation was suggested based on the prevailing involvement of Gαq-coupled pathways in this process (Figure 2) [11]. These results reveal again the difficulty to generate GPR43 KO mice without affecting GPR41, thus introducing uncertainties about their interpretation.

**Table 1. Studies related to GPR43 functionality in pathological conditions**

<table>
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<tr>
<th>Diseases</th>
<th>Observations</th>
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<th>Refs</th>
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<tr>
<td>Obesity</td>
<td>GPR43 is overexpressed in adipose tissue of obese mice and GPR43 KO mice are protected against diet-induced obesity and impaired glucose control</td>
<td>Inhibition of GPR43 to reduce fat mass accumulation</td>
<td>[14,29,31]</td>
</tr>
<tr>
<td>Inflammatory conditions</td>
<td>SCFAs induce mouse neutrophil chemotaxis through GPR43</td>
<td>Inhibition of GPR43 to reduce neutrophil recruitment To control colonic inflammation: Activation of GPR43? Inactivation of GPR43?</td>
<td>[6,12,48]</td>
</tr>
<tr>
<td>Cancer</td>
<td>GPR43 functions as a tumor suppressor in colon cancer</td>
<td>Activation of GPR43 to prevent colon cancer Activation of GPR43 to reduce leukemia progression</td>
<td>[54,22]</td>
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Studies conducted in germ-free (GF) mice highlighted a potential link between gut microbiota and the expression of FFA receptors. The conventionalization (colonization by normal mouse microbiota) of GF mice increased adiposity and decreased the expression of GPR41 and GPR43 in the distal small intestine [44]. However, another study reported that GF mice exhibited decreased intestinal expression of GPR43, GPR41, PYY, and GLP-1 as compared with conventional mice. It is worth noting that the expression of GPR43 and GPR41 was differentially affected in GF mice, with a 10% and 70% decrease, respectively. This was associated with lower levels of circulating PYY [45]. Overall, these results suggest that gut microbiota can influence the intestinal expression of SCFA receptors and the secretion of gut peptides, but further studies are needed to elucidate the underlying mechanisms.

GPR43 and inflammation

SCFAs have long been known to modulate the production of pro- and anti-inflammatory mediators [46,47]. For instance, production of prostaglandin E2 is induced by SCFAs. This process can be inhibited by pertussis toxin, suggesting the involvement of a G-protein-mediated signaling [46].

The formal proof of GPR43 involvement in the management of inflammation was simultaneously provided by two research teams. They both established the contribution of GPR43 to the recruitment of immune cells [6,48], and this observation was further confirmed by others [12]. However, these studies showed divergent findings on the potential impact of GPR43 in inflammatory diseases.

Maslowski et al. demonstrated that stimulation of GPR43 by acetate allowed resolution of a colitis-related inflammatory response. GPR43 KO mice showed exacerbated or unresolved inflammation in cases of acute and chronic colitis, arthritis, and asthma. This could be related to increased immune cell recruitment [6]. By contrast, Sina et al. reported that, in an acute colitis model, GPR43 KO mice showed an increased mortality compared with control mice, despite reduced immune cell recruitment, decreased colonic inflammation, and attenuated colonic tissue damage. The increased mortality was attributed to septic complication. In a chronic colitis model, GPR43 deficiency led to reduced colonic inflammation, without any sign of sepsis and any lethality. The authors pointed out the bipotential pathophysiological role of immune cells at the intestinal level, being a protective factor against acute bacterial transmigration, but having a detrimental role in chronic inflammatory responses [48]. Results from both studies, with their theoretical therapeutic prospects, are included in Table 1.

Clearly, GPR43 is involved in the SCFA-induced neutrophil chemotaxis in mice (Figure 2) [6,12]. However, demonstrating GPR43 contribution to human neutrophil chemotaxis remains to be accomplished. Interestingly, GLPG0974, an orally available small GPR43 inhibitor from Galapagos with undisclosed structure, has been claimed to reduce neutrophil migration. GLPG0974 is currently being tested in a second Phase I study and results are expected in early 2013 (ClinicalTrials.gov; identifier: NCT01721980). The global role of GPR43 in inflammatory conditions needs to be clarified before ruling on the therapeutic potential of GPR43 in this context. The dualistic action of SCFAs, being anti-inflammatory while recruiting neutrophils, might be one of the keys to full understanding of how SCFAs and GPR43 manage inflammation. Importantly, a comparison of several studies highlights that the biological and molecular responses to SCFAs are different from one type of immune cell to another [46,47]. This might be consistent with the various temporal roles of these cells in an inflammatory response [46]. Therefore, the different molecular pathways downstream of GPR43 remain to be elucidated.

Finally, ITF prebiotic feeding can control inflammation in rodent models of colitis, obesity, diabetes, and leukemia [22,49–51]. One can postulate that prebiotics, through their fermentation into SCFAs, might exert some of their anti-inflammatory effects in a GPR43-dependent manner, but this needs investigation.

GPR43 and cancer cell proliferation

The gut microbiota has been suggested to play a role in the onset and progression of colon cancer [52]. Butyrate and other SCFAs affect the cell cycle by inhibiting proliferation and inducing differentiation and cell death [13,53,54]. In 2009, Hatanaka et al. demonstrated the transforming activity of GPR43 in fibroblasts and showed that GPR43 transcript and protein levels were increased in gastric and colorectal cancers [55]. On the contrary, Tang et al. reported that GPR43 expression was importantly decreased in human colon adenocarcinomas and detected the presence of GPR43 mRNA in only one of nine established human colon cancer cell lines [54]. Interestingly, increasing GPR43 expression in the colon cancer cell line HCT8 using plasmid transfection sensitizes the cells to the antiproliferative action of propionate and butyrate [54].

Recent evidence from our laboratory suggests that the antiproliferative action of SCFAs on cancer cells is not limited to the GI tract. Indeed, ITF prebiotic administration to leukemic mice increased the levels of propionate in the portal vein, without modifying acetate and butyrate levels, and this was accompanied by a decreased accumulation of leukemic cells in the liver [22]. In vitro, propionate reduced leukemic cell proliferation by a cAMP level-dependent mechanism, suggesting that GPCR pathways might be involved. Furthermore, the activation of GPR43 by a phenylacetamide derivative reduced the proliferation of human and murine leukemic cells (Table 1) [22].

Additional studies are therefore warranted before ruling on the interest of GPR43 in the treatment of such malignant diseases. These studies should include, among others, clarification of GPR43 protein expression level in the GI and in other cancers, as well as in vivo investigation of the effect of GPR43 agonists on hematopoietic cancers.

Concluding remarks

GPR43 currently appears to be a potential target in the management of several pathological conditions such as obesity, inflammatory diseases, and cancer. However, contradictory results have been reported in animals, and there is a clear lack of data in humans. Therefore, complementary studies are needed to fully clarify GPR43 functions
and to determine in which condition(s) this receptor should be activated or blocked.

Until now, most of our knowledge concerning GPR43 has been obtained using KO mice. However, in these genetically deficient mice, the expression of the other SCFA receptor, GPR41, was also affected. Therefore, the conclusions based on this model must be taken carefully. This emphasizes the need to develop new pharmacological tools to ascertain the functional role of GPR43 in physiological and pathological conditions.

Finally, it is now well established that gut microbiota may deeply impact host metabolism and immunity. The discovery of GPR43 as a receptor for gut-derived metabolites provides a potential molecular link explaining these interactions. However, GPR43 involvement in the beneficial effect of dietary fibers with prebiotic properties remains to be formally demonstrated. Unraveling the mechanisms underlying the symbiotic gut microbes–host relationship may ultimately lead to the therapeutic exploitation of this crosstalk which has probably existed for thousands of years.

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