How are Turmeric and its derivative products beneficial for intestinal health?

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ABSTRACT

Turmeric is the common name for the rhizome of *Curcuma longa L.,* and has been used as a curative and digestive aide in both Chinese and Indian traditional medicine since ancient times. Investigations into the physiological actions of this particular spice have increased over the past decade. While the benefits of adding turmeric to the diet are slowly being delineated by the increasing popularity of food-supplement research, the mechanisms by which it exerts its effects are still unclear and there is little evidence to explain the poor bioavailability of turmeric and the protective/restorative effects it clearly exhibits.

The focus of this review was to assess the current scientific literature to determine the chemical characteristics of turmeric and its derivative products, and the nature of their interactions with the gut microbiota and intestinal microbiome.

Results from this analysis demonstrate that turmeric can provide numerous derivative products, through both physiological degradation and microbial fermentation, that are associated with intestinal integrity. Furthermore, a small number of papers relate turmeric/product actions as having a potential prebiotic effect on probiotic bacterial colonies such as Lactobacilli and Bifidobacterium species.

Abbreviations

ATP – Adenosine triphosphate; IBD – Irritable Bowel Disease; IEC - Intestinal Epithelial Cells; LPS – Lipopolysaccharide; ML-CK – Myosin light-chain kinase; ROS Reactive Oxygen Species; SCFA – Short-chain Fatty Acids; TCM – Traditional Chinese Medicine; TE – Turmeric Extract; UC - Ulcerative Colitis

Key Words

Curcuma longa, Turmeric, Curcumin, Microbiome, Intestinal Health

INTRODUCTION

For thousands of years the connection between the gastrointestinal tract and holistic health for human beings has been well documented. To exemplify, the ancient Indian medical practice of Ayurveda (c.1500 B.C) associates `the digestive fire' with many ailments, and remedies are focussed on not only treating the cause of disease within the digestive tract, but also the systemic symptoms which often arise when the gastrointestinal system is imbalanced [1,2]. Turmeric, the rhizome of *Curcuma Longa L.,* is an herbal remedy and culinary spice that has been commonly used within ancient and traditional medical practices to provide gastrointestinal support. Additionally, in both Ayurvedic and Traditional Chinese Medicine, the turmeric spice has also been used as a treatment for cardiovascular disease, diarrhoea, diabetes; minor burns, respiratory conditions and dental health [3,4]. Many contemporary studies are now discovering, or more accurately, rediscovering, the purported beneficial effect of turmeric for a host of common ailments; of which gastrointestinal conditions are a cardinal area of interest.

Today we are beginning to appreciate that gastrointestinal function is intricately connected with the human microbiota, an amalgamation of microbial species whose composition is as individual to the host as their biometric data, and that predominantly consists of bacteria; but also includes many species of fungi, protozoa and viruses [5.6]. With current advances in biotechnology and the development of metagenomic capabilities, researchers are now able to sequence portions of microbial DNA to identify specific taxonomic units of the intestinal microbiota using culture-independent methodologies [7]. These applications are able to suggest how

many of a certain microbial species are represented in any given sample, whilst also giving an indication into their functional role within the digestive system [8]. Using these methods, the microbial metabolism of turmeric and other herbs is beginning to be explored [9,10,11]. Interestingly, it has also been proposed that such microbial-derived degradation products account for multiple biological actions attributed to the turmeric spice [10].

A current topic of increasing interest is whether turmeric exhibits prebiotic effects. Prebiotics are defined by Gibson *et al.,* as non-digestive food ingredients which promote the growth of beneficial micro-organisms in the intestines, thus improving the health of the host [12]. Additionally, contemporary research is also beginning to focus on the effects of turmeric (the rhizome, or tuber, of the *Curcuma longa L.* perennial) on human health systems. Furthermore, turmeric and one of its many active constituents, curcumin (categorised as the polyphenolic compound diferuloylmethane), are also currently being investigated as an anti-carcinogenic; neuro-protective and hepato-protective substances [13, 14]. Because the mechanisms of action of turmeric and interactions within the body are yet to be fully understood, this review assesses the available scientific literature, and evaluates the effect of dietary turmeric, and its constituent and degradation compounds, on the colonic eco-system and intestinal environment. The critical question posed is, "Are Turmeric, and its derivative products, beneficial for intestinal health?"

INTESTINAL STRUCTURE AND FUNCTION

Intestinal microbiota

The human gastrointestinal tract is known to be populated by a diverse array of microbial species, approximated to be 10^{14} in individual cell numbers. Having a complex arrangement of species represented in the intestinal microbiome has often been linked with improved intestinal health [15, 16], presumably this is due to the wide-ranging metabolic processes and interactions between such a contrasting and diverse a community. These include such microbial-induced reactions as; deglycosylation, deglucuronidation, dihydroxylation, demethylation, demethoxylation or fermentation [17].

Emerging studies are acknowledging that the microbial content of the digestive system is a key constituent in the protection of the intestinal environment [18]. Both the abundance and diversity of microbiota contained within the intestinal tract are imperative aspects in the prevention of both infectious and intestinal-derived inflammatory conditions [19]. Furthermore, microbial dysbiosis is suspected to expedite the inflammatory process, the mechanism suspected to underly such pathologies as: (1) intestinal (e.g. Coeliac disease, Irritable Bowel Syndrome (IBS); Crohn's disease; and infectious diarrhoea), and (2) extra-intestinal health-related conditions, (e.g. asthma, gluten intolerance, cardiovascular disease, arthritis, depression, metabolic syndrome and obesity) [20, 21].

Intestinal Mucosal Function

Of significance when considering a healthy digestive tract is the mucosal lining of the viscera. The mucosa is an essential for maintaining a healthy boundary between the intestinal lumen and enterocytes of the gut wall. These epithelial cells are vulnerable to a myriad of assaults due to their absorptive function and proximity to metabolic waste products [22]. It is therefore critical that a robust and effective mucosal layer be maintained to protect such critically exposed cells.

Mucus, the major component of the mucosal layer, is a gelatinous substance formed by high molecular weight glycoproteins, or mucins, which are secreted by goblet cells into the intestinal lumen [23]. The intestinal mucosa not only protects the host from enzymatic and environmental toxins, pathogenic invasion and enzymatic degradation, it is also responsible for the supply of essential nutrients to the gut-microbiota, enabling selective colonies to thrive [24]. It is likely that the ingestion of turmeric can influence mucus-producing cells thereby providing a suitable environment for probiotic bacterial growth. Such positive selectivity enhances microbial production of secondary metabolites that can be utilized by enterocytes and importantly, mucus-producing cells in an annular context, where salutary colonies promote a nourishing and restorative microbiome.

Additionally, bacterial waste products are known to act as cell-signalling molecules. To elucidate, N-acyl amides such as 5-hydroxytryptamine (serotonin) are known to interact extensively with G protein-coupled

receptors directly that influence the intestinal physiology and the central nervous system [25]. These factors are of importance when considering the wider health benefits attributed to dietary turmeric.

TURMERIC CHEMISTRY

Turmeric Composition

Whole turmeric root, taxonomically identified in table 1, has been delineated by Chattopadhyay *et al*., as containing 6.3% protein; 5.1% fat; 3.5% various minerals; 69.4% carbohydrates and 13.1% moisture [26].

Curcumin (diferuloylmethane) is a lipophilic, polyphenolic compound which gives the turmeric spice its yellow/orange colouring, and accounts for approximately 4% of turmeric composition [27]. Curcumin is stable at the acidic pH of the stomach and the content within turmeric can be further broken down into constituents: 94% curcumin-1; 6% curcumin-2 and 0.3% curcumin-3 [28]. The essential oil of turmeric, which can be obtained by steam distillation, contains: 1% α-phellandrene; 0.6% sabinene; 1% cineol; 0.5% borneol; 25% zingiberene and 53% sesquiterpenes [29]. Furthermore, the phytoconstituents of turmeric essential oil were analysed by Singh *et al.,* using mass spectrometry, and were demonstrated to be aromatic-turmerone (24.4%), alpha-turmerone (20.5%) and beta-turmerone (11.1%) in fresh rhizome, with aromatic-turmerone (21.4%), alpha-santalene (7.2%) and aromatic-curcumene (6.6%) being determined in dry rhizome oil [30]. Such varied products, all derived from the Curcuma *longa* rhizome, can produce an array of effects when applied for medical purposes.

Degradation Products

In excess of 180 degradation compounds have been described as products of turmeric. To illustrate the complex composition of turmeric the authors have collated information from 22 publications which have been categorised in Supplementary File 1.

Of particular interest when considering the molecular flexibility of this traditional spice are the two methoxyphenol rings of curcumin which are connected by a connecting heptadienedione chain and this chain

is readily degraded in the body due to chemical instability at physiological pH by means of auto-oxidation [31]. Degradation of curcumin in this manner produces further biologically active substances; essentially; vanillin, ferulic aldehyde, ferulic acid, feruloyl methane and trans-6-(4-hydroxy-3-methoxyphenyl)-2,4-dioxo-5-hexenal; with trans-6-(4-hydroxy-3-methoxyphenyl)-2,4-dioxo-5-hexenal being the primary degradation bi-product [32]. It is currently considered that the preferential roles of these bi-products may include enzyme inhibition (acetylcholinesterase, COX-2 etc.) scavenging of reactive oxygen species (ROS), upregulation of antioxidant enzymes (superoxide dismutase, catalase and heme-oxygenase-1) and a reduction in lipid peroxidation [33], although further studies are necessary to fully elucidate the cellular and molecular effects of dietary turmeric.

Metabolic Products

A double-blind, randomized, placebo-controlled pilot study conducted by Peterson *et al*., on human subjects, noted that many of the colonic microbiota are able to bio-transform turmeric in several ways, including sequential reduction of the heptadienone backbone and demethylation [13]. Additionally, i*n vitro* analysis based upon the microbial fermentation of turmeric, curcumin and further component curcuminoids (curcumin-I, {diferuloylmethane} 80%; curcumin-II, {demethoxycurcumin}, 18%; curcumin-III, {bis-demethoxycurcumin}, 2%), using ultra high-performance liquid chromatography – ion trap mass (UPLC-MS^n), defined three major bi-products, or metabolites; tetrahydrocurcumin, dihydroferulic acid, and third substance, 1-(4-Hydroxy-3-methoxyphenyl)-2-propanol [13]. Furthermore, a review conducted by Stevens and Maier, 2016, identifies that gut-microbial metabolism of polyphenols, such as curcumin, contributes to both A-ring and C-ring cleavage of the molecule, and transformation of alkene moieties [32], both actions thereby produce alternative metabolic compounds which can be utilized by microbial and somatic cells alike.

Other studies have evidenced conjugation of turmeric, and more specifically its component curcuminoids (I, II & III), typically results in the generation of curcumin glucuronide and curcumin sulphate, again via metabolism by the intestinal microbiota [34]. These alterations to the configuration of curcumin compounds have the

potential to create numerous biological molecules which can be both chemically diverse and reactive in their own right.

POTENTIAL PREBIOTIC ACTIONS OF TURMERIC / PRODUCTS

Intestinal Microbiota Influences

With dietary components having a fundamental influence over gut microbial ecology, the addition of turmeric as a nutritional supplement is proposed to act as a prebiotic, reinforcing the salubrious microbial colonies located in the digestive tract [35, 36]. Feng *et al.*, demonstrated that turmeric has the potential to dramatically shift the overall structure of microbial composition within the gut of rats subjected to a high-fat diet toward that of healthily fed rat populations. This research indicates that curcumin increases microbial heterogeneity whilst also preventing the decline of α-diversity [37].

Several neoteric studies are beginning to unravel the complex interactions between ingestible turmeric and the gut microbiota. Feng *et al.* identified that curcumin administration augmented weight-loss in ovariectomised laboratory models via modulation of the intestinal microbiota [37]. Corresponding studies also reveal turmeric is able to alter the microbial heterogeneity within the lower digestive tract [38]. Details of the positively-influenced operational taxonomic units that have been attributed to turmeric ingestion can be found in Table 2.

In addition to the increase in biodiversity within the colonic ecosystem, Lopresti's 2018 review [39] of the bioavailability of turmeric, revealed that dietary curcumin in particular activates carbohydrate colonic fermentation in human subjects, thus enhancing beneficial short-chain fatty-acid (SCFA) production by the intestinal microbiota [39, 40]. These findings are further supported by empirical evidence collated by Peterson *et al.,* [41] who studied anaerobic cultures cultivated from human stool samples.

SCFA, predominantly acetate and butyrate, are produced when gut-friendly bacteria ferment fibre in the colon. The primary advantage of SFCA production by intestinal micro-organisms is the ability to provide the energy that is required to sustain colonic epithelial cells via butyrate production; intestinal cells are known to

derive up to 70% of their ATP from this particular SCFA [40, 41]. SCFA are also implicated in the metabolism of carbohydrate substances and dietary fats, and therefore are key factors in the digestive process [43]. A contemporary report on the effects of turmeric extract (TE), conducted by Yazdi and colleagues [38] demonstrated that as TE was resistant to the acidity of gastric juices, arriving intact as a compound in the upper intestinal tract. The study focused specifically on probiotic bacterium including *Lactobacillus rhamnosus* and *Bifidobacterium animalis* and noted increased growth of these colonies within 72 hours post-ingestion of TE. Although these findings contradict previous investigations conducted by Lu *et al.,* [44] who reported no identifiable increases to such colonies under the influence of turmeric extract. The same study [44], in accordance with the Peterson study [41], did notice a decrease in pathogenic species including *Ruminococcus* and *Clostridium* species.

INFLUENCE ON INTESTINAL MUCOSA

Intestinal Barrier Function

A recent study conducted by Ghosh *et al*. examined the effects of turmeric on the Western diet, and how turmeric affects the functionality of the intestines, concluded that dietary supplementation improved intestinal barrier function by re-establishing intestinal alkaline phosphatase activity in the outermost layer of the barrier (exposed to the intestinal lumen) [42]. Curcumin, arguably the most widely studied component of turmeric, has also been demonstrated to increase the expression of tight junction proteins, ZO-1 and Claudin-1, between individual IECs, thus reducing intestinal permeability and mitigating the immune response. NOD2/CARD15 receptor activation by turmeric degradation products is also of interest here, as this particular receptor functions to recognize bacterial cell wall components and induce the production of defensins [13, 45]. However, the molecular mechanisms as to how this occurs is not widely known and requires further research to establish this knowledge.

Mucosal Immune Influences

Dietary supplementation with turmeric has also been demonstrated to positively affect gut mucosal immunity. Wang *et al*., [35] determined that curcumin in particular attenuated intestinal inflammation by acting on a

manner of systems; including, detoxification of lipopolysaccharide (LPS), attenuation of IL-1β production, a decrease in IL-1β-induced proinflammatory signalling within IEC's; and reduced expression of myosin light-chain kinase (ML-CK), a protein which interrupts tight junction protein organization that can result in increased permeability of the intestinal wall [35]. Hence, a flourishing mucosal layer preserves intestinal integrity. Additional functions of the mucosal layer are to protect the IEC from bacterial invasion and to lubricate the passage of the intestines [46]. For these reasons, a robust mucosal layer and a thriving community of probiotic bacteria within the intestinal lumen is critical for establishing a healthy symbiotic relationship that influences both the immediate environment and wider somatic systems. Interestingly, turmeric-derived compounds, including bisabolene, polyphenolic and terpenoid structures, detailed in Supplementary file 1, have been repeatedly demonstrated to enhance immune function within the intestinal mucosa and gut associated lymphoid tissue [6, 35, 42, 45], both vital aspects of the host innate immune system. For example, the modulation of mucosal immunity by products of turmeric digestion has been suggested in a study which outlines the reduction of C-reactive protein (CRP), an acute phase reactant often used as a clinical marker to assess levels of systemic inflammation. in the presence of curcumin [47].

Further to the inhibition of pro-inflammatory cytokines and co-stimulatory molecules as a result of the action of turmeric-derived metabolites mentioned in the reviewed articles, numerous studies implicate the modulation of Dendritic Cells (DC), when treated with curcumin as suppressant. Here, reduction of activity within the p38 MAPK (mitogen-activated protein kinase) signalling pathway, a key inflammatory disease marker has been observed [48]. Additionally, an increase in IL-10, an anti-inflammatory cytokine; and reduction of NF-kB, a signal transducer and activator of the pro-inflammatory enzyme COX-2 were also described [49, 50]. Curcumin, specifically, has also been noted to moderate CD2/CD3/CD28-initiated CD4+ T-cell activation [51], and to amplify the prohibitive activity of regulatory T-cells (Treg), therefore alleviating inflammatory adulteration of the colonic mucosa [52]. Likewise, a 2015 study by Kinney *et al* has shown curcumin to suppress CD4+T-helper 2 cells which are responsible for the production of IL-4, IL-5, IL-6 and are known to assist B-cell IgE antibody secretion. Excess IgE is associated with mast cell activation and release of

219 histamine, a hormone which increases the permeability of the capillaries and initiates the inflammatory
220 response [53].

221 Future Studies

222 Current understanding of how herbs such as turmeric interact with the intestinal microbiota and with host
223 systems is still in its infancy, with contemporary studies just beginning to elucidate the elaborate mechanisms
224 by which the intestinal flora impact on the functionality of discrete biological components. Future research
225 should consider the exact nature of the interplay between intestinal microbiota and prebiotic herbs and foods.
226 There is also a need to delineate how such alterations to the microbiota affect a variety of human systems,
227 including: the cardiovascular system [54], the gut/brain axis [55], as well as modulation of immunological
228 responses and metabolism [6, 56]. To fully comprehend the dynamic reciprocity between host and microbe,
229 further research is necessary. These should include a variety of cell types: neurons, epithelial cells and
230 adipocytes, for example. Future work could examine whether there are differences between whole Turmeric,
231 active constituents such as curcumin or essential oils, or its chief degradation or metabolism products.

232 To date, human pilot studies analysing the effect of curcumin on the human microbiota, such as the one
233 undertaken by Peterson *et al.,* are beginning to emerge [13], and encouragingly these may act as vanguard for
234 subsequent clinical trials. Moreover, as both fields of research (into the microbiome and into turmeric bi-
235 products) have only recently been established, consideration should be given to the long-term effects of
236 dietary compounds on the human microbiota and also to the causal sequence of biological reactions which
237 result in a multitude of pervasive effects being established on health and well-being. In addition to this,
238 investigations into the definitive pathways of turmeric metabolism and/or fermentation within individual
239 species of colonic microbiota would also be advantageous. Future research, including high quality clinical
240 studies into the interactions of dietary turmeric and the human microbiota, is imperative if we are to fully
241 comprehend the mechanisms by which this particular spice exerts its holistic and healthful properties.

Summary and Conclusion

Mounting evidence suggests that turmeric and its constituents and degradation products may impact on the intestinal microbiome, supporting the theory that several favourable health effects can be attributed to this spice. This may partially be attributed to the prebiotic action displayed within the microbial population, alongside direct effects on intestinal mucosal function. It is only by understanding how turmeric interacts with the microbiome in its entirety that an explanation into the paradox between the low bioavailability of turmeric, its metabolites, and the notable pharmacological effects can be found. This review has revealed that the multiple health benefits the addition of turmeric into the diet are most likely attributed, not to the turmeric itself, but to the degradation and metabolic substances it provides, Figure 1. Therefore it is reasonable to conclude that the addition of turmeric into the diet is likely to both support and sustain growth of complimentary intestinal microbes and enhance diversity within the microbiota. *Prima facie*, turmeric and the degradation products generated also have impactful immunomodulatory effects within the intestinal environment.

DECLARATIONS

Ethical Approvals

No ethical approvals were required for this review

Consent for Publication

No details, images, or videos relating to an individual are used in this review.

Availability of Data

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing Interests

Vivien Rolfe works for Pukka Herbs Ltd.

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Author Contributions

Grace Russell undertook the research and writing behind this review, Dr's Vivian Rolfe and Emmanuel Adukwu instructed, supervised and helped edit the manuscript.

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TABLES AND FIGURES

Table 1. Taxonomy of the Turmeric plant

KINGDOM	Plantae (plants)
PHYLUM	Magnoliophyta (flowering plants)
CLASS	Liliopsida (monoctyledons)
ORDER	Zingiberales (gingers, bananas, birds-of-paradise etc.,)
FAMILY	Zingiberaceae (ginger family)
GENUS	Curcuma (curcuma)
SPECIES	*Curcuma longa* (common turmeric)

Legend: Taxonomic classification of Turmeric. Details adapted from [23].

Table 2. Microbial alterations noted with turmeric supplementation.

Evidence for increased Operational Taxonomic Units ↑	Evidence for decreased Operational Taxonomic Uniits ↓	References
Actinomyces spp.		**(i) , (ii), (iii), (iv)**
Akkermansia muciniphila		
Alistipes spp.		
Anaerotruncus spp.		

Bifidobacterium spp.	*Bacillus subtilis* *Blautia spp.*	**(v), (vi)**
Citrobacter spp. ***Clostridium spp.*** ***Collinsella spp.*** ***Cronobacter spp.***	*Candida albicans* *Clostridium difficile* *Coriobacterales spp.*	**(iii), (vi), (vii), (viii)**
Enterobacter spp. ***Enterococcus spp.*** ***Exiguobacterium spp.***	*(Pathogenic) Escherichia coli* *Elusimicrobia spp.* *Enterococcus fecalis*	**(ii), (v), (vi)**
Gemella spp. ***Gordonibacter spp.***		**(iii)**
Helicobacter spp.		**(ii)**
Klebsiella spp.	*Klebsiella pneumonia*	**(vi), (viii)**
Lactobacillus spp.		**(vi), (viii), (ix)**
Papillibacter spp. ***Parabacteroidetes spp.*** ***Prevotellaceae spp.*** ***Pseudomonas spp.***	*Pseudomonas aeruginosa*	**(ii), (iv), (v), (vi), (viii)**
Rikenellaceae spp.	*Ruminococcus spp.*	**(iv), (vi), (viii)**
Serratia spp ***Shewanella spp.*** ***Streptococcus spp.*** ***Sutterella spp.***	*Salmonella typhi* *Shigella flexneri* *Spirochaetae spp* *(Methicillin-resistant) Staphylococcus aureus* *Streptococcus agalactaiae*	**(ii), (iii), (v), (x)**
Thalassospira spp.	*Tenericutes spp.*	**(iii)**

Table 2. Details both the stimulatory and inhibitory effects of turmeric on specific genus and species colonies of commensal intestinal microbiota.

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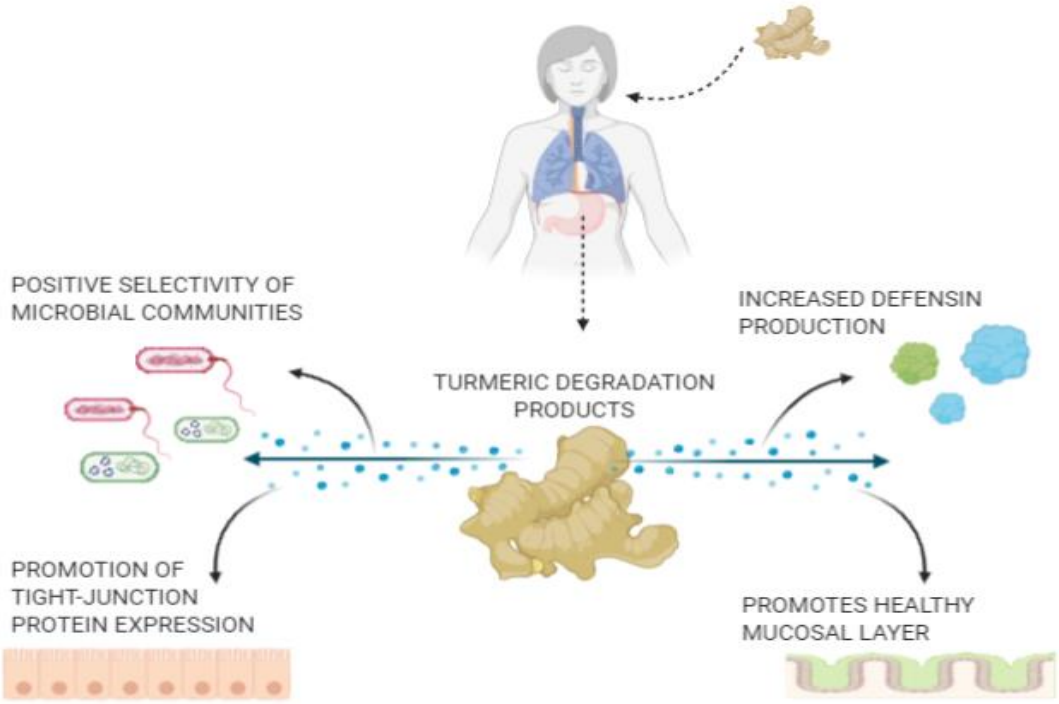
Figure 1. The effect of turmeric-derived compounds on the gastrointestinal environ.



Legend: Infographic depiction of how ingested turmeric has multi-modal affects within the human intestinal environment. Image created at www.biorender.com