EJPMR, 2026, 13(9), 518-534 **Review Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

GUT MICROBIOTA–PHYTOCHEMICAL INTERACTIONS IN ULCERATIVE COLITIS: MECHANISTIC INSIGHTS AND THERAPEUTIC OPPORTUNITIES

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DOI: https://doi.org/10.5281/zenodo.22687747

How to cite this Article: ED Padma, Balakoti Erothi*, Routhu Pratyusha, K Eswar Kumar. (2026). Gut Microbiota-Phytochemical Interactions In Ulcerative Colitis: Mechanistic Insights And Therapeutic Opportunities. European Journal of Pharmaceuticaland Medical Research, 13(9), 518–534.

Article Received on 18/08/2026 **Article Revised on 09/09/2026** **Article Published on 10/09/2026**

ABSTRACT

The mucosal inflammatory network which drives ulcerative colitis involves a series of biological interactions between epithelial barrier injury, microbial dysbiosis, defective microbial metabolism, immune activation, oxidative stress and impaired restitutaion. The relevance of phytochemicals to this disease is not one of general "anti-inflammatory" activity, but rather by their ability to reach the colonic lumen at pharmacologically relevant concentrations, to undergo microbial biotransformation and to alter the output of microbial metabolites, and to act directly at epithelial and immune interfaces that define the pathology of ulcerative colitis. The most coherent evidence for translation into clinical practice for curcumin includes in combination with mesalamine, curcumin formulations enhanced by bioenhancing agents, resveratrol in small randomized trials, indigo naturalis, and Curcumin–QingDai. The best mechanistic evidence is based on microbial tryptophan metabolism, aryl hydrocarbon receptor signalling, interleukin 22 dependent epithelial repair, urolithin formation from ellagitannins, Nrf2 mediated redox defence, nuclear factor kappa B suppression, attenuation of the inflammasome, preservation of the mucus barrier, restoration of tight junctions and partial recovery of some short chain fatty acid producing microbial functions. In this review, we have collected the recent primary and translational studies available on microbiota/phytochemical interactions and merged them with compound-specific clinical and mechanistic evidence to suggest a development framework for precision medicine, including colonic exposure, microbial metabotype, mucosal pharmacodynamics, biomarker response, endoscopic healing, histology, and safety surveillance. The therapeutic window is optimum when phytochemicals are designed as colon targeted, microbiotically dependent pharmacologic interventions, instead of as broad-based anti-inflammatory dietary supplements.

KEYWORDS: ulcerative colitis, phytochemicals, gut microbiota, curcumin, Curcumin–QingDai, urolithin A, resveratrol, berberine, baicalein, quercetin, aryl hydrocarbon receptor, interleukin 22, Nrf2, microbial metabolites.

1. INTRODUCTION

In ulcerative colitis, all the surfaces of the colon (epithelium, microbes, mucus layer, lamina propria immune cells, and microbial metabolites) are part of one disease compartment. Defect in epithelial barrier integrity, loss of mucus barrier, increased antigen penetration in the lumen, activation of innate immune system, amplification of adaptive immune system, oxidative damage and defective repair of damaged epithelium all support active disease. The disease's anatomical and biological place in the body makes ulcerative colitis an ideal disease for interventions that target the gut lumen and mucosa.[1]

Phytochemicals have been touted as an antioxidant or anti-inflammatory. This is a weak framing for pharmacology of ulcerative colitis, as it neglects the site of exposure, the metabolism of microbes, formulation, host variability, and regulatory endpoints. A more accurate model acknowledges that many of the phytochemicals have poor systemic bioavailability, but high intestinal exposure. Therefore, their apparent lack of plasma pharmacokinetics seems to be a good fit for colonic activity targeting epithelial cells, mucosal immune cells, bacterial enzymes, microbial communities and microbial metabolites.

Examples of this are curcumin, resveratrol, berberine, urolithins from ellagitannin, quercetin, baicalein, and indole compounds from QingDai. The most supportive clinical evidence for curcumin as an adjunctive therapy is found in mild to moderate UC when combined with mesalamine.[2,3] Urolithin A is an example of a microbial-metabolite because it is a metabolite of ellagitannins, which is produced in the gut and affects epithelial barrier and redox pathways.[4] Berberine, baicalein, quercetin, and QingDai-derived compounds converge on microbial tryptophan metabolism and aryl hydrocarbon receptor biology.[5–8] A smaller, but clinically consistent, clinical signal for resveratrol is oxidative and inflammatory modulation.[9,10] These compounds are thus best considered to be microbiota-conditioned mucosal pharmaceuticals.

For a modern ulcerative colitis, the development is more complex than symptom improvement. Therapy regimens are targeted toward clinical remission, endoscopic improvement or remission, normalization of biomarkers, quality of life, steroid-free clinical outcomes, and more recently histological healing. However, it is important to note that the development of phytochemicals must rely on a "translational chain" that links chemical identity, colonic exposure, microbial transformation, mucosal mechanism and accepted ulcerative colitis endpoints.

2. Ulcerative colitis as a microbial-metabolic barrier disease

The gut microbiota in ulcerative colitis is not defined by a single causative organism. The disease-associated microbial lesion is better described as loss of functional resilience. This includes reduced abundance or activity of butyrate-producing anaerobes,[11] altered mucus-associated microbial ecology, impaired tryptophan-to-indole metabolism, disturbed bile acid transformation, increased facultative anaerobe expansion, and inflammatory oxygenation of the mucosal surface. These microbial shifts do not merely accompany inflammation. They can reinforce epithelial dysfunction and immune activation by reducing protective metabolites and increasing pro-inflammatory microbial signals.

Butyrate is central because colonocytes use it as an energy substrate and because it supports epithelial hypoxia, tight junction structure, regulatory immune tone, and mucosal repair. Reduced abundance of butyrate-associated species such as *Roseburia hominis* and *Faecalibacterium prausnitzii* has been reported in ulcerative colitis, but fecal short chain fatty acid concentrations alone are not a reliable disease activity biomarker.[11,12] This apparent conflict is due to the variation between the microbial production, the epithelial uptake, the transit of stool, food, and the remaining concentration by the inflamed mucosa and oxygenation. Butyrate improving phytochemicals do not necessarily lead in a simple linear fashion to an increase in faecal butyrate levels.

Tryptophan metabolism is a more focused connection between microbes, phytochemicals, and mucosal immune cells. Tryptophan is metabolized in the gut to indole derivatives which can activate the aryl hydrocarbon receptor. The aryl hydrocarbon receptor controls epithelial barrier integrity, the biology of mucus, antimicrobial peptides, activity of innate lymphoid cells and epithelial restitution of interleukin 22. Dysregulated aryl hydrocarbon receptor ligand tone has a negative effect on epithelial defence, and restoration of targeted aryl hydrocarbon receptor ligand tone has a positive effect on mucosal repair. This is the reason why berberine, baicalein, quercetin, urolithin A, indigo naturalis and Curcumin – QingDai have been of mechanistic interest.[13,14]

The microbial-metabolic lesion is completed with bile acid metabolism and oxidative stress. The colonic bile acid pool is affected by microbial bile salt hydrolases and dehydroxylation pathways and impacts epithelial receptors and immune tone. These changes may be disrupted by inflammation. Oxidative stress at the epithelial level, triggers nuclear factor kappa B, impaired mitochondrial function, activates signalling of inflammasomes and leads to damage of tight junctions.[15] The phytochemicals which promote Nrf2 activation and inhibit NF-kB, stabilize epithelial junctions and restore microbial metabolite functions, therefore act on disease-relevant nodes, and not on peripheral pathways.

Table 1: Mechanistic modules that connect phytochemical-microbiota interactions to ulcerative colitis outcomes.

Disease module	Phytochemical–microbiota interaction	Key mucosal mechanism	Translational readout	Reference
Luminal exposure	Poorly absorbed compounds remain concentrated in the intestinal lumen	Direct epithelial and microbial contact	Fecal parent compound, fecal metabolites, mucosal biopsy exposure	[16]
Butyrate-linked barrier function	Recovery of butyrate-producing taxa or fermentation genes	Colonocyte energy support, tight-junction stability, immune regulation	Metagenomic butyrate gene capacity, mucosal inflammation, calprotectin	[11,12]
Tryptophan metabolism	Increased indole derivatives and AhR	AhR activation, IL-22 production, epithelial	Indole metabolites, CYP1A1/CYP1B1, IL-22,	[5–7]

	ligands	repair	barrier proteins	
Ellagitannin metabolism	Microbial conversion to urolithin A and related urolithins	Nrf2 activation, barrier repair, NF-κB suppression, AhR-linked signalling	Urolithin metabotype, fecal and plasma urolithin A, histology	[4,17]
Redox injury	Activation of epithelial antioxidant defence	Nrf2 and HO-1 induction, reduced epithelial oxidative stress	MDA, SOD, GSH, Nrf2, HO-1, epithelial injury score	[18,19]
Mucus layer failure	Restoration of goblet cell and mucin integrity	Increased MUC2 and improved mucus barrier	Alcian blue/PAS staining, MUC2 expression, permeability assay	[20]
Potent botanical AhR ligands	QingDai-derived indigo and indirubin-like molecules	Strong AhR pathway activation with therapeutic and safety implications	Endoscopy, clinical remission, chemical fingerprinting, cardiopulmonary surveillance	[8,21,22]

3. Microbial biotransformation as the pharmacological gateway

For several phytochemicals, microbial biotransformation is the deciding factor whether they are inactive precursors, active mucosal metabolites, or are inactive before hitting the host target. This is particularly true of polyphenols, alkaloids, flavonoids and herbal mixtures of low small-intestinal absorption. The intestinal flora of the colon contain microbial glycosidases, esterases, reductases, demethylases, dehydroxylases and ring-cleavage enzymes that change the structure and activity of the phytochemicals.

The clearest model is that of the ellagitannins. They are large polyphenols that are broken down into ellagic acid and then by the gut bacteria into urolithins. Urolithin A is more than just a marker of the diet. In experimental models of colitis it has barrier-protective and anti-inflammatory properties. There is inter-individual variation in the ability to produce urolithin A, resulting in the potential for varying active exposures across patients with ellagitannin intake.[4,17]

This is not the mere effect of dose variations but a metabotype effect due to a microbial component. Curcumin is different. It is poorly absorbed systemically and it is reduced, conjugated and may enter the colon in large quantities. The microbiota interaction seems to be characterized by high luminal exposure, reduction of the bacteria, local epithelial signalling, and minimal or short-lived microbiota community compositional effects. The low systemic exposure, high concentrations in the fecal microbiome, and no consistent remodeling of the entire microbiota at the systemic level, as observed in a recent study using high dose curcumin in people with inflammatory bowel disease in remission and healthy controls, may be due to this.[16]

Berberine is a representative of a third model. It is poorly absorbed from the gut, so is not absorbed into the blood and gut directed effects are still possible due to exposure to the gut. Berberine ameliorated experimental colitis by regulating gut microbiota-derived tryptophan metabolites, and by enhancing the aryl hydrocarbon receptor (AhR) signalling pathway.[5] Its pharmacology thus relies on the microbial metabolic redirection and not high plasma exposure.

4. Curcumin as the lead colon-facing adjunct in ulcerative colitis

Curcumin continues to be the most promising phytochemical supplement for ulcerative colitis. It is not the case that a high systemic bioavailability increases its translational value; it is based on the amount of it that is exposed in the colon. Hanai et al (2006)[2] found that patients with quiescent ulcerative colitis had fewer relapses when taking curcumin with mesalamine or sulfasalazine than when taking a placebo with the standard treatment. The induction trial by Lang et al (2015)[3] demonstrated superiority of curcumin over placebo plus mesalamine for clinical and endoscopic remission in mild to moderate active ulcerative colitis. These trials demonstrated that curcumin was as an adjunctive mucosal therapy and not as a single drug therapy.

The negative low dose curcumin trial is also significant. The study by Kedia et al. (2017) showed that there was no remission observed in mild to moderate ulcerative colitis using 450 mg/day.[23] This discovery restricts the use of curcumin for widespread therapeutic uses and indicates that dose, formulation, release, disease activity, and background therapy have significant impact on the results. More recently, 1500 mg/day was shown to be effective at reducing disease activity and inflammatory markers, and bioenhanced curcumin at 50 mg twice daily in combination with mesalamine was effective at improving clinical and endoscopic remission.[24,25] These findings suggest that the dose is not the only factor in exposure-response. The dissolution, mucosal availability, and intensity of the pharmacodynamics in the local area may be affected by the formulation chemistry.

Curcumin exerts its beneficial effects in several ulcerative colitis-related pathways in a mechanistically diverse manner. It inhibits activation of the nuclear factor

kB, decreases pro-inflammatory cytokine signalling, regulates cyclooxygenase and lipoxygenase action, induces Nrf2 activation, blocks oxidative stress, enhances the stability of epithelial junctions, diminishes inflammasome activation and affects macrophage polarization. However, in a microbiota-centred interpretation, curcumin also presents gut bacteria with high local concentrations, which may increase or decrease the activity of gut enzymes and the flux of metabolites without necessarily creating large and lasting changes in gut bacterial taxonomy.[26]

For the purposes of translational refinement, the 2026 study on the microbiome with high doses of curcumin is useful. For 8 weeks participants were given 3g twice a day. The study found almost no systemic exposure and high levels of gut microbes in the feces with no long-lasting restructuring of gut microflora. This finding doesn't make curcumin a non-gut-directed compound. Future trials ought to not be based exclusively on alpha diversity, beta diversity or change in wide taxonomic groups. Mucosal cytokines, fecal calprotectin, epithelial oxidative stress markers, fecal exposure to curcumin, microbial functional genes, and local metabolic changes may be better markers of curcumin response.

Table 2: Curcumin Evidence Interpreted through A Microbiota-Facing Pharmacology Framework.

Study context	Intervention	Key finding	Mechanistic interpretation	Reference
Maintenance of remission	Curcumin 1 g twice daily plus mesalamine or sulfasalazine	Lower relapse than placebo plus standard therapy	Adjunctive mucosal anti-inflammatory and barrier-stabilizing effect	[2]
Active mild-to-moderate disease	Curcumin plus mesalamine	Improved clinical and endoscopic remission	Enhanced response to 5-aminosalicylic acid through local mucosal pathways	[27]
Low-dose induction	Curcumin 450 mg/day	No remission-induction benefit	Insufficient exposure or pharmacodynamic intensity	[23]
Higher-dose supplementation	Curcumin 1,500 mg/day	Improved clinical activity, quality of life and selected inflammatory markers	Clinical benefit may occur without uniform cytokine suppression	[24]
Bioenhanced formulation	Hydrophilic bioenhanced curcumin 50 mg twice daily plus mesalamine	Improved clinical response and endoscopic endpoints	Formulation modifies the exposure–response relationship	(Banerje [25]
Pharmacokinetic–microbiome study	Curcumin 3 g twice daily for 8 weeks	Low plasma exposure, high fecal exposure, no sustained broad microbiota restructuring	Supports colon-facing exposure and need for functional mucosal endpoints	[16]

5. Ellagitannins and urolithin A as metabotype-dependent barrier therapy

Ellagitannins from pomegranate, berries, walnuts, and related plant materials do not act principally as intact systemic drugs. Their therapeutic meaning depends on microbial conversion into urolithins, particularly urolithin A. This conversion requires specific microbial metabolic capacity, creating a clear stratification problem. A patient with a urolithin-producing metabotype receives an active metabolite exposure that a non-producer does not receive from the same precursor intake.[28]

Urolithin A has strong mechanistic relevance to ulcerative colitis. Singh et al. (2019) showed that urolithin A and a synthetic analogue enhanced gut barrier integrity through Nrf2-dependent mechanisms and reduced inflammation in preclinical models. This is highly relevant because Nrf2 activation protects against oxidative epithelial injury, supports barrier defence, and counterbalances nuclear factor kappa B dominated inflammation. Ma et al. (2023) later showed that urolithin A alleviated DSS-induced colitis by improving gut microbiota dysbiosis, modulating microbial tryptophan metabolism, and triggering aryl hydrocarbon receptor activation. This places urolithin A at the intersection of three ulcerative colitis-relevant mechanisms: epithelial barrier repair, redox regulation, and microbial tryptophan metabolism.[17,29]

The translational implication is precise. Ellagitannin-rich interventions should not be developed as general "polyphenol therapy." They require metabotype measurement. Direct urolithin A administration can bypass microbial conversion variability, but it changes the intervention from phytochemical precursor therapy to microbial metabolite therapy. Both approaches are valid but answer different questions. Ellagitannin precursor trials test whether a patient's microbiota can generate active exposure. Urolithin A trials test whether direct metabolite delivery can repair barrier dysfunction independent of microbial conversion capacity.

6. Tryptophan metabolism, AhR, IL-22 and phytochemical-mediated epithelial repair

The aryl hydrocarbon receptor and interleukin 22 axis is one of the most disease-specific mechanisms connecting microbiota and phytochemicals in ulcerative colitis. Gut microbial tryptophan metabolites such as indole derivatives provide receptor ligands that regulate epithelial defence. Activation of aryl hydrocarbon receptor signalling in epithelial and immune compartments supports antimicrobial peptide expression, mucus barrier stability, epithelial regeneration, and interleukin 22 dependent repair.[30]

Berberine is a strong example of microbiota-conditioned tryptophan pharmacology. Jing et al. (2021) showed that berberine improved experimental colitis by regulating gut microbiota-associated tryptophan metabolites and activating aryl hydrocarbon receptor signalling.[5] This mechanism is translationally important because it links a low-bioavailability alkaloid to a measurable microbial metabolite pathway and a defined mucosal receptor. It also explains why luminal exposure may be more important than plasma exposure.

Baicalein provides a more immune-cell-specific mechanism. Li et al. (2022) showed that baicalein improved intestinal epithelial barrier function through the aryl hydrocarbon receptor and interleukin 22 pathway in group 3 innate lymphoid cells.[6] This connects phytochemical exposure to an epithelial repair circuit rather than only cytokine suppression. Interleukin 22 is especially relevant in ulcerative colitis because it supports epithelial regeneration and mucosal defence when appropriately regulated.

Quercetin has recently been linked to microbial tryptophan metabolism in DSS-induced ulcerative colitis models. Xiong et al. (2025) reported that quercetin regulated gut microbiota and tryptophan metabolism, increased indolelactic acid, activated aryl hydrocarbon receptor signalling, improved barrier proteins, and reduced inflammatory mediators.[7] The key translational point is not that quercetin is broadly anti-inflammatory. The stronger claim is that quercetin may shift a microbial metabolite pathway toward barrier-supportive aryl hydrocarbon receptor activity.

QingDai and Curcumin–QingDai extend this pathway into a high-activity clinical category. Indigo naturalis contains indigo and indirubin-like compounds with aryl hydrocarbon receptor activity. Naganuma et al. (2016) demonstrated clinical activity of indigo naturalis in ulcerative colitis,[31] while Ben-Horin et al. (2023) reported that Curcumin–QingDai was effective for response and remission in active ulcerative colitis.[32] This strengthens AhR as a therapeutic pathway but also creates a safety boundary because indigo naturalis has been associated with pulmonary arterial hypertension and colitis-like vascular adverse events.[22]

Table 3. AhR-Centered Phytochemical Mechanisms in Ulcerative Colitis.

Compound/formulation	Microbiota or ligand event	AhR-related mechanism	Evidence level	Translational limitation	REFERENCE
Berberine	Alters gut microbiota-associated tryptophan metabolites	Activates AhR and improves inflammatory injury in experimental colitis	Preclinical mechanistic	Human UC trials with metabolomics are insufficient	[5]
Baicalein	Enhances AhR and IL-22 pathway in ILC3s	Improves epithelial barrier and tight-junction function	Preclinical mechanistic	Needs human mucosal pathway validation	[6]
Quercetin	Increases indolelactic acid and regulates tryptophan metabolism	Activates AhR-linked barrier protection	Preclinical mechanistic	Human UC efficacy and responder metabotype unknown	[7]
Urolithin A	Modulates microbial tryptophan metabolism and AhR activity	Links microbial metabolite exposure to barrier repair	Preclinical mechanistic	Human UC efficacy remains insufficiently established	[17]
Indigo naturalis	Supplies indigo and indirubin-like AhR-active constituents	Potent mucosal activity in UC	Human clinical activity	Pulmonary arterial hypertension and product standardization concerns	[8,22]
Curcumin–QingDai	Combines curcumin with QingDai-derived AhR ligand activity	Clinical response and remission signal in active UC	Human randomized evidence	Requires standardized chemistry and safety surveillance	[21]

7. Nrf2, oxidative epithelial injury and redox-resolving phytochemicals

Oxidative stress is not a secondary feature of ulcerative colitis. It directly contributes to epithelial injury, tight-junction disruption, mitochondrial dysfunction, endoplasmic reticulum stress, inflammasome activation, and defective restitution. Neutrophil-derived reactive oxygen species and epithelial redox imbalance amplify mucosal damage. Nrf2 is therefore a relevant therapeutic node because it regulates antioxidant response elements, heme oxygenase 1, glutathione-related enzymes, and epithelial cytoprotection.[33]

Urolithin A is one of the strongest microbiota-derived Nrf2 activators in the colitis literature. Its capacity to enhance gut barrier integrity through Nrf2-dependent mechanisms gives it a barrier-repair identity rather than a general antioxidant label. Resveratrol also intersects with redox regulation. Human pilot trials for ulcerative colitis found that patients taking 500 mg daily for six weeks experienced better disease activity, quality of life, inflammatory markers and oxidative-antioxidative status. In preliminary studies, resveratrol has been associated with activation of Nrf2 and HO-1, modulation of the microbiota homeostasis, inhibition of the PI3K/Akt/VEGFA pathway, and decrease in epithelial injury.[18,34,35]

The Nrf2-related redox biology is also impacted by curcumin and quercetin, albeit in different ways. Curcumin has evidence from human UC trials, while quercetin has more preclinical mechanistic evidence currently. In both instances, oxidative stress readouts should be associated with mucosal outcomes. No decrease in malondialdehyde or increase in antioxidant enzyme activity is enough unless accompanied by barrier restoration, histology, and/or calprotectin, or endoscopic improvement.

8. Mucus layer, tight junctions and epithelial restitution

There is a crucial barrier in ulcerative colitis that is the mucus layer. The depletion of goblet cells, disorganization of MUC2, impaired mucus thickness and proximity of bacteria to the epithelium can drive immune activation. These phytochemicals which maintain goblet cell structure, restore expression of MUC2, or strengthen epithelial junctions, thus target a key disease process.

In experimental colitis, quercetin has been demonstrated to increase the structure of goblet cells, as well as the expression of MUC2, expression of ZO-1, expression of occludin, and inflammatory mediator profiles (Xiong et al., 2025; Jiang et al., 2024). Baicalein restores the integrity of the epithelial barrier by regulating AhR and IL-22 signalling in ILC3s (Li et al., 2022). Urolithin A enhances barrier function through Nrf2-linked mechanisms.[4] Curcumin stabilizes epithelial barrier signalling and inflammatory tone. These mechanisms converge on the same structural endpoint: reduced permeability and improved mucosal separation from luminal microbes.

Barrier repair is clinically meaningful because symptoms can improve before mucosal integrity is restored. Persistent microscopic inflammation and barrier dysfunction can sustain relapse risk. A phytochemical that reduces symptoms but does not repair epithelial injury has limited disease-modifying value. Conversely, a compound that improves barrier markers, calprotectin, endoscopy, and histology may have adjunctive maintenance potential even if symptom relief is gradual.

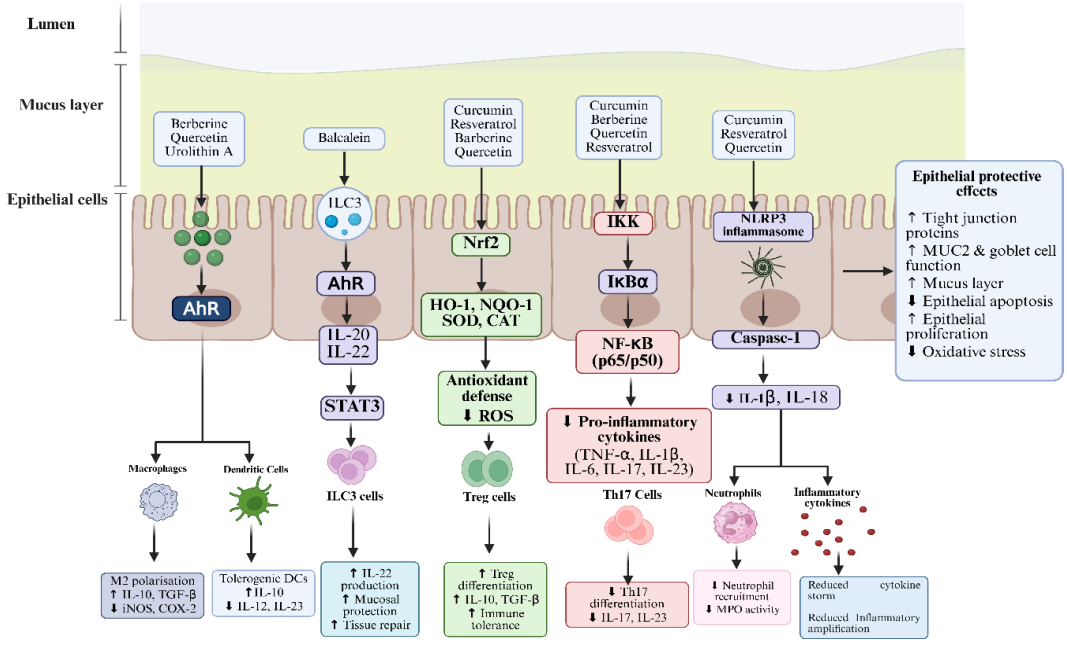

Figure 1: Integrated molecular and cellular mechanisms underlying the epithelial-protective and immunomodulatory effects of microbiota-interacting phytochemicals in ulcerative colitis.

Representative phytochemicals such as curcumin, resveratrol, berberine, quercetin, urolithin A and baicalein target a number of interrelated mucosal signalling pathways. The aryl hydrocarbon receptor (AhR) is activated and its signalling in group 3 innate lymphoid cells (ILC3s) drives IL-20/IL-22–STAT3 dependent epithelial repair, and contributes to M2 macrophage polarisation, tolerogenic dendritic cells, mucosal protection and tissue restitution. Nuclear factor erythroid 2-related factor 2 (Nrf2) activation has a beneficial effect on the antioxidant defence system by inducing heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO-1), superoxide dismutase (SOD), and catalase (CAT) which decreases the production of reactive oxygen species (ROS). Inhibition of the IKK/IκBα/NF-κB pathway decreases production of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-17, and IL-23, and inhibition of the NLRP3 inflammasome–caspase-1 axis reduces production of IL-1β and IL-18, neutrophil recruitment, myeloperoxidase activity, cytokine amplification, and inflammatory injury. The combination of these mechanisms likely promotes the differentiation of regulatory T cells and immune tolerance, suppresses Th17-associated responses, promotes integrity of epithelial barrier by increased expression of tight-junction proteins, MUC2 and goblet-cell function, restores mucus layer, decreased epithelial apoptosis and oxidative stress, and enhanced epithelial proliferation.

Table 4. Barrier-Specific Readouts for Future Phytochemical Trials in Ulcerative colitis.

Barrier domain	Mechanistic marker	Suitable sample/method	Relevant phytochemical class	Reference
Tight-junction integrity	Occludin, claudin-1, ZO-1	Biopsy western blot, immunohistochemistry, transcriptomics	Quercetin, baicalein, curcumin, urolithin A	[36,37]
Mucus barrier	MUC2, goblet cell density	PAS/Alcian blue staining, biopsy transcriptomics	Quercetin, AhR-active compounds	[20]
Epithelial redox defence	Nrf2, HO-1, GSH, SOD, MDA	Biopsy, serum and fecal oxidative markers	Urolithin A, resveratrol, curcumin	[36,37]
Repair cytokine axis	IL-22, STAT3, antimicrobial peptides	Biopsy transcriptomics, mucosal protein assays	Baicalein, QingDai-derived compounds, berberine	[36,37]
Microbial metabolite support	Butyrate, indolelactic acid, urolithin A	Fecal and serum metabolomics	Quercetin, ellagitannins, berberine	[17,36]
Clinical mucosal target	Endoscopic improvement and histological healing	Mayo endoscopic subscore, histological index	Curcumin, Curcumin–QingDai, indigo naturalis	[37,38]

9. Resveratrol as a redox and microbiota-modulating candidate

Resveratrol has smaller clinical evidence base than curcumin but remains mechanistically relevant. In randomized placebo-controlled pilot studies, 500 mg per day for six weeks improved disease activity, quality of life, inflammatory markers, and oxidative-antioxidative status in patients with ulcerative colitis.[9,10] These findings are not sufficient for definitive clinical positioning, but they provide a human signal that aligns with redox and inflammatory mechanisms observed in preclinical models.

In DSS-induced colitis models, resveratrol has been linked to gut microbiota homeostasis, reduced inflammatory cytokines, modulation of the PI3K/Akt/VEGFA pathway, and activation of Nrf2/HO-1 signalling.[18,34,35] The PI3K/Akt/VEGFA connection is relevant because angiogenesis, vascular permeability, and inflammatory tissue remodeling participate in active ulcerative colitis mucosa. However, human studies have not yet established whether resveratrol responders have distinct microbial profiles, metabolite shifts, or mucosal pathway activation.

The translational role of resveratrol is therefore narrower than broad anti-inflammatory use. It is best positioned as a candidate for oxidative epithelial injury and inflammatory redox imbalance, requiring trials that pair clinical endpoints with fecal metabolomics, microbial sequencing, biopsy Nrf2/HO-1 activity, epithelial barrier markers, and calprotectin. Without these measurements, resveratrol remains a promising but under-stratified phytochemical.

10. QingDai and Curcumin–QingDai: high activity with a narrow translational margin

Indigo naturalis and Curcumin–QingDai deserve separate treatment because they do not fit the low-potency polyphenol model. Indigo naturalis contains indigo, indirubin, and related compounds with potent biological activity, including aryl hydrocarbon receptor signalling. Randomized and short-term clinical studies have shown efficacy in ulcerative colitis.[39,40] Curcumin–QingDai has also demonstrated benefit in active ulcerative colitis, with interest in aryl hydrocarbon receptor induction as a treatment target.

The same potency creates safety concerns. Pulmonary arterial hypertension has been reported with QingDai or indigo naturalis use, and some reports describe colitis-like vascular complications.[22] These events are not compatible with casual supplement framing. They indicate that potent botanical aryl hydrocarbon receptor ligand mixtures require pharmaceutical-grade characterization, batch standardization, defined dosing, contaminant testing, stability data, cardiac and pulmonary surveillance, and long-term adverse-event capture.

Curcumin–QingDai may represent one of the most clinically active phytochemical strategies in ulcerative colitis, but it also highlights the difference between traditional botanical use and drug-development quality. The therapeutic window depends on product chemistry, dose, duration, patient selection, and monitoring. A standardized Curcumin–QingDai product should not be equated with unregulated indigo naturalis powders.

11. Formulation, delivery and local pharmacokinetics

Phytochemical translation in ulcerative colitis is inseparable from formulation. Native curcumin, hydrophilic bioenhanced curcumin, phospholipid curcumin complexes, nanoparticles, pH-sensitive colon-targeted systems, and crude turmeric preparations are different interventions. They differ in dissolution, stability, intestinal release, microbial contact, epithelial exposure, and systemic absorption. A negative trial using one formulation does not invalidate another formulation, and a positive trial cannot be generalized across all preparations.

Colon-targeted formulations are especially relevant. The desired pharmacokinetic profile for many phytochemicals in ulcerative colitis is not maximal plasma exposure. It is sufficient delivery to the inflamed colonic mucosa with controlled local concentration and acceptable safety. This reverses the conventional interpretation of low oral bioavailability.[41] For curcumin, low plasma levels and high fecal concentrations support a gut-directed model. For ellagitannins, the formulation must allow microbial conversion to urolithins. For QingDai-derived products, formulation must control active ligand exposure and reduce unpredictable toxicity.

Microbiota-sensitive delivery systems may become important. These include polysaccharide-coated formulations degraded by colonic bacteria, pH-dependent release systems, enzyme-triggered carriers, and mucoadhesive particles. Their translational value depends on whether release occurs at the inflamed mucosal site and whether the active compound or microbial metabolite reaches epithelial and immune targets. Formulation studies should therefore measure release, fecal concentration, mucosal concentration, metabolite generation, microbiota function, and pharmacodynamic response.[42]

12. Clinical-trial and regulatory translation

FDA and EMA guidance for ulcerative colitis emphasizes rigorous clinical development, appropriate patient selection, clinically meaningful endpoints, symptomatic and endoscopic assessment, safety monitoring, and maintenance of benefit.[43,44] STRIDE-II reinforces clinical remission and endoscopic healing as long-term targets, with quality of life and biomarker normalization contributing to treat-to-target care.[45] These frameworks are directly relevant to phytochemicals because symptom improvement alone is insufficient for disease-modifying claims.

A phytochemical ulcerative colitis trial should therefore include four linked layers. The first is product definition, including chemical fingerprint, dose, release profile, and stability. The second is local exposure, including fecal parent compound, microbial metabolite concentration, and preferably mucosal biopsy exposure. The third is mechanism, including targeted readouts such as AhR target genes, IL-22, Nrf2, HO-1, tight-junction proteins, MUC2, cytokines, and microbial metabolomics. The fourth is clinical outcome, including clinical remission, fecal calprotectin, endoscopic improvement, histological activity, quality of life, and steroid-free response.[46,47]

13. Safety and interaction risks

Safety assessment must be compound-specific. Curcumin has generally shown acceptable tolerability in ulcerative colitis trials, but formulation-specific absorption, gastrointestinal intolerance, gallbladder disease, bleeding risk in susceptible patients, and drug interaction potential require attention.[48] Resveratrol has short-term pilot data, but larger and longer ulcerative colitis trials are limited.[49] Berberine has interaction potential through drug transporters, cytochrome enzymes, and effects on glucose and lipid metabolism.[50] Quercetin and baicalein require dose and formulation-specific safety evaluation before human ulcerative colitis claims can be made.[51] QingDai and indigo naturalis require the strictest safety framing because pulmonary arterial hypertension and vascular colitis-like complications have been reported.[52]

Botanical complexity increases risk. A purified phytochemical, a standardized extract, a crude powder, and a multi-component traditional formulation are not interchangeable. Differences in active constituents, contaminants, adulterants, particle size, extraction solvent, storage, and batch variability can change both efficacy and toxicity. This is especially important for Curcumin–QingDai and indigo naturalis products.

Safety endpoints in future trials should include adverse-event surveillance, liver and renal function, complete blood counts, inflammatory biomarkers, cardiopulmonary evaluation when QingDai-derived products are used, concomitant medication review, pregnancy exclusion or specific reproductive safety plans, and long-term follow-up for relapse and delayed

toxicity. Phytochemical status as plant-derived material should not lower the safety standard for chronic ulcerative colitis therapy.

14. Therapeutic opportunities by ulcerative colitis endotype

The therapeutic translation of gut microbiota-phytochemical interactions is strongest when ulcerative colitis is divided into mechanistic endotypes rather than treated as a single inflammatory phenotype. Each endotype reflects a dominant mucosal lesion that can be linked to a specific phytochemical exposure pattern, microbial transformation route, pharmacodynamic marker and clinical endpoint.[53] This framework also prevents overgeneralization, because curcumin, urolithin A, resveratrol, berberine, baicalein, quercetin and Curcumin-QingDai do not share the same therapeutic logic.

14.1 Mild-to-moderate 5-aminosalicylic acid partial-response endotype

The most clinically mature phytochemical opportunity is adjunctive curcumin in patients with mild-to-moderate ulcerative colitis who remain symptomatic or endoscopically active despite 5-aminosalicylic acid therapy. This endotype is defined by residual mucosal inflammation rather than severe refractory disease. Curcumin is suitable for this phenotype because its low systemic bioavailability is offset by high intestinal exposure, allowing direct interaction with epithelial cells, mucosal immune cells and luminal microbial communities.[16,54]

The therapeutic logic is additive rather than substitutive. Mesalamine targets mucosal inflammation through cyclooxygenase, prostaglandin, leukotriene and peroxisome proliferator-activated receptor-related mechanisms, while curcumin adds nuclear factor kappa B attenuation, Nrf2 activation, inflammasome modulation, epithelial barrier support and microbiota-facing luminal activity. The positive randomized trials of curcumin with mesalamine support this adjunctive position, while the negative low-dose curcumin trial indicates that inadequate dose, formulation or colonic exposure can erase clinical benefit.[2,3,23]

This endotype should be identified by persistent symptoms with objective inflammation. Suitable baseline features include mild-to-moderate Mayo activity, elevated fecal calprotectin, endoscopic erythema, friability or erosions, and incomplete response to optimized mesalamine. The most relevant intervention is not generic turmeric powder but a standardized curcumin formulation with documented dose, release properties and tolerability. Bioenhanced curcumin preparations may allow lower nominal doses, but they require formulation-specific evaluation because enhanced absorption may alter the balance between local colonic exposure and systemic exposure.[55,56]

The translational endpoints should include clinical remission, endoscopic improvement, fecal calprotectin reduction and steroid-free maintenance. Mucosal biopsies can strengthen the mechanistic interpretation by measuring nuclear factor kappa B pathway activity, Nrf2 and HO-1 expression, cytokine transcripts, epithelial junction proteins and macrophage polarization markers. A curcumin trial without fecal or mucosal exposure data remains clinically interpretable but mechanistically incomplete.

14.2 Barrier-repair deficient endotype

A distinct therapeutic opportunity exists in patients whose dominant lesion is impaired epithelial restitution. This endotype is characterized by persistent epithelial permeability, reduced tight-junction integrity, goblet cell depletion, reduced MUC2 expression, microscopic inflammation and incomplete histological healing. These patients may show partial symptomatic improvement while retaining mucosal vulnerability and relapse risk.

Urolithin A, curcumin, baicalein, quercetin and resveratrol converge on this endotype through complementary mechanisms. Urolithin A enhances barrier integrity through Nrf2-linked cytoprotection and has also been linked to microbiota and tryptophan metabolism.[4,17] Baicalein activates the AhR and IL-22 pathway in group 3 innate lymphoid cells, creating a repair signal directed toward epithelial restoration.[57] Quercetin has been associated with improved tight-junction proteins, mucus barrier protection and microbial tryptophan metabolite modulation in experimental colitis.[7,14] Resveratrol adds redox protection and autophagy-linked epithelial barrier support. Curcumin contributes by suppressing inflammatory amplification while supporting epithelial redox and junctional stability.

This endotype is especially suitable for adjunctive maintenance strategies. The aim is not only to suppress inflammation but to strengthen the mucosal surface after inflammatory activity has begun to decline. Relevant biomarkers include ZO-1, occludin, claudin-1, MUC2, goblet cell density, epithelial apoptosis markers, crypt architecture, histological activity indices and fecal calprotectin. Where available, lactulose-mannitol permeability testing or confocal endomicroscopy can add functional barrier information.[58,59]

The strongest near-term translational candidates are curcumin and urolithin A. Curcumin already has human ulcerative colitis trial evidence, while urolithin A has a sharper barrier-repair mechanism but needs direct human ulcerative colitis testing. Baicalein and quercetin remain mechanistically valuable but clinically immature in ulcerative colitis. Their development should move through small mechanistic trials before large efficacy studies.

14.3 Tryptophan-AhR-IL-22 deficient endotype

The tryptophan-AhR-IL-22 endotype is defined by insufficient microbial generation of indole derivatives and reduced mucosal repair signalling through aryl hydrocarbon receptor pathways. This endotype is highly relevant to ulcerative colitis because AhR activation supports antimicrobial peptide production, mucus barrier stability, epithelial repair, innate lymphoid cell function and interleukin 22 dependent restitution.

Berberine, baicalein, quercetin, urolithin A and QingDai-derived compounds fit this endotype through different entry points. Berberine acts through microbial tryptophan metabolite reshaping and AhR activation.[5] Baicalein acts through AhR and IL-22 signalling in group 3 innate lymphoid cells. Quercetin increases microbial indolelactic acid and activates AhR-linked epithelial protection in experimental colitis.[7] Urolithin A connects microbial tryptophan metabolism with AhR activation and barrier repair.[17] QingDai and Curcumin-QingDai supply stronger botanical AhR ligand activity through indigo and indirubin-like constituents.

A tryptophan-AhR deficient phenotype can be investigated through fecal or serum tryptophan, kynurenine, indolelactic acid, indole-3-acetic acid, indole-3-aldehyde and related metabolites. Biopsy-level readouts should include AhR target genes such as CYP1A1 and CYP1B1, IL-22, STAT3 phosphorylation, antimicrobial peptides, MUC2 and tight-junction markers. The clinical endpoint should remain endoscopic and biomarker improvement, because pathway activation alone does not establish disease control.

This endotype also requires attention to therapeutic intensity. Berberine, baicalein, quercetin and urolithin A represent moderate pathway modulators with mainly preclinical ulcerative colitis evidence. QingDai-derived compounds represent high-intensity AhR ligand therapy with human efficacy signals but greater safety concerns. This distinction should guide trial placement. Moderate modulators are suitable for mechanistic adjunctive studies, while Curcumin-QingDai requires controlled clinical development with chemical standardization and safety surveillance.

14.4 Urolithin metabotype-dependent endotype

Ellagitannin-derived therapy is one of the clearest examples of microbiota-dependent phytopharmacology. Ellagitannins require microbial conversion to ellagic acid and then to urolithins. Patients who produce urolithin A after ellagitannin intake receive a different active exposure from non-producers. This creates a metabotype-dependent endotype in which therapeutic response depends on microbial biotransformation capacity.[28]

This endotype is particularly relevant in ulcerative colitis because active inflammation, antibiotics, diet, age and microbial depletion may alter urolithin production. A patient may consume the same ellagitannin precursor but generate insufficient urolithin A exposure because the necessary microbial conversion network is weak. Direct urolithin A administration bypasses this variability and allows cleaner pharmacological testing, whereas ellagitannin precursor therapy tests both botanical exposure and microbial conversion capacity.[60]

The ideal translational design stratifies participants into urolithin producers and non-producers before intervention. Urolithin producer status can be assessed after a standardized ellagitannin challenge using urine, plasma or fecal metabolite profiling. In urolithin producers, ellagitannin-rich standardized extracts may be tested as microbial prodrug therapy. In non-producers, direct urolithin A or microbiota-restorative co-interventions may be more rational than repeated precursor dosing.[61]

The most suitable mucosal phenotype is barrier dysfunction with oxidative epithelial injury. Pharmacodynamic readouts should include urolithin A concentration, Nrf2, HO-1, epithelial junction proteins, histological activity, calprotectin and endoscopic healing. This endotype has strong mechanistic credibility but limited direct clinical evidence in ulcerative colitis. It should therefore be presented as a high-priority translational opportunity rather than an established treatment category.

14.5 Oxidative epithelial injury endotype

Oxidative epithelial injury is a frequent and therapeutically important layer of ulcerative colitis. It is characterized by excessive reactive oxygen species, mitochondrial stress, lipid peroxidation, reduced antioxidant capacity, nuclear factor kappa B activation, epithelial apoptosis, inflammasome priming and delayed wound repair. This endotype overlaps with barrier dysfunction but is more specifically defined by redox injury.

Resveratrol, urolithin A, curcumin and quercetin are the most relevant phytochemical candidates for this phenotype. Resveratrol has pilot human evidence showing improvement in clinical activity, quality of life and oxidative-antioxidative status, supported by experimental evidence involving Nrf2 and HO-1 activation, microbiota modulation and PI3K/Akt/VEGFA attenuation.[18,34,35] Urolithin A is strongly linked to Nrf2-mediated gut barrier integrity. Curcumin activates Nrf2 while suppressing nuclear factor kappa B mediated inflammatory amplification. Quercetin combines redox activity with epithelial barrier and microbial tryptophan effects in experimental colitis models.

This endotype should be evaluated using both redox and mucosal endpoints. Suitable biomarkers include malondialdehyde, glutathione, superoxide dismutase, catalase, Nrf2, HO-1, mitochondrial injury markers, epithelial apoptosis and histological activity. Serum

oxidative markers alone are insufficient because ulcerative colitis is a mucosal disease. The strongest studies will connect redox correction to epithelial repair, fecal calprotectin reduction, endoscopic improvement and histological healing.

Resveratrol's current translational place is narrower than curcumin's. It has a human signal, but the trials are small and not deeply microbiome-instrumented. Resveratrol should therefore be positioned as a redox-focused adjunctive candidate rather than a broadly established ulcerative colitis therapy. Its future value depends on demonstrating that oxidative epithelial injury markers identify responders.[62]

14.6 High-activity botanical AhR ligand-responsive endotype

A high-activity AhR ligand-responsive endotype is suggested by the clinical activity of indigo naturalis and Curcumin-QingDai. This phenotype is likely characterized by active mucosal inflammation with impaired epithelial repair signalling and insufficient endogenous AhR ligand tone. Curcumin-QingDai is mechanistically distinctive because curcumin contributes broad mucosal anti-inflammatory and barrier-supportive effects, while QingDai-derived indigo and indirubin-like compounds provide stronger AhR pathway stimulation.[63]

This endotype has higher clinical potency but also higher translational risk. Indigo naturalis has been associated with pulmonary arterial hypertension and other serious adverse events. The opportunity is therefore not informal QingDai use but standardized, controlled and safety-monitored development of chemically defined products. Product identity, indigo and indirubin content, impurities, batch variation, particle properties and stability should be documented before clinical interpretation.[64]

The suitable clinical position is active ulcerative colitis requiring induction of response, especially where a controlled phytochemical adjunct is being tested with standard therapy. The endpoints should include clinical response, clinical remission, endoscopic improvement, fecal calprotectin reduction and safety. For mechanistic confirmation, AhR target gene induction, IL-22 signalling, epithelial repair markers and tryptophan metabolite profiles should be paired with clinical outcomes.[57]

This endotype has citation potential because it connects a clinical efficacy signal with a defined mucosal receptor pathway and a clear safety boundary. Its development will be judged by whether efficacy can be retained while reducing unpredictable toxicity through chemical standardization, dose control and monitoring.

14.7 Microbial fermentation and short-chain fatty-acid deficient endotype

A short-chain fatty-acid deficient endotype is characterized by reduced microbial fermentation capacity, loss of butyrate-producing taxa, impaired colonocyte energy support and weakened epithelial immune tolerance. This phenotype is relevant to ulcerative colitis but should not be defined only by fecal short-chain fatty-acid concentration, because fecal concentration reflects production, absorption, transit and inflammation-dependent epithelial uptake.[65]

Phytochemicals may affect this endotype indirectly by reshaping microbial ecological functions. Curcumin, resveratrol, quercetin and berberine have been reported in experimental settings to alter microbial composition and metabolic outputs, but the evidence is stronger for functional modulation than for consistent restoration of a single bacterial taxon. This endotype therefore requires metagenomic or metatranscriptomic assessment of butyrate-producing pathways rather than simple taxonomic abundance.[66]

Relevant markers include butyryl-CoA:acetate CoA-transferase genes, abundance and activity of *Faecalibacterium*, *Roseburia* and related anaerobes, fecal calprotectin, epithelial hypoxia markers, tight-junction proteins and histological inflammation. The therapeutic aim is recovery of microbial metabolic support for the epithelial barrier. Phytochemicals alone may be insufficient in severely depleted anaerobic ecosystems, but they may contribute as adjuncts when residual microbial capacity is present.[67]

Table 5: Endotype-specific positioning of microbiota-interacting phytochemicals in ulcerative colitis.

UC endotype	Dominant lesion	Best-matched phytochemical strategy	Mechanistic biomarkers	Clinical endpoints	Evidence maturity	Reference
5-ASA partial-response inflammatory endotype	Persistent mild-to-moderate mucosal inflammation despite mesalamine	Curcumin or bioenhanced curcumin as adjunct	NF-κB, Nrf2, fecal curcumin, cytokine transcripts	Clinical remission, endoscopic improvement, calprotectin reduction	Human randomized evidence	[68,69]
Barrier-repair deficient endotype	Tight-junction disruption, mucus depletion,	Urolithin A, curcumin, baicalein,	ZO-1, occludin, claudin-1, MUC2, IL-22,	Histological improvement, endoscopic	Strong preclinical, partial clinical	[68,70]

	incomplete epithelial restitution	quercetin, resveratrol	Nrf2	healing, relapse reduction	support	
Tryptophan-AhR-IL-22 deficient endotype	Reduced microbial indole signalling and impaired repair immunity	Berberine, baicalein, quercetin, urolithin A, QingDai-derived compounds	Indolelactic acid, AhR target genes, IL-22, STAT3	Biomarker reduction and mucosal healing	Strong mechanistic, emerging clinical for QingDai/CurQD	[71,72]
Urolithin metabotype-dependent endotype	Variable microbial conversion of ellagitannins to urolithin A	Ellagitannin precursor in producers, or direct urolithin A	Urolithin A exposure, Nrf2, HO-1, barrier proteins	Histological repair and calprotectin reduction	Mechanistically strong, clinical UC evidence limited	[4,17]
Oxidative epithelial injury endotype	ROS excess, mitochondrial stress, lipid peroxidation, delayed repair	Resveratrol, urolithin A, curcumin, quercetin	Nrf2, HO-1, GSH, SOD, MDA, epithelial apoptosis	Clinical activity, histology, endoscopy	Human pilot signal for resveratrol; stronger preclinical support	[68,69]
High-activity AhR ligand-responsive endotype	Active inflammation with repair-pathway insufficiency	Curcumin–QingDai or standardized indigo naturalis-derived products	AhR target genes, IL-22, indigo and indirubin exposure	Clinical response, remission, endoscopic improvement	Human efficacy signal with safety constraints	[8,21,22]
Fermentation and SCFA-deficient endotype	Reduced butyrate-producing function and epithelial metabolic support	Curcumin, resveratrol, quercetin or berberine as microbial functional modulators	Butyrate pathway genes, anaerobe function, epithelial hypoxia markers	Calprotectin reduction and mucosal healing	Mechanistic but not yet endotype-validated	[11,12]

14.8 Integration into therapeutic development

The endotype model changes how phytochemical trials should be designed. A conventional trial that randomizes an unselected ulcerative colitis population to a phytochemical supplement and measures symptoms alone will dilute mechanistic signals. A higher-value design selects patients by dominant mucosal lesion and measures whether the compound produces the predicted microbial and epithelial pharmacodynamic effect.

For curcumin, the most suitable design is add-on therapy in mild-to-moderate 5-aminosalicylic acid partial responders, with fecal curcumin exposure and mucosal inflammatory markers. For urolithin A, the design should stratify by urolithin metabotype or use direct urolithin A exposure in a barrier-repair phenotype. For berberine, baicalein and quercetin, the design should focus on tryptophan metabolites, AhR target activation and epithelial repair. For resveratrol, oxidative injury markers should be integrated with microbiome and mucosal outcomes. For Curcumin-QingDai, the design should combine efficacy endpoints with rigorous safety surveillance and phytochemical standardization.

15. Evidence conflicts and interpretation

There are studies that have shown beneficial effects of curcumin and others that have demonstrated adverse effects. This should be seen as an exposure and formulation heterogeneity and not as a contradiction. In some trials, curcumin was beneficial as adjunctive therapy, in another trial, it was not beneficial at lower concentrations and in a bioenhanced formulation, it was beneficial at higher concentrations.[2,3,23–25] The question isn't whether or not 'curcumin works' is a general statement. The question becomes what is the mucosal pharmacodynamic activity of the specific formulation, dose, exposure, background therapy and disease phenotype?

The results of the short chain fatty acid analyses are also inconclusive. There is association between the reduced bacteria that produce short chain fatty acids (SCFA) in feces and ulcerative colitis, but the concentration of SCFA in the feces is not always correlated with disease activity.[11,12] This is as one would expect as the concentration of faecal would be different from what is produced in the mucosa and used by the epithelia. Further phytochemical research should assess the capacity of the microbial genome, as well as the context in the gut (mucosa) and not just the concentration of metabolites in stool.

Urolithin A has strong mechanistic evidence and is currently under investigation in direct efficacy studies in humans with ulcerative colitis with limited data.[4,17] Not a "mechanistic weakness" but a "translational gap".

Berberine, baicalein and quercetin also possess good preclinical evidence via the tryptophan-AhR-barrier pathway, but need to be tested in humans. Despite adequate animal research, small human studies, and support human microbiota mechanisms are not well developed. QingDai and Curcumin–QingDai exhibit clinical activity, but concerns to their safety give the limits of their translational applications.

16. CONCLUSION

From colonic exposure, to the biotransformation of phytochemicals through the gut microbiota, to their pharmacodynamics at the mucosal surface, and their surveillance-grade clinical outcome, gut microbiota-phytochemical interactions provide a convincing therapeutic avenue for UC. The clinical evidence for combination with mesalamine is the most solid, and curcumin is formulating sensitive. Urolithin A is a high value microbial metabolite model that connects metabolic processes of ellagitannin, activation of Nrf2, repair of epithelial barriers and aryl hydrocarbon receptor-related tryptophan biologies. A tryptophan-AhR-IL-22 repair axis, characterized by berberine, baicalein and quercetin, has a strong link with epithelial restitution. Resveratrol is a signal of the redox and microbiota modulation, which needs more sized-up, and instrumented mechanistically trials. Curcumin–QingDai and indigo naturalis show a very good clinical activity and require a strict safety and chemical standardisation. Only when the field is able to move beyond the general use of phytochemicals, can it progress. Precision phytopharmacology is the future of this type of intervention, which is chemically defined, delivered to the colon, metabolized/conditioned by the microbiota, measured by microbial metabolic products and activation of mucosal pathways, and judged by the endpoints of ulcerative colitis (calprotectin reduction, endoscopy, histology, steroid-free remission, and relapse prevention and safety). In this context, there are no alternatives to anti-inflammatory supplements and phytochemicals are not among them. They are rational pharmacologic agents that can be developed for specific ulcerative colitis endotypes and that are colon facing and rely on microbes.

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