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REVIEW

Baicalin as a Multifunctional Regulator of Gut Health: Integrative Mechanisms Involving Inflammation, Barrier Integrity, and Gut-Organ Axis

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Abstract: Intestinal health is sustained by coordinated control of mucosal immunity, epithelial barrier integrity, and the gut microbiota and its metabolites. Disruption of these tightly coupled systems contributes to a wide spectrum of disorders, ranging from infectious enteritis and inflammatory bowel disease (IBD) to ischemia-reperfusion injury and metabolic dysfunction with extra-intestinal sequelae. Baicalin (BAI), a major flavonoid from Scutellaria baicalensis, has emerged as a multi-level regulator of gut homeostasis. Across diverse preclinical models, BAI attenuates inflammatory signaling and frequently converges on NF-κB-centered networks; it also rebalances immune responses by modulating macrophage polarization and T-cell subsets, limits oxidative and ferroptotic damage through cytoprotective programs, and restores barrier function by preserving tight junctions and mucus-layer defenses. In parallel, BAI remodels microbial community structure and microbial metabolites, including short-chain fatty acids and bile-acid signaling, providing a plausible basis for benefits along gut–organ axes such as the gut–liver and gut–metabolic axes. This review integrates mechanistic evidence across these three pillars and highlights key translational gaps, including limited oral bioavailability, incomplete causal validation of proposed targets, and the need to disentangle BAI from active metabolites. We further discuss derivative design, formulation, and combination strategies to improve exposure and accelerate clinical translation.

Keywords: gut health, baicalin, inflammation, barrier integrity, gut-organ axis

Introduction

The gut is a critical organ for maintaining systemic homeostasis and overall health, playing central roles not only in nutrient absorption and metabolic regulation but also in immune defense, inflammatory responses, and even mood regulation.[1,2] Gut health depends on the integrity of the epithelial barrier, dynamic immune balance, and the precise interactions among the intestinal microbiota.[3–5] These three components are interdependent and coordinately regulated, collectively establishing intestinal homeostasis. When the epithelial barrier is compromised, immune responses are dysregulated, or microbial composition is disturbed, intestinal permeability increases, allowing pathogenic microbes and their metabolites to breach the mucosal barrier. This can trigger persistent inflammation and oxidative stress, leading to various pathological conditions, including Inflammatory bowel disease (IBD), infectious enteritis, and metabolic disorders.[6,7] Therefore, strategies aimed at modulating immune responses, protecting epithelial integrity, and restoring microbial balance have become central to recent research on gut disease prevention and therapy. Moreover, the emerging concept of the "gut-organ axis" has highlighted the close connections between intestinal function and organs such as the liver, brain, and metabolic systems, positioning gut homeostasis as a potential target for improving systemic disorders.[8–11]Given that gut-related pathologies typically arise from coupled failures across barrier function, immune regulation, and microbiota-derived signaling, interventions capable of simultaneously modulating multiple interconnected pathways may be particularly advantageous in this setting.

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BAI is the major active flavonoid isolated from the traditional Chinese medicinal herb *Scutellaria baicalensis*.[12] Although BAI has been investigated in a wide range of inflammation- and metabolism-related conditions, a unifying feature across studies is its capacity to modulate immune and stress-response pathways.[13–25] This multi-level regulatory profile makes BAI particularly relevant to gut disorders, where disease initiation and progression typically involve coupled failures in mucosal immunity, epithelial barrier integrity, and microbiota-derived signaling. Accordingly, BAI has attracted growing attention as a candidate to restore intestinal homeostasis and potentially confer systemic benefits through gut-organ axis regulation.[17]

This review summarizes recent advances in understanding the regulatory effects of BAI on intestinal homeostasis, with a particular focus on its mechanisms in inflammation modulation, epithelial barrier preservation, and gut-organ interactions, providing theoretical foundations and research directions for its potential application in the prevention and treatment of gut-related diseases.

The Role of Baicalin in Various Intestinal Diseases

BAI, a natural flavonoid derived from *Scutellaria baicalensis* Georgi, exhibits potent anti-inflammatory, antioxidant, and immunoregulatory properties, demonstrating broad protective effects in multiple intestinal disorders. Extensive studies have shown that BAI exerts systemic protective effects in infectious, inflammatory, and metabolic intestinal diseases by regulating inflammation, oxidative stress, and epithelial barrier homeostasis through multiple pathways (Figure 1 and Table 1).

Infectious intestinal diseases, caused by bacteria, viruses, fungi, or parasites, are characterized by diarrhea, mucosal damage, and intestinal dysfunction.[56] In models of infection-induced intestinal injury, such as deoxynivalenol (DON) and avian pathogenic Escherichia coli (APEC), BAI significantly alleviates intestinal damage. It reduces the overactivation of inflammatory pathways, downregulates pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), and enhances antioxidant

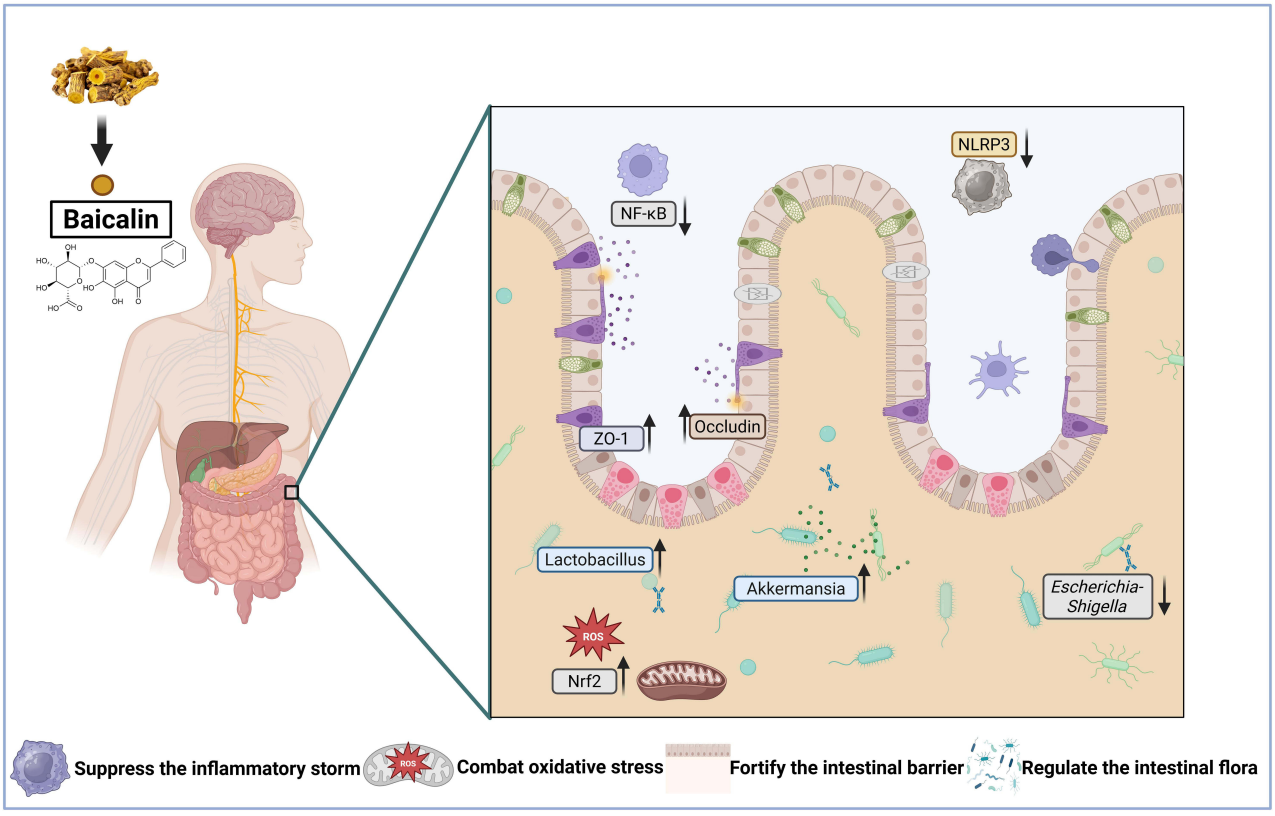

Figure 1 Baicalein alleviates intestinal inflammation and oxidative damage and promotes tissue repair through synergistic effects.

Table 1 High-Level Evidence Map of Baicalin-Related Interventions in Intestinal Protection

Major Effect	Disease Contexts/ Representative Models	Convergent Phenotypic Outcomes	Key Mechanism Modules	Representative References
Inflammation suppression (core hub)	IBD/colitis; endotoxemia; infection-associated enteritis	Reduces mucosal inflammation and injury; lowers key cytokines; improves disease indices	TLR4/CD14–MyD88–NF-κB; MAPK/PI3K/JAK-STAT	[26–32]
Immune reprogramming	IBD/colitis; infection-associated inflammation	Shifts immune balance toward resolution; reduces pro-inflammatory polarization and supports regulatory programs	Th17/Treg (JAK2/STAT3); M1→M2 (IRF4/IRF5); FOXP3/IL-10	[27,31,33]
Barrier repair (tight junction + mucus)	Colitis; infection; inflammatory epithelial injury; immune-mediated injury	Restores barrier integrity and permeability; improves villus/goblet features	TJ proteins (ZO-1/occludin/claudins); MLCK axis; NLRP6/IL-18–MUC2; autophagy (AMPK/mTOR)	[34–37]
Epigenetic/structural barrier stabilization	Epithelial injury models	Stabilizes junctional complexes and preserves epithelial integrity	miR-191a/ZO-1 regulation	[38]
Regulated inflammatory cell death	LPS/ATP epithelial injury; DSS-colitis derivatives	Attenuates inflammatory cell death and mucosal damage	PARP1–NF-κB; NLRP3 inflammasome/pyroptosis cascade	[39,40]
Antioxidant cytoprotection (redox program)	DON toxicity; endotoxemia; colitis; oxidative stress injury	Enhances antioxidant defenses; reduces ROS and lipid peroxidation; supports epithelial survival	AMPK–Nrf2; SOD/CAT/GSH-Px; ROS–MAPK	[41–45]
Anti-ferroptosis in ischemic injury	Intestinal ischemia–reperfusion; OGD/R in IEC-6	Prevents lipid peroxidation-driven injury; preserves mitochondria and barrier	Nrf2–GPX4/xCT; iron/lipid ROS control	[46]
Microbiota and metabolite remodeling	Infection; DON; metabolic and hypertensive models; FMT validation	Restores microbial ecology; increases beneficial taxa and metabolites linked to barrier/immune homeostasis	SCFA-producing taxa; SCFAs; microbiota–metabolite axis	[26,47–50]
Gut–organ axis outcomes and translation enablers	Gut-iver; gut-metabolic /cardiovascular; formulations/ combos	Improves distal organ phenotypes alongside gut homeostasis; exposure/biotransformation optimization may amplify effects	Microbiota–bile acids (FXR/GPBAR1); β-glucuronidase–metabolite conversion; combinations/ complexes/derivatives	[32,36,40, 51–55]

enzyme activities (SOD, GSH-Px, CAT), thereby mitigating oxidative stress, improving villus morphology, maintaining tight junction protein expression (ZO-1, Occludin, Claudin), and restoring barrier function.[26,34,41,57]

IBD is a chronic, relapsing, immune-mediated disorder of the gastrointestinal tract, primarily comprising ulcerative colitis (UC) and Crohn's disease (CD). Experimental colitis models, including TNBS- and DSS-induced colitis, are widely used to investigate IBD pathogenesis and to evaluate potential therapeutic candidates.[42] In these models, BAI has been repeatedly reported to alleviate disease activity and histopathological injury, which is accompanied by attenuation of mucosal inflammatory signaling and restoration of immune homeostasis. Mechanistically, available evidence suggests that BAI frequently converges on NF-κB–centered inflammatory networks, rebalances immune-cell phenotypes (such as macrophage polarization and T-cell subset distribution), and promotes mucosal healing by supporting epithelial barrier repair, including preservation of tight junction proteins and mucus-layer defenses.[27–29,33,35,58]

Intestinal ischemia–reperfusion (II/R) injury, caused by transient interruption and subsequent restoration of intestinal blood flow, leads to structural and functional damage due to oxidative stress, inflammation, and cell injury.[30,59] In II/R models, BAI mitigates ferroptosis, reduces lipid peroxidation and oxidative damage, restores tight junction protein expression, and alleviates tissue inflammation, thereby improving intestinal barrier function.[60]

In metabolic-related intestinal dysfunction, BAI also modulates gut microbiota composition and short-chain fatty acid (SCFA) production, improving intestinal barrier integrity and microbial homeostasis in high-fat diet or hypertension-induced models. Additionally, BAI can be metabolized via β-glucuronidase (β-GUS) to baicalein, enhancing the generation and absorption of active metabolites and thereby improving bioavailability and pharmacological activity.[46–49]

Multidimensional Protective Mechanisms of Baicalin in Intestinal Health

Anti-Inflammatory and Immune-Modulating Effects

Inflammation is essential for intestinal defense, yet sustained activation can amplify mucosal injury by coupling cytokine storms, immune-cell imbalance, and barrier breakdown.[51,61,62] Across disease contexts-including IBD, infection-associated enteritis, and toxin-triggered injury-evidence consistently indicates that BAI exerts a convergent anti-inflammatory program that suppresses pro-inflammatory signaling while reprogramming immune-cell phenotypes toward resolution (Figure 2).

At the pathway level, BAI most frequently maps onto a pattern-recognition-to-NF-κB-centered inflammatory hub, with recurrent involvement of PI3K/AKT-, MAPK-, and JAK/STAT-linked amplification loops.[26,28,29,31,33,36,39,43,52,63,64] Rather than reiterating individual pathway readouts across models, the literature supports a common outcome profile: reduced mucosal pro-inflammatory mediators and adhesion/inflammatory effector molecules, alongside increased anti-inflammatory signals such as IL-10. Notably, several studies suggest that BAI may act at upstream checkpoints (eg., CD14) or interact with nuclear regulators (eg., PARP1), providing plausible mechanistic entry points for dampening LPS-driven inflammation at its source.[28,52]

Importantly, BAI's anti-inflammatory effects are not limited to signaling suppression; they are frequently accompanied by immune-cell rebalancing that may mechanistically explain sustained mucosal improvement in IBD and related inflammatory settings. Reported immunomodulatory patterns include reduced Th17-associated activity via inhibition of JAK2/STAT3 phosphorylation and attenuation of IL-17A output, as well as suppression of M1 macrophage polarization linked to IL-17/NF-κB signaling.[58] In parallel, BAI can promote pro-resolving macrophage features, for example by shifting IRF4/IRF5 balance toward M2 polarization.[35] In infection-induced inflammation models, similar immune rebalancing is described together with microbiota-associated changes (eg., enrichment of beneficial Lactobacillus species), suggesting that immune and microbial layers may be coordinated rather than independent.[26,32,41] Additional nodes such as p38 MAPK inhibition and PPARγ activation have also been implicated as part of an anti-inflammatory homeostatic shift.[64] Consistent with an "immune-microbiota-metabolite" perspective, BAI-associated metabolite changes (eg., baicalein, lactate, indole) have been proposed to further reinforce anti-inflammatory states.[32] In some settings, rational combinations may amplify these effects; for instance, BAI plus emodin has been reported to enhance anti-inflammatory efficacy through concurrent targeting of CD14/TLR4/NF-κB and PPARγ-related pathways.[43]

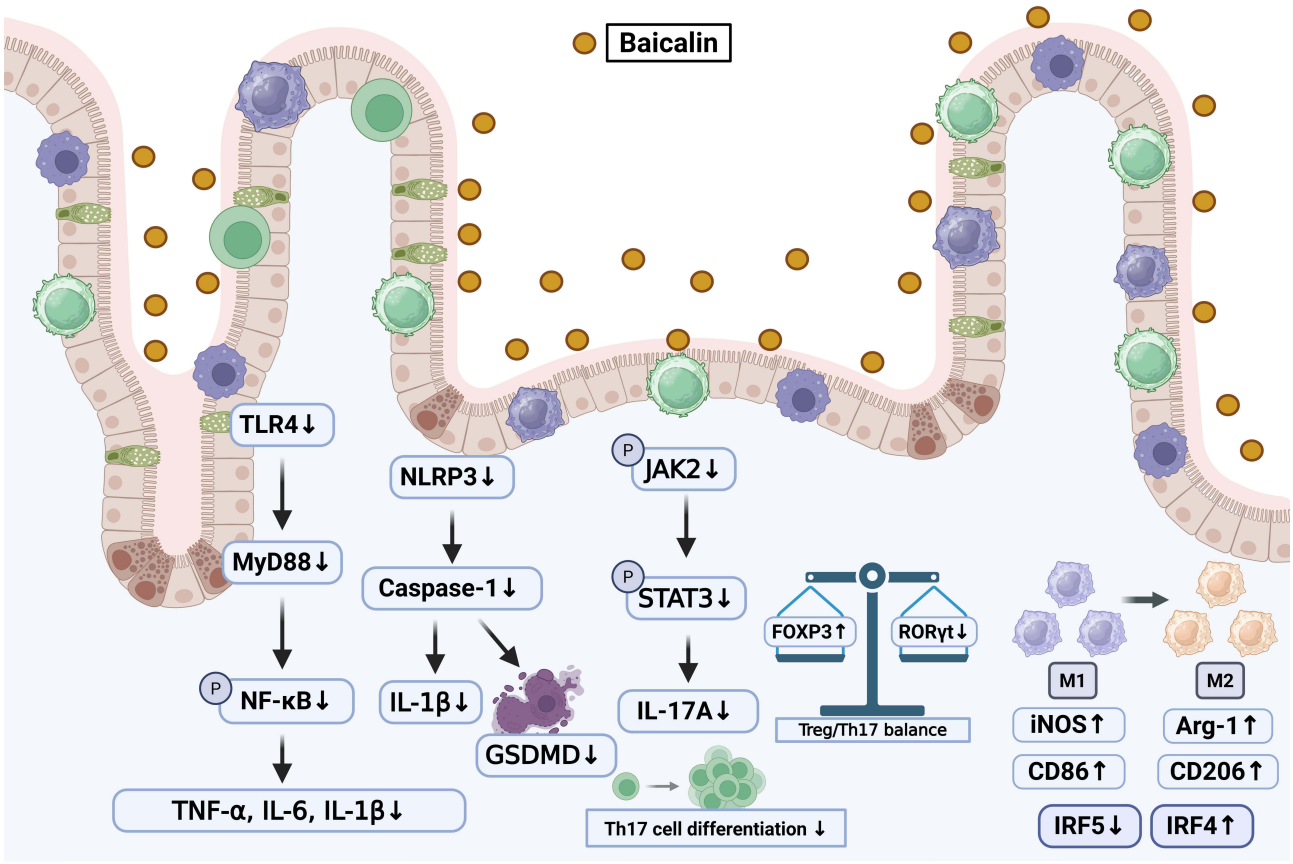

Figure 2 Baicalein reshapes a healthy intestinal immune microenvironment by targeting multiple key signaling pathways, synergistically inhibiting pro-inflammatory responses and promoting immune tolerance.

Although anti-inflammatory and immune-modulating effects are supported across multiple preclinical contexts, mechanistic interpretation often remains correlational and relies on pathway markers rather than causal validation. Future studies should prioritize standardized comparisons of dose and administration route across disease stages in IBD and infection-associated inflammation,[62] together with stronger necessity and sufficiency designs to verify key entry nodes such as CD14 and PARP1 and to determine whether immune reprogramming is a true driver, rather than a by-product, of mucosal healing.[28,35,52,58] Clearer separation of barrier-mediated secondary effects from primary immune targeting, as discussed in Section 3.3, will further improve interpretability.

Antioxidant and Cytoprotective Effects

Oxidative stress and cellular injury are common denominators across IBD, toxin-induced injury, infection-associated inflammation, and ischemia-related intestinal damage.[65,66] Beyond immunosuppression, evidence indicates that BAI engages cytoprotective programs that stabilize epithelial viability and redox balance, thereby limiting downstream tissue injury (Figure 3).

A consistent observation across diverse stressors is that BAI enhances endogenous antioxidant capacity, typically reflected by increased SOD, CAT, and GSH-Px activities with concomitant reductions in lipid peroxidation markers such as MDA.[31,44,57,67] Mechanistically, the AMPK/Nrf2 axis emerges as a recurrent integrator of this antioxidant phenotype. In oxidative models, BAI can promote Nrf2 nuclear translocation and downstream antioxidant gene induction, and AMPK knockdown markedly attenuates the protection, supporting AMPK/Nrf2 as a central cytoprotective route in these settings.[67] In DON-induced toxicity, BAI-associated redox improvement is reported together with reduced inflammatory activation and preservation of villus architecture, implying that cytoprotection and inflammation control are tightly

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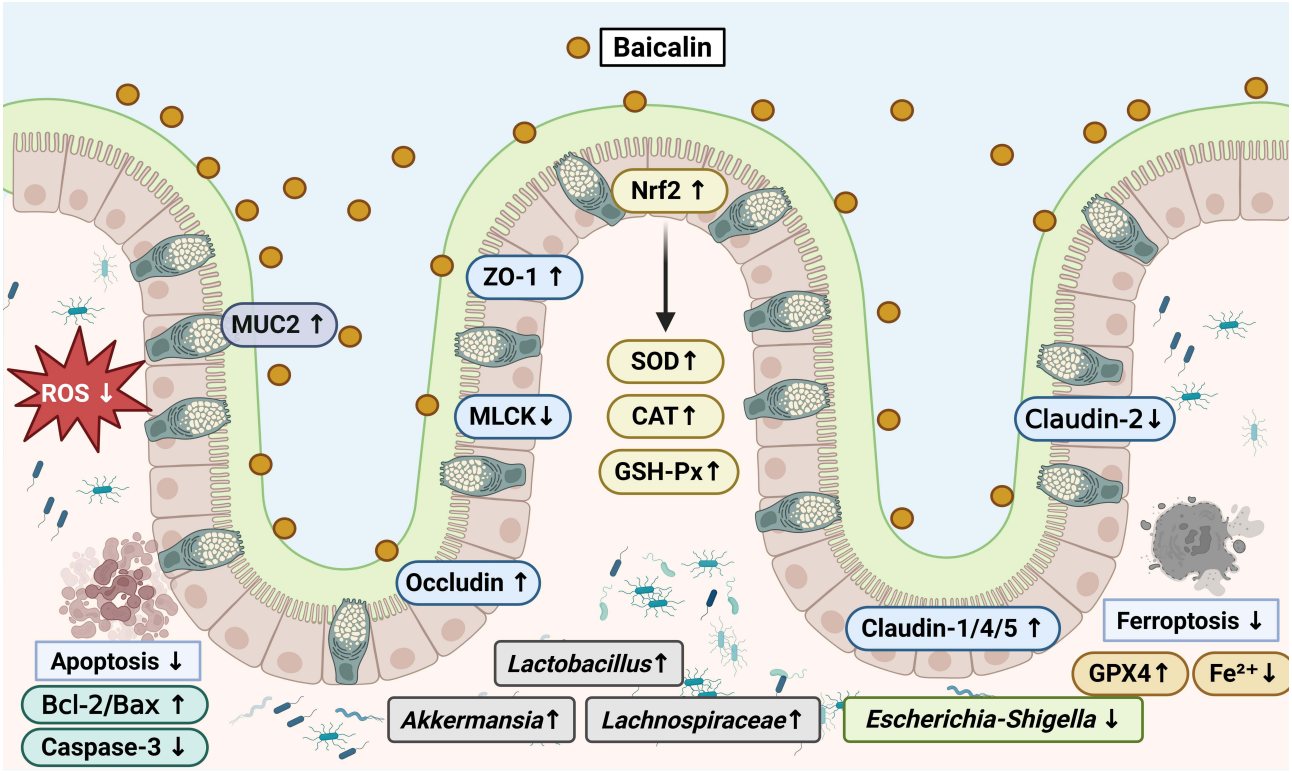

Figure 3 Baicalein builds a solid multi-layered intestinal defense system by enhancing tight junctions, promoting mucus secretion, improving antioxidant capacity and regulating the microbiota.

coupled during mucosal recovery.[67] In DON-induced toxicity, BAI-associated redox improvement is reported together with reduced inflammatory activation and preservation of villus architecture, implying that cytoprotection and inflammation control are tightly coupled during mucosal recovery.[57]

In severe injury contexts, particularly intestinal ischemia–reperfusion, BAI has been linked to suppression of ferroptosis-related damage, providing a mechanistic explanation for protection beyond conventional antioxidant readouts. Studies suggest that BAI can mitigate iron overload and lipid peroxidation through the Nrf2/GPX4 axis, restoring GPX4 and xCT expression, maintaining mitochondrial membrane potential, and preserving redox balance; these effects are reported to be reversible by Nrf2 or GPX4 inhibitors, supporting a causal anti-ferroptotic component in II/R injury.[60]

Additional stress-signaling nodes may contribute; for example, modulation of ROS/MAPK pathways has been described in inflammatory models, with decreased p-ERK and p-p38 phosphorylation and docking-based suggestions of direct interaction.[34] However, such target engagement requires further biochemical confirmation.

BAI also appears to limit epithelial loss by influencing apoptosis-related pathways, reducing pro-apoptotic mediators while increasing anti-apoptotic Bcl-2, consistent with reduced epithelial apoptosis in colitis-related contexts.[31,44] The reported inhibition of IKK/IκB/NF-κB signaling suggests a plausible bidirectional coupling between oxidative stress and inflammatory programs, enabling combined anti-apoptotic and anti-inflammatory tissue protection.[31]

While antioxidant and cytoprotective signatures are repeatedly observed, the field would benefit from standardized, time-resolved in vivo readouts linking redox/mitochondrial metrics to permeability and clinical endpoints.[65,66] Given that BAI's effects often co-occur with reduced inflammation, experiments that isolate primary cytoprotection from secondary anti-inflammatory improvement are needed. Anti-ferroptotic claims in II/R are strengthened by inhibitor-based reversals, but broader validation of target engagement and disease-stage dependence remains essential.[60] Finally, docking-based inferences should be supported by direct binding/functional assays to avoid overinterpretation.[34]

Barrier Restoration and Gut Microbiota Homeostasis

The epithelial barrier and gut microbiota form an interdependent ecological–structural unit that is essential for intestinal function and systemic health.[45,68] Barrier disruption and dysbiosis can mutually reinforce inflammation, infection susceptibility, and metabolic disturbances.[69,70] Across disease contexts, BAI is repeatedly associated with improvements in barrier integrity and microbiota–metabolite homeostasis, suggesting a coordinated mechanism that extends beyond single-pathway suppression (Figure 3).

On the structural side, BAI and its derivatives consistently promote tight junction preservation and permeability reduction, typically reflected by increased ZO-1, occludin, and claudin-family expression along with improved villus morphology and goblet-cell features in injury models.[41] In infection-associated enteritis, BAI improves mucosal architecture and upregulates barrier proteins and antimicrobial peptides, often in parallel with restrained inflammatory pathway activation.[26,41,71] In epithelial injury models driven by inflammatory mediators, BAI or derivatives can reduce MLCK-associated junctional disruption via TNF-α/MLCK/ZO-1-linked mechanisms, with docking results suggesting that derivative-specific interactions may contribute to suppressing inflammatory signaling.[39,72] Beyond signaling, barrier stabilization may also involve epigenetic regulation; for example, BAI-mediated downregulation of miR-191a can relieve repression on ZO-1 and improve barrier function in IEC-6 cells.[73] Mucus-layer and goblet-cell repair programs have additionally been linked to NLRP6/IL-18 activity and enhanced MUC2 secretion, providing another structural route through which BAI may reinforce barrier defenses.[27]

On the ecological side, BAI is frequently reported to reshape microbiota composition and microbial metabolites, including restoration of diversity and enrichment of beneficial taxa under toxin exposure, antibiotic perturbation, and metabolic stress.[38] In antibiotic-disrupted piglets, microbiota restoration accompanied by changes in MAPK and calcium signaling has been linked to improved metabolic and energy homeostasis.[48] In high-fat diet–related settings, enrichment of SCFA-producing bacteria (eg., Akkermansia and Roseburia) and increased acetate/butyrate levels align with improved glucose tolerance and insulin sensitivity, suggesting that microbiota–metabolite remodeling may contribute to systemic benefits (see Section 3.4).[46,47]

Under complex stress states, barrier protection may involve additional regulated processes: BAI can suppress NET formation in hyperglycemic conditions and preserve tight junction integrity,[50] while derivatives such as BNE have been linked to microbiota shifts and reduced ROS/ERK/NLRP3-associated pyroptosis in DSS-induced colitis.[74] In immune-mediated injury such as aGVHD, BAI has been reported to enhance AMPK/mTOR-dependent autophagy and mitochondrial recovery, supporting barrier integrity; these effects are sensitive to autophagy inhibition.[40]

Although barrier and microbiota improvements are consistently described, causality is not always established: microbiota shifts may be drivers or consequences of mucosal healing. Designs such as fecal microbiota transplantation or controlled microbiota depletion are important for demonstrating directionality, especially when ecological remodeling is proposed as a therapeutic mechanism.[48] Moreover, overlap between barrier-structural pathways and inflammatory suppression complicates attribution; future studies should more clearly separate primary epithelial mechanisms from immune-mediated secondary effects.[39,72,73] Finally, linking microbiota/metabolite changes to defined host targets and to permeability/endotoxemia readouts will strengthen mechanistic coherence across contexts.[46,47]

Gut-Organ Axis Regulatory Effects

The "gut-organ axis" framework highlights how intestinal microbiota and their metabolites can influence distal organ physiology through immune, metabolic, and neuroendocrine pathways.[37,75,76] Because permeability and microbial product translocation can propagate systemic inflammation and metabolic disruption, interventions that restore intestinal barrier and microecology may plausibly yield multi-organ benefits.[77] Accumulating evidence suggests that BAI can exert systemic protective effects along gut–organ axes, but mechanistic clarity depends on demonstrating a coherent chain from intestinal regulation to distal outcomes (Figure 4).

Along the gut-liver axis, BAI has been reported to ameliorate combined gut and liver pathology in settings where antibiotic- or stress-associated dysbiosis compromises barrier function. In lincomycin-exposed neonatal mice, BAI improves gut and liver injury phenotypes while reshaping microbiota composition (increasing beneficial genera and

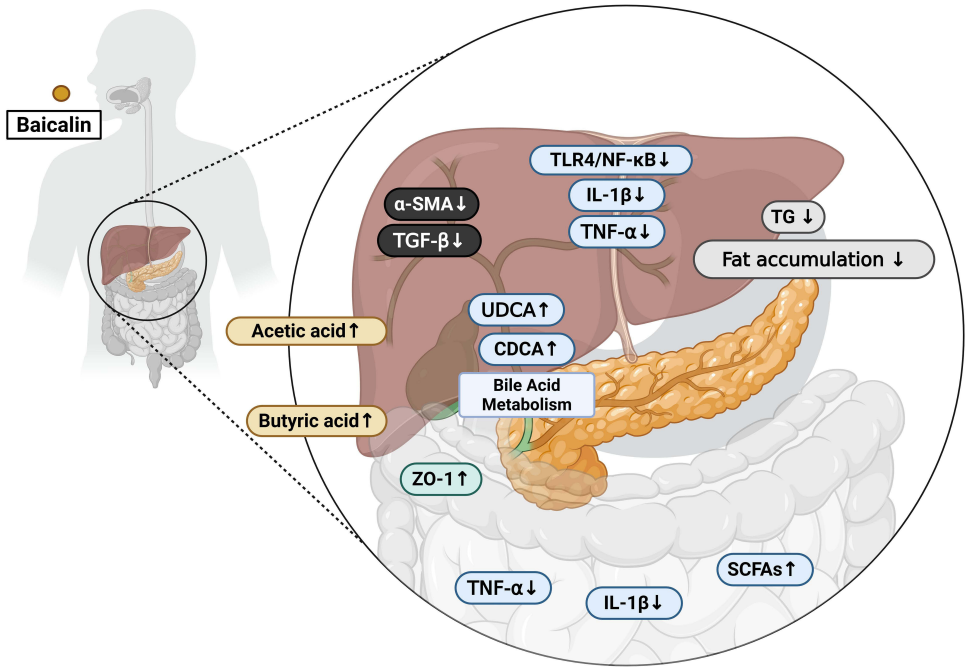

Figure 4 Baicalein alleviates damage and metabolic disorders in distant organs such as the liver by repairing the intestinal barrier, regulating the microbiota and their metabolites, reducing the entry of harmful substances into the bloodstream, and generating beneficial signals. It is mediated by the gut-liver axis.

decreasing opportunistic pathogens), and transcriptomic signals suggest normalization of immune programs and hepatic metabolic pathways, including bile acid secretion and lipid catabolism.[78] In heat-stressed pregnant mice, BAI reduces liver injury markers and modulates lipid metabolism genes while improving villus morphology and tight junction protein expression; microbiota changes further support bidirectional gut–liver regulation in this context.[53] These models collectively support an axis-level interpretation in which intestinal barrier/microbiota recovery aligns with reduced hepatic stress and improved metabolic handling.

Along the gut–metabolic and gut–cardiovascular axes, BAI-associated remodeling of microbiota and SCFA profiles provides a plausible mechanistic bridge to systemic metabolic improvements. In high-fat diet–induced type 2 diabetes models, enrichment of SCFA-producing bacteria and elevated acetate/propionate/butyrate levels coincide with improved glucose tolerance, insulin sensitivity, and lipid profiles.[46] Similarly, in spontaneously hypertensive rats, increased SCFA production and enrichment of beneficial taxa occur alongside strengthened barrier function and reduced inflammatory gene expression, suggesting that intestinal homeostasis may contribute to improved systemic inflammatory tone and vascular phenotype.[47] Together, these findings support a generalizable hypothesis: by stabilizing the barrier–microbiota–metabolite network, BAI may reduce systemic inflammatory signaling and improve distal metabolic/cardiovascular outcomes.

Notably, some studies explicitly aim to strengthen axis-level efficacy by improving intestinal exposure or metabolite conversion. For example, co-administration strategies can enhance β-glucuronidase activity and promote conversion to active metabolites, potentially increasing bioavailability and reinforcing bile acid and lipid metabolism regulation.[49] Likewise, highly water-soluble complexes have been linked to microbiota remodeling, secondary bile acid production, receptor activation, and integrated anti-inflammatory/antioxidant/barrier effects in colitis contexts.[54] These approaches highlight how optimizing exposure and microbiota-associated signaling may amplify gu-organ outcomes, while also underscoring the need for rigorous pharmacokinetic-pharmacodynamic integration.

Axis-level conclusions remain predominantly preclinical and are often associative; stronger linkage requires permeability and endotoxemia-related measures, metabolite profiling, and temporal coupling of intestinal and distal organ readouts.[77] Additionally, disentangling the contributions of BAI versus microbiota-generated metabolites is essential when conversion is invoked as a mechanism or a formulation rationale.[49] Finally, prioritizing clinically actionable axes and defining responder phenotypes will be critical for translation beyond animal models.[37,75,76]

Advances in Baicalin Derivatives for Intestinal Protection

BAI and its various derivatives exhibit significant potential in intestinal protection through multi-target and multi-pathway synergistic mechanisms.[55] The BCU has been shown to effectively mitigate intestinal injury caused by APEC infection. Its protective mechanisms involve inhibition of AKT/NF-κB phosphorylation, thereby reducing intestinal inflammation and oxidative stress, while upregulating tight junction proteins (ZO-1, Occludin, Claudin1/3) and chemical barrier factors (MUC2, AvBD2), enhancing antioxidant enzyme activity, and improving intestinal structural integrity.[71]

BME demonstrates pronounced protective effects in LPS-induced intestinal barrier injury in mice. BME directly binds to the NF-κB P65 protein, suppressing its activity, and blocks the TNF-α/MLCK/ZO-1 signaling pathway, thereby restoring tight junction protein expression, reducing pro-inflammatory cytokines, and increasing anti-inflammatory mediators, ultimately improving intestinal barrier function.[39]

BNE has shown efficacy in UC models by modulating gut microbiota composition, increasing the abundance of beneficial bacteria such as Lachnospiraceae, reducing pro-inflammatory bacteria such as Clostridia-UCG-014, and inhibiting the ROS/ERK/p-ERK/NLRP3 signaling pathway to suppress pyroptosis-related protein expression, thereby significantly alleviating colonic inflammation.[74]

Additionally, Baicalin-Mg regulates gut microbiota and secondary bile acid metabolism via the microbiota–bile acid axis, activates FXR and GPBAR1 receptors, and downregulates NF-κB and PPAR-α signaling, markedly reducing intestinal inflammation and mucosal damage. Its water solubility is approximately 2000-fold higher than that of conventional baicalin, providing a promising strategy to overcome the bioavailability limitations of traditional BAI.[54]

Overall, these studies highlight that baicalin derivatives exert intestinal protective effects through multiple mechanisms, including anti-inflammatory and antioxidant actions, barrier repair, and gut microbiota modulation, positioning them as potential therapeutic agents for intestinal protection and the treatment of inflammatory bowel diseases.

Discussion

Intestinal health is fundamental to overall physiological homeostasis, influencing not only nutrient digestion and absorption but also immune defense, metabolic regulation, and neuropsychological function.[79] Intestinal homeostasis depends on the coordinated integrity of the epithelial barrier, dynamic immune regulation, and balanced gut microbiota.[1,80,81] Disruption of this delicate balance, referred to as gut dysregulation, can trigger persistent inflammation, oxidative stress, and mucosal barrier damage, thereby predisposing to a variety of diseases.[82,83] Gut dysregulation is closely associated not only with IBD but also with infectious enteritis, intestinal ischemia–reperfusion injury, metabolic syndrome, and gut–brain axis dysfunction.[84–86] Consequently, restoring intestinal homeostasis, repairing the mucosal barrier, and re-establishing microbial balance have emerged as critical strategies and research priorities for the prevention and treatment of intestinal disorders.

Recent studies indicate that BAI and its derivatives exert multi-target and systemic regulatory effects in maintaining intestinal homeostasis. BAI modulates immune balance and suppresses inflammation by downregulating pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-17A) and upregulating anti-inflammatory mediators (IL-10) through the inhibition of multiple signaling pathways, including TLR4/NF-κB, PI3K/AKT, MAPK, and JAK/STAT.[26–28,31–33,35,36,41,43,52,58,63,64] It also enhances antioxidant defenses and protects epithelial integrity by activating AMPK/Nrf2 and Nrf2/GPX4 pathways, increasing antioxidant enzyme activity, reducing oxidative stress, and inhibiting apoptosis.[34,38,39,47,50,57,67,72–74] Furthermore, BAI promotes mucosal repair by upregulating tight junction proteins (ZO-1, Occludin, Claudin) and modulates gut microbiota composition, increasing short-chain fatty acid (SCFA)-producing bacteria and their metabolites, thereby improving intestinal function through the microbiota–metabolism–immune axis.[26,39,41,71–73]

BAI also extends its protective effects via the gut-organ axis. It exhibits anti-inflammatory, antioxidant, and metabolic regulatory roles along the gut-liver, gut-metabolic, and gut-cardiovascular axes.[46,47,53,78] Derivatives such as BME, BNE, BCU, and Baicalin-Mg) demonstrate improved barrier repair, anti-pyroptotic effects, and microbiota modulation, offering enhanced pharmacological efficacy and bioavailability, and providing new avenues for clinical translation and drug development.[39,54,71,74]

Despite its promising multi-target advantages, the clinical translation of BAI faces several challenges. Its poor water solubility and low oral bioavailability limit in vivo efficacy; thus, derivative modifications, nano-delivery systems, and

metal coordination strategies represent effective approaches to enhance pharmacokinetic properties. In addition, the precise systemic targets and signaling networks regulated by BAI remain incompletely elucidated; future studies integrating multi-omics approaches (metabolomics, transcriptomics, microbiomics) and systems pharmacology are required to dissect its comprehensive mechanisms. Moreover, clinical evidence supporting BAI in IBD and metabolic intestinal disorders is still limited, warranting large-scale, randomized controlled trials to validate its efficacy and safety.

Overall, BAI, as a multifunctional natural compound, demonstrates substantial potential for maintaining intestinal health by coordinating inflammation, oxidative stress, epithelial barrier integrity, and gut-organ axis networks. Its multi-dimensional mechanisms provide valuable insights for the development of novel intestinal protective and anti-inflammatory therapeutics and serve as a model for the modernization of traditional Chinese medicine.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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