Potential for anti-angiogenic therapy targeting the receptor for advanced glycation end products/VEGF axis in ulcerative colitis (Review)

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Abstract. Ulcerative colitis (UC), a major form of inflammatory bowel disease, has a global incidence of ~10.6 per 100,000 individuals. The long-term side effects and dependency issues associated with conventional UC therapies have become increasingly evident, highlighting the need for more effective and safer treatment options. In previous years, clinical research on small-molecule targeted drugs against UC has achieved notable progress; however, the underlying pathogenesis and therapeutic mechanisms of UC still require deeper investigation. The receptor for advanced glycation end products (RAGE) is a pattern recognition receptor that binds both pathogen-associated molecular patterns and damage-associated molecular patterns, thereby mediating inflammatory and cellular stress responses. Concurrently, vascular endothelial growth factor (VEGF), a key regulator of angiogenesis, is markedly upregulated in patients with UC and associates with disease severity. The RAGE/VEGF signaling axis has thus emerged as a notable target for antiangiogenic therapy in UC. Interventions aimed at disrupting the interaction between RAGE and its ligands, inhibiting RAGE pathway activation or suppressing VEGF upregulation have demonstrated promising potential to alleviate symptoms and slow disease progression. The present review summarizes previous advances in UC-targeted therapeutics and elucidates the role of the RAGE/VEGF axis in UC pathophysiology, highlighting the potential mechanisms and clinical prospects of antiangiogenic strategies targeting this pathway.

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Contents

1. Introduction

Ulcerative colitis (UC) is a chronic, non-specific inflammatory bowel disease (IBD) that is characterized by persistent inflammation and ulceration of the colonic mucosa. Patients with UC typically present with abdominal pain, diarrhea and stools containing blood and mucus (1). Although the precise pathogenesis of UC remains to be fully elucidated, it is generally understood to result from the multifactorial interplay of environmental factors, immune dysregulation, gut microbiota imbalance and genetic predispositions (2). Histopathological features include inflammatory cell infiltration within the lamina propria and excessive secretion of proinflammatory cytokines such as IL-6 and TNF-α (3). Globally, the prevalence of UC is ~10.6 per 100,000 individuals (4), driven by an aging population and improved diagnostic recognition. With disease progression, the risk of colonic malignancy also increases (5). In Asian populations, westernization of diets has been identified as a key contributor to the increasing prevalence. Evidence from a large cohort of 500,000 Chinese participants highlights two high-risk dietary patterns associated with increased risk of UC: i) The traditional Northern diet, consisting of high wheat and low rice intake; and ii) a modern diet rich in animal-based foods and fruits. Notably, frequent egg consumption was associated with increased susceptibility to late-onset UC, whereas spicy food intake

showed a protective association (6). Similarly, a Japanese study has attributed the pathogenesis of UC to reduced intake of dietary fiber, fermented foods containing probiotics and plant-based nutrients, accompanied by higher consumption of refined carbohydrates and animal fats (7). Pan-Asian analyses further support these findings, indicating that 'Westernized' diets, characterized by elevated refined sugar, red meat and linoleic acid, promote UC development, while fiber-rich fruits and vegetables exert protective effects (8).

Mechanistically, these dietary factors are considered to impair gut barrier integrity, alter gut microbial composition and amplify proinflammatory signaling cascades. Acute severe colitis is experienced by ~15% of patients with UC, with >30% ultimately requiring colectomy (9). Therapeutically, monoclonal antibodies targeting key cytokines have been increasingly used to manage corticosteroid-refractory UC (10-12). However, their long-term efficacy is limited by adverse effects and the gradual loss of therapeutic response in some patients (13), underscoring the need for continued investigation into UC pathogenesis and the development of novel treatment strategies.

The receptor for advanced glycation end products (RAGE), first identified in 1992, is a transmembrane protein belonging to the immunoglobulin (Ig) receptor superfamily (10). Structurally, RAGE comprises three domains, extracellular, transmembrane and intracellular, and exists in both membrane-bound and soluble forms. Owing to its unique molecular configuration, RAGE is one of the few pattern recognition receptors capable of binding both pathogen-associated molecular patterns and damage-associated molecular patterns (DAMPs). Initially discovered for its ability to interact with AGEs implicated in diabetes (14), RAGE has since been shown to bind a wide array of non-glycation ligands, including protein S100 (S100) calgranulins, high-mobility group box 1 (HMGB1) and amyloid β (Aβ) protein (15). Although this is most abundantly expressed in lung tissue, RAGE signaling contributes to the pathogenesis of numerous chronic inflammatory diseases affecting multiple organs, including diabetic vascular complications (16), cardiovascular disease (17), cancer (18), Alzheimer's disease (AD) (19) and various infection-related and autoimmune disorders (20). Previous studies have revealed elevated RAGE expression in UC (21) and Crohn's disease (22). Furthermore, several DAMP ligands, including calprotectin (23), lactoferrin (24), S100A calgranulins (25) and HMGB1 (26), are recognized biomarkers of disease activity and prognosis in IBD. Other receptor systems implicated in UC, including toll-like receptors (TLRs) (27), C-type lectin receptors (28) and nucleotide-binding oligomerization domain-like receptors (29), have been well characterized. However, the contribution of RAGE to UC pathogenesis and its potential as a therapeutic target remain inadequately understood. The present review, therefore, highlights the pathobiological importance of RAGE in UC, summarizing previous advances in clinical and translational research and exploring its implications for targeted therapeutic intervention.

2. Other targeted therapeutic pathways in UC

Currently, the primary pharmacologic options for treating UC include corticosteroids, aminosalicylates, immunomodulators and antibiotics. However, the widespread clinical application of these drugs is constrained by high costs, notable toxicities and frequent disease recurrence (30). Although a previous study has explored dose de-escalation strategies using immunomodulators such as thiopurines and methotrexate, these regimens have shown limited efficacy in patients with moderate-to-severe UC compared with biologic therapies and small-molecule targeted drugs (31). To address these limitations, a new generation of small-molecule targeted therapies has been developed, offering distinct advantages such as high oral bioavailability, reduced risk of immunogenicity and lower manufacturing costs (32). These agents represent a promising alternative to conventional biologics in UC management. Approaches primarily targeting cellular subsets or broad immune modulation are beyond the scope of the present discussion and are therefore not included in the classification stated in the present review.

IL-12/23. The IL-12 family has unique heterodimeric cytokines, including the IL-12, IL-23, IL-27 and IL-35 cytokines; this heterodimeric property confers a unique set of connectivity and functional interactions in these cytokines (33). Despite their similar structural features, the members of the IL-12 family have distinct properties. Among them, IL-12 and IL-23 play key roles in intestinal homeostasis and inflammation and are involved in the pathogenesis of IBD (34). The main contributions of IL-12 and IL-23 to UC pathogenesis are the induction of T helper (Th)1 and Th17 cell differentiation, respectively (35); thus, the inflammatory effects of IL-12 and IL-23 provide a theoretical rationale for the development of blocking agents targeting UC. Inhibitors targeting IL-12/23 attenuate the Th1/Th17-mediated adaptive immune response, which is a notable contributor to UC pathogenesis (36).

JAK/STAT. JAK is a non-receptor tyrosine protein kinase located downstream of different inflammatory cytokines. As an intracellular-signaling mediator, JAK interacts with STAT so as to induce phosphorylation of STAT and activate the target transcription molecules (11). The JAK/STAT pathway is an important signaling pathway that allows extracellular proinflammatory cytokines to relay inflammatory signals to the nucleus via membrane receptors. Several cytokines that are notably associated with immunity and intestinal stromal cell homeostasis, such as IL-6, IL-10, IL-2 and IL-22, as well as cytokines that act as mediators of pathological responses in UC, such as IFN-γ, IL-12, IL-23 and IL-9, are dependent on JAK/STAT-mediated signaling (37,38). When JAK/STAT signaling is blocked, the nucleus cannot receive extracellular chemical signals, which reduces inflammation. Thus, JAK inhibitors can simultaneously block multiple inflammatory pathways. Demonstrably, JAK inhibitors can broadly affect the immunopathogenesis of UC, influencing factors such as the inflammatory response, intestinal epithelial barrier and fibrosis (11).

The diversity of therapeutic targets identified thus far underscores the multifactorial nature of UC pathogenesis. Agents targeting cytokines, such as TNF-α (39-52) and IL-12/23 (40,53-56), intracellular signaling pathways, such as the JAK/STAT pathway (57-67), epithelial barrier integrity, such as mucin-2, phosphodiesterase 4 (PDE4) inhibitors (68,69) and lymphocyte trafficking, for example sphingosine 1-phosphate receptor (70-74), have demonstrated clinical efficacy

in mediating UC (11,12,72,75), with the detailed clinical trial data of these targeted agents systematically summarized in Table SI (39-56,58-74); however, these therapies typically modulate discrete components of the inflammatory cascade or adaptive immune response. By contrast, RAGE represents a distinct signaling axis, primarily activated by DAMPs generated during tissue stress and injury (76). Functioning as a sensor of persistent inflammation and cellular injury, RAGE activation amplifies oxidative stress, perpetuates chronic inflammation and contributes to fibrotic remodeling, key pathological processes not fully addressed by current biologics or small molecule inhibitors (77). The following sections examine the mechanistic role of RAGE and its ligands in UC pathogenesis and discuss the potential of targeting this axis as a novel therapeutic strategy.

3. RAGE signaling pathway in UC

Introduction to the RAGE molecule. The RAGE gene is located on chromosome 6 within the major histocompatibility complex class III region, which harbors numerous genes that are important to both adaptive and innate immune function (78). RAGE is a 50-55 kDa type I transmembrane glycoprotein composed of an extracellular region containing three Ig-like domains, a variable, a constant 1 and a constant 2 domain (Fig. 1). Ligand binding predominantly occurs within the variable domain (79). The extracellular region adjoins a single transmembrane segment, followed by a short, charged cytoplasmic tail, the latter being important for intracellular signal transduction (80,81). Notably, truncation of this cytoplasmic domain abolishes downstream RAGE signaling and markedly attenuates RAGE-mediated pathological effects (82,83). In addition to the membrane-bound full-length RAGE (FL-RAGE), two soluble isoforms, soluble RAGE (sRAGE) and endogenous secretory RAGE (esRAGE), have been identified. The former arises from proteolytic cleavage of membrane-bound RAGE, whereas esRAGE is produced through alternative mRNA splicing. Both soluble forms can bind circulating RAGE ligands, acting as 'decoy' receptors that prevent ligand engagement with FL-RAGE and thereby dampen inflammatory signaling (84,85).

Interactions between cell-surface RAGE and its ligands initiate a cascade of intracellular events that promote proinflammatory phenotypes both *in vitro* and *in vivo*, implicating this pathway in the pathophysiology of numerous diseases (84). In addition to binding endogenous DAMPs, RAGE can also be activated by pathogen-associated molecular patterns such as bacterial lipopolysaccharide (86), viral proteins (87), parasite-derived proteins (88) and bacterial DNA (76). Ligand engagement activates multiple downstream signaling networks, including the diaphanous-related formin 1 (89), MAPK (90), PI3K/Akt (91) and toll-interleukin 1 receptor domain-containing adaptor protein (92) pathways, culminating in NF-κB activation. Notably, RAGE signaling forms a self-sustaining positive feedback loop with NF-κB: Inflammatory stimuli activate NF-κB, which subsequently upregulates RAGE expression, further amplifying and prolonging inflammatory responses (93).

RAGE expression has been detected in diverse cell types, including endothelial cells (ECs), vascular smooth muscle cells, monocytes and macrophages, granulocytes, adipocytes and various tumor cells (94). Aberrant RAGE expression has also been implicated in the pathogenesis of numerous diseases, such as diabetes (95), atherosclerosis (96), rheumatoid arthritis (97), AD (19), cardiovascular diseases (98) and chronic immune-mediated and inflammatory disorders (84). Furthermore, RAGE has been associated with tumor initiation and progression across multiple types of cancer (99).

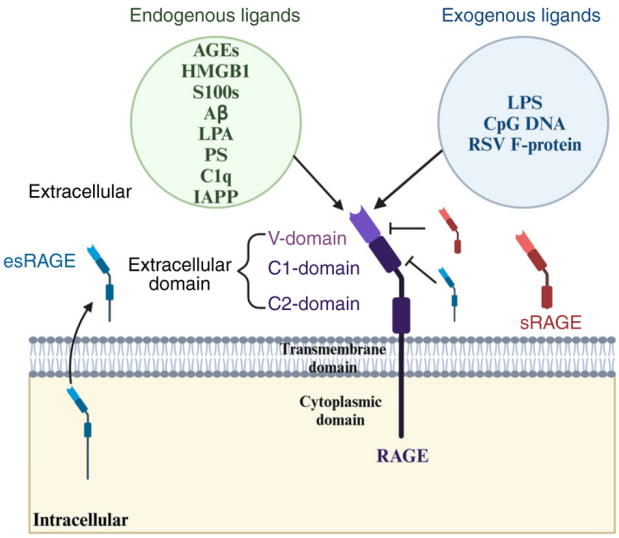

Figure 1. RAGE is a multi-ligand pattern recognition receptor. RAGE binds to a variety of ligands, including endogenous ligands (DAMPs) and exogenous ligands (pathogen-associated molecular patterns). sRAGE and esRAGE have a blocking effect on the RAGE pathway. AGEs, advanced glycation end products; RAGE, receptor for advanced glycation end products; DAMPs, damage-associated molecular patterns; sRAGE, soluble RAGE; esRAGE, endogenous secretory RAGE; HMGB1, high-mobility group box 1; S100s, protein S100s; Aβ, amyloid β; LPA, lysophosphatidic acid; PS, phosphatidylserine; C1q, complement protein C1q; IAPP, islet amyloid polypeptide; CpG, 5'-C-phosphate-G-3'; RSV F-protein, respiratory syncytial virus fusion protein.

Upstream activation signal of RAGE in UC. The binding of RAGE ligands to membrane-bound RAGE initiates receptor activation and triggers a cascade of intracellular signaling events. Increasing evidence identifies RAGE as an important mediator in the pathogenesis of numerous chronic inflammatory disorders (100-102). Multiple molecular mechanisms appear to contribute to disease initiation and persistence in patients with UC, particularly those amplifying proinflammatory signaling (103,104). Notably, both RAGE and its ligands exhibit elevated expression in intestinal epithelial cells from patients with UC and experimental colitis models, and are localized predominantly in inflamed mucosal regions (105-108). This interaction of RAGE and its ligands plays an important role in sustaining mucosal injury and perpetuating intestinal inflammation.

In UC, chronic inflammation and mucosal damage promote the accumulation of AGEs, which interact with RAGE to exacerbate inflammatory signaling. AGEs are naturally formed during aging however, their formation is accelerated under conditions of hyperglycemia and oxidative stress, such as in diabetes mellitus (81). The binding of AGEs to RAGE activates the NF-κB and MAPK signaling pathways (90), stimulating the release of proinflammatory cytokines, including IL-6

and TNF-α, thereby aggravating mucosal inflammation and driving UC progression (21). AGEs are generated through the Maillard reaction, a non-enzymatic process in which reducing sugars react with proteins, lipids or DNA (109). This reaction proceeds from the formation of reversible Schiff bases and Amadori intermediates to stable, irreversible AGEs via oxidative rearrangements (110). Given that diabetes is a frequent comorbidity among patients with UC (111), strategies aimed at glycemic control, through dietary interventions, hypoglycemic agents or inhibition of glycation reactions, may effectively suppress AGE production and attenuate intestinal inflammation. Inhibitors of AGE synthesis, including aminoguanidine, which has been evaluated in acetic acid- (112) and TNF-α-induced rat and murine colitis models (113), metformin, tested in oxazolone- (114), acetic acid- (115) and dextran sulfate sodium (DSS)-induced models (116), and pioglitazone, previously assessed in acute and chronic DSS-driven murine colitis (117,118), consistently alleviate inflammation and reduce colonic mucosal injury across experimental settings. Although some clinical evidence supports these findings, translational validation remains limited (119).

Another therapeutic strategy involves preventing AGE-RAGE binding, which can be achieved via soluble receptor analogs, receptor antagonists or post-receptor signaling inhibitors. In UC, blockade of this binding suppresses inflammatory cascades, preserves mucosal integrity and modulates immune responses (120). Statins, for instance, interrupt the positive feedback loop between the AGE-RAGE axis and C-reactive protein expression, thereby reducing inflammation and oxidative stress (121). Statins, as a potential preventive and therapeutic strategy for UC, have been shown to attenuate colitis severity in animal models (122-124). However, clinical investigations evaluating the disease-modifying and preventive potential of statins in UC have yielded limited and inconsistent findings (125-127). Current epidemiologic evidence is insufficient to support the use of statins for the prevention or treatment of UC (128).

Low-molecular-weight heparin acts as a competitive RAGE antagonist by displacing AGE ligands, leading to notable anti-inflammatory and antioxidant effects in UC, as supported by clinical evidence (129-131). Collectively, AGEs contribute to UC pathogenesis through multiple mechanisms that sustain inflammation and tissue injury. Elucidating these pathways may yield novel therapeutic targets and provide mechanistic insight into AGE-RAGE-mediated intestinal pathology.

HMGB1 was the second ligand identified to bind RAGE following the discovery of AGEs (132). HMGB1 is a highly-conserved nuclear protein comprising two N-terminal DNA-binding domains and an acidic C-terminal domain. It is broadly expressed in multiple tissues, including the brain, heart, lungs, liver, spleen, kidneys and lymphatic organs, and can be localized in the nucleus, cytoplasm and extracellular milieu (133). Under resting conditions, HMGB1 predominantly resides within the nucleus; however, upon stimulation by lipopolysaccharide, 5'-C-phosphate-G-3' DNA, TNF-α or IL-1, various immune cells, particularly monocytes and neutrophils, actively secrete HMGB1 (134). Passive release also occurs from necrotic cells (134). Both actively and passively released HMGB1 can bind high-affinity receptors such as TLR2, TLR4 and RAGE on target cells (135-137). These interactions drive immune cell activation, cytokine release and downstream inflammatory cascades (138,139). RAGE-HMGB1 binding activates multiple tumor-associated signaling pathways, including the ERK1/2, p38 MAPK and NF-κB pathways, thereby promoting cancer progression and metastasis (140).

In the context of UC, blockade of HMGB1/TLR4 or HMGB1/RAGE signaling markedly attenuates inflammation in experimental models (141,142). Clinically, fecal HMGB1 levels correlate strongly with disease severity and mucosal activity in UC (143-145), highlighting its promise as a non-invasive biomarker for both overt and subclinical intestinal inflammation (26,146). Therapeutic strategies targeting HMGB1 remain in early development, but preclinical evidence suggests potential efficacy. Pharmacological agents such as dapagliflozin (141) and several natural compounds, including isoliquiritin (147), 20(S)-protopanaxadiol saponins (148) and matrine (149), have demonstrated anti-HMGB1 effects in experimental models. Nonetheless, the majority of these interventions remain confined to animal experimental stages (147,148,150), and rigorous clinical validation is required to confirm their safety, pharmacokinetics and therapeutic benefit. To date, HMGB1-targeted therapies have not entered routine clinical practice, although ongoing advances warrant close attention to emerging evidence.

The S100 protein family constitutes one of the largest subgroups of calcium-binding proteins, exhibiting distinct biological functions and tissue-specific expression patterns (151). Extracellular S100 proteins interact with several receptors, including RAGE, TLR4, fibroblast growth factor receptor 1 and G-protein coupled receptors (152). Through these interactions, they promote the transcription of proinflammatory mediators such as TNF-α, IL-1β, IL-6 and IL-8, induce reactive oxygen species generation and regulate apoptosis (102). Although RAGE binding is considered a common feature of numerous S100 proteins (153), only specific members, including S100A1, S100A2, S100A4-9, S100A11-13, S100B and S100P, have been experimentally validated as RAGE ligands *in vivo* (154). Among these, S100A8/A9, also known as calprotectin, is predominantly expressed by neutrophils and is markedly elevated in IBD. The notable stability of calprotectin in fecal samples has established it as a robust biomarker of intestinal inflammation (155,156). Functionally, calprotectin contributes to epithelial barrier dysfunction by disrupting cytoskeletal organization and tight junction integrity via TLR4- and RAGE-dependent pathways in endothelial and epithelial cells (157). Calprotectin further compromises EC integrity by downregulating junctional proteins and increasing vascular permeability (158). The quinoline-3-carboxamide derivative ABR-215757 binds S100A9 and S100A8/A9 complexes, blocking their interactions with TLR4 and RAGE, thereby exerting potent anti-inflammatory effects across several experimental models (159-161). Localized targeting of calprotectin in UC mucosa using monoclonal antibodies represents a promising therapeutic strategy, supported by successful outcomes in preclinical models of atherosclerosis (162).

Beyond HMGB1 and S100 proteins, several other endogenous RAGE ligands have been identified, including Aβ (15), lysophosphatidic acid (LPA) (163), phosphatidylserine (164),

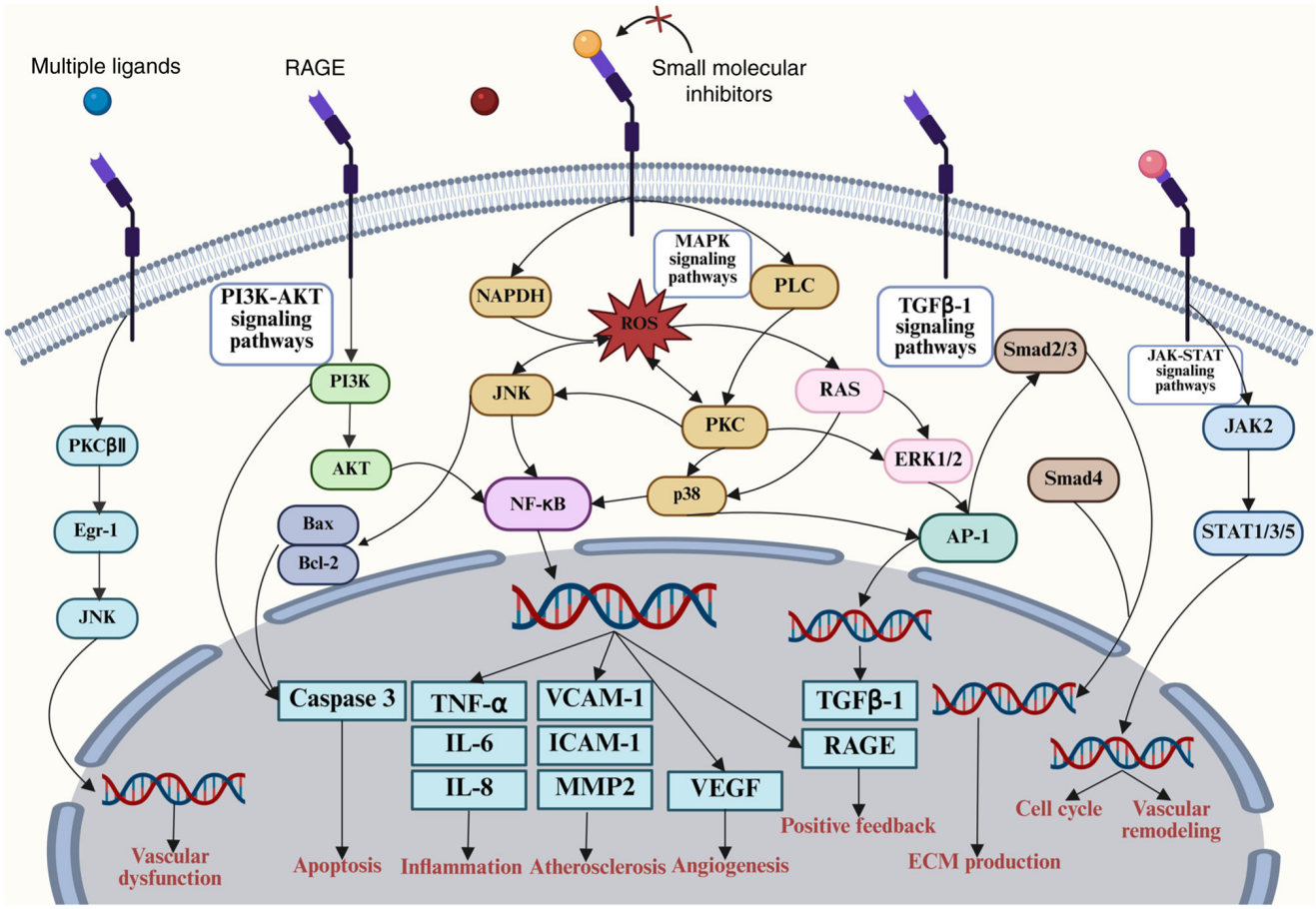

Figure 2. Schematic diagram of RAGE signaling. The interaction of RAGE with ligands leads to the activation of the NADPH, ROS, PI3K/AKT, RAS/ERK, MAPK, TGFβ-1 and JAK/STAT pathways, which further activate intracellular transcription factors such as NF-κB, Egr-1, AP-1 and STAT3. Transcription factors cause a series of functional changes in the nucleus such as vascular dysfunction, apoptosis, inflammation, atherosclerosis, angiogenesis, ECM production, cell cycle and vascular remodeling. RAGE, receptor for advanced glycation end products; PKCβII, protein kinase C βII; Egr-1, Early growth response-1; JNK, c-Jun N-terminal kinase; PI3K, Phosphatidylinositol-3 kinase; AKT, Protein kinase B; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma/leukemia-2; NAPDH, Nicotinamide adenine dinucleotide phosphate; ROS, Reactive oxygen species; MAPK, Mitogen-activated protein kinase; PLC, Phospholipase C; PKC, Protein kinase C; TNF-α, Tumor necrosis factor-α; NF-κB, Nuclear factor kappa B; IL-, Interleukin; ERK1/2, Extracellular signal-regulated kinase 1/2; JAK, Janus kinase; STAT, Signal transducer and activator of transcription; VCAM-1, Vascular cell adhesion molecule-1; ICAM-1, Intercellular adhesion molecule-1; MMP-2, Matrix metalloproteinase-2; VEGF, Vascular endothelial growth factor; TGF-β, Transforming growth factor-β; ECM, Extracellular matrix.

complement protein C1q (165) and islet amyloid polypeptide (166). Although the involvement of DAMPs in UC remains insufficiently characterized, emerging evidence suggests that they contribute to disease pathogenesis or to comorbid conditions associated with UC. For instance, modulation of adrenergic receptor signaling can preserve intestinal barrier integrity in UC partly through the presenilin 1/β-secretase-1/Aβ axis, conferring antioxidant, anti-inflammatory and antifibrotic effects (164). Similarly, bamboo leaf flavonoids downregulate Aβ expression in the brain, ameliorating both AD and UC-like inflammation (167). Furthermore, inhibition of the autotaxin/LPA axis reduces chronic intestinal inflammation by suppressing Th17 cell differentiation (168,169). Despite these insights, to the best of our knowledge, no current studies have directly demonstrated that these ligands exert anti-UC effects specifically through RAGE signaling. Further mechanistic and translational investigations are therefore warranted to delineate their roles within RAGE-dependent inflammatory networks.

Downstream pathways of RAGE in UC. Ligand binding to RAGE activates multiple downstream signaling cascades implicated in the pathogenesis of UC (Fig. 2). These include the Ras/MEK/ERK1/2S (170), stress-activated protein kinase/JNK (171), MAPK/p38 (172), PI3K/AKT (173), JAK/STAT (174), Rho GTPase (175) and vascular endothelial growth factor (VEGF) (176) pathways. Collectively, these cascades activate the transcription factors NF-κB, STAT3, activator protein 1 and early growth response-1, which subsequently induce the synthesis and secretion of vascular cell adhesion protein 1, intercellular adhesion molecule 1, matrix metalloproteinase-2, IL-1, IL-6 and TNF-α (15,177-180). DAMP-mediated RAGE activation drives UC pathogenesis via three interconnected mechanisms: i) Rho GTPase modulation alters gut microbiota composition and metabolites, promoting disease progression (175); ii) JAK/STAT signaling regulates inflammatory mediators and immune cell activation (181); and iii) MAPK pathway activation induces mitochondrial dysfunction (182), autophagy (183), oxidative stress (184) and apoptosis (185). Collectively, these pathways underscore the

central role of RAGE in UC pathogenesis by orchestrating inflammation, disrupting intestinal barrier integrity and dysregulating immune responses. Thus, identifying and characterizing RAGE-associated downstream targets may offer novel insights into UC pathophysiology and reveal new therapeutic strategies.

4. RAGE-angiogenesis-UC

Angiogenesis as a new component of UC pathogenesis. Angiogenesis, the formation of new capillaries from pre-existing blood vessels in adult tissues, is a multistep process involving EC proliferation, migration, differentiation, lumen formation and maturation, ultimately expanding the microvascular network (186,187). This process represents a double-edged sword: While important for wound healing and tissue repair, it also contributes to pathological tissue remodeling in cancer and chronic inflammatory diseases. Beyond oncology, angiogenesis plays a key role in several chronic inflammatory disorders such as atherosclerosis, rheumatoid arthritis and psoriasis (188-193). Although angiogenesis has been implicated in UC (194), quantitative characterization of mucosal vascular remodeling during active inflammation remains limited. However, increasing evidence from clinical and experimental studies demonstrates notable angiogenesis in UC and Crohn's disease, with elevated vascular density associating with IBD severity (195-200).

In UC, the colonic mucosa undergoes recurrent cycles of ulceration and regeneration. This dynamic process increases local neovascularization and enhances the recruitment of leukocytes, nutrients and oxygen to inflamed regions (194,201). The expansion of the vascular network during inflammation is accompanied by notable structural and functional changes in blood vessels. Functionally, these changes promote inflammation through several mechanisms: i) Enhanced leukocyte infiltration; ii) augmented nutrient delivery that sustains metabolically active immune responses; and iii) EC activation, which drives local cytokine, chemokine and metalloproteinase production (202). Consequently, angiogenesis and inflammation form a self-perpetuating, chronic cycle.

Hypoxia serves as a central trigger in inflammation-induced angiogenesis. Inflammatory and immune cells migrate to hypoxic sites, where they release angiogenic mediators, including growth factors, cytokines, proteases and nitric oxide, which stimulate EC activation and vascular remodeling. The resulting neovascularization amplifies inflammation by increasing the delivery of oxygen, nutrients and inflammatory mediators to affected tissues (203,204). In UC, this excessive angiogenesis enlarges the endothelial surface area and enhances vascular permeability, promoting plasma extravasation and worsening IBD severity (199). Notably, the neovessels formed during active UC differ from those generated during normal physiological angiogenesis. UC-induced vessels are structurally immature, highly permeable, poorly perfused, prone to stenosis and thrombosis and display hypersensitivity to growth factors, features that exacerbate mucosal injury and sustain chronic inflammation (205,206). Collectively, inflammation and angiogenesis in UC exist in a reciprocal, self-amplifying relationship that drives disease progression (207-210).

RAGE mediates UC angiogenesis. Angiogenesis is coordinated through a balance of pro- and anti-angiogenic molecules. Although the VEGF family is a central player, the angiogenic cascade in UC involves the complex interplay of multiple factors, receptors and isoforms (211). VEGF is the most extensively studied angiogenic factor in IBD, with elevated levels in circulation and the intestinal mucosa associating with disease activity (212,213). The VEGF family comprises several isoforms, such as VEGF-A, -B, -C, -D and -E, and placental growth factor (PlGF), which exert their effects primarily by binding to three tyrosine kinase receptors: VEGFR1, VEGFR2 and VEGFR3 (214). Although VEGFR2 is the primary mediator of pathological angiogenesis, driving EC proliferation, permeability and survival, the roles of other receptors and isoforms are increasingly recognized. VEGFR1, which has a higher affinity for VEGF-A than other isoforms but weaker tyrosine kinase activity than other VEGFRs, acts as a decoy receptor, thereby fine-tuning the availability of VEGF for VEGFR2 (215). The VEGF2 ligands, VEGF-B and PlGF, are upregulated in inflammation and modulate VEGFR1-specific signaling, influencing monocyte recruitment and inflammatory angiogenesis (216). Furthermore, the neuropilin (NRP) co-receptors NRP1 and NRP2, which bind specific VEGF-A isoforms, enhance VEGFR2-signaling complex formation and signaling potency (217).

The specific splice variants of VEGF-A are notably important. The pro-angiogenic VEGF-Axxx isoforms, such as VEGF-A164, dominate in the inflammatory milieu of UC (218). By contrast, the anti-angiogenic VEGF-Axxxb isoforms, such as VEGF-A164b, are often downregulated, creating a permissive environment for neovascularization (57). Previous evidence suggests that restoring the balance of isoforms toward VEGF-A164b can ameliorate experimental colitis (57). VEGF-C, primarily known for lymphangiogenesis via VEGFR3, can also contribute to blood vessel angiogenesis in chronic inflammation (219).

Under the inflammatory environment of UC, cytokines such as TNF-α and IL-1β can activate the RAGE-signaling pathway, which, in turn, promotes the expression and release of VEGF (21). Alterations in the extracellular matrix and oxidative stress, both hallmarks of UC, further amplify RAGE activation and its downstream pro-angiogenic signals (77,177,220). The downstream signaling of VEGFR2 exhibits notable crosstalk with RAGE-activated pathways. VEGFR2 activates the ERK1/2/MAPK pathway via Ras, which is important for EC proliferation and migration (221). VEGFR2 also activates PI3K, leading to the activation of AKT, a central regulator of cell survival, and small GTPases such as Rac, which guides cytoskeletal dynamics and EC motility (222,223). Notably, both RAGE and VEGFR2 signaling converge on NF-κB activation, creating a feed-forward loop that amplifies the production of proinflammatory cytokines and sustains the angiogenic response (224). Supporting this interconnection, neutralizing RAGE has been shown to markedly inhibit AGE-induced activation of both the VEGF and NF-κB pathways (224), while RAGE silencing also inhibits VEGF expression and angiogenesis in colorectal cancer models (225).

Beyond VEGF, other angiogenic factor families are active in UC. The angiopoietin (Ang)/Ang-1 receptor (Tie2) system is important for vascular maturation and stability. Ang-1,

produced by pericytes, activates Tie2 to promote vessel quiescence and integrity (226). In UC, the balance is shifted toward Ang-2, which is stored in and released from endothelial Weibel-Palade bodies upon inflammatory stimuli. Ang-2 acts as a context-dependent antagonist of Tie2, destabilizing vessels, priming them to be more responsive to VEGF and promoting vascular leakage and inflammation (227). Platelet-derived growth factors (PDGFs), particularly PDGF-BB produced by ECs and platelets, are important for recruiting pericytes and vascular smooth muscle cells in order to stabilize newly formed vessels. PDGF-BB is also associated with M1 macrophages and has demonstrated notable potential diagnostic value for active IBD (228).

Despite the central role of VEGF and its synergistic partners in UC angiogenesis, drug development targeting VEGF has predominantly focused on oncology. The majority of mechanistic insights into the RAGE/VEGF axis are derived from diabetes-related lesions and tumors (229-231). Consequently, there is a notable gap in the comprehension of the precise mechanisms and therapeutic potential involved in targeting the RAGE/VEGF network and its associated angiogenic factors, specifically in UC. Future research should therefore explore multi-target strategies that co-regulate RAGE, specific VEGF isoforms and parallel pathways such as the Ang-2/Tie2 pathway to achieve effective vascular normalization in UC.

Therapeutic strategies targeting angiogenesis in UC. RAGE knockdown is safe in animal models, supporting the feasibility of developing RAGE-targeted drugs (232). However, to the best of our knowledge, no anti-RAGE drug has been approved for the treatment of UC to date. Several investigations are exploring strategies that interfere with RAGE activation, including antagonistic ligands, RAGE gene deletion or small-molecule inhibitors (120,233,234). Among these, FPS-ZM1 (77,235) binds to the V-type domain of RAGE, thereby preventing its interaction with multiple ligands such as AGEs (84,236-238), HMGB1 (84,239-241), S100B (84,242) and Aβ (243). Other RAGE antagonists or inhibitors (Table SII) (84,236-244), including azeliragon, alagebrium and Tanshinone IIA (241,243,244), have been primarily developed for other RAGE-related conditions, such as neurodegenerative disorders, diabetes, tumors and inflammatory diseases (237,245,246). As aforementioned, angiogenesis is a multifactorial process involving numerous cells, molecules and signaling pathways, all of which may serve as potential therapeutic targets in UC (21,208,210). Beyond conventional anti-inflammatory agents, such as 5-aminosalicylic acid derivatives, glucocorticoids and biologics, which indirectly modulate VEGF-mediated angiogenesis (247,248), direct anti-VEGF therapies have gained attention as potential adjunctive treatments. Representative agents include receptor tyrosine kinase inhibitors, such as axitinib and sunitinib, and monoclonal antibodies such as bevacizumab, as well as investigational compounds such as rapatinib, hesperidin and sorafenib (249-251). These agents inhibit VEGF activity, suppress new vessel formation and consequently reduce vascular density and permeability in the colonic mucosa, leading to attenuation of inflammatory responses and tissue injury (247-251). Despite these promising mechanisms, clinical outcomes of antiangiogenic drugs in UC remain suboptimal, and further preclinical and clinical studies are warranted to validate their efficacy and safety.

5. Outlooks

Although numerous innovative drugs and biologics have been approved for UC treatment in previous years, the complex multifactorial pathogenesis of UC continues to limit therapeutic efficacy. Furthermore, individualized therapy in UC remains underdeveloped, and the lack of reliable prognostic biomarkers complicates the selection of optimal therapeutic regimens (40,47,50,54). Although sRAGE and esRAGE function as both biomarkers and natural inhibitors of RAGE-mediated pathology, their large recombinant protein structures hinder their practical use as therapeutic agents. Consequently, current research is increasingly focused on developing small-molecule inhibitors that can selectively target the extracellular ligand-binding domains of RAGE or its intracellular signaling cascades (252-254).

Nevertheless, several key questions remain regarding the long-term safety, pharmacodynamics and physiological impact of RAGE blockade in humans. Further studies are required to elucidate the molecular properties of potent RAGE inhibitors and to clarify the systemic consequences of chronic RAGE inhibition. In parallel, although VEGF-based antiangiogenic therapies have been successfully used in clinical trials against various tumors (255-257), their application in chronic inflammatory diseases such as UC is still in its infancy. Antiangiogenic therapy may represent a promising adjunctive approach to preventing inflammation recurrence and persistence in UC. Given that angiogenesis involves multiple interdependent steps, regulated by growth and survival factors, adhesion molecules and proteases, intestinal angiogenesis in UC provides a multidisciplinary array of potential pharmacological targets (258-260). Despite being generally considered low in toxicity, antiangiogenic agents warrant comprehensive evaluation to determine their effects on normal physiological angiogenesis and mucosal healing dynamics. Consequently, combined targeting of RAGE ligands and VEGF may offer a synergistic and effective therapeutic strategy for UC. Translation to clinical applications will require careful evaluation of human tolerability and maintaining an appropriate physiological-pathological angiogenesis balance.

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Authors' contributions

CX designed the manuscript concept. CX and YL wrote the manuscript. KH, LW, YH, DZ and FH participated in writing and reviewing the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

1. Nakase H, Uchino M, Shinzaki S, Matsuura M, Matsuoka K, Kobayashi T, Saruta M, Hirai F, Hata K, Hiraoka S, *et al*: Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. J Gastroenterol 56: 489-526, 2021.
2. Kobayashi T, Siegmund B, Le Berre C, Wei SC, Ferrante M, Shen B, Bernstein CN, Danese S, Peyrin-Biroulet L and Hibi T: Ulcerative colitis. Nat Rev Dis Primers 6: 74, 2020.
3. Li J, Wang H, Zheng Z, Luo L, Wang P, Liu K, Namani A, Jiang Z, Wang XJ and Tang X: Mkp-1 cross-talks with Nrf2/Ho-1 pathway protecting against intestinal inflammation. Free Radic Biol Med 124: 541-549, 2018.
4. Hracs L, Windsor JW, Gorospe J, Cummings M, Coward S, Buie MJ, Quan J, Goddard Q, Caplan L, Markovinović A, *et al*: Global evolution of inflammatory bowel disease across epidemiologic stages. Nature 642: 458-466, 2025.
5. Du L and Ha C: Epidemiology and pathogenesis of ulcerative colitis. Gastroenterol Clin North Am 49: 643-654, 2020.
6. Song S, Wu Z, Lv J, Yu C, Sun D, Pei P, Pan L, Yang L, Chen Y, Du H, *et al*: Dietary factors and patterns in relation to risk of later-onset ulcerative colitis in Chinese: A prospective study of 0.5 million people. Aliment Pharmacol Ther 59: 1425-1434, 2024.
7. Kanai T, Matsuoka K, Naganuma M, Hayashi A and Hisamatsu T: Diet, microbiota, and inflammatory bowel disease: Lessons from Japanese foods. Korean J Intern Med 29: 409-415, 2014.
8. Prideaux L, Kamm MA, De Cruz PP, Chan FK and Ng SC: Inflammatory bowel disease in Asia: A systematic review. J Gastroenterol Hepatol 27: 1266-1280, 2012.
9. Turner D, Walsh CM, Steinhart AH and Griffiths AM: Response to corticosteroids in severe ulcerative colitis: A systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol 5: 103-110, 2007.
10. Kim TW, Shin JS, Chung KS, Lee YG, Baek NI and Lee KT: Anti-inflammatory mechanisms of koreanaside A, a lignan isolated from the flower of forsythia koreana, against LPS-induced macrophage activation and DSS-induced colitis mice: The crucial role of AP-1, NF-κB, and JAK/STAT Signaling. Cells 8: 1163, 2019.
11. Salas A, Hernandez-Rocha C, Duijvestein M, Faubion W, McGovern D, Vermeire S, Vetrano S and Vande Casteele N: JAK-STAT pathway targeting for the treatment of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 17: 323-337, 2020.
12. Straatmijer T, Biemans VBC, Visschedijk M, Hoentjen F, de Vries A, van Bodegraven AA, Bodelier A, de Boer NKH, Dijkstra G, Festen N, *et al*: Superior effectiveness of tofacitinib compared to vedolizumab in Anti-TNF-experienced ulcerative colitis patients: A nationwide dutch registry study. Clin Gastroenterol Hepatol 21: 182-191.e2, 2023.
13. Savelkoul EHJ, Thomas PWA, Derikx L, den Broeder N, Römkens TEH and Hoentjen F: Systematic review and Meta-analysis: Loss of response and need for dose escalation of infliximab and adalimumab in ulcerative colitis. Inflamm Bowel Dis 29: 1633-1647, 2023.
14. Schmidt AM, Vianna M, Gerlach M, Brett J, Ryan J, Kao J, Esposito C, Hegarty H, Hurley W, Clauss M, *et al*: Isolation and characterization of two binding proteins for advanced glycosylation end products from bovine lung which are present on the endothelial cell surface. J Biol Chem 267: 14987-14997, 1992.
15. Jangde N, Ray R and Rai V: RAGE and its ligands: From pathogenesis to therapeutics. Crit Rev Biochem Mol Biol 55: 555-575, 2020.
16. Yamagishi S, Fukami K and Matsui T: Crosstalk between advanced glycation end products (AGEs)-receptor RAGE axis and dipeptidyl peptidase-4-incretin system in diabetic vascular complications. Cardiovasc Diabetol 14: 2, 2015.
17. Zhang L, He J, Wang J, Liu J, Chen Z, Deng B, Wei L, Wu H, Liang B, Li H, *et al*: Knockout RAGE alleviates cardiac fibrosis through repressing endothelial-to-mesenchymal transition (EndMT) mediated by autophagy. Cell Death Dis 12: 470, 2021.
18. Rigiracciolo DC, Nohata N, Lappano R, Cirillo F, Talia M, Adame-Garcia SR, Arang N, Lubrano S, De Francesco EM, Belfiore A, *et al*: Focal Adhesion Kinase (FAK)-Hippo/YAP transduction signaling mediates the stimulatory effects exerted by S100A8/A9-RAGE system in triple-negative breast cancer (TNBC). J Exp Clin Cancer Res 41: 193, 2022.
19. Guan L, Mao Z, Yang S, Wu G, Chen Y, Yin L, Qi Y, Han L and Xu L: Dioscin alleviates Alzheimer's disease through regulating RAGE/NOX4 mediated oxidative stress and inflammation. Biomed Pharmacother 152: 113248, 2022.
20. Li Y, Qin M, Zhong W, Liu C, Deng G, Yang M, Li J, Ye H, Shi H, Wu C, *et al*: RAGE promotes dysregulation of iron and lipid metabolism in alcoholic liver disease. Redox Biol 59: 102559, 2023.
21. Duan ZL, Wang YJ, Lu ZH, Tian L, Xia ZQ, Wang KL, Chen T, Wang R, Feng ZY, Shi GP, *et al*: Wumei Wan attenuates angiogenesis and inflammation by modulating RAGE signaling pathway in IBD: Network pharmacology analysis and experimental evidence. Phytomedicine 111: 154658, 2023.
22. Huang YF, Li QP, Dou YX, Wang TT, Qu C, Liang JL, Lin ZX, Huang XQ, Su ZR, Chen JN and Xie YL: Therapeutic effect of Brucea javanica oil emulsion on experimental Crohn's disease in rats: Involvement of TLR4/NF-κB signaling pathway. Biomed Pharmacother 114: 108766, 2019.
23. Jukic A, Bakiri L, Wagner EF, Tilg H and Adolph TE: Calprotectin: From biomarker to biological function. Gut 70: 1978-1988, 2021.
24. Gisbert JP, McNicholl AG and Gomollon F: Questions and answers on the role of fecal lactoferrin as a biological marker in inflammatory bowel disease. Inflamm Bowel Dis 15: 1746-1754, 2009.
25. Däbritz J, Langhorst J, Lügering A, Heidemann J, Mohr M, Wittkowski H, Krummenerl T and Foell D: Improving relapse prediction in inflammatory bowel disease by neutrophil-derived S100A12. Inflamm Bowel Dis 19: 1130-1138, 2013.
26. Palone F, Vitali R, Cucchiara S, Pierdomenico M, Negroni A, Aloi M, Nuti F, Felice C, Armuzzi A and Stronati L: Role of HMGB1 as a suitable biomarker of subclinical intestinal inflammation and mucosal healing in patients with inflammatory bowel disease. Inflamm Bowel Dis 20: 1448-1457, 2014.
27. Kordjazy N, Haj-Mirzaian A, Haj-Mirzaian A, Rohani MM, Gelfand EW, Rezaei N and Abdolghaffari AH: Role of toll-like receptors in inflammatory bowel disease. Pharmacol Res 129: 204-215, 2018.
28. Iliev ID, Funari VA, Taylor KD, Nguyen Q, Reyes CN, Strom SP, Brown J, Becker CA, Fleshner PR, Dubinsky M, *et al*: Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. Science 336: 1314-1317, 2012.
29. Zhen Y and Zhang H: NLRP3 inflammasome and inflammatory bowel disease. Front Immunol 10: 276, 2019.
30. Le Berre C, Honap S and Peyrin-Biroulet L: Ulcerative colitis. Lancet 402: 571-584, 2023.
31. Chhibba T and Ma C: Is there room for immunomodulators in ulcerative colitis? Expert Opin Biol Ther 20: 379-390, 2020.
32. Coskun M, Vermeire S and Nielsen OH: Novel targeted therapies for inflammatory bowel disease. Trends Pharmacol Sci 38: 127-142, 2017.
33. Vignali DA and Kuchroo VK: IL-12 family cytokines: Immunological playmakers. Nat Immunol 13: 722-728, 2012.
34. Verstockt B, Salas A, Sands BE, Abraham C, Leibovitzh H, Neurath MF and Vande Casteele N; Alimentiv Translational Research Consortium (ATRC): IL-12 and IL-23 pathway inhibition in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 20: 433-446, 2023.

35. Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM and Cua DJ: IL-12 and IL-23 cytokines: From discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med 21: 719-729, 2015.
36. Ogino H, Fukaura K, Iboshi Y, Nagamatsu Y, Okuno H, Nishioka K, Nishihara Y, Tanaka Y, Chinen T, Ihara E and Ogawa Y: Role of the IL-23-T-bet/GATA3 axis for the pathogenesis of ulcerative colitis. Inflammation 44: 592-603, 2021.
37. O'Shea JJ and Plenge R: JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. Immunity 36: 542-550, 2012.
38. Villarino AV, Kanno Y and O'Shea JJ: Mechanisms and consequences of Jak-STAT signaling in the immune system. Nat Immunol 18: 374-384, 2017.
39. Croft NM, Faubion WA Jr, Kugathasan S, Kierkus J, Ruemmele FM, Shimizu T, Mostafa NM, Venetucci M, Finney-Hayward T, Sanchez Gonzalez Y, *et al*: Efficacy and safety of adalimumab in paediatric patients with moderate-to-severe ulcerative colitis (ENVISION I): A randomised, controlled, phase 3 study. Lancet Gastroenterol Hepatol 6: 616-627, 2021.
40. Feagan BG, Sands BE, Sandborn WJ, Germinaro M, Vetter M, Shao J, Sheng S, Johanns J and Panés J; VEGA Study Group: Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): A randomised, double-blind, controlled, phase 2, proof-of-concept trial. Lancet Gastroenterol Hepatol 8: 307-320, 2023.
41. Harris MS, Hartman D, Lemos BR, Erlich EC, Spence S, Kennedy S, Ptak T, Pruitt R, Vermeire S and Fox BS: AVX-470, an orally delivered anti-tumour necrosis factor antibody for treatment of active ulcerative colitis: Results of a First-in-Human trial. J Crohns Colitis 10: 631-640, 2016.
42. Hartman DS, Tracey DE, Lemos BR, Erlich EC, Burton RE, Keane DM, Patel R, Kim S, Bhol KC, Harris MS and Fox BS: Effects of AVX-470, an oral, locally acting anti-tumour necrosis factor antibody, on tissue biomarkers in patients with active ulcerative colitis. J Crohns Colitis 10: 641-649, 2016.
43. Hibi T, Imai Y, Senoo A, Ohta K and Ukyo Y: Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: A phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). J Gastroenterol 52: 1101-1111, 2017.
44. Panés J, Colombel JF, D'Haens GR, Schreiber S, Panaccione R, Peyrin-Biroulet L, Loftus EV Jr, Danese S, Tanida S, Okuyama Y, *et al*: Higher vs standard adalimumab induction and maintenance dosing regimens for treatment of ulcerative colitis: SERENE UC trial results. Gastroenterology 162: 1891-1910, 2022.
45. Rutgeerts P, Feagan BG, Marano CW, Padgett L, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Zhang H, Colombel JF, *et al*: Randomised clinical trial: A placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis. Aliment Pharmacol Ther 42: 504-514, 2015.
46. Sandborn WJ, Targan SR, Byers VS, Rutty DA, Mu H, Zhang X and Tang T: Andrographis paniculata extract (HMPL-004) for active ulcerative colitis. Am J Gastroenterol 108: 90-98, 2013.
47. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, Danese S, Colombel JF, Törüner M, Jonaitis L, Abhyankar B, Chen J, Rogers R, *et al*: Vedolizumab versus Adalimumab for Moderate-to-severe ulcerative colitis. N Engl J Med 381: 1215-1226, 2019.
48. Schreiber S, Ben-Horin S, Leszczyszyn J, Dudkowiak R, Lahat A, Gawdis-Wojnarska B, Pukitis A, Horynski M, Farkas K, Kierkus J, *et al*: Randomized controlled trial: Subcutaneous vs intravenous infliximab CT-P13 maintenance in inflammatory bowel disease. Gastroenterology 160: 2340-2353, 2021.
49. Suzuki Y, Motoya S, Hanai H, Matsumoto T, Hibi T, Robinson AM, Mostafa NM, Chao J, Arora V, Camez A, *et al*: Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. J Gastroenterol 49: 283-294, 2014.
50. Syversen SW, Jørgensen KK, Goll GL, Brun MK, Sandanger Ø, Bjørlykke KH, Sexton J, Olsen IC, Gehin JE, Warren DJ, *et al*: Effect of therapeutic drug monitoring vs standard therapy during maintenance infliximab therapy on disease control in patients with immune-mediated inflammatory diseases: A randomized clinical trial. JAMA 326: 2375-2384, 2021.
51. Tajiri H, Arai K, Kagimoto S, Kunisaki R, Hida N, Sato N, Yamada H, Nagano M, Susuta Y, Ozaki K, *et al*: Infliximab for pediatric patients with ulcerative colitis: A phase 3, open-label, uncontrolled, multicenter trial in Japan. BMC Pediatr 19: 351, 2019.
52. Tang T, Targan SR, Li ZS, Xu C, Byers VS and Sandborn WJ: Randomised clinical trial: Herbal extract HMPL-004 in active ulcerative colitis-a double-blind comparison with sustained release mesalazine. Aliment Pharmacol Ther 33: 194-202, 2011.
53. D'Haens G, Higgins PDR, Peyrin-Biroulet L, Sands BE, Lee S, Moses RE, Redondo I, Escobar R, Hunter Gibble T, Keohane A, *et al*: Extended induction and prognostic indicators of response in patients treated with mirikizumab with moderately to severely active ulcerative colitis in the LUCENT trials. Inflamm Bowel Dis 30: 2335-2346, 2024.
54. Danese S, Sands BE, Abreu MT, O'Brien CD, Bravatà I, Nazar M, Miao Y, Wang Y, Rowbotham D, Leong RWL, *et al*: Early symptomatic improvement after ustekinumab therapy in patients with ulcerative colitis: 16-week data from the UNIFI trial. Clin Gastroenterol Hepatol 20: 2858-2867.e5, 2022.
55. Peyrin-Biroulet L, Allegretti JR, Rubin DT, Bressler B, Germinaro M, Huang KG, Shipitofsky N, Zhang H, Wilson R, Han C, *et al*: Guselkumab in patients with moderately to severely active ulcerative colitis: QUASAR phase 2b induction study. Gastroenterology 165: 1443-1457, 2023.
56. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, *et al*: Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 381: 1201-1214, 2019.
57. Cromer WE, Ganta CV, Patel M, Traylor J, Kevil CG, Alexander JS and Mathis JM: VEGF-A isoform modulation in an preclinical TNBS model of ulcerative colitis: Protective effects of a VEGF164b therapy. J Transl Med 11: 207, 2013.
58. Danese S, Vermeire S, Zhou W, Pangan AL, Siffledeen J, Greenbloom S, Hébuterne X, D'Haens G, Nakase H, Panés J, *et al*: Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: Results from three phase 3, multicentre, double-blind, randomised trials. Lancet 399: 2113-2128, 2022.
59. Feagan BG, Danese S, Loftus EV Jr, Vermeire S, Schreiber S, Ritter T, Fogel R, Mehta R, Nijhawan S, Kempiński R, *et al*: Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): A phase 2b/3 double-blind, randomised, placebo-controlled trial. Lancet 397: 2372-2384, 2021.
60. Gros B, Goodall M, Plevris N, Constantine-Cooke N, Elford AT, O'Hare C, Noble C, Jones GR, Arnott ID and Lees CW: Real-world cohort study on the effectiveness and safety of filgotinib use in ulcerative colitis. J Crohns Colitis 19: jjad187, 2023.
61. Sandborn WJ, Ghosh S, Panes J, Schreiber S, D'Haens G, Tanida S, Siffledeen J, Enejosa J, Zhou W, Othman AA, *et al*: Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis. Gastroenterology 158: 2139-2149.e14, 2020.
62. Sandborn WJ, Nguyen DD, Beattie DT, Brassil P, Krey W, Woo J, Situ E, Sana R, Sandvik E, Pulido-Rios MT, *et al*: Development of Gut-selective pan-janus kinase inhibitor TD-1473 for ulcerative colitis: A translational medicine programme. J Crohns Colitis 14: 1202-1213, 2020.
63. Sandborn WJ, Peyrin-Biroulet L, Quirk D, Wang W, Nduaka CI, Mukherjee A, Su C and Sands BE: Efficacy and safety of extended induction with tofacitinib for the treatment of ulcerative colitis. Clin Gastroenterol Hepatol 20: 1821-1830.e3, 2022.
64. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, *et al*: Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 376: 1723-1736, 2017.
65. Sands BE, Sandborn WJ, Feagan BG, Lichtenstein GR, Zhang H, Strauss R, Szapary P, Johanns J, Panes J, Vermeire S, *et al*: Peficitinib, an oral Janus Kinase inhibitor, in moderate-to-severe ulcerative colitis: Results from a randomised, phase 2 study. J Crohns Colitis 12: 1158-1169, 2018.
66. Singh A, Midha V, Kaur K, Mahajan R, Singh D, Kaur R, Kohli A, Chawla A, Sood K, Bansal N and Sood A: Tofacitinib versus oral prednisolone for induction of remission in moderately active ulcerative colitis [ORCHID]: A prospective, open-label, randomized, pilot study. J Crohns Colitis 18: 300-307, 2024.
67. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S and Niezychowski W; Study A3921063 Investigators: Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 367: 616-624, 2012.
68. Danese S, Neurath MF, Kopoń A, Zakko SF, Simmons TC, Fogel R, Siegel CA, Panaccione R, Zhan X, Usiskin K and Chitkara D: Effects of apremilast, an oral inhibitor of phosphodiesterase 4, in a randomized trial of patients with active ulcerative colitis. Clin Gastroenterol Hepatol 18: 2526-2534.e9, 2020.

69. Schreiber S, Keshavarzian A, Isaacs KL, Schollenberger J, Guzman JP, Orlandi C and Hanauer SB: A randomized, placebo-controlled, phase II study of tetomilast in active ulcerative colitis. Gastroenterology 132: 76-86, 2007.
70. Danese S, Panaccione R, Abreu MT, Rubin DT, Ghosh S, Dignass A, Afzali A, Wolf DC, Chiorean MV, Vermeire S, *et al*: Efficacy and safety of approximately 3 years of continuous ozanimod in moderately to severely active ulcerative colitis: Interim analysis of the true north Open-label extension. J Crohns Colitis 18: 264-274, 2024.
71. Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, Ghosh S, Petersen A, Hua SY, Lee JH, *et al*: Ozanimod as induction and maintenance therapy for ulcerative colitis. N Engl J Med 385: 1280-1291, 2021.
72. Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S, Hanauer SB, Ghosh S, Smith H, Cravets M, Frohna PA, *et al*: Ozanimod induction and maintenance treatment for ulcerative colitis. N Engl J Med 374: 1754-1762, 2016.
73. Sandborn WJ, Peyrin-Biroulet L, Zhang J, Chiorean M, Vermeire S, Lee SD, Kühbacher T, Yacyshyn B, Cabell CH, Naik SU, *et al*: Efficacy and safety of etrasimod in a phase 2 randomized trial of patients with ulcerative colitis. Gastroenterology 158: 550-561, 2020.
74. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, Dubinsky MC, Panes J, Yarur A, Ritter T, Baert F, Schreiber S, Sloan S, *et al*: Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): Two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet 401: 1159-1171, 2023.
75. Sánchez de Medina F, Romero-Calvo I, Mascaraque C and Martínez-Augustin O: Intestinal inflammation and mucosal barrier function. Inflamm Bowel Dis 20: 2394-2404, 2014.
76. Sims GP, Rowe DC, Rietdijk ST, Herbst R and Coyle AJ: HMGB1 and RAGE in inflammation and cancer. Annu Rev Immunol 28: 367-388, 2010.
77. Body-Malapel M, Djouina M, Waxin C, Langlois A, Gower-Rousseau C, Zerbib P, Schmidt AM, Desreumaux P, Boulanger E and Vignal C: The RAGE signaling pathway is involved in intestinal inflammation and represents a promising therapeutic target for inflammatory bowel diseases. Mucosal Immunol 12: 468-478, 2019.
78. Sugaya K, Fukagawa T, Matsumoto K, Mita K, Takahashi E, Ando A, Inoko H and Ikemura T: Three genes in the human MHC class III region near the junction with the class II: Gene for receptor of advanced glycosylation end products, PBX2 homeobox gene and a notch homolog, human counterpart of mouse mammary tumor gene int-3. Genomics 23: 408-419, 1994.
79. Fritz G: RAGE: A single receptor fits multiple ligands. Trends Biochem Sci 36: 625-632, 2011.
80. Hudson BI, Kalea AZ, Del Mar Arriero M, Harja E, Boulanger E, D'Agati V and Schmidt AM: Interaction of the RAGE cytoplasmic domain with diaphanous-1 is required for ligand-stimulated cellular migration through activation of Rac1 and Cdc42. J Biol Chem 283: 34457-34468, 2008.
81. Kalea AZ, Schmidt AM and Hudson BI: RAGE: A novel biological and genetic marker for vascular disease. Clin Sci (Lond) 116: 621-637, 2009.
82. Harja E, Bu DX, Hudson BI, Chang JS, Shen X, Hallam K, Kalea AZ, Lu Y, Rosario RH, Oruganti S, *et al*: Vascular and inflammatory stresses mediate atherosclerosis via RAGE and its ligands in apoE-/- mice. J Clin Invest 118: 183-194, 2008.
83. Huttunen HJ, Fages C and Rauvala H: Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF-kappaB require the cytoplasmic domain of the receptor but different downstream signaling pathways. J Biol Chem 274: 19919-19924, 1999.
84. Hudson BI and Lippman ME: Targeting RAGE signaling in inflammatory disease. Annu Rev Med 69: 349-364, 2018.
85. Piarulli F, Lapolla A, Ragazzi E, Susana A, Sechi A, Nollino L, Cosma C, Fedele D and Sartore G: Role of endogenous secretory RAGE (esRAGE) in defending against plaque formation induced by oxidative stress in type 2 diabetic patients. Atherosclerosis 226: 252-257, 2013.
86. Deng M, Tang Y, Li W, Wang X, Zhang R, Zhang X, Zhao X, Liu J, Tang C, Liu Z, *et al*: The endotoxin delivery protein HMGB1 mediates caspase-11-dependent lethality in sepsis. Immunity 49: 740-753.e7, 2018.
87. Angioni R, Bonfanti M, Caporale N, Sánchez-Rodríguez R, Munari F, Savino A, Pasqualato S, Buratto D, Pagani I, Bertoldi N, *et al*: RAGE engagement by SARS-CoV-2 enables monocyte infection and underlies COVID-19 severity. Cell Rep Med 4: 101266, 2023.
88. Tsubokawa D, Lee JM, Hatta T, Mikami F, Maruyama H, Arakawa T, Kusakabe T and Tsuji N: Characterization of the RAGE-binding protein, Strongyloides venestatin, produced by the silkworm-baculovirus expression system. Infect Genet Evol 75: 103964, 2019.
89. Senatus L, Egaña-Gorroño L, López-Díez R, Bergaya S, Aranda JF, Amengual J, Arivazhagan L, Manigrasso MB, Yepuri G, Nimma R, *et al*: DIAPH1 mediates progression of atherosclerosis and regulates hepatic lipid metabolism in mice. Commun Biol 6: 280, 2023.
90. Chiappalupi S, Sorci G, Vukasinovic A, Salvadori L, Sagheddu R, Coletti D, Renga G, Romani L, Donato R and Riuzzi F: Targeting RAGE prevents muscle wasting and prolongs survival in cancer cachexia. J Cachexia Sarcopenia Muscle 11: 929-946, 2020.
91. Tian M, Tang Y, Huang T, Liu Y and Pan Y: Amelioration of human peritoneal mesothelial cell co-culture-evoked malignant potential of ovarian cancer cells by acacetin involves LPA release-activated RAGE-PI3K/AKT signaling. Cell Mol Biol Lett 26: 51, 2021.
92. Sakaguchi M, Murata H, Aoyama Y, Hibino T, Putranto EW, Ruma IM, Inoue Y, Sakaguchi Y, Yamamoto K, Kinoshita R, *et al*: DNAX-activating protein 10 (DAP10) membrane adaptor associates with receptor for advanced glycation end products (RAGE) and modulates the RAGE-triggered signaling pathway in human keratinocytes. J Biol Chem 289: 23389-23402, 2014.
93. Bierhaus A, Schiekofer S, Schwaninger M, Andrassy M, Humpert PM, Chen J, Hong M, Luther T, Henle T, Klöting I, *et al*: Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. Diabetes 50: 2792-2808, 2001.
94. Goldin A, Beckman JA, Schmidt AM and Creager MA: Advanced glycation end products: Sparking the development of diabetic vascular injury. Circulation 114: 597-605, 2006.
95. Le Bagge S, Fotheringham AK, Leung SS and Forbes JM: Targeting the receptor for advanced glycation end products (RAGE) in type 1 diabetes. Med Res Rev 40: 1200-1219, 2020.
96. Mocanu CA, Fuior EV, Voicu G, Rebleanu D, Safciuc F, Deleanu M, Fenyo IM, Escriou V, Manduteanu I, Simionescu M and Calin M: P-selectin targeted RAGE-shRNA lipoplexes alleviate atherosclerosis-associated inflammation. J Control Release 338: 754-772, 2021.
97. Lai PH, Wang TH, Zhang NY, Wu KC, Yao CJ and Lin CJ: Changes of blood-brain-barrier function and transfer of amyloid beta in rats with collagen-induced arthritis. J Neuroinflammation 18: 35, 2021.
98. Selejan SR, Linz D, Mauz M, Hohl M, Huynh AKD, Speer T, Wintrich J, Kazakov A, Werner C, Mahfoud F and Böhm M: Renal denervation reduces atrial remodeling in hypertensive rats with metabolic syndrome. Basic Res Cardiol 117: 36, 2022.
99. Turovskaya O, Foell D, Sinha P, Vogl T, Newlin R, Nayak J, Nguyen M, Olsson A, Nawroth PP, Bierhaus A, *et al*: RAGE, carboxylated glycans and S100A8/A9 play essential roles in colitis-associated carcinogenesis. Carcinogenesis 29: 2035-2043, 2008.
100. Bierhaus A, Stern DM and Nawroth PP: RAGE in inflammation: A new therapeutic target? Curr Opin Investig Drugs 7: 985-991, 2006.
101. Chuah YK, Basir R, Talib H, Tie TH and Nordin N: Receptor for advanced glycation end products and its involvement in inflammatory diseases. Int J Inflam 2013: 403460, 2013.
102. Sparvero LJ, Asafu-Adjei D, Kang R, Tang D, Amin N, Im J, Rutledge R, Lin B, Amoscato AA, Zeh HJ, *et al*: RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. J Transl Med 7: 17, 2009.
103. Moura FA, Goulart MOF, Campos SBG and da Paz Martins AS: The close interplay of Nitro-oxidative stress, advanced glycation end products and inflammation in inflammatory bowel diseases. Curr Med Chem 27: 2059-2076, 2020.
104. Yadav V, Varum F, Bravo R, Furrer E, Bojic D and Basit AW: Inflammatory bowel disease: Exploring gut pathophysiology for novel therapeutic targets. Transl Res 176: 38-68, 2016.
105. Foell D, Kucharzik T, Kraft M, Vogl T, Sorg C, Domschke W and Roth J: Neutrophil derived human S100A12 (EN-RAGE) is strongly expressed during chronic active inflammatory bowel disease. Gut 52: 847-853, 2003.
106. Hu Z, Wang X, Gong L, Wu G, Peng X and Tang X: Role of high-mobility group box 1 protein in inflammatory bowel disease. Inflamm Res 64: 557-563, 2015.
107. Manolakis AC, Kapsoritakis AN, Tiaka EK and Potamianos SP: Calprotectin, calgranulin C, and other members of the s100 protein family in inflammatory bowel disease. Dig Dis Sci 56: 1601-1611, 2011.

108. Yamasaki H, Mitsuyama K, Masuda J, Kuwaki K, Takedatsu H, Sugiyama G, Yamada S and Sata M: Roles of high-mobility group box 1 in murine experimental colitis. Mol Med Rep 2: 23-27, 2009.
109. Brownlee M: Advanced protein glycosylation in diabetes and aging. Annu Rev Med 46: 223-234, 1995.
110. Yamagishi S and Matsui T: Pathologic role of dietary advanced glycation end products in cardiometabolic disorders, and therapeutic intervention. Nutrition 32: 157-165, 2016.
111. Maconi G, Furfaro F, Sciurti R, Bezzio C, Ardizzone S and de Franchis R: Glucose intolerance and diabetes mellitus in ulcerative colitis: Pathogenetic and therapeutic implications. World J Gastroenterol 20: 3507-3515, 2014.
112. Farghaly HS and Thabit RH: L-arginine and aminoguanidine reduce colonic damage of acetic acid-induced colitis in rats: Potential modulation of nuclear factor-κB/p65. Clin Exp Pharmacol Physiol 41: 769-779, 2014.
113. Mouzaoui S, Rahim I and Djerdjouri B: Aminoguanidine and curcumin attenuated tumor necrosis factor (TNF)-α-induced oxidative stress, colitis and hepatotoxicity in mice. Int Immunopharmacol 12: 302-311, 2012.
114. El-Mahdy NA, El-Sayad ME, El-Kadem AH and Abu-Risha SE: Metformin alleviates inflammation in oxazolone induced ulcerative colitis in rats: Plausible role of sphingosine kinase 1/sphingosine 1 phosphate signaling pathway. Immunopharmacol Immunotoxicol 43: 192-202, 2021.
115. Pandey A, Verma S and Kumar VL: Metformin maintains mucosal integrity in experimental model of colitis by inhibiting oxidative stress and pro-inflammatory signaling. Biomed Pharmacother 94: 1121-1128, 2017.
116. Shaaban AA, Abdelhamid AM, Shaker ME, Cavalu S, Maghiar AM, Alsayegh AA, Babalghith AO, El-Ahwany E, Amin NA, Mohammed OA, *et al*: Combining the HSP90 inhibitor TAS-116 with metformin effectively degrades the NLRP3 and attenuates inflammasome activation in rats: A new management paradigm for ulcerative colitis. Biomed Pharmacother 153: 113247, 2022.
117. da Rocha GHO, de Paula-Silva M, Broering MF, Scharf PRDS, Matsuyama LSAS, Maria-Engler SS and Farsky SHP: Pioglitazone-mediated attenuation of experimental colitis relies on cleaving of annexin A1 released by macrophages. Front Pharmacol 11: 591561, 2020.
118. Matsunaga H, Hokari R, Kurihara C, Okada Y, Takebayashi K, Okudaira K, Watanabe C, Komoto S, Nakamura M, Tsuzuki Y, *et al*: Omega-3 fatty acids exacerbate DSS-induced colitis through decreased adiponectin in colonic subepithelial myofibroblasts. Inflamm Bowel Dis 14: 1348-1357, 2008.
119. El-Haggar SM, Hegazy SK, Maher MM, Bahgat MM and Bahaa MM: Repurposing metformin as adjuvant therapy in patients with ulcerative colitis treated with mesalamine: A randomized controlled double-blinded study. Int Immunopharmacol 138: 112541, 2024.
120. Lin J, Wang C, Yang G, Liu Y, Da Y, Zhou W, Zhou H, Wang F, Fan Z, Hou L, *et al*: Targeting the cell adhesion related ligands MAC1 with Indirubin to inhibit AGE-RAGE signaling and mitigate colitis in an mouse model. Phytomedicine 149: 157504, 2025.
121. Paradela-Dobarro B, Raposeiras-Roubín S, Rodiño-Janeiro BK, Grigorian-Shamagian L, García-Acuña JM, Aguiar-Souto P, Jacquet-Hervet M, Reino-Maceiras MV, González-Juanatey JR and Alvarez E: Statins modulate feedback regulation mechanisms between advanced glycation end-products and C-reactive protein: Evidence in patients with acute myocardial infarction. Eur J Pharm Sci 49: 512-518, 2013.
122. Côté-Daigneault J, Mehandru S, Ungaro R, Atreja A and Colombel JF: Potential immunomodulatory effects of statins in inflammatory bowel disease. Inflamm Bowel Dis 22: 724-732, 2016.
123. Ikeda M, Takeshima F, Isomoto H, Shikuwa S, Mizuta Y, Ozono Y and Kohno S: Simvastatin attenuates trinitrobenzene sulfonic acid-induced colitis, but not oxazalone-induced colitis. Dig Dis Sci 53: 1869-1875, 2008.
124. Naito Y, Katada K, Takagi T, Tsuboi H, Isozaki Y, Handa O, Kokura S, Yoshida N, Ichikawa H and Yoshikawa T: Rosuvastatin, a new HMG-CoA reductase inhibitor, reduces the colonic inflammatory response in dextran sulfate sodium-induced colitis in mice. Int J Mol Med 17: 997-1004, 2006.
125. Ungaro R, Chang HL, Côté-Daigneault J, Mehandru S, Atreja A and Colombel JF: Statins associated with decreased risk of new onset inflammatory bowel disease. Am J Gastroenterol 111: 1416-1423, 2016.
126. Khalil D, Boktor M, Mortensen EM, Frei CR and Mansi I: Comparison of frequency of inflammatory bowel disease and noninfectious gastroenteritis among statin users versus nonusers. Am J Cardiol 115: 1396-1401, 2015.
127. Dhamija P, Hota D, Kochhar R, Sachdev A and Chakrabarti A: Randomized clinical trial: Atorvastatin versus placebo in patients with acute exacerbation of mild to moderate ulcerative colitis. Indian J Gastroenterol 33: 151-156, 2014.
128. Peppas S, Piovani D, Peyrin-Biroulet L, Danese S and Bonovas S: Statins and inflammatory bowel disease: Where do we stand? Eur J Intern Med 75: 10-14, 2020.
129. Chande N, McDonald JW, Macdonald JK and Wang JJ: Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. Cochrane Database Syst Rev: CD006774, 2010 doi: 10.1002/14651858.CD006774.pub3.
130. Yan Y, Sun Y, Wang P, Zhang R, Huo C, Gao T, Song C, Xing J and Dong Y: Mucoadhesive nanoparticles-based oral drug delivery systems enhance ameliorative effects of low molecular weight heparin on experimental colitis. Carbohydr Polym 246: 116660, 2020.
131. Yazeji T, Moulari B, Beduneau A, Stein V, Dietrich D, Pellequer Y and Lamprecht A: Nanoparticle-based delivery enhances anti-inflammatory effect of low molecular weight heparin in experimental ulcerative colitis. Drug Deliv 24: 811-817, 2017.
132. Hori O, Brett J, Slattery T, Cao R, Zhang J, Chen JX, Nagashima M, Lundh ER, Vijay S, Nitecki D, *et al*: The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system. J Biol Chem 270: 25752-25761, 1995.
133. Erlandsson Harris H and Andersson U: Mini-review: The nuclear protein HMGB1 as a proinflammatory mediator. Eur J Immunol 34: 1503-1512, 2004.
134. Kang R, Zhang Q, Zeh HJ III, Lotze MT and Tang D: HMGB1 in cancer: Good, bad, or both? Clin Cancer Res 19: 4046-4057, 2013.
135. Dong Xda E, Ito N, Lotze MT, Demarco RA, Popovic P, Shand SH, Watkins S, Winikoff S, Brown CK, Bartlett DL, *et al*: High mobility group box I (HMGB1) release from tumor cells after treatment: Implications for development of targeted chemoimmunotherapy. J Immunother 30: 596-606, 2007.
136. Tang D, Kang R, Zeh HJ III and Lotze MT: High-mobility group box 1 and cancer. Biochim Biophys Acta 1799: 131-140, 2010.
137. Tian J, Avalos AM, Mao SY, Chen B, Senthil K, Wu H, Parroche P, Drabic S, Golenbock D, Sirois C, *et al*: Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. Nat Immunol 8: 487-496, 2007.
138. Scaffidi P, Misteli T and Bianchi ME: Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 418: 191-195, 2002.
139. Yanai H, Ban T, Wang Z, Choi MK, Kawamura T, Negishi H, Nakasato M, Lu Y, Hangai S, Koshiba R, *et al*: HMGB proteins function as universal sentinels for nucleic-acid-mediated innate immune responses. Nature 462: 99-103, 2009.
140. Huang CY, Chiang SF, Chen WT, Ke TW, Chen TW, You YS, Lin CY, Chao KSC and Huang CY: HMGB1 promotes ERK-mediated mitochondrial Drp1 phosphorylation for chemoresistance through RAGE in colorectal cancer. Cell Death Dis 9: 1004, 2018.
141. Arab HH, Al-Shorbagy MY and Saad MA: Activation of autophagy and suppression of apoptosis by dapagliflozin attenuates experimental inflammatory bowel disease in rats: Targeting AMPK/mTOR, HMGB1/RAGE and Nrf2/HO-1 pathways. Chem Biol Interact 335: 109368, 2021.
142. Chen L, Li J, Ye Z, Sun B, Wang L, Chen Y, Han J, Yu M, Wang Y, Zhou Q, *et al*: Anti-high mobility group box 1 neutralizing-antibody ameliorates dextran sodium sulfate colitis in mice. Front Immunol 11: 585094, 2020.
143. Davé SH, Tilstra JS, Matsuoka K, Li F, DeMarco RA, Beer-Stolz D, Sepulveda AR, Fink MP, Lotze MT and Plevy SE: Ethyl pyruvate decreases HMGB1 release and ameliorates murine colitis. J Leukoc Biol 86: 633-643, 2009.
144. Maeda S, Hikiba Y, Shibata W, Ohmae T, Yanai A, Ogura K, Yamada S and Omata M: Essential roles of high-mobility group box 1 in the development of murine colitis and colitis-associated cancer. Biochem Biophys Res Commun 360: 394-400, 2007.

145. Palone F, Vitali R, Cucchiara S, Mennini M, Armuzzi A, Pugliese D, D'Incà R, Barberio B and Stronati L: Fecal HMGB1 reveals microscopic inflammation in adult and pediatric patients with inflammatory bowel disease in clinical and endoscopic remission. Inflamm Bowel Dis 22: 2886-2893, 2016.
146. Vitali R, Stronati L, Negroni A, Di Nardo G, Pierdomenico M, del Giudice E, Rossi P and Cucchiara S: Fecal HMGB1 is a novel marker of intestinal mucosal inflammation in pediatric inflammatory bowel disease. Am J Gastroenterol 106: 2029-2040, 2011.
147. Miao Z, Gu M, Raza F, Zafar H, Huang J, Yang Y, Sulaiman M, Yan J and Xu Y: Isoliquiritin ameliorates ulcerative colitis in rats through caspase 3/HMGB1/TLR4 dependent signaling pathway. Curr Gene Ther 24: 73-92, 2024.
148. Chen J, Lu P, Liu J, Yang L, Li Y, Chen Y, Wang Y, Wan J and Zhao Y: 20(S)-Protopanaxadiol saponins isolated from Panax notoginseng target the binding of HMGB1 to TLR4 against inflammation in experimental ulcerative colitis. Phytother Res 37: 4690-4705, 2023.
149. Sun K, Lin W, Hong Q, Chen S, Li J and Qiu S: Matrine: A promising treatment for ulcerative colitis by targeting the HMGB1/NLRP3/caspase-1 pathway. Comb Chem High Throughput Screen 28: 654-663, 2025.
150. Zhu N, Ge X, Zhang L, Chen X, Xiang W and Mei Q: HMGB1 exacerbates intestinal barrier damage by inducing ferroptosis through the TLR4/NF-κB/GPX4 pathway in ulcerative colitis. Mediators Inflamm 2025: 2395557, 2025.
151. Gonzalez LL, Garrie K and Turner MD: Role of S100 proteins in health and disease. Biochim Biophys Acta Mol Cell Res 1867: 118677, 2020.
152. Donato R, Cannon BR, Sorci G, Riuzzi F, Hsu K, Weber DJ and Geczy CL: Functions of S100 proteins. Curr Mol Med 13: 24-57, 2013.
153. Xiao X, Yang C, Qu SL, Shao YD, Zhou CY, Chao R, Huang L and Zhang C: S100 proteins in atherosclerosis. Clin Chim Acta 502: 293-304, 2020.
154. Gross SR, Sin CG, Barraclough R and Rudland PS: Joining S100 proteins and migration: For better or for worse, in sickness and in health. Cell Mol Life Sci 71: 1551-1579, 2014.
155. Bjarnason I: The use of fecal calprotectin in inflammatory bowel disease. Gastroenterol Hepatol (N Y) 13: 53-56, 2017.
156. Rammes A, Roth J, Goebeler M, Klempt M, Hartmann M and Sorg C: Myeloid-related protein (MRP) 8 and MRP14, calcium-binding proteins of the S100 family, are secreted by activated monocytes via a novel, tubulin-dependent pathway. J Biol Chem 272: 9496-9502, 1997.
157. Wang L, Luo H, Chen X, Jiang Y and Huang Q: Functional characterization of S100A8 and S100A9 in altering monolayer permeability of human umbilical endothelial cells. PLoS One 9: e90472, 2014.
158. Viemann D, Barczyk K, Vogl T, Fischer U, Sunderkötter C, Schulze-Osthoff K and Roth J: MRP8/MRP14 impairs endothelial integrity and induces a caspase-dependent and -independent cell death program. Blood 109: 2453-2460, 2007.
159. Bengtsson AA, Sturfelt G, Lood C, Rönnblom L, van Vollenhoven RF, Axelsson B, Sparre B, Tuvesson H, Ohman MW and Leanderson T: Pharmacokinetics, tolerability, and preliminary efficacy of paquinimod (ABR-215757), a new quinoline-3-carboxamide derivative: Studies in lupus-prone mice and a multicenter, randomized, double-blind, placebo-controlled, repeat-dose, dose-ranging study in patients with systemic lupus erythematosus. Arthritis Rheum 64: 1579-1588, 2012.
160. Brunmark C, Runström A, Ohlsson L, Sparre B, Brodin T, Aström M and Hedlund G: The new orally active immunoregulator laquinimod (ABR-215062) effectively inhibits development and relapses of experimental autoimmune encephalomyelitis. J Neuroimmunol 130: 163-172, 2002.
161. Karussis DM, Lehmann D, Slavin S, Vourka-Karussis U, Mizrachi-Koll R, Ovadia H, Kalland T and Abramsky O: Treatment of chronic-relapsing experimental autoimmune encephalomyelitis with the synthetic immunomodulator linomide (quinoline-3-carboxamide). Proc Natl Acad Sci USA 90: 6400-6404, 1993.
162. Maiseyeu A, Badgeley MA, Kampfrath T, Mihai G, Deiuliis JA, Liu C, Sun Q, Parthasarathy S, Simon DI, Croce K and Rajagopalan S: In vivo targeting of inflammation-associated myeloid-related protein 8/14 via gadolinium immunonanoparticles. Arterioscler Thromb Vasc Biol 32: 962-970, 2012.
163. Rai V, Touré F, Chitayat S, Pei R, Song F, Li Q, Zhang J, Rosario R, Ramasamy R, Chazin WJ and Schmidt AM: Lysophosphatidic acid targets vascular and oncogenic pathways via RAGE signaling. J Exp Med 209: 2339-2350, 2012.
164. Nasser S, Abdallah DM, Ahmed KA, Abdel-Mottaleb Y and El-Abhar HS: The novel anti-colitic effect of β-adrenergic receptors via modulation of PS1/BACE-1/Aβ axis and NOTCH signaling in an ulcerative colitis model. Front Pharmacol 13: 1008085, 2022.
165. Son M, Porat A, He M, Suurmond J, Santiago-Schwarz F, Andersson U, Coleman TR, Volpe BT, Tracey KJ, Al-Abed Y and Diamond B: C1q and HMGB1 reciprocally regulate human macrophage polarization. Blood 128: 2218-2228, 2016.
166. Abedini A, Cao P, Plesner A, Zhang J, He M, Derk J, Patil SA, Rosario R, Lonier J, Song F, *et al*: RAGE binds preamyloid IAPP intermediates and mediates pancreatic β cell proteotoxicity. J Clin Invest 128: 682-698, 2018.
167. Zhang T, Jia C, Ran L, Shi J, Amarmend T and Li H: The alleviative effects comparison of four flavonoids from bamboo leaves on ulcerative colitis in an Alzheimer mouse model. CNS Neurosci Ther 30: e14620, 2024.
168. Dong YL, Duan XY, Liu YJ, Fan H, Xu M, Chen QY, Nan Z, Wu H and Deng SJ: Autotaxin-lysophosphatidic acid axis blockade improves inflammation by regulating Th17 cell differentiation in DSS-induced chronic colitis mice. Inflammation 42: 1530-1541, 2019.
169. Wang Z, Shi W, Tian D, Qin H, Vallance BA, Yang H, Yu HB and Yu Q: Autotaxin stimulates LPA2 receptor in macrophages and exacerbates dextran sulfate sodium-induced acute colitis. J Mol Med (Berl) 98: 1781-1794, 2020.
170. Takahashi S, Yoshimura T, Ohkura T, Fujisawa M, Fushimi S, Ito T, Itakura J, Hiraoka S, Okada H, Yamamoto K and Matsukawa A: A novel role of Spred2 in the colonic epithelial cell homeostasis and inflammation. Sci Rep 6: 37531, 2016.
171. You BH, Chae HS, Song J, Ko HW, Chin YW and Choi YH: α-Mangostin ameliorates dextran sulfate sodium-induced colitis through inhibition of NF-κB and MAPK pathways. Int Immunopharmacol 49: 212-221, 2017.
172. Wei YY, Fan YM, Ga Y, Zhang YN, Han JC and Hao ZH: Shaoyao decoction attenuates DSS-induced ulcerative colitis, macrophage and NLRP3 inflammasome activation through the MKP1/NF-κB pathway. Phytomedicine 92: 153743, 2021.
173. Li C, Gong L, Jiang Y, Huo X, Huang L, Lei H, Gu Y, Wang D, Guo D and Deng Y: Sanguisorba officinalis ethyl acetate extract attenuates ulcerative colitis through inhibiting PI3K-AKT/NF-κB/STAT3 pathway uncovered by single-cell RNA sequencing. Phytomedicine 120: 155052, 2023.
174. Salari-Sharif P and Abdollahi M: Phosphodiesterase 4 inhibitors in inflammatory bowel disease: A comprehensive review. Curr Pharm Des 16: 3661-3667, 2010.
175. Yang J, Pei G, Sun X, Xiao Y, Miao C, Zhou L, Wang B, Yang L, Yu M, Zhang ZS, *et al*: RhoB affects colitis through modulating cell signaling and intestinal microbiome. Microbiome 10: 149, 2022.
176. Adini A, Ko VH, Puder M, Louie SM, Kim CF, Baron J and Matthews BD: PR1P, a VEGF-stabilizing peptide, reduces injury and inflammation in acute lung injury and ulcerative colitis animal models. Front Immunol 14: 1168676, 2023.
177. Adamopoulos C, Piperi C, Gargalionis AN, Dalagiorgou G, Spilioti E, Korkolopoulou P, Diamanti-Kandarakis E and Papavassiliou AG: Advanced glycation end products upregulate lysyl oxidase and endothelin-1 in human aortic endothelial cells via parallel activation of ERK1/2-NF-κB and JNK-AP-1 signaling pathways. Cell Mol Life Sci 73: 1685-1698, 2016.
178. Byun K, Yoo Y, Son M, Lee J, Jeong GB, Park YM, Salekdeh GH and Lee B: Advanced glycation end-products produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases. Pharmacol Ther 177: 44-55, 2017.
179. Reynaert NL, Gopal P, Rutten EPA, Wouters EFM and Schalkwijk CG: Advanced glycation end products and their receptor in age-related, non-communicable chronic inflammatory diseases; Overview of clinical evidence and potential contributions to disease. Int J Biochem Cell Biol 81: 403-418, 2016.
180. Xu Y, Toure F, Qu W, Lin L, Song F, Shen X, Rosario R, Garcia J, Schmidt AM and Yan SF: Advanced glycation end product (AGE)-receptor for AGE (RAGE) signaling and up-regulation of Egr-1 in hypoxic macrophages. J Biol Chem 285: 23233-23240, 2010.

181. Spalinger MR, Sayoc-Becerra A, Ordookhanian C, Canale V, Santos AN, King SJ, Krishnan M, Nair MG, Scharl M and McCole DF: The JAK inhibitor tofacitinib rescues intestinal barrier defects caused by disrupted Epithelial-macrophage interactions. J Crohns Colitis 15: 471-484, 2021.
182. Han J, Zhao Q, Basmadjian C, Désaubry L and Theiss AL: Flavaglines ameliorate experimental colitis and protect against intestinal epithelial cell apoptosis and mitochondrial dysfunction. Inflamm Bowel Dis 22: 55-67, 2016.
183. Zhou M, Xu W, Wang J, Yan J, Shi Y, Zhang C, Ge W, Wu J, Du P and Chen Y: Boosting mTOR-dependent autophagy via upstream TLR4-MyD88-MAPK signalling and downstream NF-κB pathway quenches intestinal inflammation and oxidative stress injury. EBioMedicine 35: 345-360, 2018.
184. Hwang J, Jin J, Jeon S, Moon SH, Park MY, Yum DY, Kim JH, Kang JE, Park MH, Kim EJ, *et al*: SOD1 suppresses pro-inflammatory immune responses by protecting against oxidative stress in colitis. Redox Biol 37: 101760, 2020.
185. Hayakawa Y, Hirata Y, Nakagawa H, Sakamoto K, Hikiba Y, Otsuka M, Ijichi H, Ikenoue T, Tateishi K, Akanuma M, *et al*: Apoptosis signal-regulating kinase 1 regulates colitis and colitis-associated tumorigenesis by the innate immune responses. Gastroenterology 138: 1055-1067.e1-e4, 2010.
186. Eelen G, Treps L, Li X and Carmeliet P: Basic and therapeutic aspects of angiogenesis updated. Circ Res 127: 310-329, 2020.
187. Sajib S, Zahra FT, Lionakis MS, German NA and Mikelis CM: Mechanisms of angiogenesis in microbe-regulated inflammatory and neoplastic conditions. Angiogenesis 21: 1-14, 2018.
188. Roldán-Montero R, Pérez-Sáez JM, Cerro-Pardo I, Oller J, Martinez-Lopez D, Nuñez E, Maller SM, Gutierrez-Muñoz C, Mendez-Barbero N, Escola-Gil JC, *et al*: Galectin-1 prevents pathological vascular remodeling in atherosclerosis and abdominal aortic aneurysm. Sci Adv 8: eabm7322, 2022.
189. Elshabrawy HA, Chen Z, Volin MV, Ravella S, Virupannavar S and Shahrara S: The pathogenic role of angiogenesis in rheumatoid arthritis. Angiogenesis 18: 433-448, 2015.
190. Dudley AC and Griffioen AW: Pathological angiogenesis: Mechanisms and therapeutic strategies. Angiogenesis 26: 313-347, 2023.
191. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, *et al*: Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 383: 120-128, 2020.
192. Tarnawski AS and Ahluwalia A: The critical role of growth factors in gastric ulcer healing: The cellular and molecular mechanisms and potential clinical implications. Cells 10: 1964, 2021.
193. Vagnucci AH Jr and Li WW: Alzheimer's disease and angiogenesis. Lancet 361: 605-608, 2003.
194. Carmeliet P: Angiogenesis in health and disease. Nat Med 9: 653-660, 2003.
195. Danese S, Sans M, de la Motte C, Graziani C, West G, Phillips MH, Pola R, Rutella S, Willis J, Gasbarrini A and Fiocchi C: Angiogenesis as a novel component of inflammatory bowel disease pathogenesis. Gastroenterology 130: 2060-2073, 2006.
196. Danese S, Sans M, Spencer DM, Beck I, Doñate F, Plunkett ML, de la Motte C, Redline R, Shaw DE, Levine AD, *et al*: Angiogenesis blockade as a new therapeutic approach to experimental colitis. Gut 56: 855-862, 2007.
197. Chidlow JH Jr, Langston W, Greer JJ, Ostanin D, Abdelbaqi M, Houghton J, Senthilkumar A, Shukla D, Mazar AP, Grisham MB and Kevil CG: Differential angiogenic regulation of experimental colitis. Am J Pathol 169: 2014-2030, 2006.
198. Maconi G, Sampietro GM, Russo A, Bollani S, Cristaldi M, Parente F, Dottorini F and Bianchi Porro G: The vascularity of internal fistulae in Crohn's disease: An in vivo power Doppler ultrasonography assessment. Gut 50: 496-500, 2002.
199. Spalinger J, Patriquin H, Miron MC, Marx G, Herzog D, Dubois J, Dubinsky M and Seidman EG: Doppler US in patients with crohn disease: Vessel density in the diseased bowel reflects disease activity. Radiology 217: 787-791, 2000.
200. Hatoum OA and Binion DG: The vasculature and inflammatory bowel disease: Contribution to pathogenesis and clinical pathology. Inflamm Bowel Dis 11: 304-313, 2005.
201. Folkman J and Shing Y: Angiogenesis. J Biol Chem 267: 10931-10934, 1992.
202. Szekanecz Z and Koch AE: Vascular endothelium and immune responses: Implications for inflammation and angiogenesis. Rheum Dis Clin North Am 30: 97-114, 2004.
203. Colgan SP, Furuta GT and Taylor CT: Hypoxia and innate immunity: Keeping Up with the HIFsters. Annu Rev Immunol 38: 341-363, 2020.
204. Ucuzian AA, Gassman AA, East AT and Greisler HP: Molecular mediators of angiogenesis. J Burn Care Res 31: 158-175, 2010.
205. Danese S, Papa A, Saibeni S, Repici A, Malesci A and Vecchi M: Inflammation and coagulation in inflammatory bowel disease: The clot thickens. Am J Gastroenterol 102: 174-186, 2007.
206. Ginnan R, Guikema BJ, Halligan KE, Singer HA and Jourd'heuil D: Regulation of smooth muscle by inducible nitric oxide synthase and NADPH oxidase in vascular proliferative diseases. Free Radic Biol Med 44: 1232-1245, 2008.
207. Benelli R, Lorusso G, Albini A and Noonan DM: Cytokines and chemokines as regulators of angiogenesis in health and disease. Curr Pharm Des 12: 3101-3115, 2006.
208. Chidlow JH Jr, Shukla D, Grisham MB and Kevil CG: Pathogenic angiogenesis in IBD and experimental colitis: New ideas and therapeutic avenues. Am J Physiol Gastrointest Liver Physiol 293: G5-G18, 2007.
209. Deban L, Correale C, Vetrano S, Malesci A and Danese S: Multiple pathogenic roles of microvasculature in inflammatory bowel disease: A Jack of all trades. Am J Pathol 172: 1457-1466, 2008.
210. Pousa ID, Maté J and Gisbert JP: Angiogenesis in inflammatory bowel disease. Eur J Clin Invest 38: 73-81, 2008.
211. Hicklin DJ and Ellis LM: Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 23: 1011-1027, 2005.
212. Algaba A, Linares PM, Fernández-Contreras ME, Ordoñez A, Trápaga J, Guerra I, Chaparro M, de la Poza G, Gisbert JP and Bermejo F: Relationship between levels of angiogenic and lymphangiogenic factors and the endoscopic, histological and clinical activity, and acute-phase reactants in patients with inflammatory bowel disease. J Crohns Colitis 7: e569-579, 2013.
213. Frysz-Naglak D, Fryc B, Klimacka-Nawrot E, Mazurek U, Suchecka W, Kajor M, Kurek J and Stadnicki A: Expression, localization and systemic concentration of vascular endothelial growth factor (VEGF) and its receptors in patients with ulcerative colitis. Int Immunopharmacol 11: 220-225, 2011.
214. Yamazaki Y and Morita T: Molecular and functional diversity of vascular endothelial growth factors. Mol Divers 10: 515-527, 2006.
215. Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, Moldovan IM, Roman AL and Mihu CM: Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis. Rom J Morphol Embryol 59: 455-467, 2018.
216. Shibuya M: VEGF-VEGFR system as a target for suppressing inflammation and other diseases. Endocr Metab Immune Disord Drug Targets 15: 135-144, 2015.
217. Sarabipour S and Mac Gabhann F: VEGF-A121a binding to Neuropilins-A concept revisited. Cell Adh Migr 12: 204-214, 2018.
218. Sandor Z, Deng XM, Khomenko T, Tarnawski AS and Szabo S: Altered angiogenic balance in ulcerative colitis: A key to impaired healing? Biochem Biophys Res Commun 350: 147-150, 2006.
219. Tacconi C, Schwager S, Cousin N, Bajic D, Sesartic M, Sundberg JP, Neri D and Detmar M: Antibody-mediated delivery of VEGFC ameliorates experimental chronic colitis. ACS Pharmacol Transl Sci 2: 342-352, 2019.
220. Koutroubakis IE, Tsiolakidou G, Karmiris K and Kouroumalis EA: Role of angiogenesis in inflammatory bowel disease. Inflamm Bowel Dis 12: 515-523, 2006.
221. Simons M, Gordon E and Claesson-Welsh L: Mechanisms and regulation of endothelial VEGF receptor signalling. Nat Rev Mol Cell Biol 17: 611-625, 2016.
222. Dimmeler S and Zeiher AM: Akt takes center stage in angiogenesis signaling. Circ Res 86: 4-5, 2000.
223. Fryer BH and Field J: Rho, Rac, Pak and angiogenesis: Old roles and newly identified responsibilities in endothelial cells. Cancer Lett 229: 13-23, 2005.
224. Chen YJ, Chan DC, Chiang CK, Wang CC, Yang TH, Lan KC, Chao SC, Tsai KS, Yang RS and Liu SH: Advanced glycation end-products induced VEGF production and inflammatory responses in human synoviocytes via RAGE-NF-κB pathway activation. J Orthop Res 34: 791-800, 2016.
225. Liang H, Zhong Y, Zhou S and Peng L: Knockdown of RAGE expression inhibits colorectal cancer cell invasion and suppresses angiogenesis in vitro and in vivo. Cancer Lett 313: 91-98, 2011.

226. Sha L, Zhao Y, Li S, Wei D, Tao Y and Wang Y: Insights to Ang/Tie signaling pathway: Another rosy dawn for treating retinal and choroidal vascular diseases. J Transl Med 22: 898, 2024.
227. Fagiani E and Christofori G: Angiopoietins in angiogenesis. Cancer Lett 328: 18-26, 2013.
228. Fang Z, Qu S, Ji X, Zheng C, Mo J, Xu J, Zhang J and Shen H: Correlation between PDGF-BB and M1-type macrophage in inflammatory bowel disease: A case-control study. BMC Gastroenterol 24: 417, 2024.
229. Chen X, Zhang L, Zhang IY, Liang J, Wang H, Ouyang M, Wu S, da Fonseca ACC, Weng L, Yamamoto Y, *et al*: RAGE expression in tumor-associated macrophages promotes angiogenesis in glioma. Cancer Res 74: 7285-7297, 2014.
230. Lan J, Luo H, Wu R, Wang J, Zhou B, Zhang Y, Jiang Y and Xu J: Internalization of HMGB1 (High Mobility Group Box 1) promotes angiogenesis in endothelial cells. Arterioscler Thromb Vasc Biol 40: 2922-2940, 2020.
231. Zheng J, Zhu W, He F, Li Z, Cai N and Wang HH: An aptamer-based antagonist against the receptor for advanced glycation end-products (RAGE) blocks development of colorectal cancer. Mediators Inflamm 2021: 9958051, 2021.
232. Soro-Paavonen A, Watson AM, Li J, Paavonen K, Koitka A, Calkin AC, Barit D, Coughlan MT, Drew BG, Lancaster GI, *et al*: Receptor for advanced glycation end products (RAGE) deficiency attenuates the development of atherosclerosis in diabetes. Diabetes 57: 2461-2469, 2008.
233. Ming L, Ji J, Luo Z, Zhao Z, Li M, Sun R, Lu W, Chen Y and Huang Q: Sishen pill alleviates DSS induced colitis through AGE/RAGE/NLRP3 pathway based on transcriptomics analysis. J Ethnopharmacol 356: 120818, 2026.
234. He X, Zhou C, Shang R and Wang X: Acanthoside B attenuates NLRP3-mediated pyroptosis and ulcerative colitis through inhibition of tAGE/RAGE pathway. Allergol Immunopathol (Madr) 53: 112-122, 2025.
235. Zhang J, Jiao Y, Hou S, Tian T, Yuan Q, Hao H, Wu Z and Bao X: S100A4 contributes to colitis development by increasing the adherence of Citrobacter rodentium in intestinal epithelial cells. Sci Rep 7: 12099, 2017.
236. Aljohi A, Matou-Nasri S, Liu D, Al-Khafaji N, Slevin M and Ahmed N: Momordica charantia extracts protect against inhibition of endothelial angiogenesis by advanced glycation endproducts in vitro. Food Funct 9: 5728-5739, 2018.
237. Watson AM, Gray SP, Jiaze L, Soro-Paavonen A, Wong B, Cooper ME, Bierhaus A, Pickering R, Tikellis C, Tsorotes D, *et al*: Alagebrium reduces glomerular fibrogenesis and inflammation beyond preventing RAGE activation in diabetic apolipoprotein E knockout mice. Diabetes 61: 2105-2113, 2012.
238. Zhang M, Li Y, Rao P, Huang K, Luo D, Cai X and Xiao J: Blockade of receptors of advanced glycation end products ameliorates diabetic osteogenesis of adipose-derived stem cells through DNA methylation and Wnt signalling pathway. Cell Prolif 51: e12471, 2018.
239. Arab HH, Abd El-Aal SA, Eid AH, Arafa EA, Mahmoud AM and Ashour AM: Targeting inflammation, autophagy, and apoptosis by troxerutin attenuates methotrexate-induced renal injury in rats. Int Immunopharmacol 103: 108284, 2022.
240. He F, Gu L, Cai N, Ni J, Liu Y, Zhang Q and Wu C: The HMGB1-RAGE axis induces apoptosis in acute respiratory distress syndrome through PERK/eIF2α/ATF4-mediated endoplasmic reticulum stress. Inflamm Res 71: 1245-1260, 2022.
241. Tang Z, Yang G, Liao Z, Chen F, Chen S, Wang W, Huo G, Sun X and Wang X: Tanshinone IIA reduces AQP4 expression and astrocyte swelling after OGD/R by inhibiting the HMGB1/RAGE/NF-κB/IL-6 pro-inflammatory axis. Sci Rep 12: 14110, 2022.
242. Shihui M, Shirong Y, Jing L, Jingjing H, Tongqian W, Tian T, Chenyu W and Fang Y: S100A4 reprofiles lipid metabolism in mast cells via RAGE and PPAR-gamma signaling pathway. Int Immunopharmacol 128: 111555, 2024.
243. Ding B, Lin C, Liu Q, He Y, Ruganzu JB, Jin H, Peng X, Ji S, Ma Y and Yang W: Tanshinone IIA attenuates neuroinflammation via inhibiting RAGE/NF-κB signaling pathway in vivo and in vitro. J Neuroinflammation 17: 302, 2020.
244. Liu W, Wu C, Wang Q, Kuang L and Le A: Tanshinone IIA relieves arthritis by inhibiting autophagy of fibroblast-like synoviocytes via matrix metalloproteinase9/receptor for advanced glycation end product/toll-like receptor 9 signal axis in mice with collagen-induced arthritis. Phytother Res 37: 1391-1404, 2023.
245. Parthasarathy G, Mauer AS, Golla N, Daniel PV, Kim LH, Sidhu GS, Marek GW III, Loeuillard E, Krishnan A, Lee HSK, *et al*: Macrophage RAGE activation is proinflammatory in NASH. JCI Insight 9: e169138, 2024.
246. Zhang C, Wang L, Xu Y, Huang Y, Huang J, Zhu J, Wang W, Li W, Sun A, Li X, *et al*: Discovery of novel dual RAGE/SERT inhibitors for the potential treatment of the comorbidity of Alzheimer's disease and depression. Eur J Med Chem 236: 114347, 2022.
247. Algaba A, Linares PM, Encarnación Fernández-Contreras M, Figuerola A, Calvet X, Guerra I, de Pousa I, Chaparro M, Gisbert JP and Bermejo F: The effects of infliximab or adalimumab on vascular endothelial growth factor and angiopoietin 1 angiogenic factor levels in inflammatory bowel disease: Serial observations in 37 patients. Inflamm Bowel Dis 20: 695-702, 2014.
248. Deng X, Tolstanova G, Khomenko T, Chen L, Tarnawski A, Szabo S and Sandor Z: Mesalamine restores angiogenic balance in experimental ulcerative colitis by reducing expression of endostatin and angiostatin: Novel molecular mechanism for therapeutic action of mesalamine. J Pharmacol Exp Ther 331: 1071-1078, 2009.
249. Knod JL, Crawford K, Dusing M and Frischer JS: Murine colitis treated with multitargeted tyrosine kinase inhibitors. J Surg Res 200: 501-507, 2016.
250. Liu XM, Zhu WT, Jia ML, Li YT, Hong Y, Liu ZQ and Yan PK: Rapamycin liposomes combined with 5-fluorouracil inhibits angiogenesis and tumor growth of $APC^{((Min/+))}$ mice and AOM/DSS-induced colorectal cancer mice. Int J Nanomedicine 17: 5049-5061, 2022.
251. Tang T, Abu-Sbeih H, Ma W, Lu Y, Luo W, Foo WC, Richards DM, Halperin DM, Ge PS and Wang Y: Gastrointestinal injury related to antiangiogenesis cancer therapy. Clin Colorectal Cancer 19: e117-e123, 2020.
252. Meijer B, Hoskin T, Ashcroft A, Burgess L, Keenan JI, Falvey J, Gearry RB and Day AS: Total soluble and endogenous secretory receptor for advanced glycation endproducts (RAGE) in IBD. J Crohns Colitis 8: 513-520, 2014.
253. Făgărășan A and Săsăran MO: The predictive role of plasma biomarkers in the evolution of aortopathies associated with congenital heart malformations. Int J Mol Sci 23: 4993, 2022.
254. Yilmaz Y, Yonal O, Eren F, Atug O and Hamzaoglu HO: Serum levels of soluble receptor for advanced glycation endproducts (sRAGE) are higher in ulcerative colitis and correlate with disease activity. J Crohns Colitis 5: 402-406, 2011.
255. van der Heijden MS, Powles T, Petrylak D, de Wit R, Necchi A, Sternberg CN, Matsubara N, Nishiyama H, Castellano D, Hussain SA, *et al*: Predictive biomarkers for survival benefit with ramucirumab in urothelial cancer in the RANGE trial. Nat Commun 13: 1878, 2022.
256. Heil F, Babitzki G, Julien-Laferriere A, Ooi CH, Hidalgo M, Massard C, Martinez-Garcia M, Le Tourneau C, Kockx M, Gerber P, *et al*: Vanucizumab mode of action: Serial biomarkers in plasma, tumor, and skin-wound-healing biopsies. Transl Oncol 14: 100984, 2021.
257. Soria JC, Mauguen A, Reck M, Sandler AB, Saijo N, Johnson DH, Burcoveanu D, Fukuoka M, Besse B and Pignon JP; meta-analysis of bevacizumab in advanced NSCLC collaborative group: Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol 24: 20-30, 2013.
258. Eder P, Korybalska K, Linke K and Witowski J: Angiogenesis-related proteins-their role in the pathogenesis and treatment of inflammatory bowel disease. Curr Protein Pept Sci 16: 249-258, 2015.
259. Mateescu RB, Bastian AE, Nichita L, Marinescu M, Rouhani F, Voiosu AM, Benguş A, Tudoraşcu DR and Popp CG: Vascular endothelial growth factor-key mediator of angiogenesis and promising therapeutical target in ulcerative colitis. Rom J Morphol Embryol 58: 1339-1345, 2017.
260. Xu X, Ying H, Wang X, Hong W and Zhang M: Identification of Angiogenesis-related gene signatures and prediction of potential therapeutic targets in ulcerative colitis using integrated bioinformatics. J Inflamm Res 17: 11699-11717, 2024.