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REVIEW

AMPK in Intestinal Health and Disease: A Multifaceted Therapeutic Target for Metabolic and Inflammatory Disorders

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Abstract: The intestines play essential roles in nutrient absorption and immune function and help maintain a protective barrier. Disruptions to its function can result in various diseases, including metabolic disorders, inflammation, and cancer. As a key regulator of cellular energy levels, 5'-adenosine monophosphate-activated protein kinase (AMPK) is essential for intestinal health. Beyond its established metabolic role, emerging evidence suggests that AMPK exerts profound effects on intestinal cell physiology, influencing cell proliferation and differentiation, inflammation, autophagy, barrier integrity, and smooth muscle contractility. Here, we explore the structure and regulation of AMPK, as well as its diverse roles in intestinal diseases and potential as a therapeutic target. Our findings reveal that AMPK is a multifaceted regulator of intestinal health, modulating various cellular processes and intestinal diseases. It plays a dual role in cancer, acting as both a tumor suppressor and promoter, and it regulates inflammatory pathways, autophagy, tight junction formation, and smooth muscle contractility. Both natural and synthetic AMPK activators offer promise as therapeutic agents. This review of AMPK's mechanisms and activators offers valuable insights for developing novel therapies for intestinal disorders. Further research is needed to fully define AMPK's roles and therapeutic potential.

Keywords: AMPK, AMPK activators, intestinal diseases, intestinal inflammation, intestinal cancer

Introduction

The intestinal tract is a pivotal site for various essential bodily functions, such as nutrient absorption, immune response modulation, and maintenance of the intestinal barrier. Pathological alterations to the intestines result in several intestinal diseases, including metabolic disorders, inflammatory conditions, and cancerous formations.[1]

Among the myriad signaling molecules that orchestrate intestinal cellular functions, 5'-adenosine monophosphate-activated protein kinase (AMPK), a highly conserved serine/threonine (Ser/Thr) kinase, is a central regulator and metabolic sensor that responds to changes in cellular energy status. Beyond its established role in cellular energy metabolism, emerging evidence suggests that AMPK exerts profound effects on intestinal cell physiology, influencing cell proliferation, differentiation, inflammatory responses, apoptosis, autophagy, epithelial barrier integrity, and smooth muscle contractility.[2–4] These diverse effects highlight AMPK's crucial role in regulating various intestinal functions, including nutrient absorption, ion transport, inflammation control, maintenance of gut barrier integrity, and intestinal mobility.[2,3,5] Dysregulation of AMPK has been associated with the development of intestinal diseases.[6] Indeed, AMPK signaling is disrupted in several intestinal disorders. Studies have shown that administering AMPK activators can protect against intestinal damage and toxicity.[7] Conversely, models lacking AMPK subunits exhibit increased intestinal permeability and heightened susceptibility to colitis.[3,7,8] Furthermore, AMPK's protective effects extend to suppressing inflammation and reducing reactive oxygen species (ROS) production within the intestine.[9]

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This comprehensive review explores the intricate regulatory mechanisms governing AMPK activation and its pathophysiological implications, while examining diverse exogenous AMPK activators. Moreover, we present growing evidence supporting AMPK's potential as a therapeutic target across multiple pathological conditions, with particular emphasis on inflammation and cancer applications.

A Glance at AMPK

Structure of AMPK

AMPK is a heterotrimeric protein complex composed of three distinct subunits: the α, β, and γ subunits. The α subunit, the core of AMPK, contains a catalytic domain responsible for phosphorylating target substrates and flanking N-terminal kinase and C-terminal regulatory domains that facilitate phosphate transfer and modulate activity, respectively. The β subunit stabilizes the entire complex and potentially senses energy levels via its glycogen-binding domain. The γ subunit, with its four cystathionine β-synthase (CBS) domains, binds adenosine monophosphate (AMP)/adenosine triphosphate (ATP) to sense cellular energy levels and regulate the complex's activity.[4,10,11]

The key activation site of the α subunit's kinase domain is located at Thr172. Phosphorylation of Thr172 by upstream kinases, such as liver kinase B1 (LKB1) and Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) β, is crucial for AMPK activation.[11,12] Notably, the α subunit has two isoforms: α1 and α2. The α1 isoform, which is linked to gene polymorphism rs10074991, is associated with a decreased risk of cancer susceptibility.[13] The α2 isoform is important for neutrophil-mediated vascular repair and muscle differentiation, as it regulates genes that encode muscle creatinine kinase (MCK), pepsinogen C (PGC)-1α1, PGC-1α4, and cytochrome c.[14,15] However, its phosphorylation is reduced during bladder ischemia.[16]

The β subunit acts as a scaffold, stabilizing the trimeric AMPK complex through interactions with the other subunits, and regulates glycogen metabolism via its glycogen-binding domain.[4,10,11] This subunit has two isoforms, β1 and β2, which exhibit distinct tissue distribution patterns. For instance, the β1 isoform is crucial for both erythrocyte development and glucose homeostasis, and mice lacking the β1 isoform exhibit reduced kidney fibrosis, elevated blood sugar, and microcytic anemia with splenomegaly.[17,18] In contrast, upregulation of the β2 isoform promotes adipogenesis.[19] Interestingly, both the β1 and β2 isoforms determine gene expression during cardiac stem cell differentiation.[20] It is also worth noting that myristoylation of the β subunit can suppress AMPK[21] and that inhibition of this myristoylation can activate AMPK and prevent mice from developing high-fat diet-induced obesity and hepatic steatosis.[22]

The γ subunit of AMPK serves as a cellular energy sensor through its four CBS domains that bind adenine nucleotides, including AMP and ATP. This binding allows AMPK to detect changes in the AMP-to-ATP ratio, a key indicator of energy level. When energy is low (high AMP level), AMP binding allosterically activates AMPK via conformational changes in the γ subunit.[10,23] Conversely, a high ATP level inhibits AMPK activation. Furthermore, prolyl isomerase 1 (Pin1) suppresses AMPK phosphorylation in the CBS domain.[24] The γ subunit has three isoforms (γ1, γ2, and γ3) that have distinct functions. The γ1 isoform was found to regulate glucose metabolism in the liver and skeletal muscle in metformin-treated AMPK$\gamma1^{H151R}$ transgenic mice.[25,26] Other studies have shown that the γ2 isoform is crucial for heart rate control and that the γ3 isoform regulates human lipoprotein metabolism.[27,28]

Regulation of AMPK

AMPK senses cellular energy depletion through its ability to detect rising levels of AMP and adenosine diphosphate (ADP). When energy stress occurs, the increase in cellular AMP results in AMP outcompeting ATP for binding to AMPK, and this binding triggers a conformational change in AMPK that activates its kinase.[29] When there are high levels of ADP, it can bind to and activate AMPK via the same mechanism.[12] Notably, ADP dominantly controls AMPK activation in skeletal muscle cells during exercise.[30] Furthermore, AMP binding to the γ subunit of AMPK enhances AMPK activation through Thr172 phosphorylation by upstream kinases, such as LKB1 and CaMKKβ.[10,11,23,31,32]

Interestingly, when activated LKB1 contains mutations, it can still support cancer cell viability, proliferation, and metastasis.[33] Additionally, the AMPK inhibitor BAY-3827 can increase phosphorylation at Thr172 without activating AMPK, indicating the presence of additional AMPK regulatory mechanisms.[34] It has also been reported that protein

phosphatase 2C (PP2C) and PH-domain leucine-rich repeat protein phosphatase 2 (PHLPP2) can deactivate AMPK by removing the phosphate group from Thr172, and this has been shown to induce various cellular processes, including cell death.[35,36] Other studies have shown that AMPK can also be activated by high intracellular calcium levels, a hallmark of cellular stress, via CaMKKβ[37] and that inhibition of CaMKKβ by STO-609 suppresses AMPK activation in LKB1-deficient cell lines.[38] The CaMKKβ-dependent pathway that results in AMPK activation is described in detail elsewhere.[39]

It is important to note that AMPK can also be activated by other conditions. For example, low glucose or low oxygen (hypoxia) can activate AMPK as a cellular response to metabolic stress.[40] Interestingly, hypoxia can trigger AMPK activation via a pathway involving reactive oxygen species (ROS)-mediated CaMKKβ activation.[41] Collectively, AMPK regulation is shown in Figure 1.

Energy Regulation by AMPK

Acting as a cellular energy switch, AMPK regulates carbohydrate, lipid, and protein metabolism by catalyzing the phosphorylation of various key metabolic enzymes. In 1987, AMPK was first found to regulate fat and cholesterol production. AMPK has a direct effect on these processes by inhibiting acetyl coenzyme A carboxylase (ACC)1, which is crucial for fatty acid synthesis, and 3-hydroxy-4-methylglutaryl coenzyme A (HMG-CoA) reductase, the key enzyme in cholesterol production.[42] Furthermore, AMPK promotes beta oxidation by inhibiting ACC2, an enzyme that suppresses this process. Additionally, AMPK inactivates sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate-responsive element-binding protein (ChREBP), two transcription factors that promote fat synthesis. These actions position AMPK as a promising target for treating fatty liver disease and dyslipidemia.[43]

Given that AMPK has been implicated in blood sugar regulation, it is being assessed as a target for treating type 2 diabetes mellitus (T2DM). Studies have shown that AMPK can inhibit gluconeogenesis and glycogen synthesis in the liver and that it can promote glucose uptake by skeletal muscle cells by enhancing glucose transporter (GLUT) 4 translocation and cell-surface expression.[44,45] AMPK also enhances the translocation of GLUT1; however, more studies are necessary to confirm this phenomenon and its effects in living organisms.[46]

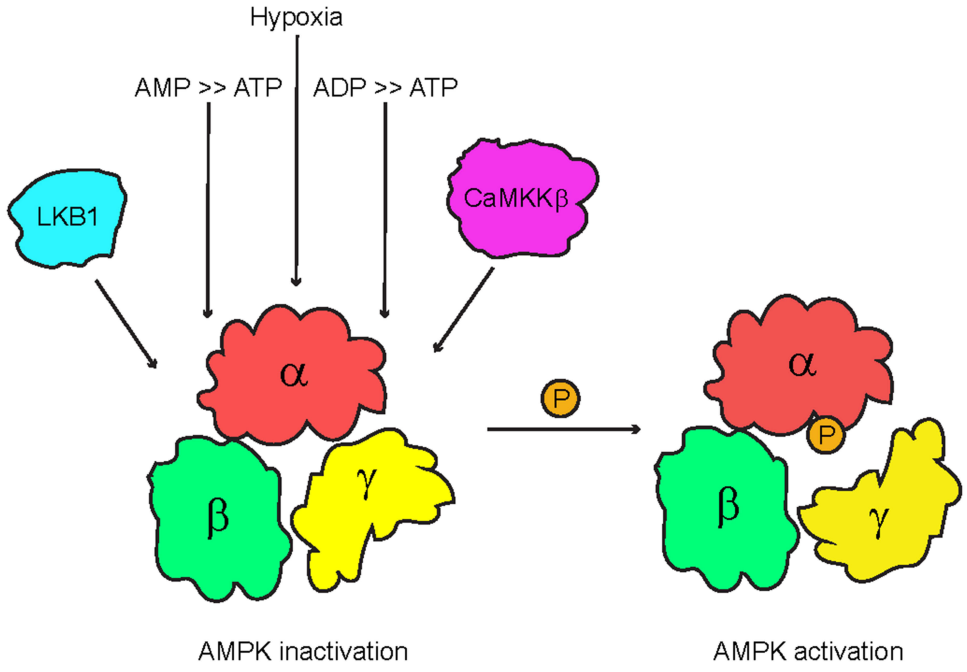

Figure 1 Several mechanisms regulate the activation of AMPK. AMPK is composed of three subunits: the alpha subunit (AMPKα), which has a phosphorylation binding site; the beta subunit (AMPKβ), which stabilizes the entire complex; and the gamma subunit (AMPKγ), which acts as an AMP/ATP energy sensor. Phosphorylation by LKB1 or CaMKKβ can trigger AMPK activation. Elevated levels of AMP or ADP compete with ATP, promoting AMPK activation. Additionally, hypoxia can also stimulate AMPK activation. This activation results from a conformational change in AMPKγ, which reveals the phosphorylation binding site.

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Under stress conditions, cells prioritize energy conservation by ceasing protein synthesis. AMPK triggers this process by terminating three key signaling pathways: translation initiation via suppressing mammalian target of rapamycin complex 1 (mTORC1), translation elongation by activating eukaryotic elongation factor 2 kinase (eEF2K), and ribosome biosynthesis through the inhibitory phosphorylation of Transcriptional initiation factor 1A (TIF-1A).[47–49]

Key Biological Activities of AMPK in Intestinal Diseases

The intestines are vital organs responsible for nutrient absorption and act as the first line of defense against external pathogens. Maintaining intestinal health is crucial for overall well-being, as their disruption can lead to various diseases, including IBD and colorectal cancer. AMPK plays a pivotal role in regulating cellular metabolism and stress responses. Emerging evidence suggests that AMPK plays a crucial role in maintaining intestinal health by exerting various biological activities.

This section delves into the key biological activities of AMPK in intestinal health and disease, focusing on its roles as (i) a growth suppressor, (ii) an inflammation and stress modulator, (iii) an autophagy inducer, and (iv) a regulator of gut barrier function (Figure 2). By understanding these versatile functions of AMPK can pave the way for exploring its therapeutic potential in addressing various intestinal disorders and promoting gut health.

AMPK and Growth Suppression

AMPK is known to modulate the function and metabolism of tumor cells.[50] It has been found to not only regulate diverse cellular responses pivotal to tumor cell growth, proliferation, and survival but also suppress tumor cells by regulating oncogenic metabolic processes and promoting cell-cycle arrest and pathways related to glucose, lipid, and protein biosynthesis.[51] Given these findings, and the fact that AMPK has been shown to significantly arrest the cell cycle in a variety of tumor cell types (notably, melanoma and lung, colorectal, liver, and prostate cancer cells), it has potential as a therapeutic target in multiple types of cancer.[52,53]

In colorectal cancer (CRC), the third most common type of cancer, tumor cells perform aerobic glycolysis—also known as the Warburg effect—to promote tumor metastasis and remodel the tumor microenvironment.[54,55] AMPK

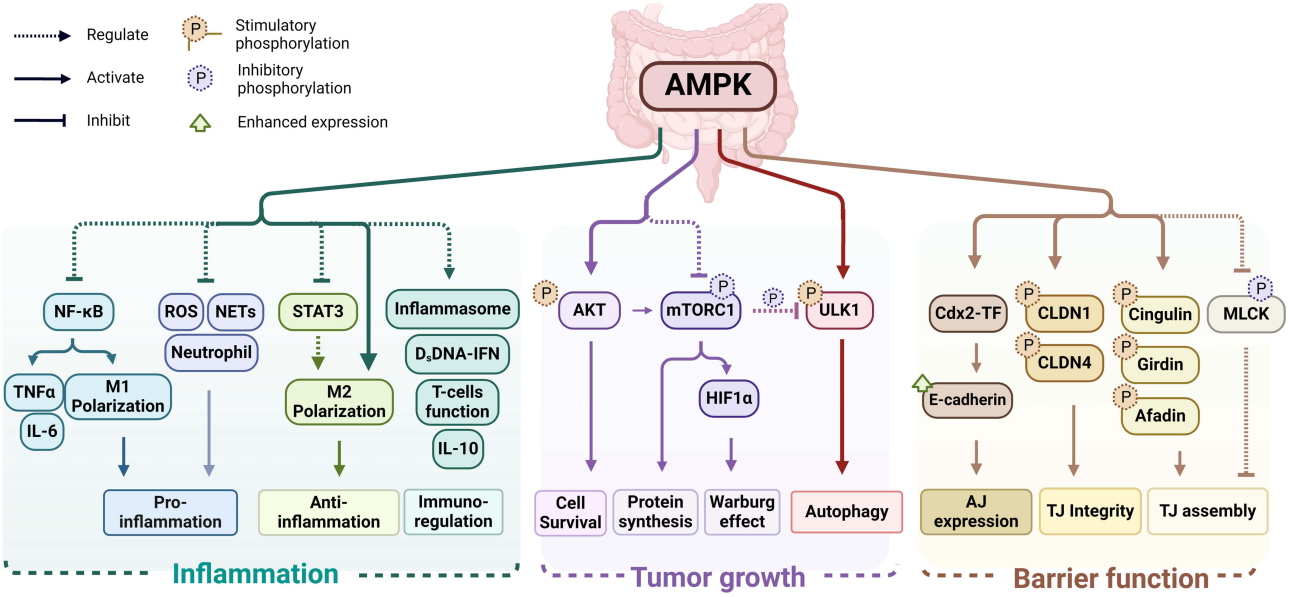


Figure 2 AMPK influences diverse functions of GI cells, including inflammation, tumor genesis, and barrier function, through the manipulation on myriad signaling pathways. The impact of AMPK on inflammation was explicit in modulating the differentiation and activities of immune cells by suppressing pro-inflammatory macrophages and neutrophils, while boosting M2 polarization and other anti-inflammatory mediators. Tumor reduction was relevant to the role of AMPK. Active AMPK phosphorylates downstream to dampen the protein synthesis and proliferation yet preserve survival and autophagy. Lastly, a wide range of barriers forming junctional proteins are regulated by AMPK. AMPK promotes the expression of adherent junctions, strengthens the tight junction cross-linking, and enzymatically regulates the tight junction scaffolding modulators. This figure was created with BioRender.com/ Mahidol University.

activation has been shown to counteract tumor progression by dampening the Warburg effect in tumor cells and inhibiting cell growth via the inactivation of the mammalian target of rapamycin (mTOR) signaling and suppression of hypoxia-inducible factor-1 alpha (HIF-1α), implicating the tumor-suppressor role of LKB1, the upstream AMPK kinase.[56,57] In addition, relatively lower levels of phosphorylated AMPK have been found in patients with CRC.[58] It should also be noted that pharmacological activation of AMPK with 5-aminoimidazole-4-carboxamide-ribonucleoside (AICAR) alone or in combination with chemotherapies has been reported to be cytotoxic and induce cell apoptosis in CRC cells, demonstrating the benefits of targeting AMPK in cancer therapy.[51,59] In contrast, AMPK also reportedly promotes tumor cell survival and protects tumor cells against cellular stress via oncogenic phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling.[50,60] Treating CRC stem cells with the known AMPK inhibitor compound C has been shown to result in cell death.[60] Hence, current evidence indicates that AMPK plays the dual roles of tumor promoters and tumor suppressors in tumorigenesis, depending on the context.

AMPK and Inflammation and Stress

Inflammatory processes are typically initiated when stimuli are detected, such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Subsequently, intracellular inflammatory signaling pathways and molecules are activated, such as nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), Janus kinase-signal transducers and activators of transcription (JAK-STAT), and inflammasomes, and these are extensively reviewed in the literature.[61,62]

Given its well-established role as a regulator of cellular energy and metabolic homeostasis, AMPK has garnered considerable attention in immunology regarding its potential applications in the treatment of inflammation and related diseases. Both pro-inflammatory and anti-inflammatory signals can influence AMPK activity.[63] Compound C (an AMPK inhibitor) has been shown to suppress stimulator of interferon genes (STING)-mediated production of interferon (IFN)-β and tumor necrosis factor (TNF),[64] as well as the production of type I IFN in response to double-stranded DNA (dsDNA)-dependent type I IFN induction.[65] AMPK also plays a role in the interleukin (IL)-10-mediated anti-inflammatory process.[66] AICAR (an AMPK activator) can reduce inflammation by preventing the nuclear translocation of the NF-κB p65 subunit.[67] Additionally, AICAR inhibits the IL-6-mediated signal transducer and activator of transcription 3 (STAT3) phosphorylation in HepG2 cells.[68] Treating mice with another AMPK activator, A-769662, before exposing them to lipopolysaccharide (LPS), reduces LPS-induced IL-6 secretion and lung injury.[69] Notably, AICAR ameliorates 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced acute colitis in mice.[70]

Inflammasome is a cellular component involved in innate immunity that consists of multiprotein complexes activated by various stimuli. When activated, it releases pro-inflammatory cytokines (IL-1β and IL-18) and triggers a type of inflammation-related cell death called pyroptosis. Activation of the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome plays a significant role in colitis in mice, with deficiencies in inflammasome components exacerbating the disease in dextran sulfate sodium (DSS)-induced colitis models.[71,72] AMPK has been found to regulate the activation of the NLRP3 inflammasome caused by different stimuli, including autophagy, mitochondria, endoplasmic reticulum (ER) stress, and sirtuin (SIRT)1.[73–76] However, there is a need for further research in this area, as AMPK inhibition has been reported to cause both NLRP3 inflammasome activation and inhibition.[77,78]

Beyond its role in immune signaling, AMPK is crucial for immune cell function, especially in T cells and macrophages. These cells are key players in various inflammatory diseases, and their functioning affects disease outcomes. Here, we focus on one such inflammatory disease: colitis, a multifactorial disease with various etiologies, including infection, inflammation, autoimmunity, ischemia, and drug-induced factors. Colitis can partially be attributed to abnormal T-cell metabolism, with high glucose consumption worsening colitis in T cell transfer colitis models.[79] AMPK has been shown to facilitate metabolic adaptation in T cells when nutrients are limited or altered[80] and to be essential for T-cell expansion but not to influence the fate or differentiation of T cells in T cell-mediated chronic colitis.[80] Interestingly, mice that lacked T cells and received AMPKα-deficient CD4+ T cells were found to develop less severe colitis.[81] Mogrol, an active compound in some traditional Chinese medicines, was found to alleviate the severity of DSS-induced colitis in mice through AMPK activation.[82]

Metformin treatment reduces regulatory T cell (Treg) numbers, and AMPKα1-deficient Tregs have decreased suppressive function.[83,84] AMPK enhances the suppressive function of Tregs by directly phosphorylating forkhead box P3 (FoxP3).[84] However, the role that AMPK plays in Treg function remains unclear, as some studies have shown no significant differences in the suppressive function of Tregs and AMPK-deficient Tregs.[80]

The polarization of macrophages into the pro-inflammatory (M1) or anti-inflammatory (M2) phenotype significantly influences the development of various inflammatory diseases, including colitis.[85] Similar to the situation in T cells, AMPK plays a pivotal role in regulating macrophage homeostasis and functions. AMPKα1-deficient macrophages fail to polarize into the M2 phenotype and exhibit impaired phagocytic activity in murine models of muscle regeneration.[86] Furthermore, AMPKβ1-deficient mouse macrophages tend toward the M1 phenotype, with upregulation of pro-inflammatory cytokine mRNA (ie, TNF-α, IL-6, and IL-1β mRNA) after palmitate stimulation.[87] Treating mouse bone marrow-derived macrophages (BMDMs) with metformin inhibits LPS-induced pro-inflammatory cytokine (TNF-α and IL-1β) secretion and promotes anti-inflammatory cytokine (IL-10) secretion.[88]

Neutrophils are essential for combating infections; however, they can also contribute to the pathogenesis of colitis. Neutrophil infiltration is common in ulcerative colitis (UC) and correlates with disease severity.[89] Furthermore, neutrophil extracellular traps (NETs), which are released by neutrophils to combat pathogens, contribute to ongoing intestinal inflammation in UC.[90] A novel highly potent AMPK activator, IM156, has been found to inhibit LPS-induced ROS production and NET formation in mouse neutrophils.[91] In another study, it was found that AMPK regulates the neutrophil secretion of matrix metalloproteinases 8 (MMP-8), the zinc-dependent proteolytic enzymes that contribute to several pathological processes.[92]

A major challenge in translating preclinical AMPK findings to the clinic is the context-specificity of its effects, which vary depending on the inflammatory stimulus, cell type, disease model, and the specific AMPK modulator used. Conflicting data, particularly regarding NLRP3 inflammasome activation and Treg function, highlight the need for standardized protocols and rigorous analysis. While some AMPK-mediated inflammatory mechanisms are known, many remain unclear, hindering the development of targeted therapies. Furthermore, the interplay between AMPK and the gut microbiota, a key player in intestinal inflammation, requires further investigation, as it could significantly impact disease development and treatment.

AMPK and Autophagy

Autophagy serves as a cellular quality control system, ensuring that cellular homeostasis is maintained by degrading and recycling cellular components. It helps cells conserve energy for survival and provides protection against various stressors, particularly under glucose deprivation conditions.[93–95] In non-starved cells, autophagy involves the selective degradation of damaged cellular components.[96] Autophagy also plays a pivotal role in preserving intestinal balance, mediating the interplay between the gut microbiota and immune system and enhancing host defense against intestinal pathogens.

Patients with inflammatory bowel disease (IBD) exhibit defective autophagy, which is associated with mutation of the *ATG16L1* gene and impaired intestinal barrier integrity.[97]

When the nutrient supply is sufficient, mTORC1 phosphorylates UNC-51-like kinase 1 (ULK1) at Ser757, which disrupts the AMPK–ULK1 complex and impedes autophagy. AMPK has been found to have dual, opposing effects on autophagy. Activating AMPK with AICAR, A769662, and metformin inhibits autophagy,[98–102] whereas AMPK can phosphorylate and activate ULK1 at Ser317 and Ser777 to promote autophagy under glucose starvation.[102,103]

In CRC, autophagy can have either pro- or anti-tumorigenic effects, depending on the genetic mutation(s) present and the tumor type and stage.[104–106] Autophagy can bolster tumor development by stabilizing the fate of cells and enabling cellular tolerance to environmental stress. Conversely, it can induce apoptosis and cell death in tumor cells, highlighting its implications for CRC treatment strategies and treatment resistance.[107,108]

In several studies, CRC patients were found to have higher levels of various proteins, such as microtubule-associated protein 1 light chain 3 beta (LC3B), Beclin 1 (BECN1), lysosome-associated membrane glycoprotein 3 (LAMP3), and autophagy-related proteins (eg, ATG5 and ATG7).[105–107] It was also reported that suppression of ATG5 and ATG7 resulted in tumor-specific AMPK activation and consequent AMPK-induced cell cycle arrest and cell death, which suggests that these autophagy markers

have pro-tumorigenic activity and are potential targets in CRC therapy.[109–112] In addition, the level of ATG10 was found to be relevant to tumor metastasis.[113] However, in other studies, BECN1, LC3B, and ATG5 loss correlated with poor prognosis in CRC patients.[110] Furthermore, knocking down ATG5 or ATG7 has been shown to ameliorate apoptosis in CRC cells by suppressing autophagy, suggesting that autophagy has an anti-tumorigenic function.[114,115] These findings imply that autophagy has dual effects on CRC development. To sum up, they highlight the importance of AMPK in autophagy-related diseases and underscore its potential as a therapeutic target. However, more research is needed to understand its mechanisms and develop effective intervention for IBD and CRC.

AMPK also plays a role in smooth muscle contractility, particularly in functional gastrointestinal disorders like diabetic gastroparesis (DGP). DGP is a common complication of diabetes mellitus, marked by impaired gastric motility, which is associated with oxidative stress and apoptosis of gastric smooth muscle cells (GSMCs), impairing gastric emptying.[2] This GSMC apoptosis gradually increases in diabetes, driven by pathways such as PI3K-AKT-mTOR and AMPK-mTOR.[116] Recent studies have focused on AMPK's contribution in these effects, particularly under hyperglycemic conditions.[117] Interestingly, AMPK activity exhibits a biphasic pattern in diabetes: decreasing in early stages but subsequently increasing as the disease progresses.[118] This later increase in AMPK activity contributes to GSMC apoptosis by modulating key proteins, including p53 and Bcl-2.[119] Furthermore, AMPK promotes a metabolic shift from mitochondrial respiration to glycolysis, leading to cellular dysfunction and reduced muscle contraction.[2] In contrast to its detrimental role in DGP, AMPK can exert protective effects in cardiomyocytes, by maintaining cellular energy homeostasis and mitigating oxidative stress.[120] However, within smooth muscle itself, AMPK's actions can be complex. For instance, pro-inflammatory cytokines can induce hypercontractility in intestinal smooth muscle through an NF-κB/PKA pathway that inhibits AMPK and subsequently activates MLCK, ultimately increasing muscle contraction.[121] This apparent paradox, where AMPK can be both detrimental and protective in smooth muscle, highlights the need for further research to fully elucidate AMPK's precise role in DGP and to explore its potential as a therapeutic target.

AMPK and Gut Barrier Function

The gastrointestinal barrier, established by the epithelial lining, is part of the physical defense system that separates the body from the external environment. Tight junctions between epithelial cells regulate the paracellular transport of some nutrients and solutes across this barrier, while limiting the entry of noxious substances into the body. In this section, the involvement of AMPK in the regulation of paracellular permeability in the gut epithelium and in leakage-associated gastrointestinal diseases is discussed.

Tight junctions comprise a string of transmembrane molecules and dynamically aggregated cytoplasmic proteins. The transmembrane proteins that primarily contribute to epithelial integrity at cell–cell junctions include occludin, claudins, and junctional adhesion molecules (JAMs). These proteins bind to cytoplasmic anchoring proteins, such as zonula occludens-1 (ZO-1), cingulin, and afadin, which are connected to the cytoskeleton's filamentous actins and microtubules.[122]

In 2006, the first evidence of AMPK's involvement in the control of tight junctions was obtained using MDCK cells; it was found that AMPK can promote the reassembly of ZO-1 in the paracellular area.[123] Since then, several studies have shown that activating AMPK, via LKB1 or CaMKKβ activation, can enhance tight junction assembly and gut epithelial barrier integrity.[124–129] Recent research has identified several tight junction components as downstream targets of AMPK and two primary pathways that mediate this activity. First, the direct phosphorylation of tight junction proteins has been reported. AMPK-mediated phosphorylation of claudin-1 has been shown to prevent its degradation, and occludin binding was found to be promoted by AMPK-mediated phosphorylation of claudin-4.[130,131] However, further studies are required to validate this activity in gut epithelial cells. Second, the phosphorylation of scaffold proteins has been reported. AMPK-mediated phosphorylation of cingulin has been demonstrated to improve the tight junction–cytoskeleton interaction by enhancing microtubule binding while reducing actin affinity.[132,133] In addition, the actin-binding protein Girdin, which is crucial for maintaining apical polarity, can be directly phosphorylated by AMPK under energy deprivation conditions.[134] Furthermore, AMPK indirectly regulates tight junction permeability through the phosphorylation of afadin and myosin light-chain kinase (MLCK), which are involved in F-actin remodeling.[135,136] These mechanisms have primarily been observed in studies conducted with non-gut cells; however, these findings suggest that similar mechanisms occur in the

gut. In short, AMPK promotes tight junction assembly and preserves tight junction integrity in response to cellular stress via the phosphorylation of claudin and tight junction scaffold proteins.

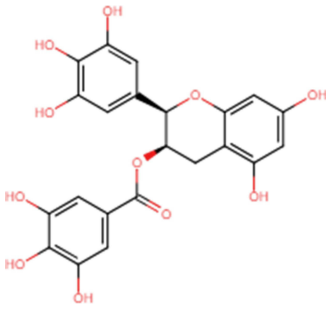
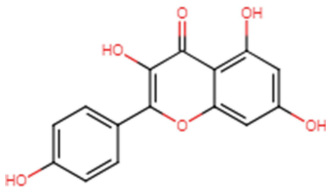
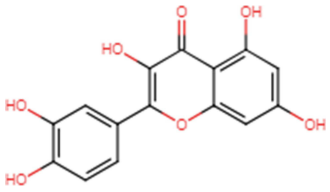
AMPK Activators

Natural Compounds

Given that AMPK plays a critical role in numerous bodily systems, researchers are actively exploring ways to stimulate its activity, particularly through the use of various natural compounds. These compounds are attractive due to their accessibility, potential for therapeutic development, and often lower toxicity compared to synthetic counterparts. Natural products, especially those used in traditional medicine, offer a rich source of bioactive compounds for managing various health conditions, including metabolic and inflammatory disorders. This is highlighted in several previous studies, which emphasizes the importance of bridging traditional knowledge with modern scientific research to unlock the therapeutic potential of these compounds.[137,138] However, these studies also acknowledge the limitations of natural compounds, such as variability in composition and potency, and the need for further research to validate their efficacy and safety. This aligns with the growing interest in AMPK activators for treating conditions like diabetes, inflammation, cancer, and metabolic disorders. A list of natural AMPK activators can be found in Table 1.

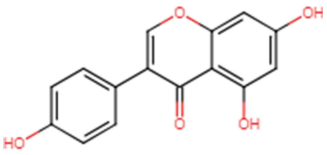
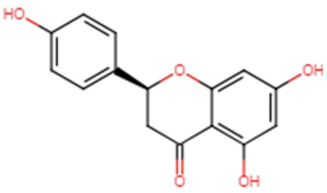
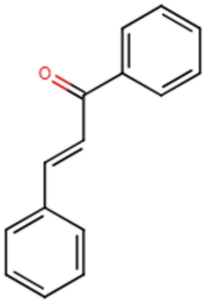
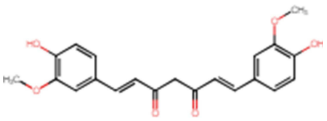
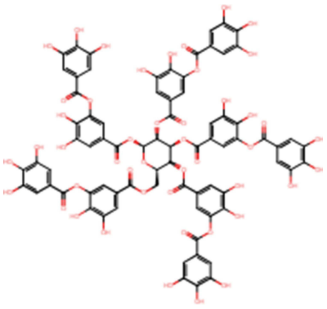
Polyphenols, particularly flavonoids, are promising natural AMPK activators. Flavonoids have been extensively studied due to the potential benefits they offer to people with various health conditions, including cancer, inflammation, autophagy, diabetes,

Table 1 AMPK Natural Activators

Compound Name	Natural Sources	Chemical Structure	Action(s)	References
Polyphenols				
Epigallocatechin gallate (EGCG)	Abundant in green tea extract		- Activate CaMKKβ and LKB1 - Suppress cancer cell proliferation through AMPK activation/COX-2 inhibition - Reduce inflammatory bowel disease risk	[139–144]
Kaempferol	Various vegetables and fruits include tomatoes, hops, red grapes, and strawberries		- Induce autophagy through AMPK and AKT signaling in SK-HEP-1 human hepatic cancer cells - Stimulate glucose uptake in skeletal muscle cells via an AMPK/AKT mechanism - Regulate hepatic lipid accumulation through activation of SIRT1/AMPK signaling	[145–147]
Quercetin	Mostly in citrus, red onions, berries, cherries, broccoli, leafy vegetables, spices, legumes, tea, and cocoa		- Improve lipid metabolism by modulating gut microbial and AMPK/PPARα signaling pathways in broilers - Modulate AMPK/SIRT1/NF-κB signaling to inhibit inflammatory/oxidative stress responses in diabetic high-fat diet-induced atherosclerosis in rat - Reduce cardiovascular and inflammatory bowel disease risk	[148–151]

(*Continued*)

Table 1 (Continued).

Compound Name	Natural Sources	Chemical Structure	Action(s)	References
Genistein	Mainly from soy product		- Attenuate the vascular smooth muscle cell senescence via an LKB1–AMPK-dependent mechanism - Activate SIRT1-AMPK signaling pathway to reduce fat accumulation in chicken hepatocytes	[152,153]
Naringenin	Commonly in citrus fruits such as grapefruit		- Alleviate NAFLD by increasing energy expenditure and regulating autophagy via activating AMPK directly (AMPKγ1) and indirectly (CaMKKβ/AMPK/ACC pathway)	[154]
Chalcone and derivatives	Various angiosperm, citrus fruits, apple, licorice		- Inhibit CFTR Cl^- channel activity via CaMKKβ-AMPK pathways	[155]
Curcumin	Mostly in the rhizome of *Curcuma longa* or turmeric and others *Curcuma spp.*		- Induce autophagy via activating the AMPK signaling in lung adenocarcinoma cells	[156]
Tannin and derivatives	Tea, coffee, cacao, peas, some leafy and green vegetables		- Induce senescence and impaired autophagy leading to cell death via SIRT1/AMPK signaling in HCC cells	[157]

(*Continued*)

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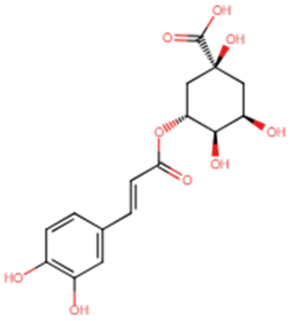
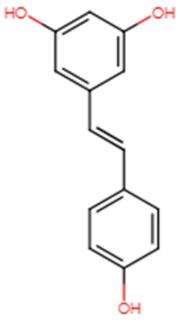
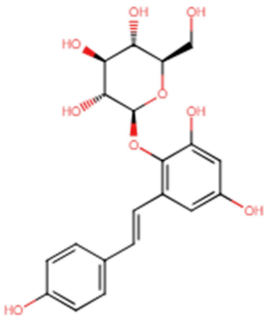
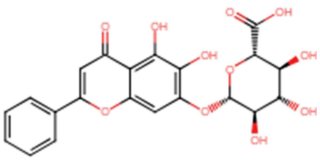
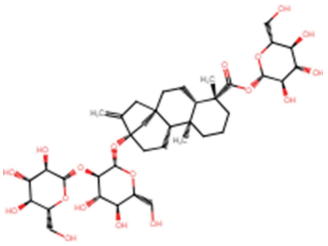
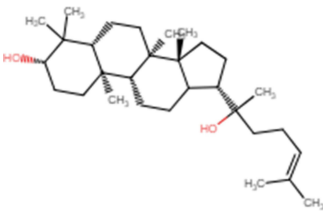
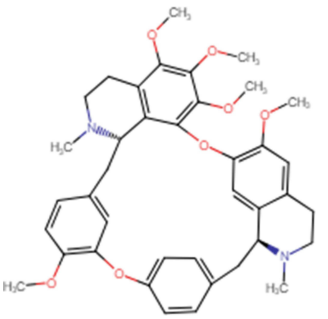
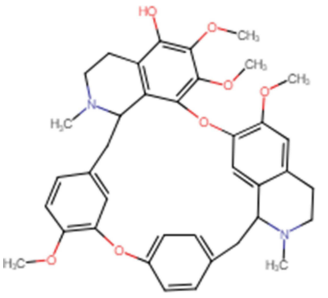
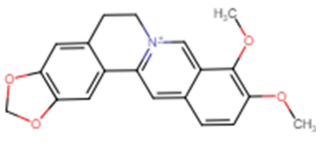
Table 1 (Continued).

Compound Name	Natural Sources	Chemical Structure	Action(s)	References
Chlorogenic acid	Artichokes, burdock, carrots, coffee beans, eggplants, grapes, kiwi, pears, plums, potatoes, and tea		- Suppress tumor growth via AMPK pathways	[158]
Resveratrol	Red wines, peanut, berry, and grapes		- Activate SIRT1-LKB1-AMPK pathway - Regulate insulin sensitivity via SIRT1/AMPK signaling pathway	[159]
Glycosides				
Stilbene glycoside	Berries, peanuts, wines and		- Alleviate inflammatory damage by mitophagy via AMPK-related PINK1/Parkin signaling - Promote mitochondrial autophagy via SIRT3/AMPK signaling in ischemic neuron	[160,161]
Flavonoid C-glycosides: baicalin	Mostly derived from the root of *Scutellaria baicalensis*, also known as Chinese skullcap		- Have anti-depressant effect through activating AMPK/PGC-1alpha pathway - Induce autophagy through the AMPK-mTOR pathway protects human skin fibroblasts	[162,163]

(*Continued*)

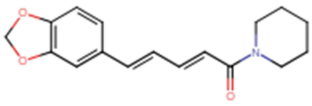
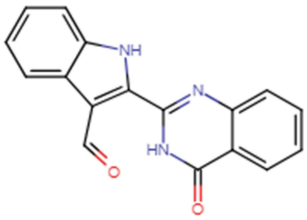
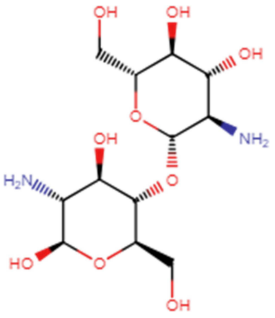
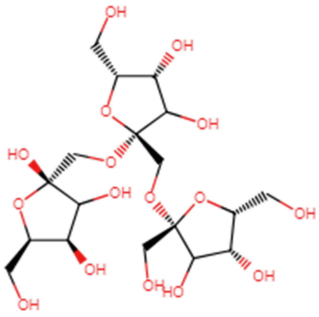
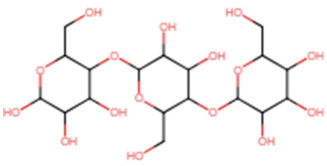
Table 1 (Continued).

Compound Name	Natural Sources	Chemical Structure	Action(s)	References
Stevioside	The leaves of *Stevia rebaudiana*		- Have anti-adipogenic effect and beta-oxidation by activating AMPK in 3T3-L1 cells - Reduce cardiovascular risk- Improved cardiometabolic risk in T2DM patient - Alleviate lipopolysaccharide-induced intestinal mucosal damage in broiler chickens	[164–167]
Ginsenoside	Mainly from ginseng		- Have anti-diabetic and anti-lipidemic effects in hepatic through activating AMPK and downstream GLUT4/ACC/G6Pase/SREBP signaling pathways.	[168]
Alkaloids				
Hernandezine	Traditional Chinese herbal medicine *Thalictrum spp.*		- Induce autophagic cell death in drug-resistant cancers through AMPK pathways - Alleviate hyperglycemia in T2D mouse models via AMPK/ACC signaling pathways	[169,170]
Thalidezine	Traditional Chinese herbal medicine *Thalictrum glandulosissimum*		- Induce autophagic cell death in HeLa cells through AMPK pathways	[171]
Berberine	Barberry, goldthread, grape, and turmeric		- Stimulate glycolysis and activation of the AMPK pathway - Reduce cholesterol and blood sugar levels in hypercholesterolemic and T2DM patients, respectively - Restore intestinal barrier function in IBD cats	[172–175]

(*Continued*)

https://doi.org/10.2147/DDDT.S507489

Table 1 (Continued).

Compound Name	Natural Sources	Chemical Structure	Action(s)	References
Piperine	Mainly black pepper (*Piper nigrum*), and other *Piper* species		- Activate CAMKK/AMPK signaling pathway to promote glucose uptake in skeletal muscle - Attenuate HFD-induced obesity by activating AMPK and PPARδ signaling pathway - Reduce oxidative stress and inflammation in hemodialysis patients	[176–178]
Bouchardatine	Plant *Bouchardatia neurococca*		- Increase the capacity of energy expenditure in adipose tissues and liver through SIRT1-LKB1-AMPK pathway	[179]
Oligosaccharides				
Chitosan oligosaccharides (COS)	Prepared from chitin, which is found in the exoskeletons of arthropods and insects, as well as the cell walls of fungi		- Prevent afatinib-induced barrier disruption and Cl^- secretion through AMPK, PI3K/AKT, and ERK signaling in T84 cells - Restore gut microbiota to improve antioxidant activity of CHD patients	[180,181]
Fructooligosaccharides (FOS)	Onions, garlic, leeks, asparagus, bananas, and chicory root		- Induce tight junction assembly via CaMKKβ-AMPK pathway in intestinal epithelial cells - Improve gut microbiota of IBD patient	[182,183]
Galactooligosaccharides (GOS)	Mainly from human/mammal milk		- Alleviate the small intestinal oxidative stress and dysfunction of LPS-challenged suckling piglets involving the AMPK pathway	[184]

obesity, and fatty liver disease.[185] The flavonoids epigallocatechin gallate (EGCG), kaempferol, quercetin, genistein, and naringenin are well-known examples of potent AMPK activators.[185,186] EGCG, found abundantly in green tea extract, has been shown to suppress cancer cell proliferation by activating AMPK and subsequently inhibiting cyclooxygenase-2 (COX-2) in HT-29 colon cancer cells.[139] Furthermore, EGCG can partially counteract insulin secretion by activating AMPK and mitigating the insulin-lowering effects of glutamate dehydrogenase in primary human myocytes.[140] EGCG can also activate CaMKKβ and LKB1, the upstream kinases of AMPK, by increasing cytosolic calcium and phosphorylation, respectively.[141–143] Kaempferol, a flavonol found in various plants (eg, grapes, kale, and strawberries), can activate AMPK, leading to enhanced glucose uptake in skeletal muscle, and induce autophagy by inhibiting mTOR in human hepatic cancer cells.[145,146] Moreover, kaempferol can reduce lipid accumulation and attenuate nonalcoholic fatty liver disease (NAFLD) via SIRT1/AMPK signaling in an in vivo mouse model of T2DM.[147] Quercetin, found in abundance in grapes, apples, and onions, has been shown to modulate the AMPK/SIRT1/NF-κB pathway, suppressing inflammation and oxidative stress in diabetic rats with atherosclerosis.[148] In addition, quercetin can activate AMPK via LKB1, stimulating peroxisome proliferator-activated receptor (PPAR)α expression and decreasing lipid accumulation in the abdominal fat of broiler chickens.[149] Similarly, genistein, a compound found in soy products, can activate AMPK through SIRT1 and LKB1, leading to autophagy and reduced lipid accumulation.[152,153] Naringenin from citrus fruits, especially grapefruit, has been found to increase phosphorylation directly at AMPKα and CaMKKβ to alleviate NAFLD and regulate autophagy.[154] Other polyphenols, including chalcone, curcumin, tannin, chlorogenic acid, and resveratrol, have also been demonstrated to activate AMPK, either directly or through its upstream kinases.[155–159] Clinical trials have investigated several natural compounds from this group, including EGCG and Quercetin. While EGCG has been studied for its impact on cognition, mood, and brain function, its mechanism of action remains unclear.[187] Quercetin's anti-inflammatory and antioxidant properties have also been explored in clinical trials. One study, using a supplement combining quercetin with resveratrol, pterostilbene, Morin hydrate, δ-tocotrienol, riboflavin, and nicotinic acid, demonstrated a reduction in cardiovascular risk factors.[150] Furthermore, both EGCG and quercetin have demonstrated a reduction in the risk of adverse outcomes for individuals with Inflammatory Bowel Disease.[144,151]

Glycosides, a class of compounds characterized by a sugar moiety linked to a non-sugar component, can effectively activate AMPK. Of particular note is the C-glycosides subgroup, which includes stilbene glycoside and flavonoid C-glycosides. Stilbene glycoside has demonstrated potential in mitigating neurodegenerative diseases and neuroinflammation by activating AMPK and modulating the SIRT3, PTEN-induced kinase 1 (PINK1)/Parkin, and Tet methylcytosine dioxygenase 2 (Tet2) signaling pathways.[160,161,188] Flavonoid C-glycosides, such as baicalin, which is found in members of the *Lamiaceae* plant family, can mediate autophagy through AMPK activation and downstream pathways, such as the PGC-1α and mTOR signaling pathways.[162,163] Additionally, other glycosides (eg, O-glycoside, stevioside, and ginsenoside) have been shown to activate AMPK and regulate fatty acid metabolism.[164,168,189] Regarding the application of these compounds, stevioside, commonly found in stevia, is a prominent and widely recognized substance in this group. It is used as a sugar substitute and has been shown to reduce cardiovascular risk. Studies supplementing individuals with T2DM with stevioside for 24 weeks have demonstrated improved cardiometabolic risk in diabetic patients with an increase in total caloric intake and a decrease in BMI, waist circumference, waist-hip ratio, and fat mass index in the obese group.[165,166] However, there is limited clinical research on its effects on gastrointestinal diseases, with most studies conducted on animals. For example, one study found that stevioside supplementation can alleviate lipopolysaccharide-induced intestinal mucosal damage through anti-inflammatory and antioxidant effects in broiler chickens.[167]

Alkaloids have also been shown to activate AMPK and thus have various biological effects. For example, hernandezine and thalidezine can induce autophagy, which indicates that they could potentially be utilized in cancer treatment.[169,171] Additionally, it has been suggested that due to their AMPK-stimulating activity, hernandezine, berberine, and piperine could be used to reduce glucose for alleviating diabetes symptoms.[170,172,176] Moreover, AMPK activation by alkaloids such as piperine and bouchardatine can contribute to reduce lipid metabolism, potentially alleviating obesity and metabolic disorders.[177,179] Clinical trials investigating this group of compounds are still limited. However, some promising findings have emerged. For instance, piperine, found in black pepper, has been shown to reduce oxidative stress and inflammation in hemodialysis patients when combined with turmeric.[178] Berberine, another compound in this group, has demonstrated cholesterol-lowering effects in patients with high cholesterol and can also reduce blood sugar levels in individuals with type 2 diabetes.[173,174] In regards to intestinal health, a study

in cats showed that berberine helped restore intestinal mucosal barrier function, suggesting a potential benefit for Inflammatory Bowel Disease (IBD).[175]

Oligosaccharides, including chitosan oligosaccharides (COS), fructooligosaccharides (FOS), and galactooligosaccharides (GOS), are prebiotics that can improve gut microecology and protect the gut barrier. COS, derived from chitin found in marine animal shells, have been shown to promote intestinal tight junctions by activating AMPK through the calcium-sensing receptor (CaSR)–phospholipase C (PLC)–inositol triphosphate (IP3) receptor pathway in T84 colon cancer cells.[127,180] Similarly, FOS can strengthen the intestinal barrier by activating AMPK through the CaSR–PLC–CaMKKβ pathway.[182] Additionally, GOS have been found to alleviate intestinal oxidative stress and dysfunction in LPS-challenged suckling piglets by activating AMPK and improving the expression of heme oxygenase-1 (HO-1) and nicotinamide adenine dinucleotide phosphate (NADPH).[184] Many compounds in this group are commonly used in supplements, leading to a considerable number of clinical trials. For example, research on FOS has shown its impact on gut microbiota, which in turn affects various conditions like IBD.[183,190] Similarly, chitosan oligosaccharide (COS) is widely used, particularly in supplements. Clinical trials have demonstrated that COS can modulate gut microbiota, leading to improved antioxidant activity and protection against coronary heart disease (CHD).[181]

While this is just a glimpse of the existing research on natural AMPK activators, it's clear that these compounds hold significant promise. Studying them not only deepens our understanding of metabolic regulation but also opens doors to new AMPK-based therapies and interventions for a wide range of health issues.

Synthetic Compounds and Repositioned Drugs

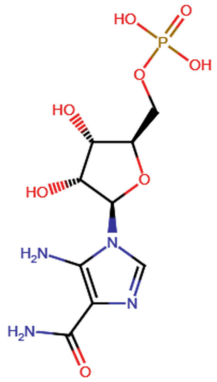
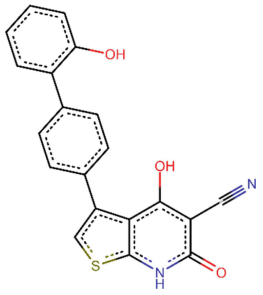
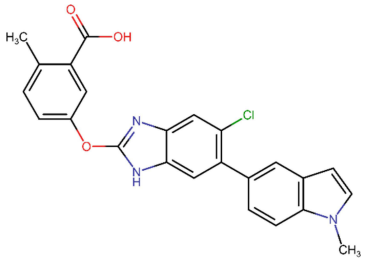
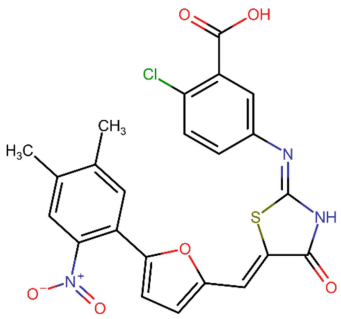
In recent years, synthetic compounds and small molecules have emerged as powerful tools for modulating AMPK activity. By targeting specific sites on the AMPK protein, these molecules can activate AMPK, leading to a cascade of cellular responses. These compounds offer a precise and controlled approach to study AMPK signaling and its potential therapeutic applications, particularly in intestinal diseases such as IBD and colorectal cancer. A list of synthetic AMPK activators is provided in Table 2.

Numerous synthetic compounds have been identified as AMPK activators. AICAR, a nucleotide analog, has been a cornerstone in AMPK research for decades. It is primarily known for its ability to activate AMPK by mimicking AMP, a key allosteric activator. However, AICAR's biological effects extend beyond AMPK modulation.[191] Several studies have demonstrated its potential in cancer therapy; it has been shown to induce differentiation of acute myeloid leukemia cells.[228] Additionally, it activates large tumor suppressor kinase 1 and 2 (Lat1 and Lat2) in AMPK-double-knockout murine embryonic cells, suggesting a broader range of cellular targets.[229] Despite its versatility, AICAR is still widely used as a positive control in AMPK-activation experiments, underscoring its reliability and significance in this field.[230] From a clinical perspective, AICAR shows therapeutic potential by enhancing glucose transport and strengthening barrier function, while simultaneously reducing inflammatory cell infiltration.[3,192]

A-769662 directly activates AMPK through an allosteric mechanism, bypassing the need for changes in AMP or ADP levels or upstream kinases.[193] With an EC_{50} of approximately 0.39 μM, it effectively stimulates AMPK activity.[231] Studies have demonstrated that A-769662 has anti-inflammatory properties, showing that it reduces LPS-induced inflammation in the heart and lungs and inhibits IL-6 expression in inflammatory arthritis.[232,233] Additionally, it can mitigate acute lung injury caused by sepsis through its AMPK-activating effect.[234] A-769662 also exhibits AMPK-independent effects. It can inhibit glucose uptake in adipocytes, suppress insulin-induced nitric oxide synthesis and AKT phosphorylation in endothelial cells, and enhance intracellular calcium and ATP release from astrocytes.[235–237] Collectively, A-769662 is a promising AMPK activator with a broader range of biological activities.

Compound 991, a benzimidazole derivative, is an even more potent AMPK activator than A-769662; it has an EC_{50} of approximately 0.09 μM and effectively activates AMPK through an allosteric mechanism.[231] Compound 991 exhibits selectivity for the β1 isoform of AMPK, leading to its phosphorylation and activation. Notably, it demonstrates a stronger preference for the γ2 isoform compared to the γ1 and γ3 isoforms, although it can also activate the γ1 and γ3 isoforms in skeletal muscle cells.[194] Furthermore, compound 991 has been shown to protect osteoblasts from dexamethasone-induced damage by activating AMPK.[238] In summary, compound 991's potency, selectivity, and ability to target various AMPK subunits make it a valuable tool for studying the mechanisms of AMPK in experimental settings.

Table 2 Synthetic Compounds and Repositioned Drugs

Compound name	Chemical structure	Action (s)	References
5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)		- Activate AMPK through an allosteric mechanism - Enhance glucose transport and gut barrier integrity - Decrease inflammatory cell migration	[3,191,192]
A-769662		- Activate AMPK through an allosteric mechanism - Prevent glucose transport in adipose tissue	[193]
Compound 991		- Activate β1 subunit of AMPK, leading to its phosphorylation and activation - Activate γ1, γ2, and γ3 subunits of AMPK - Protect osteoblasts from dexamethasone toxicity	[194]
PT-1		- Activate γ1 subunit of AMPK	[195]

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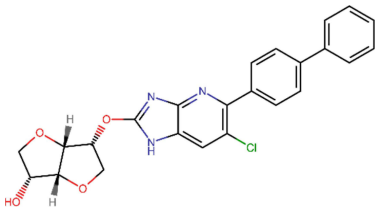
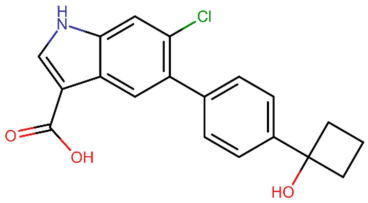
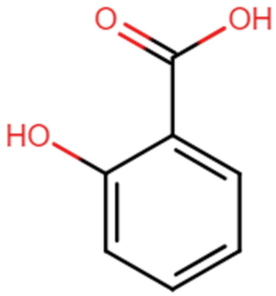
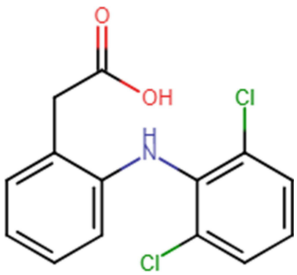
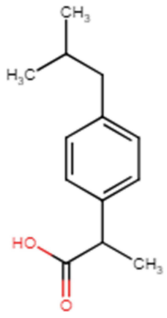
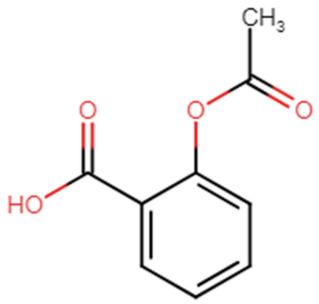
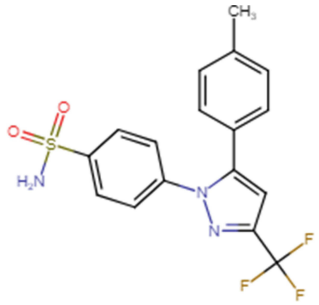
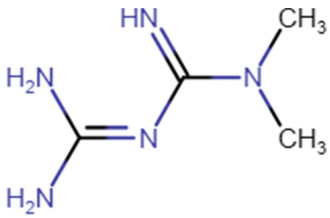
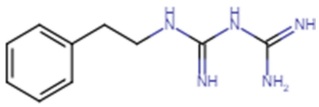
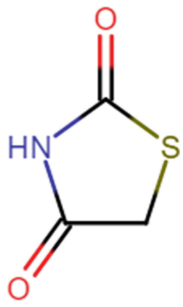
https://doi.org/10.2147/DDDT.S507489

Table 2 (Continued).

Compound name	Chemical structure	Action (s)	References
MK-8722		- Activate β1 subunit of AMPK - Inhibit pancreatic cancer cell growth and regulate fat metabolism in ovarian cancer cells	[196,197]
PF-06409577		- Activate AMPK through an allosteric mechanism - Prevent kidney cyst formation and reduce CFTR activity by targeting the mTOR pathway	[198,199]
NSAIDs			
Salicylic acid		- Enhance insulin sensitivity and inhibit lipogenesis in liver when combined with metformin	[200]
Diclofenac		- Inhibit cAMP-induced chloride secretion via AMPK activation in intestinal cells	[201]
Ibuprofen		- Activate AMPK in liver and neuronal cells	[202]

(*Continued*)

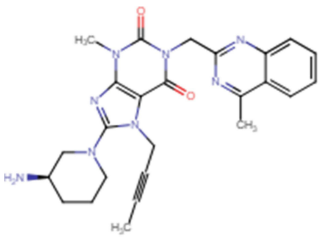
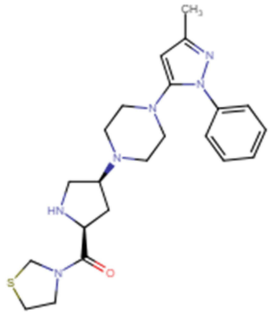
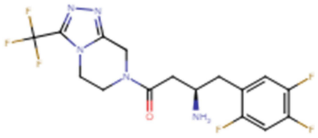
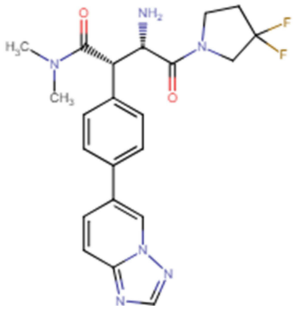
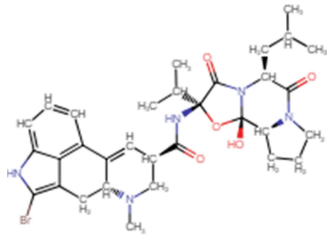
Table 2 (Continued).

Compound name	Chemical structure	Action (s)	References
Aspirin		- Suppress breast cancer cell proliferation by AMPK-mediated mTORC1 inhibition and autophagy	[203]
Celecoxib		- Inhibit the proliferation and survival of CML by activating the AMPK/β-catenin/mTORC1/2 signaling pathway	[204]
Antidiabetic drugs			
Metformin		- Enhance AMPK activity by elevating AMP levels and inhibiting mitochondrial respiration - Promote LKB1-dependent AMPK phosphorylation and prevent its dephosphorylation by protein phosphatase - Suppress NF-κB, thereby exerting anti-inflammatory effect - Interact with PTEN2 to suppress the activity of v-ATPase, thereby preventing AMPK activation	[205–209]
Phenformin		- Enhance keratinocyte differentiation in a skin carcinogenesis mouse model - Reduce proinflammatory cytokines in a skin cancer mouse model via down regulation of c- Myc expansion - Inhibit cell growth, induce apoptosis, and promote autophagy in cholangiocarcinoma and breast cancer cells - Inhibit T- ALL development via AMPK activation	[210–214]
Thiazolidinedione		- Enhance insulin sensitivity by regulating the expression and release of adiponectin - Trigger AMPK and inhibits platelet aggregation	[215,216]

(*Continued*)

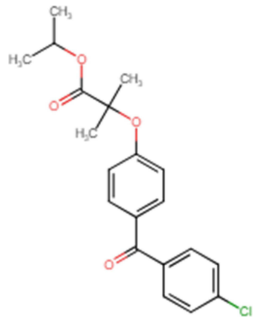
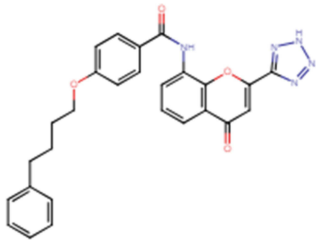
https://doi.org/10.2147/DDDT.S507489

Table 2 (Continued).

Compound name	Chemical structure	Action (s)	References
Dipeptidyl peptidase-4 inhibitors	 Linagliptin  Teneligliptin  Sitagliptin  MK-0626	- Downregulate the expression of hepatic lipogenic gene in NAFLD models - Reduce adipose tissue inflammation and fatty liver by modulating adiponectin and AMPK - Improve endothelial function and reduce vascular aging through AMPK/SIRT1/Nrf2 activation - Mitigate the symptoms of colitis caused by acetic acid through the regulation of AMPK/SIRT1/PGD-1a and JAK2/STAT3 pathways	[217–222]
Bromocriptine		- Improve glycemic control and insulin sensitivity in patients with type 2 diabetes - Decrease the levels of GLUT2, thereby improving insulin sensitivity and decreasing fat accumulation in the liver - Inhibit CaMKK2 phosphorylation, leading to AMPK activation in prostate cancer	[223–225]

(*Continued*)

Table 2 (Continued).

Compound name	Chemical structure	Action (s)	References
Fenofibrate		- Enhance AMPK/eNOS signaling in HUVECs	[226]
Pranlukast		- Prevent cyst enlargement in renal epithelial cells through CaMKKβ/AMPK/mTOR-mediated mechanism	[227]

PT-1 directly activates AMPK (independent of the AMP or ADP level) by binding to the γ1 isoform within the kinase domain.[236] This interaction stimulates all three AMPK subunits. PT-1 has an EC_{50} of approximately 0.3 μM.[239] While PT-1 stimulates all three γ isoforms, it has been observed to inhibit the respiratory chain in human cells, suggesting potential off-target effects.[195]

MK-8722 is a highly potent small-molecule AMPK activator that acts in an allosteric manner and targets the β1 isoform.[194,238] MK-8722-mediated activation leads to increased AMPK phosphorylation and activity.[196,197] Interestingly, MK-8722 exhibits anti-cancer properties. It suppresses the proliferation, migration, and invasion of pancreatic cancer cells and modulates lipid metabolism in epithelial ovarian cancer cells.[240,241] Additionally, MK-8722 induces early-stage autophagy; therefore, it may play a role in cancer cell death.[241]

PF-06409577 is a potent and selective allosteric activator of AMPK that directly binds to AMPK and induces strong and sustained AMPK activation.[196,197] Its EC_{50} for AMPK activation is approximately 7 nM, and it stimulates all three AMPK subunits.[198,199] This molecule also inhibits renal cyst formation and cystic fibrosis transmembrane conductance regulator (CFTR) activity via the mTOR pathway.[242]

Additionally, drug repositioning has gained significant attention as a strategy to identify novel AMPK activators. By leveraging these approaches, researchers have discovered a diverse range of compounds that can activate AMPK. Repositioned drugs also are listed in Table 2.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylate are available as over-the-counter (OTC) analgesics and anti-inflammatory agents. Salicylic acid, an active metabolite of acetyl-salicylic acid (aspirin), has been documented to activate AMPK; hence, it could potentially be used to mitigate intestinal inflammation via multiple pathways.[243–245] In addition, aspirin has been shown to inhibit breast cancer cell proliferation by AMPK-dependent mTORC1 inhibition and autophagy activation.[203] Interestingly, the combination of metformin and salicylate promotes insulin sensitivity and inhibits lipogenesis in the liver via AMPK activation.[200] Moreover, salicylate can suppress CRC metastasis via AMPK-mediated inhibition of c-MYC.[246] Therefore, it has been shown that this well-known and popular drug (salicylate) can modulate the cell's energy status by activating AMPK. Other NSAIDs, such as diclofenac and ibuprofen, reportedly

activate AMPK in intestinal, liver, and neuronal cells.[201,202] In addition, celecoxib halts chronic myelogenous leukemia (CML) cell proliferation and survival via AMPK/β-catenin/mTORC1/2 pathway.[204]

Metformin, a biguanide widely used as a first-line antidiabetic drug, activates AMPK through multiple mechanisms. Initially, it was thought to indirectly increase AMPK activity by increasing AMP levels and inhibiting mitochondrial respiration.[205] However, recent studies have revealed more complex interactions. Metformin can directly modulate the AMPK heterotrimeric complex, promoting its phosphorylation by LKB1 and preventing its dephosphorylation by protein phosphatase.[206,207] This activity contributes to metformin's anti-inflammatory effects, mediated by the inhibition of NF-κB.[208] Extending beyond its primary anti-hyperglycemic and anti-inflammatory functions, metformin has also been found to have metabolic, cardioprotective, neuroprotective, anti-cancer, and anti-microbial activity.[208] It was recently demonstrated that at a low dose, metformin binds to the presenilin enhancer 2 (PEN2) subunit of γ-secretase to form a complex that inhibits vacuolar-type ATPase (V-ATPase) and AMPK activation, independent of AMP levels.[209] In addition to its AMPK-activating effects, metformin has shown promise as a therapeutic agent for the treatment of a range of health conditions, including diabetes, inflammation, and liver disease, as well as for gut microbiota regulation.[247–250] Like metformin, phenformin can activate AMPK by increasing the intracellular AMP level. However, its potential extends beyond glucose regulation.[251] Studies have demonstrated that phenformin has anti-tumor effects, particularly in skin and breast cancers. For example, it enhanced keratinocyte differentiation in a mouse skin carcinogenesis model and suppressed pro-inflammatory cytokines in keratinocytes via downregulation of *c-Myc* expression.[210,211] Moreover, phenformin has been shown to inhibit cell growth and promote apoptosis and autophagy in cholangiocarcinoma and breast cancer cells.[212,213] In another study, it was found that oral phenformin therapy suppressed the progression of T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) by activating AMPK in a cell-autonomous manner.[214] Despite its promising effects, phenformin's clinical use is limited due to its association with lactic acidosis, a severe side effect.[211] As a result, it remains primarily a research tool for studying AMPK activation.[252] Thiazolidinedione (TZD) is an insulin-sensitizing agent used in the treatment of T2DM that binds to the nuclear receptor PPARγ in adipocytes and thus stimulates adipogenesis.[253] This action enhances insulin sensitivity by upregulating the expression and release of adiponectin, an adipokine that activates AMPK.[215] Two other members of the same class of drugs, rosiglitazone and pioglitazone, also trigger AMPK activation, and platelet aggregation is inhibited in these cases. Hence, AMPK is a potential therapeutic target due to this anti-platelet aggregation activity of rosiglitazone and pioglitazone.[216] Finally, it has been revealed that dipeptidyl peptidase-4 (DPP4) inhibitors, the antidiabetic drugs that prevent the cleavage of incretin hormones by DPP4, increase the level of AMPK and suppress hepatic lipogenic gene expression in NAFLD models.[217–219] Sitagliptin has been shown to inhibit adipose tissue inflammation and fatty liver disease by regulating adiponectin and AMPK levels.[220] Saxagliptin has been found to improve endothelial aging by modulating the AMPK/SIRT1/nuclear factor erythroid 2-related factor 2 (Nrf2) pathway.[221] Additionally, linagliptin has demonstrated efficacy in alleviating acetic acid-induced colitis through the regulation of the AMPK/SIRT/peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) and JAK2/STAT3 pathways.[222]

Bromocriptine, a dopamine D2 receptor agonist used in patients with prolactinomas, acromegaly, Parkinson's disease, and hyperprolactinemia-associated conditions, has been shown to effectively control blood glucose levels and improve insulin resistance in individuals with T2DM.[223] It lowers GLUT2 levels and postprandial insulin resistance, thereby relieving fatty liver conditions that involve AMPK activation.[224] Additionally, bromocriptine has been found to reduce the phosphorylation of CaMKK2 and thus activate it and subsequently AMPK in a prostate cancer model.[225]

Fenofibrate, an agonist of PPARα, is prescribed for managing dyslipidemia and slowing the progression of atherosclerotic events in patients with T2DM.[254,255] It reportedly activates AMPK and upregulates endothelial nitric oxide synthase (eNOS) in human umbilical vein endothelial cells (HUVECs).[226]

Pranlukast, a cysteinyl leukotriene receptor 1 (CysLT1) antagonist, is indicated for the treatment of asthma due to its capacity to inhibit chloride secretion in bronchial epithelial cells.[256] In this example of drug repositioning, pranlukast has been shown to inhibit cyst progression in renal epithelial cells via activation of the CaMKKβ/AMPK/mTOR pathway.[227]

In conclusion, AMPK activators, including natural compounds, synthetic compounds, and repositioned drugs, hold great promise as therapeutic agents for various diseases, especially those affecting the gastrointestinal tract. By activating AMPK, these compounds can modulate cellular metabolism, reduce inflammation, and promote tissue repair. Further research is needed to fully elucidate the mechanisms of action of these compounds and to identify novel AMPK

activators with improved efficacy and safety profiles. Ultimately, the development of effective AMPK activators could significantly impact the treatment of a wide range of diseases.

Future Perspectives and Conclusions

AMPK, a key regulator of cellular energy stores, is essential for intestinal health. Beyond its established metabolic role, emerging evidence suggests that AMPK exerts profound effects on intestinal cell physiology, influencing cell proliferation and differentiation, inflammation, autophagy, and barrier integrity. AMPK is activated by changes in the AMP-to-ATP ratio, which lead to conformational changes that activate the kinase and trigger various physiological activities. AMPK plays a dual role in intestinal diseases, acting as both a tumor suppressor and promoter. It can act as a tumor suppressor by regulating oncogenic metabolic processes and promoting cell cycle arrest. Conversely, it can act as a tumor promoter by activating oncogenic signaling. In the contexts of inflammation and autophagy, AMPK can influence both pro-inflammatory and anti-inflammatory signals, affecting cytokine production and inflammasome activation. Moreover, AMPK plays a crucial role in immune cell function, regulating T-cell metabolism and macrophage polarization. To maintain the integrity of the gut barrier, AMPK promotes the assembly of tight junctions and preserves their integrity by phosphorylating claudin and tight junction scaffold proteins. These actions are crucial for preventing leakage-associated gastrointestinal diseases. Research on the role of AMPK in gastrointestinal diseases remains limited. A key challenge is the context-dependent nature of AMPK's activity, as it can function as both a tumor suppressor and a tumor promoter. A more thorough understanding of the specific conditions that determine its role in different tissues and disease states is crucial. Future studies should focus on identifying these contextual cues—including genetic mutations, microenvironmental factors, and upstream signaling pathways—to better predict and ultimately control AMPK's effects. Furthermore, the precise mechanisms involved often remain unclear, likely because most experiments are conducted in vitro or in vivo, limiting the ability to observe the complex interplay of factors present in actual disease. Undiscovered crosstalk with other signaling pathways may also contribute to this complexity. Finally, the relatively short duration of some studies may not fully capture the long-term dynamics of chronic gastrointestinal diseases, highlighting the need for more longitudinal research.

Given the benefits associated with AMPK activation, numerous AMPK activators have been developed—both natural and synthetic. These activators have shown promising effects that can potentially be harnessed for the treatment of various health conditions, including diabetes, inflammation, cancer, and metabolic disorders. While the therapeutic potential of AMPK activation is promising, several challenges need to be overcome to fully realize its clinical applications. One major hurdle is AMPK's widespread expression throughout the body, raising concerns about potential off-target effects. To address this, the development of tissue- or cell-specific AMPK modulators is crucial. This may involve exploring novel drug delivery systems, such as nanotechnology-based approaches, which offer enhanced bioavailability, targeted delivery, and controlled release of therapeutic agents.[257] Additionally, a more comprehensive understanding of the complex molecular mechanisms underlying AMPK's diverse actions is essential. This knowledge will enable the design of highly specific and effective AMPK-targeted therapies, minimizing the risk of unintended consequences. A critical, yet often overlooked, aspect is the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of AMPK activators, especially those derived from natural compounds. Many natural AMPK activators lack comprehensive PK/PD data, hindering their clinical translation. Future studies must prioritize establishing the absorption, distribution, metabolism, and excretion (ADME) properties of these compounds, along with their dose-response relationships and duration of action. This includes determining optimal routes of administration, assessing bioavailability, and identifying potential drug-drug interactions. Preclinical studies should rigorously evaluate potential toxicities associated with long-term or excessive AMPK activation, optimizing dosage regimens and monitoring for adverse effects. In addition, anticipating and overcoming potential resistance mechanisms, particularly in cancer, will be essential for the long-term efficacy of AMPK-based therapies. Future investigations should explore combination therapies and strategies to prevent or reverse resistance development, ultimately maximizing the therapeutic benefit of AMPK activation. Finally, the development of new drugs, whether from novel compounds or through repurposing existing ones, is a complex and expensive process. It requires a rigorous approach that encompasses all stages of drug development, from in silico studies

and in vitro experiments to in vivo testing and clinical trials. This comprehensive process demands significant financial investment and sustained effort to ensure the safety and efficacy of new therapies.

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Author Contributions

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

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Disclosure

The authors report no declarations of interest.

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