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Review

The Endocannabinoid System in Aging: Physiological Changes and Therapeutic Opportunities

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Abstract

Aging is accompanied by progressive molecular damage, chronic low-grade inflammation, metabolic dysfunction, and declining tissue homeostasis. The endocannabinoid system (ECS)—comprising endocannabinoids, their receptors and other molecular targets, and the enzymes responsible for ligand synthesis and degradation—regulates neural activity, immune responses, energy metabolism, autophagy, and tissue repair. This review summarizes age-associated changes in ECS components across the brain and peripheral organs and evaluates their potential contributions to age-related disease. Although many studies indicate reduced endocannabinoid tone or receptor abundance with age, the direction and functional consequences of these changes are strongly dependent on tissue, cell type, sex, and disease state. In the aging brain, preserved or enhanced cannabinoid signaling may support synaptic plasticity and limit neuroinflammation, whereas excessive peripheral cannabinoid receptor type 1 (CB1) signaling may promote insulin resistance, steatosis, and metabolic dysfunction. Preclinical evidence supports selective modulation of CB1, cannabinoid receptor type 2 (CB2), and related targets, but clinical evidence in older adults remains limited. Diet and exercise also influence ECS activity and may offer lower-risk approaches to restoring physiological balance. Overall, therapeutic strategies should prioritize receptor selectivity, tissue targeting, dose, route, age, sex, and comorbidities rather than generalized ECS activation or inhibition.

Keywords: aging; cannabinoids; endocannabinoid system; inflammaging; metabolism; metabolic dysfunction

1. Introduction

Aging is characterized by the progressive accumulation of cellular and tissue damage, accompanied by the buildup of cellular debris, chronic inflammatory responses, functional decline, and metabolic reprogramming. These changes occur at every level of biological organization, from damaged molecules and dysfunctional cells to impaired tissues and organs, ultimately resulting in a decline in overall organismal function [1].

Although aging is a multifactorial process, many of the molecular and cellular changes that accompany it can be organized within the framework of the hallmarks of aging. The original framework identified nine interconnected processes that contribute to the progressive loss of physiological integrity with age [2], and its recent revision expanded this model to twelve hallmarks: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis [3]. These processes are not independent; rather, they form an interconnected network in which deterioration of one component can initiate or amplify changes in others. For example, genomic and mitochondrial damage can promote cellular senescence and inflammatory signaling, whereas impaired proteostasis and autophagy facilitate the accumulation of damaged macromolecules and organelles. Similarly, persistent senescent cells contribute to altered intercellular communication and chronic inflammation through the senescence-associated secretory phenotype (SASP), while age-associated changes in nutrient sensing, stem-cell function, and the microbiome further reduce the capacity of tissues to maintain homeostasis and recover from physiological stress. Thus, aging is increasingly viewed not as the consequence of a single dominant mechanism but as the progressive failure of interacting cellular maintenance, metabolic, regenerative, and communication systems [3].

Several homeostatic systems counteract the physiological processes underlying aging and disease. While the nervous system provides rapid responses to physiological disturbances, the endocrine and immune systems coordinate short-, medium-, and long-term homeostatic responses, with the respiratory, circulatory, renal, and integumentary systems serving as major effectors in maintaining physiological stability. Importantly, not all organs and physiological systems age at the same rate; current evidence suggests that the circulatory and endocrine systems exhibit particularly pronounced age-related decline [4,5].

One homeostatic regulatory network that receives comparatively little attention in the context of aging is the endocannabinoid system (ECS). The ECS comprises three core elements: endogenous lipid mediators, principally anandamide (N-arachidonoylethanolamine; AEA) and 2-

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arachidonoylglycerol (2-AG); cannabinoid receptors, especially cannabinoid receptors type 1 (CB1) and cannabinoid receptor type 2 (CB2); and enzymes that synthesize and degrade these ligands. Diacylglycerol lipases α and β (DAGLα/β) generate 2-AG, whereas monoacylglycerol lipase (MAGL) hydrolyzes it to arachidonic acid and glycerol. N-Acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) contributes to AEA synthesis, and fatty acid amide hydrolase (FAAH) degrades AEA to arachidonic acid and ethanolamine [6]. AEA and 2-AG can function as retrograde synaptic messengers [7]. Structurally related N-acylethanolamines share elements of AEA metabolism and engage overlapping molecular targets [8]; they are discussed only where they inform age-related ECS regulation.

CB1 and CB2 are G-protein-coupled receptors with complex, context-dependent signaling. CB1 is abundant in the central nervous system, particularly in axons and presynaptic terminals, and is also expressed in glial cells and peripheral tissues [9]. CB2 is enriched in microglia and circulating immune-cell populations and is expressed in several peripheral organs. Although CB2 expression is often increased in activated inflammatory cells and in inflammatory and neurodegenerative conditions, receptor activation generally suppresses pro-inflammatory signaling and cytokine production. Thus, increased CB2 expression in diseased tissues may reflect both accumulation or activation of CB2-expressing immune cells and a compensatory negative-feedback response aimed at limiting inflammation [10]. CB1 may exert similar anti-inflammatory effects where it is expressed. Receptor abundance varies substantially among tissues, developmental stages, cell states, and pathological conditions [11].

Although CB1 and CB2 are the canonical cannabinoid receptors, endocannabinoids also interact with numerous additional molecular targets, including transient receptor potential vanilloid 1 (TRPV1), orphan GPCRs such as GPR18, GPR19, GPR55 (sometimes referred to as CB3), and GPR119, as well as the nuclear receptors peroxisome proliferator-activated receptor α (PPARα) and PPARγ [12]. Furthermore, both CB1 and CB2 form homo- and heterodimers with other receptors. CB1 has been shown to heterodimerize with dopamine D2, μ-opioid (MOR), orexin-1 (OX1), serotonin 5-HT2A, and adenosine A2A receptors, thereby modulating numerous aspects of brain function [13,14,15]. Similarly, CB2 forms heteromers with N-methyl-D-aspartate (NMDA) receptors and several other GPCRs, contributing to immune regulation, neuroprotection, and anti-inflammatory signaling [15,16]. Additional receptor interactions likely remain to be identified. For example, CB1 may also heterodimerize with the delta-opioid receptor (DOR), as subthreshold concentrations of CB1 ligands significantly enhance DOR signaling in the cerebral cortex [17].

The ECS plays a fundamental role throughout human life, from fertility, implantation, and embryonic development to the regulation of cognition, emotion, mood, sleep, appetite, energy metabolism, and immune function [18,19,20,21]. It intersects with several hallmarks of aging and may therefore influence aging through multiple mechanisms rather than a single pathway. ECS signaling has been linked to altered nutrient sensing and mitochondrial function through its effects on cellular metabolism and energy homeostasis, while modulation of autophagy and proteostasis may influence the accumulation of damaged cellular components [22]. The ECS also regulates cellular senescence, stem-cell function, and intercellular communication, particularly through its effects on inflammatory and immune signaling [23,24]. These actions are especially relevant to chronic inflammation, a major integrative hallmark of aging, as cannabinoid signaling can modulate cytokine production and immune-cell activity. Thus, age-related alterations in ECS activity may affect several interconnected hallmarks of aging, providing a mechanistic basis for its potential role in healthy aging and age-related disease.

Collectively, the available evidence suggests that the ECS is an important regulator of healthy aging and that disruption of endocannabinoid signaling may contribute to the premature onset of age-related diseases and accelerate the aging process. In this review, we summarize current knowledge regarding age-associated alterations in the ECS and their potential contribution to healthy aging and age-related pathologies.

2. Age-Related Physiological and Pathological Changes in the ECS

The ECS is a vital homeostatic regulator that supports our health through antioxidant and anti-inflammatory actions, as well as by facilitating the clearance of misfolded and damaged macromolecules [22]. Although the antioxidant effects of cannabinoids are well established [25], there is debate about whether cannabinoid receptors are necessary for these properties. *In vitro* studies have demonstrated that certain cannabinoids can protect cultured neurons against oxidative injury through CB1-independent mechanisms [26]. Separately, N-arachidonoyldopamine (NADA) has been shown to possess antioxidant and neuroprotective properties in experimental neuronal models. Conversely, in astrocytes, cannabinoids mitigated oxidative damage in a CB1 receptor-dependent manner [27].

The clearance of malfunctioning macromolecules may rely on activation of CB1 receptors located on lysosomes and endosomes. At physiological levels, endocannabinoids (eCBs) enhance lysosomal stability and integrity [28]. Autophagy, a crucial process for molecular turnover, appears to be influenced by the ECS. Both endo- and phytocannabinoids (pCBs) induce autophagy in various cancer cells, partially through CB1 receptor activation [29,30,31]. Altered autophagosomal and lysosomal turnover has been observed in healthy tissues of Cnr1−/− mice [22]. Additionally, the

CB2 receptor may play a key role in autophagy, as its inhibition in spinal neurons reduced this process [32] (Fig. 1A).

Aging is accompanied by gradual and often organ-specific functional decline, together with substantial remodeling of ECS components. Several animal and human studies report age-associated changes in circulating or tissue endocannabinoids; however, the direction and magnitude vary by ligand, tissue, sex, metabolic state, and analytical method [33,34,35] (Fig. 1B).

To identify recurring patterns, we surveyed studies that combined aging-related terms with measures of gene expression, RNA sequencing, protein abundance, or ECS components. Approximately 30 relevant studies were identified. Despite marked tissue specificity, several trends emerged. CB1 protein declined in the reproductive tract of aged mice, whereas TRPV1, FAAH, and DAGLβ increased [36]. Reduced CB1 expression has also been reported in the aged small intestine and in selected brain regions, whereas other brain regions show unchanged or even increased expression, and components of the ECS also undergo complex age-dependent changes in the female reproductive tract [37,38,39]. PPARα expression declined in several metabolic and immune contexts, including aged rat kidney, heart, and liver and human monocytes [40,41,42,43]. Serotonergic signaling generally decreased with age [44], and Adora3 expression declined in aged mouse heart [45]. These patterns should be interpreted as tissue-specific observations rather than evidence of uniform systemic ECS decline.

We also examined the Human Cell Aging Transcriptome Atlas (HCATA; https://www.htcatlas.org), which integrates single-cell RNA-sequencing datasets from 76 publications, encompassing approximately 92 million cells and 3475 tissue-level samples from more than 50 tissue types across ages 0–103 years [46]. Across the tissues examined, *CNR1*, *CNR2*, *TRPV1*, *GPR119*, *GABBR1–3*, and *ADORA1/3* showed no significant age-associated change.

Several other receptor-related genes exhibited cell-type-specific regulation. *GPR55* was upregulated in CD4+ and CD8+ T cells and pancreatic α-cells, whereas *TRPV3* was upregulated in the whole-brain dataset. *PPARG* was downregulated in CD4+ T cells and hepatocytes but modestly upregulated in excitatory neurons. *PPARA* was downregulated in monocytes. *HTR1A*, which encodes the 5-hydroxytryptamine receptor 1A, was upregulated in neurons and oligodendrocytes but downregulated in endocrine and pancreatic cell populations.

Genes involved in endocannabinoid metabolism were also regulated in a cell-type-specific manner. *MGLL* gene encoding MAGL enzyme was downregulated in skeletal muscle cells and pancreatic α-cells but moderately upregulated in oligodendrocytes. N-acyl phosphatidylethanolamine phospholipase D (*NAPEPLD*), *FAAH1*, and *FAAH2* were downregulated in oligodendrocytes. *DAGLA* and *DAGLB* were downregulated in M2 macrophages, and *DAGLA* was reduced in a heterogeneous all-cell dataset containing endothelial, pulmonary, immune, and epithelial populations.

Thus, HCATA does not support a universal age-associated reduction in every ECS component. Rather, it reveals a predominant—but heterogeneous—decline in selected receptors and metabolic enzymes, with the strongest changes in immune and neural populations (Fig. 1B). These findings support the hypothesis that impaired ECS signaling may contribute to inflammaging and neurodegeneration, while emphasizing that causal relationships remain to be established.

A recent study reported lower baseline plasma concentrations of anandamide (AEA) and the endocannabinoid-like N-acylethanolamine docosatetraenylethanolamide (DEA) in older adults (55–71 years) compared with younger adults (21–24 years). Linoleoylethanolamide (LEA) concentrations were also lower in older adults, but relative to middle-aged adults (25–54 years). No statistically significant age-group differences were observed for 2-arachidonoylglycerol (2-AG), palmitoylethanolamide (PEA), stearoylethanolamide (SEA), or oleoylethanolamide (OEA) [35]. The following sections examine age-associated ECS changes across organs in rodents and humans.

2.1 Brain

The ECS contributes to synaptic plasticity, adult neurogenesis, and glial regulation and therefore may influence several processes that become compromised during brain aging. Endocannabinoids function as signaling molecules in neural progenitor cells during both embryonic development and adulthood [47]. Activation of cannabinoid receptors can promote progenitor-cell proliferation, neurogenesis, and neuronal diversification [48,49,50]. Proliferative and neurogenic responses to excitotoxic stress also depend partly on CB1 signaling, and deletion of CB1 impairs neurogenesis in mice [51,52].

The ECS also regulates synaptic activity and neuronal survival. Its components vary among brain regions and neuronal subtypes; in the hippocampus, for example, CB1 expression is substantially higher in GABAergic interneurons than in glutamatergic neurons [53]. CB1-mediated retrograde signaling suppresses presynaptic neurotransmitter release and thereby regulates neuronal excitability and synaptic transmission [7]. During excessive glutamatergic activity, endocannabinoid signaling can function as a circuit breaker that limits excitotoxic neuronal injury [54]. The ECS may additionally influence age-sensitive neurotrophic pathways. Brain-derived neurotrophic factor (BDNF) expression declines with age, whereas cannabinoid-receptor agonists can increase BDNF expression in experimental models, and restoration of BDNF signaling improves synaptic plasticity in aged animals [55,56,57]. Observa-

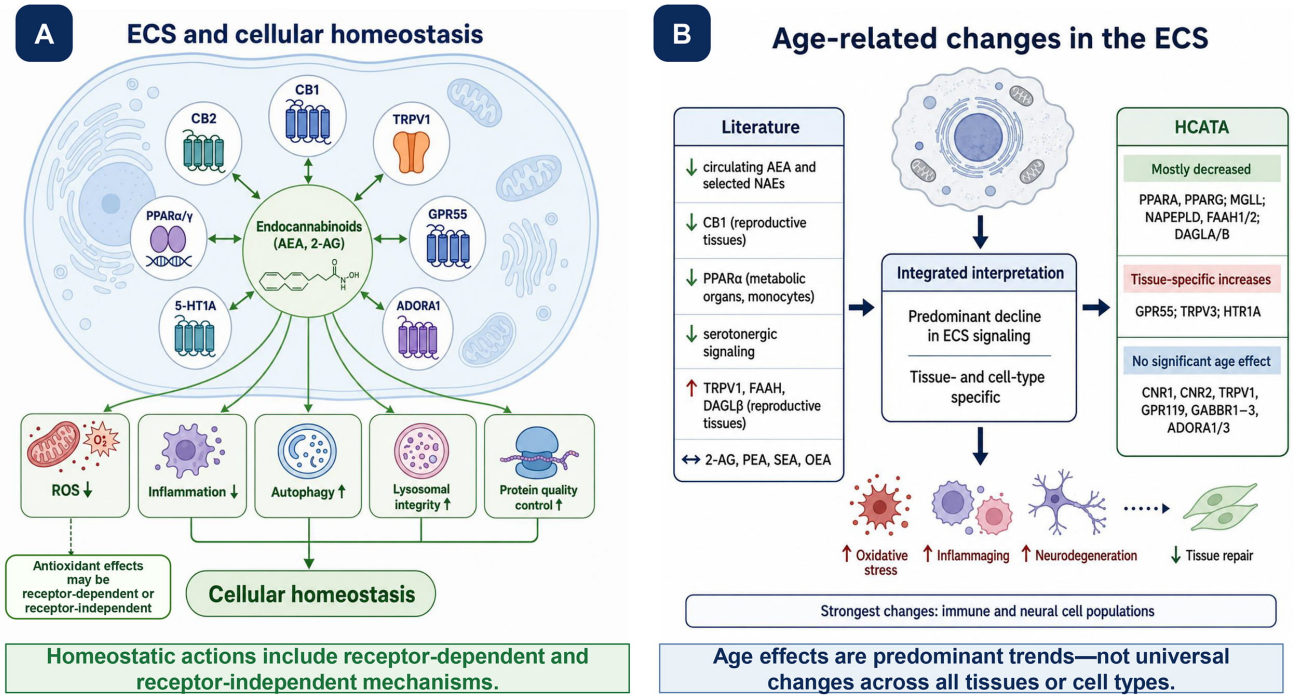


Fig. 1. Endocannabinoid-system regulation of cellular homeostasis and age-associated remodeling. (A) Endocannabinoids, principally anandamide (AEA) and 2-arachidonoylglycerol (2-AG), signal through canonical cannabinoid receptors CB1 and CB2 and through additional targets, including TRPV1, GPR55, peroxisome proliferator-activated receptors (PPARα/γ), the serotonin receptor 5-HT1A, and the adenosine receptor ADORA1. Collectively, these pathways may reduce reactive oxygen species (ROS) and inflammation, promote autophagy and lysosomal integrity, and support protein-quality control and cellular homeostasis. Antioxidant actions may involve both receptor-dependent and receptor-independent mechanisms. (B) Integration of published experimental and human evidence with analysis of the Human Cell Aging Transcriptome Atlas (HCATA) indicates predominantly reduced, but highly tissue- and cell-type-specific, ECS signaling with age. Published findings include lower circulating AEA and selected N-acylethanolamines (NAEs), reduced CB1 abundance in selected tissues, decreased PPARα expression in metabolic organs and monocytes, and reduced serotonergic signaling, together with component-specific increases in TRPV1, FAAH, and DAGLβ in reproductive tissues. HCATA data similarly suggest decreased expression of several receptors and metabolic enzymes, particularly in immune and neural populations, while some genes show tissue-specific or bidirectional regulation and others show no significant age association in the tissues analyzed. Such remodeling may contribute to oxidative stress, inflammaging, neurodegeneration, and impaired tissue repair. Arrows indicate predominant reported directions and should not be interpreted as universal changes across all tissues. Abbreviations: 2-AG, 2-arachidonoylglycerol; AEA, anandamide; DAGL, diacylglycerol lipase; ECS, endocannabinoid system; FAAH, fatty-acid amide hydrolase; HCATA, Human Cell Aging Transcriptome Atlas; MGLL, monoacylglycerol lipase; NAE, N-acylethanolamine; NAPEPLD, N-acyl phosphatidylethanolamine phospholipase D; ROS, reactive oxygen species. Schematic illustration created with assistance from OpenAI ChatGPT image-generation tools and subsequently reviewed and edited by the authors. All biological content was verified by the authors for scientific accuracy. Red arrows indicate upregulation of pathogenic processes, while green arrow indicates downregulation of protective processes.

tions in cannabis users also support an association between cannabinoid exposure and BDNF regulation, although the direction of causality and clinical relevance remain uncertain [58].

Cannabinoid signaling also regulates glial activity. Astrocytes and microglia express both CB1 and CB2, although CB2 is generally more prominent in activated microglia [59]. Activation of glial CB2 attenuates inflammatory responses in experimental models, supporting an important role for this receptor in cannabinoid-mediated control of neuroinflammation [60]. This function may become particularly relevant during aging. Although total neuronal numbers remain relatively stable in several brain regions during healthy aging, white-matter integrity and the number or integrity of myelinated axons decline [61,62,63]. Consequently, changes in neuronal function and connectivity contribute substantially to age-associated brain-volume loss. Aging is also accompanied by reduced neuronal restraint of pro-inflammatory microglia, promoting chronic microglial activation that can contribute to cognitive impairment [64].

Physiological brain aging involves progressive changes in synaptic plasticity, neurogenesis, mitochondrial

and metabolic function, proteostasis, and glial homeostasis, accompanied by a gradual increase in neuroinflammatory signaling. These processes do not necessarily involve extensive neuronal loss but can reduce neuronal resilience and contribute to age-associated cognitive decline. The ECS intersects with several of these mechanisms through regulation of neurotransmitter release, neurogenesis, mitochondrial function, and glial inflammatory responses, positioning it as an important component of the homeostatic response to brain aging [22,34].

Against this physiological background, aging produces region-, sex-, species-, and method-dependent changes in brain ECS components. Rodent studies generally show high CB1 expression and agonist binding in adulthood, followed by reductions in older animals [38]. Autoradiographic studies have identified decreased CB1 binding in several cortical regions and basal-ganglia nuclei of aged rodents [37,65]. Consistent with these observations, CNR1 expression in the whole mouse hemisphere decreases with age [66]. Human post-mortem evidence has similarly indicated higher CB1 expression in younger than in older individuals [67].

Aging also alters brain concentrations of endogenous cannabinoid ligands and the expression of their metabolic enzymes. Hippocampal 2-AG levels decrease with age in mice, potentially because of reduced DAGLα mRNA expression and increased MAGL expression [68]. In contrast, anandamide remains relatively stable in the hippocampus but decreases in the caudate-putamen and medial prefrontal cortex, illustrating the regional specificity of age-associated changes in endocannabinoid tone [33].

These molecular changes may have functional consequences. Age-associated ECS decline has been linked to reduced food intake in old animals and to impaired learning and memory in CB1-deficient mice [69]. Mice lacking Cnr1 exhibit accelerated deterioration of spatial learning and a progressive loss of hippocampal principal neurons with age [70]. This neuronal loss does not appear to result from reduced neurogenesis. Instead, CB1-deficient animals display increased hippocampal neuroinflammation, greater astrocyte and microglial density, and elevated IL-6 expression. Selective deletion of CB1 from forebrain GABAergic, but not glutamatergic, neurons reproduces this phenotype, suggesting that CB1 activity in hippocampal GABAergic neurons protects against age-associated cognitive decline by limiting pyramidal-cell degeneration and neuroinflammation [70]. Importantly, hippocampus-specific deletion of CB1 in adult mice is sufficient to impair memory, enhance local glial activation and TNFα expression, and reduce dentate-gyrus cell proliferation, supporting a local role for hippocampal CB1 signaling in limiting age-associated neuroinflammation and maintaining neural plasticity [71].

Conversely, enhancing cannabinoid signaling can partially reverse age-associated functional changes: chronic low-dose THC restored cognitive performance, hippocampal synaptic-marker expression, spine density, and a more youthful hippocampal transcriptional profile in aged mice through a CB1-dependent mechanism [72].

Nevertheless, changes in receptor abundance or ligand binding do not necessarily produce proportional changes in signaling capacity. In aged rats, cortical CB1 binding-site density is reduced, whereas measured receptor signaling remains largely preserved, suggesting compensatory enhancement of receptor efficiency or downstream signaling [38]. Moreover, rodent findings may not generalize directly to humans. A positron-emission tomography study using [^{18}F]MK-9470 reported increased CB1 binding with age in women, but not in men, with the strongest differences observed in the basal ganglia, lateral temporal cortex, and hippocampus [73]. Thus, although rodent studies generally indicate age-associated reductions in CB1 abundance or binding across cortical and subcortical regions, their functional consequences remain inconsistent, and interpretation must account for species, sex, brain region, radioligand, and assay method.

Neurodegenerative disease introduces an additional layer of ECS remodeling that should be distinguished from physiological aging. Characterizing these changes in the human brain is difficult because regional molecular measurements are commonly limited to post-mortem tissue. Nevertheless, substantial alterations in ECS components have been reported in several brain diseases, sometimes resembling—but not necessarily resulting from—the changes observed during healthy aging. Post-mortem analyses of Alzheimer's disease (AD) brains have demonstrated reduced CB1 expression in cortical regions [74,75], consistent with findings in aged rats [76]. However, CB1 abundance does not appear to correlate with the degree of cognitive impairment or with established AD markers [75].

Pathological aging exaggerates several processes already present at lower levels during physiological aging, including synaptic dysfunction, impaired cellular homeostasis, oxidative stress, and chronic neuroinflammation. In AD, these changes occur alongside Aβ accumulation, tau pathology, progressive synaptic failure, and sustained activation of microglia and astrocytes. Because the ECS regulates synaptic transmission, neuronal resilience, and glial inflammatory responses, disease-associated changes in ECS components may represent either loss of protective signaling or compensatory responses to ongoing pathology. Distinguishing these mechanisms from physiological age-related ECS remodeling is therefore essential when interpreting findings from neurodegenerative tissue [34,77].

In contrast to CB1, CB2 expression increases in AD brains, particularly in activated microglia associated with amyloid-rich plaques [74]. CB2 abundance also correlates with Aβ42 levels and amyloid-plaque burden [75]. Importantly, this upregulation likely reflects not only increased microglial activation but also a compensatory response, as activation of CB2 generally suppresses pro-inflammatory

microglial signaling and may therefore provide negative feedback limiting neuroinflammation [74]. FAAH is likewise increased in plaque-associated reactive astrocytes and may enhance the production of AEA-derived metabolites, including arachidonic acid, potentially contributing to AD-associated inflammatory signaling [78].

Other endocannabinoid-responsive receptors also undergo disease- and cell-type-specific changes. In dementia, TRPV1 is upregulated in both glutamatergic and GABAergic neurons, whereas TRPM8 is downregulated in glutamatergic neurons but upregulated in GABAergic neurons [79]. Serotonergic signaling may also interact with age-dependent ECS remodeling: hippocampal 5-HT1A receptor density decreases with age, while cannabinoid treatment increases its density more effectively in aged than in young rats [80].

Overall, healthy brain aging is characterized by region-, sex-, and species-specific remodeling of cannabinoid receptors, endogenous ligands, and metabolic enzymes rather than by a uniform decline in ECS activity. The apparent magnitude and direction of these changes also depend on the methods used to measure them. Neurodegenerative disease introduces additional, pathology-associated alterations, including microglial CB2 upregulation, plaque-associated FAAH enrichment, and cell-type-specific changes in noncanonical ECS-responsive receptors. Nevertheless, several age-related ECS changes appear relatively consistent in the hippocampus, including reduced CB1 availability and declining 2-AG signaling, although the magnitude and functional consequences of these changes vary among studies and experimental approaches. Thus, ECS changes observed in neurodegenerative tissue should not be interpreted simply as an acceleration of normal aging. Rather, the available evidence supports dynamic, region- and context-dependent remodeling of the ECS, with neurodegenerative pathology superimposing additional changes on those associated with physiological aging (Fig. 2, Ref. [78]).

2.2 Intestine

The gastrointestinal tract contains one of the largest peripheral endocannabinoid systems, with abundant CB1 receptor expression in the enteric nervous system and lower expression in intestinal epithelial and submucosal cells [81,82]. In contrast, CB2 receptors are expressed predominantly by immune cells within the lamina propria, suggesting a primary role in regulating intestinal immune responses [82]. The ECS plays a central role in maintaining intestinal homeostasis by regulating epithelial barrier integrity, gastrointestinal motility, immune responses, visceral sensation, and local inflammation [20]. Stimulation of cannabinoid receptors reduces inflammation, gastric acid secretion, emesis, and intestinal motility [83]. Apical applications of delta-9-tetrahydrocannabinol (THC) or cannabidiol (CBD), the main phytocannabinoids, to epithelial cells increase their permeability. In addition, basolateral application of eCBs to epithelial cells also induces TRPV1 receptor expression [84]. Cannabinoid-mediated inhibition of peristalsis appears to result from suppression of excitatory cholinergic neurons, inhibitory VIPergic neurons (expressing vasoactive intestinal polypeptide), and sensory neurons [85].

Normal intestinal permeability depends on proper distribution of tight junction proteins such as zonula occludens-1 (ZO-1), claudins, and occludins [86]. Although THC, CBD, and endocannabinoids increase ZO-1 expression, only endocannabinoids reduce claudin-1 expression, indicating that different cannabinoids may differentially regulate epithelial barrier integrity [84].

Several components of the ECS undergo age-dependent changes that likely contribute to impaired intestinal homeostasis. The expression of CB1 decreases in the small intestine of aged rats compared with young ones [39]. Aging and age-related diseases are associated with impaired function of the intestinal mucosal barrier [87] and gut dysmotilities. For example, decreased FAAH is associated with slow transit constipation [88] and GPR55 expression increases in a streptozotocin mouse model of gastroparesis [89]. CB2 expression tends to increase in patients with inflammatory bowel disease (IBD) [82], while circulating eCB levels decrease [90].

Recent work has identified a molecular mechanism linking age-related CB1 decline to impaired epithelial barrier function. In senescent intestinal epithelial cells, reduced CB1 signaling increases miR-191-5p expression, leading to NF-κB activation, reduced ZO-1 expression, and increased epithelial permeability. Pharmacological activation of CB1 with ACEA reverses these changes, suggesting that CB1 signaling preserves intestinal barrier integrity during aging [39].

ECS activity is also strongly influenced by the gut microbiota and diet. Dysbiosis may partly arise from CB1 overactivation [91]. In obese mice, a high-fat diet alters gut microbiota and changes expression of ECS components, including *Napepld*, *Cnr1*, *Faah*, and AEA levels, leading to increased intestinal permeability and adipogenesis [91]. Also, *Napepld* deletion in white adipocytes or intestinal epithelial cells induces dysbiosis [92], and antibiotics can alter *Napepld* levels, contributing to dysbiosis [93]. The importance of microbiota for the proper function of ECS was evident in germ-free mice, which show significantly altered expression of CB1, GPR18, GPR55, and PPARα in the gut [94]. Changes in *Gpr18* and *Gpr55* expression are particularly pronounced. Fecal microbiota transfer from conventionally raised donor mice to germ-free male mice reversed changes in receptor expression and lipid mediator levels, especially in the ileum and jejunum [94]. Changes in specific bacterial families, including *Akkermansiaceae* and *Veillonellaceae*, whether introduced artificially, or modi-

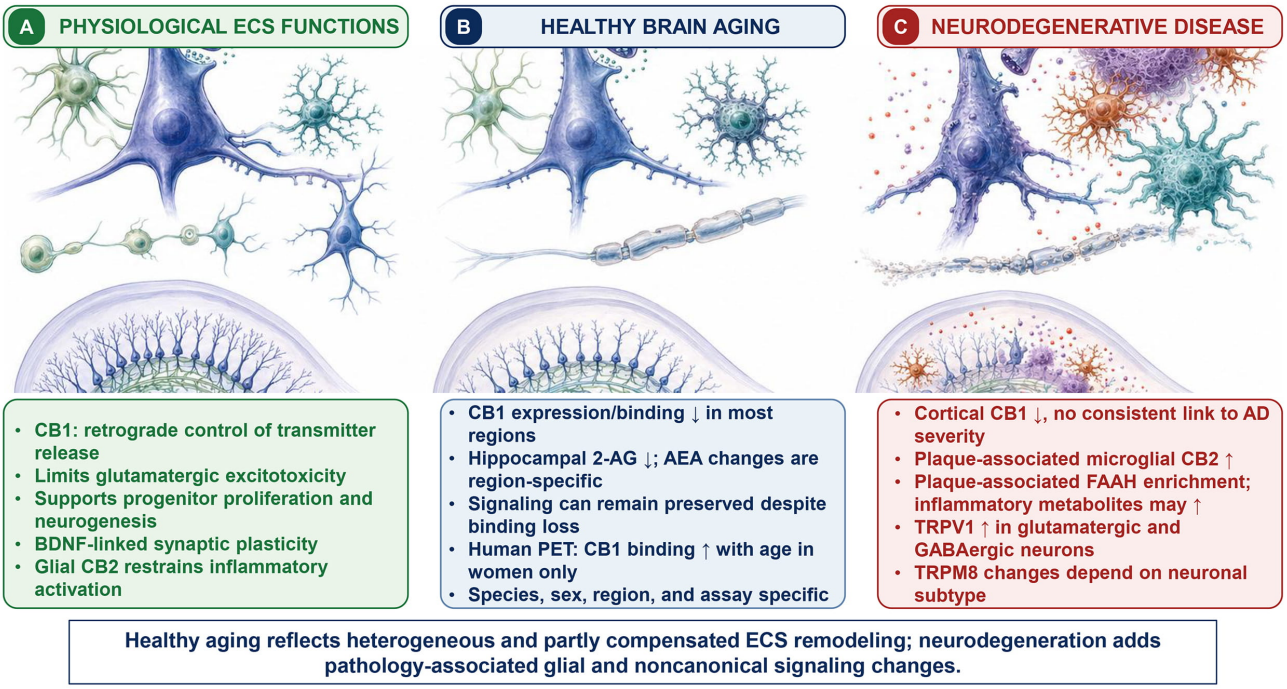


Fig. 2. Context-specific remodeling of the brain endocannabinoid system with aging and neurodegenerative disease. (A) Under physiological conditions, CB1-mediated retrograde signaling regulates neurotransmitter release and limits excessive glutamatergic activity, while cannabinoid signaling supports progenitor-cell proliferation, adult neurogenesis, BDNF-associated synaptic plasticity, and neuronal survival. Glial CB2 signaling can restrain microglial activation and neuroinflammation. (B) Healthy brain aging is associated with heterogeneous changes in ECS components. Most rodent studies report reduced CB1 expression or ligand binding in cortical and subcortical regions, together with lower hippocampal 2-AG and region-specific changes in AEA. However, receptor signaling can remain relatively preserved despite reduced binding-site density, suggesting compensatory changes in receptor efficiency or downstream signaling. Human findings are limited and may differ by sex; notably, PET imaging has shown increased CB1 binding with age in women but not in men. (C) Neurodegenerative disease is associated with additional pathology-related remodeling of the ECS. In Alzheimer's disease, reduced neuronal CB1 expression has been reported in some studies, although findings are inconsistent and CB1 abundance does not consistently correlate with disease severity or established pathological markers. In contrast, CB2 receptors are enriched in microglia associated with amyloid-β plaques, whereas FAAH expression and activity are increased in reactive astrocytes surrounding these plaques. These cell-type-specific alterations suggest that ECS components may participate in the glial responses accompanying Alzheimer's pathology [78]. Dementia is also associated with neuronal-subtype-specific changes in TRPV1 and TRPM8. Collectively, these observations indicate that healthy aging produces region-, sex-, species-, and assay-dependent ECS changes, whereas neurodegenerative disease adds distinct glial and noncanonical signaling alterations. Arrows indicate predominant reported directions and not universal effects. Abbreviations: 2-AG, 2-arachidonoylglycerol; AD, Alzheimer's disease; AEA, anandamide; BDNF, brain-derived neurotrophic factor; CB1/CB2, cannabinoid receptors type 1 and type 2; ECS, endocannabinoid system; FAAH, fatty-acid amide hydrolase; PET, positron-emission tomography; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid 1. Schematic illustration created with assistance from OpenAI ChatGPT image-generation tools and subsequently reviewed and edited by the authors. All biological content was verified by the authors for scientific accuracy.

fied by diet, are known to alter eCB levels, and thus may influence human health and healthy aging [95,96,97].

Together, these findings indicate that healthy aging is accompanied by reduced CB1 signaling in the intestine, whereas chronic inflammatory disorders often exhibit compensatory alterations in cannabinoid receptor expression and circulating eCB levels (Fig. 3). These findings support the concept of a bidirectional gut microbiota–ECS axis, in which microbial composition regulates endocannabinoid signaling while ECS activity, in turn, influences epithelial integrity and microbial homeostasis. Disruption of ECS homeostasis contributes to impaired intestinal barrier function, dysbiosis, chronic inflammation, and altered gastrointestinal motility, making the intestinal ECS a promising therapeutic target for promoting gut health during aging.

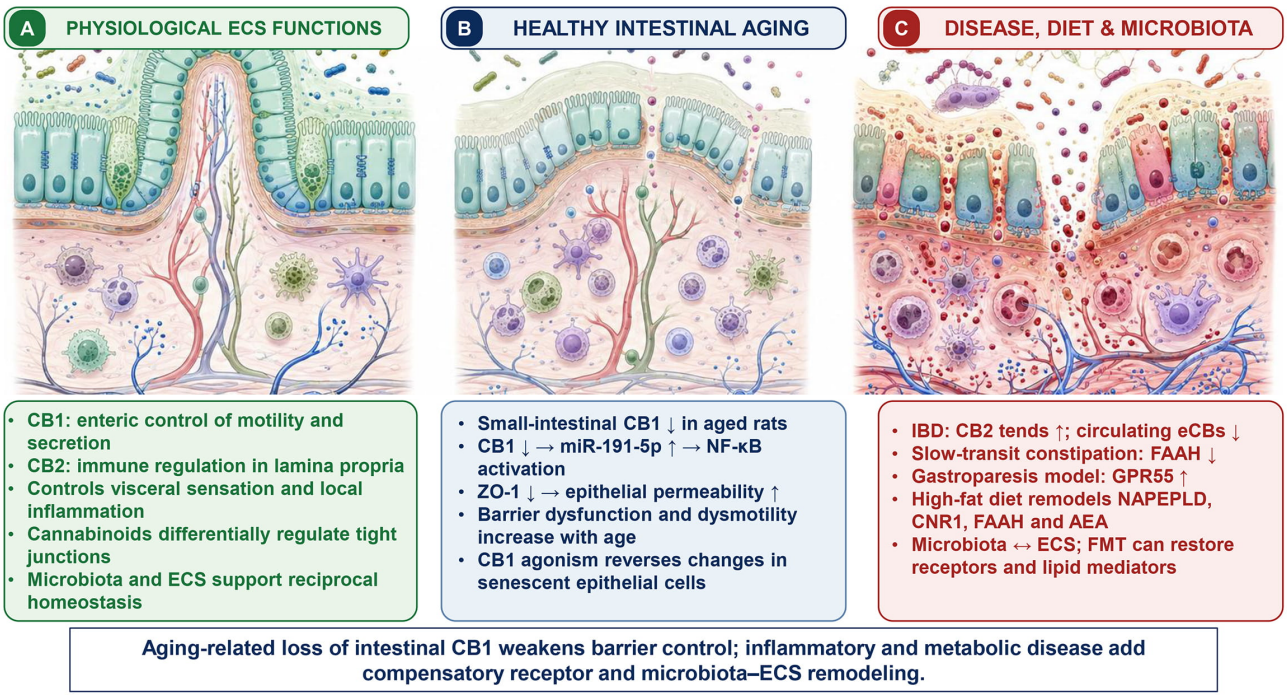


Fig. 3. Intestinal endocannabinoid-system functions and remodeling during aging and disease. (A) Under physiological conditions, abundant CB1 expression in the enteric nervous system contributes to the regulation of gastrointestinal motility, secretion, visceral sensation, and local neural activity. CB2 receptors, expressed predominantly by immune cells in the lamina propria, participate in the control of intestinal inflammation. Cannabinoids also differentially regulate epithelial tight-junction proteins and permeability, while reciprocal interactions between the ECS and gut microbiota contribute to barrier and microbial homeostasis. (B) Healthy intestinal aging is associated with reduced small-intestinal CB1 expression and impaired epithelial-barrier function. In senescent intestinal epithelial cells, reduced CB1 signaling increases miR-191-5p expression and NF-κB activity, decreases ZO-1 expression, and increases epithelial permeability. Pharmacological CB1 activation reverses these changes experimentally, suggesting that CB1 signaling helps preserve barrier integrity during aging. (C) Inflammatory, motility, and metabolic disorders produce additional context-specific alterations. CB2 expression may increase in inflammatory bowel disease, reflecting both increased expression in inflamed tissues and the accumulation of CB2-expressing activated immune cells; CB2 signaling may in turn provide a counter-regulatory mechanism limiting intestinal inflammation. Circulating and tissue endocannabinoid concentrations also change in a disease- and context-dependent manner. Reduced FAAH is associated with slow-transit constipation, and increased GPR55 expression has been reported in an experimental gastroparesis model. High-fat feeding and obesity alter the microbiota and intestinal expression or abundance of NAPEPLD, CNR1, FAAH, and AEA. Germ-free and microbiota-transfer studies further demonstrate that microbial composition can modify intestinal cannabinoid receptors and lipid mediators, supporting a bidirectional microbiota–ECS relationship. Thus, aging-related loss of intestinal CB1 may weaken epithelial-barrier control, whereas inflammatory and metabolic diseases add compensatory receptor changes and broader microbiota–ECS dysregulation. Arrows indicate predominant reported directions and not universal effects. Schematic illustration created with assistance from OpenAI ChatGPT image-generation tools and subsequently reviewed and edited by the authors. All biological content was verified by the authors for scientific accuracy. Abbreviations: AEA, anandamide; CB1/CB2, cannabinoid receptors type 1 and type 2; CNR1, gene encoding CB1; eCB, endocannabinoid; ECS, endocannabinoid system; FAAH, fatty-acid amide hydrolase; FMT, fecal microbiota transfer; GPR55, G-protein-coupled receptor 55; IBD, inflammatory bowel disease; NAPEPLD, N-acyl phosphatidylethanolamine phospholipase D; NF-κB, nuclear factor κB; ZO-1, zonula occludens-1.

2.3 Liver

The physiological role of the ECS in the healthy liver remains incompletely understood, largely because cannabinoid receptors are expressed at relatively low levels under basal conditions. CB1 receptors are present in whole-liver tissue, hepatocytes, and hepatic vascular endothelial cells, whereas CB2 receptors are primarily expressed in Kupffer cells [98]. Various pathological conditions like fibrosis [99], cirrhosis [100] and cancer [101] cause higher levels of expression of cannabinoid receptors. Similarly, in patients with metabolic dysfunction, diabetes and obesity, ECS components are also upregulated [102]. Moreover, overactivation of CB1 receptor in the liver enhances hepatic insulin resistance and lipogenesis [103]. In addition to the

classical cannabinoid receptors, GPR55 also contributes to hepatic metabolic regulation. GPR55 deficiency impairs insulin sensitivity, whereas receptor overexpression promotes lipogenesis and suppresses β-oxidation, thereby contributing to steatosis and steatohepatitis [104]. These observations suggest that the ECS participates in regulating hepatic hemodynamics, fibrogenesis, and lipid metabolism.

Endocannabinoids also exert additional effects in the liver. They inhibit inflammatory responses in Kupffer cells and activate quiescent hepatic stellate cells via CB1 receptors [105]. Also, CB1 signaling promotes hepatocyte apoptosis, lipogenesis, and hepatic steatosis [106].

Hepatic ECS activation is also observed in chronic liver diseases, including hepatitis B, hepatitis C, and alcohol-associated liver fibrosis, where CB1 and CB2 receptor expression increases in proportion to disease severity [107,108,109].

Direct evidence describing age-dependent alterations of the hepatic ECS remains remarkably limited. Nevertheless, ECS activation is consistently observed in several liver disorders whose incidence increases with age—including obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), fibrosis, cirrhosis, and hepatocellular carcinoma—suggesting that dysregulation of hepatic cannabinoid signaling may contribute more to pathological aging than to physiological aging.

2.4 Muscle, Pancreas, and Adipose Tissue

The ECS is a major regulator of whole-body energy homeostasis through its actions in skeletal muscle, pancreas, liver, and adipose tissue, where it influences food intake, energy expenditure, glucose homeostasis, insulin secretion, and insulin sensitivity [110,111]. Overactivation of CB1 receptors in skeletal muscle promotes insulin resistance [112].

It was reported that CB1 expression in skeletal muscle was approximately 25% higher in older adults (>65 years) compared with young males (20–27 years), while CB2 expression remained similar across age groups [113]. Resistance exercise increased CB1 expression by 11% and CB2 expression by 37% in older adults. Notably, increased CB2 expression correlated positively with markers of muscle catabolism (FOXO3a) and regenerative capacity (Pax7, MyoD). These findings suggest that aging skeletal muscle retains considerable ECS plasticity and remains responsive to physiological stimuli such as resistance exercise.

Within the pancreas, the islets of Langerhans contain an autonomous ECS, as β-cells possess all enzymes required for eCB synthesis and degradation [114]. Cannabinoid receptors are present on both α- and β-cells and likely contribute to insulin regulation [115]. Pharmacological activation of CB1 and CB2 receptors has been shown to stimulate insulin secretion in mouse MIN6 β-cells and potentiate glucose-stimulated insulin secretion in isolated mouse pancreatic islets [116]. However, the effects of anandamide (AEA) appear to depend on experimental conditions: AEA inhibited glucose-stimulated insulin secretion in freshly isolated rat islets but enhanced secretion following overnight culture [117]. In contrast, AEA increased basal insulin secretion and insulin content in isolated rat islets without enhancing glucose-stimulated secretion. However, overstimulation of CB receptors correlates with hyperinsulinemia, hyperglycemia, and lipogenesis, suggesting detrimental effects on islet function [115]. High-fat diets further increase ECS tone in islets by upregulating eCB synthesis enzymes and downregulating degradation enzymes [118].

Animal studies show that the autonomous islet ECS also regulates obesity-induced inflammation [119]. Endogenous CB1 ligands and synthetic agonists inhibit glucose-stimulated insulin secretion, contributing to β-cell maladaptation during chronic nutrient overload and inflammation [120].

The effects of ECS activation on insulin secretion appear to depend on the duration and magnitude of receptor activation. Acute activation may enhance glucose-stimulated insulin secretion, whereas chronic ECS overactivation during obesity promotes β-cell dysfunction and insulin resistance.

Because aging is accompanied by progressive insulin resistance and increased visceral adiposity, age-related alterations in adipose ECS signaling may substantially contribute to metabolic dysfunction [121]. Circulating AEA and 2-AG levels are typically elevated in individuals with metabolic conditions such as obesity [122,123], adiposity and insulin resistance [124]. Also, CB1 expression in visceral adipose tissue positively correlates with BMI [125]. Overall, increased CB1 expression is associated with poorer metabolic health: CB1 levels are higher in adipose tissue of overweight/obese adults compared with lean individuals [125,126], although some studies report conflicting findings [122,124]. Hyperactivation of CB1 signaling contributes to hyperphagia, insulin resistance, glucose intolerance, and impaired lipid homeostasis [122]. Interestingly, whereas CB1 expression increases in adipose tissue during obesity, central CB1 receptor availability decreases, indicating that aging and metabolic disease affect ECS regulation in a highly tissue-specific manner [125].

To investigate CB1 function in myogenesis and insulin resistance, researchers generated CB1 receptor knockout mice [127]. CB1R−/− mice exhibited significantly reduced diet- and age-induced insulin resistance and enhanced insulin signaling. CB1 deficiency resulted in elevated IL-6 secretion, reduced myostatin expression, and enhanced downstream AKT and MAPK signaling, leading to increased expression of myogenic genes, greater muscle mass, and improved lean-to-fat ratio—effects most pronounced in obese and aging animals. In this context, transient IL-6 production promotes skeletal muscle regeneration and glucose uptake rather than chronic inflammation. These mice also showed increased energy expenditure, im-

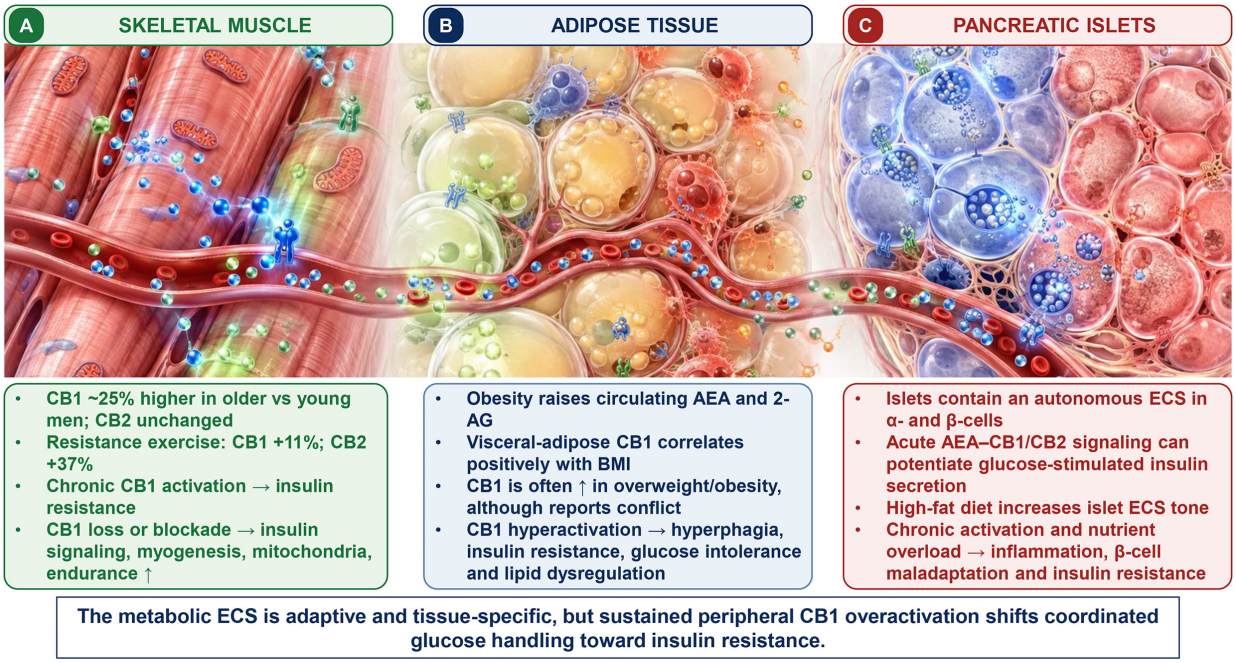


Fig. 4. ECS remodeling across metabolic tissues. The endocannabinoid system coordinates glucose and energy homeostasis through tissue-specific actions in skeletal muscle, adipose tissue, and pancreatic islets. (A) In skeletal muscle, CB1 expression is higher in older than younger men, while resistance exercise increases both CB1 and CB2 expression, demonstrating retained ECS plasticity. Chronic CB1 activation promotes insulin resistance, whereas genetic deletion or pharmacological inhibition of CB1 improves insulin signaling, myogenesis, mitochondrial function, and endurance. (B) Obesity and visceral adiposity are frequently associated with elevated circulating anandamide (AEA) and 2-arachidonoylglycerol (2-AG) and increased adipose CB1 expression, although findings vary among studies. Sustained CB1 activation promotes hyperphagia, insulin resistance, glucose intolerance, and impaired lipid homeostasis. (C) Pancreatic α- and β-cells contain an autonomous ECS that modulates insulin secretion. Acute AEA-mediated activation of CB1 and CB2 can potentiate glucose-stimulated insulin secretion, whereas high-fat feeding and chronic ECS overactivation promote islet inflammation, β-cell maladaptation, and insulin resistance. Collectively, physiological ECS signaling supports metabolic adaptation, but sustained peripheral CB1 overactivation shifts coordinated glucose handling toward metabolic dysfunction. Arrow up indicates increase, while arrow down indicates decrease. AEA, anandamide; CB1/CB2, cannabinoid receptor type 1/type 2; ECS, endocannabinoid system; 2-AG, 2-arachidonoylglycerol. Schematic illustration created with assistance from OpenAI ChatGPT image-generation tools and subsequently reviewed and edited by the authors. All biological content was verified by the authors for scientific accuracy.

proved mitochondrial performance, and enhanced physical endurance.

Similar findings have been reported by other groups. Consistent with genetic studies, pharmacological inhibition of CB1 receptors reversed age-related metabolic dysfunction, improved insulin sensitivity, and enhanced skeletal muscle regeneration in several murine models [128,129,130].

In summary, these findings indicate that chronic activation of peripheral CB1 signaling contributes to age-associated metabolic dysfunction, obesity, and insulin resistance, whereas inhibition of CB1 activity improves metabolic homeostasis and skeletal muscle function (Fig. 4). These observations identify peripheral CB1 receptors as promising therapeutic targets for combating metabolic aspects of aging.

2.5 Bone

Bone remodeling is influenced by the ECS through regulation of osteoblast and osteoclast activity, making this system relevant to age-related bone loss. Female *Cnr1*−/− mice exhibit reduced peak bone mass [131], whereas female *Cnr2*−/− mice develop age-dependent bone loss secondary to reduced bone formation [132]. Importantly, these effects are sexually dimorphic. Both male and female CB1-deficient mice show low bone mass, decreased bone formation, and increased osteoclast numbers [131]. However, male CB1−/− mice, unlike females, display increased trabecular bone mass accompanied by cortical expansion.

CB1 and CB2 receptors share limited homology and respond to distinct ligands. Their combined role in bone development was examined in female mice from birth to old age [133]. Combined deletion of *Cnr1* and *Cnr2* accelerated bone accumulation during early postnatal development, suggesting that CB1/CB2 signaling contributes

to embryonic bone formation. By three months of age, *Cnr1/2−/−* mice exhibited increased trabecular bone mass and cortical thickness. By twelve months of age, age-related declines in bone mass and strength were present but significantly less pronounced in *Cnr1/2−/−* mice, indicating that dual receptor deficiency protects against age-related bone loss and weakening. These findings indicate that the effects of cannabinoid receptors on bone are highly context-dependent and vary according to receptor subtype, developmental stage, sex, and age.

Dual receptor-deficient mice were also protected against ovariectomy-induced bone loss. Furthermore, estrogen treatment partially reversed age-related bone changes in older females (>9 months), with more pronounced effects in *Cnr1/2−/− mice* [133].

Human studies also support an involvement of the ECS in bone homeostasis: heavy recreational cannabis users exhibit low bone mineral density and increased bone turnover [134]. Unfortunately, no male/female comparison was performed.

Among non-classical ECS-related receptors, GPR55 influences osteoclast differentiation *in vitro* and bone mass *in vivo*. Male GPR55-deficient mice show increased bone mass and resorption, while the GPR55 antagonist cannabidiol inhibits osteoclast formation induced by the GPR55 agonist lysophosphatidylinositol [135].

Collectively, these findings indicate that the ECS contributes to the regulation of bone remodeling and skeletal aging through multiple receptor-dependent mechanisms. The effects of cannabinoid signaling are highly dependent on receptor subtype, sex, and developmental stage. Although preclinical studies suggest that modulation of CB1, CB2, and GPR55 signaling may influence age-related bone loss, additional clinical studies are needed before these pathways can be considered therapeutic targets for osteoporosis or other skeletal disorders associated with aging.

2.6 Heart

Cannabinoids modulate multiple aspects of cardiovascular physiology and generally exert cardioprotective effects under pathological conditions, although the outcome depends on the receptor subtype activated and the disease context.

Cannabinoids reduce tissue injury and arrhythmias following myocardial infarction, although their effects depend on the receptor subtype involved [136]. Activation of CB1 receptors decreases cardiomyocyte contractility, whereas CB2 receptor stimulation exerts the opposite effect [137]. Consistent with these findings, rodent models of cardiomyopathy demonstrate that CB1 activation promotes cardiomyocyte injury, collagen deposition, and hypertrophy, while CB2 signaling mediates cardioprotective, antifibrotic, and antihypertrophic effects [138]. CB2 activation may also attenuate the progression of atherosclerosis by limiting lesion development [139].

FAAH knockout mice, which exhibit elevated anandamide but not 2-AG, exhibit attenuated age-related cardiac dysfunction compared with wild-type animals [140,141]. This suggests that high anandamide levels may protect the aging heart. FAAH−/− mice also display reduced oxidative stress and inflammation, including reduced expression of gp91phox, TNF-α, and inducible nitric oxide synthase (iNOS), all of which typically increase with age.

Age-related changes in cardiac ECS components have also been observed in humans. Protein expression of both CB1 and CB2 receptors decreases in cardiomyocytes with age in older individuals (>50 years) compared with younger ones. Sex-specific differences were noted: in younger men, CB1 expression was lower and CB2 expression higher than in women [142]. In older individuals, CB1 expression was higher and CB2 lower in males compared with females. CB1 receptors were also detected in the intercalated discs of older hearts [142]. Because intercalated discs are essential for coordinated electrical and mechanical coupling between cardiomyocytes, increased localization of CB1 receptors in these structures may represent a compensatory adaptation to age-related alterations in ECS signaling. However, the functional significance of this observation remains unknown.

Overall, available evidence suggests that aging is accompanied by sex-specific alterations in cardiac ECS signaling. While total CB1 and CB2 receptor expression generally declines with age, activation of these receptors produces distinct functional outcomes, with CB1 signaling often associated with adverse cardiac remodeling and CB2 signaling exerting predominantly cardioprotective effects.

2.7 Kidney

The ECS contributes to the regulation of renal homeostasis and is expressed throughout the nephron and renal vasculature. Most renal cell types can synthesize and degrade endocannabinoids, forming an autonomous renal ECS [143]. Under physiological conditions, ECS signaling regulates renal hemodynamics, tubular sodium reabsorption, and urinary protein excretion [144,145]. ECS signaling becomes dysregulated in several kidney diseases, often involving altered cannabinoid receptor expression. Elevated CB1 receptor expression occurs in obesity [146] and diabetic nephropathy [147], accompanied by downregulation of CB2 receptors [148]. Exposure of renal cells to high albumin or glucose concentrations also decreases CB2 expression [149].

Both CB1 and CB2 appear to contribute to the progression of renal fibrosis. CB2 mediates fibrogenesis in renal tubular cells in aging mouse kidneys [150]. In an accelerated aging model, CB2 expression was upregulated in kidneys of 24-month-old mice [151]. CB2 overexpression or activation with the agonist AM1241 reduced expression of PGC-1α, a key regulator of mitochondrial biogenesis, and promoted cellular senescence in cultured human

renal proximal tubular cells. These effects were blocked by ICG-001, an inhibitor of β-catenin signaling. Conversely, CB2 deletion significantly inhibited β-catenin activation, preserved mitochondrial integrity, and reduced renal tubular cell senescence and kidney fibrosis [151].

Collectively, available evidence suggests that ECS signaling becomes dysregulated in several renal disorders associated with aging. Whereas CB1 receptor expression is increased in metabolic kidney diseases such as obesity-associated nephropathy and diabetic nephropathy, CB2 signaling appears to contribute to age-related renal fibrosis and tubular senescence. These findings indicate that the functional consequences of ECS activation are highly context dependent and may vary according to receptor subtype and disease state.

2.8 Skin

Components of the ECS are expressed throughout the skin, including in keratinocytes, hair follicles, sebaceous and sweat glands, sensory nerve endings, and resident immune and structural cells such as macrophages and fibroblasts [152]. The ECS acts as a neuro-immuno-endocrine regulator of skin homeostasis, regulating sensory perception (pain and itch), immune responses (including inflammation and allergic reactions), and epidermal proliferation and differentiation [152,153]. Accordingly, ECS dysregulation has been implicated in numerous skin disorders, including acne and seborrhea, pruritus, chronic inflammatory and autoimmune conditions such as psoriasis, atopic dermatitis, and allergic dermatitis, as well as various skin cancers [153].

Although many skin functions regulated by the ECS deteriorate during aging, direct evidence demonstrating age-related changes in ECS components in human skin remains limited. Nevertheless, CB1-deficient mice develop structural skin abnormalities that resemble several features of cutaneous aging, suggesting that reduced CB1 signaling may contribute to age-related skin deterioration [154].

Taken together, the limited available evidence suggests that reduced ECS activity may contribute to impaired skin homeostasis during aging. However, direct studies examining age-dependent changes in cannabinoid receptors, endocannabinoid levels, and metabolic enzymes in healthy human skin remain scarce.

We summarized all age-associated changes in the ECS described above into Table 1 (Ref. [36,39,40,42,46,65,68,73,94,98,103,113,127,131,132,135,140,141,142,150,151,152,154]).

3. Therapeutic Modulation of the ECS in Aging

Age- or disease-associated ECS dysregulation may be targeted with phytocannabinoids, synthetic cannabinoids, inhibitors of endocannabinoid metabolism, or receptor-selective agonists and antagonists. The therapeutic objective, however, should be normalization of tissue-specific signaling rather than generalized ECS activation.

Many pCBs exert significant biological effects in both animals and humans. THC acts as a weak partial agonist of CB1 and CB2 receptors, producing antiemetic, neuroprotective, anticancer, and anti-inflammatory effects, while also generating psychoactive outcomes. In contrast, CBD functions as a negative allosteric modulator of CB1 and a partial/inverse agonist of CB2, demonstrating neuroprotective, anti-inflammatory, antipsychotic, and antiseizure properties without THC-induced intoxication [12,155]. Other minor pCBs, such as cannabigerol, cannabichromene, and Δ9-tetrahydrocannabivarin, also exhibit distinct pharmacological activities and often modulate the effects of THC and CBD.

CB1 agonists such as THC decrease neuronal activity, locomotion, and cognitive function, making them desirable only in specific contexts involving neuronal overstimulation (e.g., pain, anxiety, post-traumatic stress). Importantly, THC effects are dose-dependent: lower doses may be beneficial and are sometimes appropriate for older adults. This reflects a biphasic dose–response pattern in which low doses produce effects opposite to those seen at high doses. Because ECS tone changes with age, and likely varies across tissues, it is essential to determine dose-, age-, and time-dependent effects of eCBs, pCBs, and sCBs used for supplementation in healthy and pathological aging [156].

The following sections evaluate cannabinoid-based strategies for age-associated neurological and peripheral disorders, with emphasis on evidence strength, tissue specificity, and safety.

3.1 Brain Aging and Neurological Disorders

Given the central role of the ECS in neuronal signaling and the age-associated decline in ECS activity, pharmacological modulation of cannabinoid signaling has emerged as a promising strategy to counteract neurological dysfunction during aging. Therapeutic approaches include supplementation with pCBs, sCBs, or compounds that enhance endogenous cannabinoid signaling.

Clinical interest in cannabinoids is reflected by the approval of several cannabinoid-based medicines for neurological disorders. They include nabiximols (also known as Sativex), a roughly equal mixture of THC and CBD, with small amounts of other minor cannabinoids and terpenes, for the treatment of spasticity and neuropathic pain in multiple sclerosis, and a purified botanical cannabidiol (known as Epidiolex) for the treatment of several forms of pediatric epilepsy, including Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex [157].

Several independent studies have demonstrated that low-dose THC improves cognitive performance in aged, but not young, mice. Beneficial effects have been reported

Table 1. Age-associated changes in ECS components across tissues and organ systems.

System	Age-associated ECS findings	Trend	Evidence base	Functional interpretation	Key limitations	Representative references
Cross-tissue/ HCATA	Predominant decreases in selected receptors and metabolic enzymes; CNR1, CNR2, TRPV1, GPR119, GABBR1–3, and ADORA1/3 unchanged in analyzed tissues.	Heterogeneous; mostly ↓	Human single-cell transcriptomics	Strongest remodeling in immune and neural populations; may contribute to inflammaging.	Transcript abundance does not establish protein abundance or pathway activity; datasets are uneven across tissues.	[46]
Brain	Rodent CB1 abundance/binding often ↓; human PET reported age-related ↑ binding in women; hippocampal 2-AG ↓ in mice; disease may induce microglial CB2 ↑.	Mixed, region- and sex-specific	Rodent tissue and knockout studies; human post-mortem and PET	CB1 signaling may preserve synaptic plasticity and limit excitotoxicity; CB2 may restrain neuroinflammation.	Species, sex, brain region, ligand, and assay strongly affect conclusions.	[65,68,73]
Intestine	CB1 ↓ in aged rat small intestine; reduced CB1 signaling linked to senescent epithelial barrier dysfunction; disease states show compensatory receptor changes.	Generally, CB1 ↓ in healthy aging	Rodent aging and cell models; human disease studies	Reduced signaling may impair barrier integrity and motility; microbiota–ECS interactions are bidirectional.	Healthy aging data are sparse; disease, obesity, diet, and microbiota are major confounders.	[39,94]
Liver	Direct aging evidence limited; PPARα ↓ in aged liver. CB1/CB2 and eCB tone often ↑ in fibrosis, cirrhosis, obesity, and metabolic liver disease.	Aging: limited/PPARα ↓; disease: ECS ↑	Rodent aging; experimental and human liver disease	Excessive hepatic CB1 promotes lipogenesis, insulin resistance, and fibrosis.	Pathological activation should not be interpreted as normal aging.	[42,98,103]
Muscle, adipose, pancreas	Skeletal-muscle CB1 ~25% higher in older adults; resistance exercise ↑ CB1/CB2. Obesity increases adipose and islet ECS tone.	Often ↑ in metabolic disease	Small human exercise study; rodent knockout and diet models	Excessive peripheral CB1 contributes to insulin resistance; muscle ECS remains plastic in older adults.	Age and metabolic disease are difficult to separate; limited intervention data in older humans.	[113,127]
Bone	Cnr1/Cnr2 deletion produces age-, sex-, and compartment-dependent skeletal phenotypes; GPR55 affects osteoclast differentiation and bone mass.	Receptor- and sex-specific	Mouse knockout studies; observational human cannabis-use data	ECS regulates osteoblast–osteoclast balance and bone remodeling.	Knockout phenotypes are developmental; heavy cannabis use does not identify a receptor mechanism.	[131,132,135]
Heart	CB1 and CB2 protein ↓ with age in human cardiomyocytes, with sex-specific patterns; FAAH deficiency attenuates cardiac aging in mice.	Generally ↓ receptors; AEA elevation may protect	Human histology; mouse genetic studies	CB1 and CB2 can have opposing effects on contractility, fibrosis, and injury responses.	Small human datasets; receptor abundance does not equal signaling activity.	[140,141,142]

Table 1. Continued.

System	Age-associated ECS findings	Trend	Evidence base	Functional interpretation	Key limitations	Representative references
Kidney	PPARα ↓ with age; CB2 contributes to tubular mitochondrial dysfunction and fibrosis in aging models; CB1 ↑ in diabetic nephropathy.	Context-dependent	Rodent aging and renal disease models	CB1 blockade may protect metabolic kidney disease; CB2 effects vary by cell state and model.	Physiological aging and metabolic nephropathy must be distinguished.	[40,150,151]
Skin	Direct human aging data are limited; Cnr1-null mice develop aging-like skin structural abnormalities.	Possible ↓ CB1 activity	Mouse knockout; skin-cell and disease studies	Reduced ECS activity may impair barrier function, inflammation control, and wound repair.	Developmental knockout effects and limited healthy-human longitudinal data.	[152,154]
Reproductive tract	CB1 protein ↓, whereas TRPV1, FAAH, and DAGLβ ↑ in aged female mouse reproductive tissues.	Mixed component-specific change	Aged female mice	Suggests coordinated remodeling rather than uniform ECS decline.	Single organ system, sex, and species; functional consequences remain uncertain.	[36]

Summary of reported changes in ECS receptors, endogenous ligands, metabolic enzymes, and related signaling components during physiological aging and age-associated disease. Evidence is organized by tissue or organ system and includes human single-cell transcriptomic analyses, human imaging and histological studies, rodent aging models, genetically modified animals, cell models, and disease-associated observations. Reported directions are heterogeneous and frequently depend on species, sex, cell type, anatomical region, metabolic state, and experimental method. Disease-associated ECS activation—particularly in obesity, fibrosis, diabetes, and other metabolic conditions—should not be assumed to represent normal aging. Arrows indicate predominant reported directions rather than universal effects.

following both chronic administration (1–3 mg/kg/day) and even a single ultra-low dose (0.002 mg/kg), resulting in sustained improvements in learning and memory lasting several weeks [72,158,159].

Mechanistically, these effects have been attributed primarily to CB1 receptor activation and downstream induction of Sirtuin-1 (SIRT1), a protein deacetylase with neuroprotective, memory and learning improvement capacities [159]. Sirtuins are induced by exercise and diet and are known to have inhibitory effect on mTOR activity, promoting health and longevity [160].

Prolonged THC administration (3 mg/kg/day) produced tissue-specific effects on mTOR signaling and systemic metabolism in aged mice [161]. In the brain, treatment transiently increased mTOR activity and metabolites associated with energy production, followed by increased synthesis of synaptic proteins. In adipose tissue, mTOR activity decreased; plasma amino-acid and carbohydrate profiles shifted toward patterns associated with caloric restriction. This temporal and tissue-specific response is mechanistically intriguing, but its geroprotective relevance requires confirmation beyond this preclinical model.

Neuroinflammation is a major contributor to age-related neurodegeneration; consequently, therapies that suppress chronic microglial activation may promote healthy brain aging. The mixed CB1/CB2 agonist WIN-55,212-2 reduced age-associated microglial activation, increased anti-inflammatory cytokine production, and stimulated hippocampal neurogenesis in aged rats [162].

Cannabinoids may also influence serotonergic neurotransmission. Administration of the synthetic cannabinoid dexanabinol restored hippocampal 5-HT receptor density more effectively in aged than in young rats [80].

Experimental evidence from cellular and animal models suggests that cannabinoids target multiple pathological features of Alzheimer's disease. Endocannabinoids improve neuronal survival following exposure to amyloid β and reduce Tau hyperphosphorylation, while activation of CB1 and CB2 receptors attenuates gliosis, improves cognitive performance, and reduces tau pathology in transgenic mouse models [163,164,165,166].

Collectively, preclinical studies indicate that pharmacological modulation of ECS signaling may preserve cognitive function and attenuate age-related neurodegeneration. Although these findings support cannabinoids as promising geroprotective and neuroprotective agents, robust clinical trials in older adults remain limited, and further studies are required to establish their long-term efficacy and safety.

3.2 Gastrointestinal Disorders

Because the ECS regulates intestinal motility, epithelial barrier integrity, and inflammation—processes that change with age—pharmacological modulation may influence age-associated gastrointestinal dysfunction [39]. However, intestinal effects vary substantially with ligand, receptor target, dose, route, disease state, and treatment duration.

The effects of cannabinoids on gastrointestinal motility are relatively consistent, with both eCBs and pCBs generally reducing gastric emptying and intestinal motility. Clinical studies with dronabinol, a synthetic non-selective cannabinoid receptor agonist, demonstrated delayed gastric emptying and reduced postprandial colonic motility and tone [167,168]. These actions may be therapeutically beneficial in selected conditions, including refractory nausea, vomiting, and anorexia [169]. Similarly, THC reduces gastroesophageal reflux, whereas CBD has shown potential benefits in patients with gastroparesis [170,171].

The effects of cannabinoids on intestinal permeability are considerably more complex and often contradictory, varying with the cannabinoid tested, experimental model, route of administration, and duration of treatment. Interestingly, endogenous and exogenous cannabinoids appear to exert distinct effects on epithelial barrier function. eCBs may increase intestinal permeability and promote inflammation, whereas pCBs generally restore cytokine-induced barrier dysfunction and reduce abnormal permeability [84,172].

Consistent with these observations, several experimental studies have demonstrated anti-inflammatory effects of cannabinoids in colitis models [173]. CBD combined with fish oil reduced intestinal permeability and attenuated DSS-induced colitis, although CBD alone was ineffective in one study [174,175]. Clinical evidence is similarly mixed. High-THC cannabis improved symptoms in ulcerative colitis and Crohn's disease while maintaining circulating endocannabinoid levels and reducing steroid dependence [90,176]. In contrast, CBD failed to improve symptoms in patients with irritable bowel syndrome or Crohn's disease [177,178].

Collectively, available evidence indicates that cannabinoids can modulate intestinal motility, inflammation, and epithelial barrier function. However, the therapeutic effects remain highly context-dependent, varying according to cannabinoid composition, dose, route of administration, and disease state. Given that physiological aging is itself associated with reduced gastrointestinal motility [179], indiscriminate activation of cannabinoid signaling may exacerbate constipation and delayed gastric emptying. Consequently, despite encouraging findings in inflammatory bowel diseases, current evidence does not support the routine use of cannabinoids to treat age-associated gastrointestinal dysfunction.

3.3 Visceral Pain

Unlike CB1 receptors, CB2 receptors are expressed predominantly on peripheral immune cells, including immune cells within the intestinal lamina propria, although they are also present in other intestinal cell populations and visceral sensory pathways. Their predominantly peripheral

distribution and limited psychoactive effects make CB2 receptors attractive therapeutic targets for the treatment of intestinal inflammation and visceral pain without the psychoactive adverse effects associated with central CB1 receptor activation.

Accordingly, the selective CB2 receptor full agonist olorinab (formerly APD371) demonstrated robust visceral analgesic effects in several preclinical models of pancreatitis, trinitrobenzene sulfonic acid-induced colitis, and chronic visceral hypersensitivity [180]. The therapeutic potential of selective CB2 activation has also been investigated clinically. In the phase IIb CAPTIVATE randomized placebo-controlled trial involving 273 patients with irritable bowel syndrome, olorinab, a peripherally acting selective CB2 agonist, did not significantly reduce average abdominal pain scores compared with placebo in the overall study population. However, a prespecified subgroup analysis revealed a significant improvement among patients with moderate-to-severe baseline abdominal pain receiving olorinab at 50 mg three times daily (p = 0.014), suggesting a potential benefit in selected patients that requires further confirmation [181]. In contrast, THC failed to provide analgesic benefit in a phase II clinical trial evaluating patients with chronic abdominal, pancreatic, and postsurgical pain [182]. Together, these findings suggest that selective peripheral CB2 receptor activation may represent a more promising therapeutic strategy for visceral pain than nonselective activation of cannabinoid receptors.

3.4 Liver, Pancreatic, and Kidney Disorders

High-fat feeding promotes hepatic steatosis and insulin resistance, conditions whose prevalence increases with age. Hepatocyte-specific disruption of CB1 protects mice from high-fat-diet-induced steatosis and insulin resistance [183]. In experimental metabolic liver disease, CB2 agonism can reduce inflammation and fibrosis [184], whereas CB1 inhibition attenuates alcohol-associated fibrosis and complications of cirrhosis [108,185]. CBD also reduced hepatic steatosis and fibrogenic responses in experimental models, potentially through suppression of NLRP3 inflammasome activation and inhibition of collagen synthesis and fibroblast migration [186,187].

Collectively, experimental studies indicate that excessive hepatic CB1 signaling promotes steatosis, fibrosis, and insulin resistance, whereas CB1 inhibition and, in some contexts, CB2 activation are hepatoprotective. Most evidence remains preclinical. A recent meta-analysis reported an inverse association between cannabis use and metabolic dysfunction-associated steatotic liver disease, but observational associations cannot establish a protective effect or identify the responsible cannabinoid mechanism [188].

Experimental studies consistently indicate that excessive CB1 signaling contributes to obesity-associated β-cell dysfunction, insulin resistance, and pancreatic inflammation. Accordingly, pharmacological or genetic inhibition of CB1 improves metabolic function in several animal models, whereas CB2 activation appears to attenuate pancreatic inflammation and pain. Specifically, obesity-induced inflammation in islets, β-cell damage and apoptosis can be mitigated by CB1 receptor blockers [114]. Similarly, treatment of wild-type mice with CB2 receptor antagonist resulted in improved insulin sensitivity. Deletion of the receptor in mice resulted in a lower body weight gain and normal insulin sensitivity in *Cb2* $^{-/-}$ mice fed a high-fat diet [189].

In acute pancreatitis, disease progression is worsened by activation of the CB1 receptors, at least in animal models [190]. In a mouse model of cerulein-induced acute pancreatitis, administration of HU210, a synthetic agonist of both CB1 and CB2 receptors, reduced abdominal pain-related behavior, pancreatic inflammation, and histopathological injury. Pharmacological blockade of either CB1 or CB2 attenuated HU210-induced analgesia, whereas combined blockade of both receptors reversed its anti-inflammatory effects [191]. The ability to modulate pain with cannabinoids in chronic pancreatitis has been associated with deactivation of pro-inflammatory pathways (p38 MAP kinase, mTOR and ERK pathways) [192]. However, these encouraging preclinical findings have not yet translated into clinical benefit, as THC (namisol) failed to reduce cytokine production or pain in randomized clinical trials of chronic pancreatitis [182,193].

Similarly, CB1 receptor is hyperactivated in kidneys in diabetic nephropathy. Across multiple experimental models of diabetic nephropathy, including chemically induced diabetes, db/db mice, and Zucker diabetic fatty rats, CB1 receptor blockade consistently reduced albuminuria, preserved glomerular filtration, decreased tubular apoptosis, and improved metabolic abnormalities [147,194,195,196,197].

Overall, these findings identify excessive peripheral CB1 signaling as a shared contributor to metabolic and inflammatory injury in the liver, pancreas, and kidneys. CB1 inhibition generally improves tissue function in preclinical models, whereas the effects of CB2 modulation are more tissue- and disease-dependent. Nevertheless, the limited and sometimes negative clinical evidence emphasizes that therapeutic efficacy, safety, and receptor selectivity must be established in human studies before ECS-targeted interventions can be recommended for age-associated metabolic disorders.

3.5 Muscle Degeneration and Metabolic Dysfunction

Skeletal muscle aging is characterized by progressive insulin resistance, mitochondrial dysfunction, and sarcopenia. Consistent with these changes, CB1 receptor expression is increased in aged skeletal muscle, particularly in individuals with obesity and metabolic disorders.

Genetic deletion of Cnr1 has been used to examine CB1 function in myogenesis and insulin resistance [127]. CB1-deficient mice were protected against diet- and age-

associated insulin resistance and showed enhanced myogenesis, reduced myostatin expression, increased AKT and MAPK signaling, greater muscle mass, a higher lean-to-fat mass ratio, improved mitochondrial function, greater energy expenditure, and enhanced endurance. Because several outcomes may reflect systemic rather than muscle-autonomous effects, tissue-specific validation remains important.

Consistent with genetic studies, pharmacological inhibition of CB1 receptors reversed several age-associated metabolic abnormalities in mice, improved skeletal muscle regeneration, enhanced glucose tolerance and insulin sensitivity, suppressed chronic low-grade inflammation, and reduced lipogenic gene expression [128,129,130].

Collectively, these findings suggest that CB1 receptor antagonism represents a promising strategy to improve insulin sensitivity, preserve skeletal muscle mass, and counteract obesity-associated sarcopenia during aging [127]. However, most supporting evidence originates from animal studies, and clinical validation in older adults remains necessary.

3.6 Skin Aging

Cannabinoids are highly lipophilic molecules that readily penetrate the epidermis and dermis, making them attractive candidates for topical drug delivery. Owing to their anti-inflammatory, antioxidant, and wound-healing properties, cannabinoids have attracted considerable interest for the treatment of inflammatory skin disorders and age-related skin changes.

Clinical and preclinical studies have demonstrated therapeutic benefits in psoriasis, eczema, acne, dermatitis, chronic pruritus, wound healing, fibrosis, and even melanoma [198,199]. In a mouse model of contact allergic dermatitis, intraperitoneal administration of palmitoylethanolamide (PEA), an endocannabinoid-related lipid mediator, reduced scratching behavior, mast cell accumulation, and inflammatory changes. Pharmacological antagonist experiments suggested that both CB2 and PPARα signaling contributed to its antipruritic effects [200]. Topical formulations containing CBD and THC also promoted wound healing in clinical settings. Preliminary clinical observations suggest that topical cannabis-based preparations may have potential applications in wound management. In a small prospective, open-label study involving two patients with non-uremic calciphylaxis and chronic leg ulcers, topical cannabis-based medicines were associated with complete wound closure after a mean of 76.3 days of treatment [201]. However, the uncontrolled design and very small sample size preclude definitive conclusions regarding treatment efficacy. Separately, a case series of three pediatric patients with epidermolysis bullosa reported faster wound healing, reduced blistering, and pain improvement following self-initiated topical cannabidiol (CBD) use; one patient was able to discontinue oral opioid analgesics [202].

Using a previously established stress-induced premature senescence (SIPS) model of skin aging developed in our laboratory [203], we demonstrated that both THC and CBD reduced several hallmarks of cellular senescence, including senescence-associated β-galactosidase activity and cyclin D1 expression, while improving cell viability, cellular morphology, SASP, and wound healing in a dose-dependent manner. Notably, THC promoted wound healing more effectively than several established modulators of nutrient-sensing pathways, including metformin, rapamycin, and triacetylresveratrol [198].

Because chronic inflammation, impaired wound healing, and accumulation of senescent cells are hallmark features of skin aging, these findings suggest that cannabinoids may not only treat inflammatory skin disorders but also promote healthier skin aging.

We summarized proposed therapeutic modulations of the ECS in various diseases and aging in Fig. 5 and Table 2 (Ref. [60,72,113,127,129,145,146,150,157,159,162,167,168,176,178,180,181,183,184,198,200,201,204,205]).

4. Diet, Exercise, and Healthy Aging

Endocannabinoids are synthesized from membrane phospholipid-derived fatty acid precursors; consequently, dietary composition has a major influence on endocannabinoid production and circulating eCB levels. In addition, metabolic status, inflammation, oxidative stress, and aging alter endocannabinoid bioavailability and degradation [33].

The availability of the polyunsaturated fatty acid precursors arachidonic acid (AA) and docosahexaenoic acid (DHA) declines with age, particularly after 65 years [204]. These changes may contribute to age-related decrease or increase in AEA and docosatetraenylethanolamide (DEA) concentrations [204]. In a cross-sectional study of 1277 individuals, age-associated increases in circulating DHA and EPA, alongside reductions in several omega-6 fatty acids was reported [206], while in a cross-sectional comparison of adults aged 21–71 years, significantly lower circulating concentrations of AEA and DEA in older adults (55–71 years) than in younger adults (21–24 years) were found [35]. In contrast, endocannabinoid-like N-acylethanolamines, including PEA, SEA, OEA, and LEA, appear to be influenced more strongly by dietary composition and metabolic health [205,207].

The Mediterranean diet can modulate circulating endocannabinoids and related N-acylethanolamines. During a three-year Mediterranean diet intervention in older adults with metabolic syndrome, circulating 2-AG concentrations decreased persistently, whereas AEA and most measured N-acylethanolamines declined transiently during the first six months before generally returning toward baseline, with notable sex-dependent associations with weight loss and insulin resistance [208]. Responses appear sex-dependent: women generally have higher circulating N-

Table 2. Therapeutic and lifestyle strategies that modulate the endocannabinoid system in age-associated conditions.

Indication/system	Strategy or agent	Primary target	Evidence level	Reported outcome	Age-specific relevance and limitations	Representative references
Brain aging/ cognition	Low-dose THC	CB1/CB2; downstream SIRT1 and mTOR	Preclinical: aged mice	Improved learning, memory, synaptic protein synthesis, and metabolic profiles in aged—but not young—mice.	Dose is biphasic; psychoactive, cognitive, cardiovascular, and fall risks require geriatric trials.	[72,159]
Neuroinflammation	WIN-55,212-2 and CB2-directed agonism	CB1/CB2, especially glial CB2	Preclinical: aged rodents	Reduced microglial activation and increased anti-inflammatory signaling and hippocampal neurogenesis.	Non-selective agonism limits translation; long-term safety in older adults is unknown.	[60,162]
MS spasticity/ neuropathic pain	Nabiximols (THC:CBD)	CB1/CB2 and additional cannabinoid targets	Approved/clinical	Reduces MS-related spasticity; used for selected pain indications in some jurisdictions.	Evidence is not specific to biological aging; dizziness, sedation, and interactions are relevant in older adults.	[157]
Epilepsy	Purified CBD (Epidiolex)	Multiple non-CB1 mechanisms	Approved/clinical	Reduces seizures in defined pediatric epileptic syndromes.	Not evidence for treating age-related cognitive decline; hepatic metabolism and drug interactions require monitoring.	[157]
Visceral pain/IBS	Olorinab	Peripheral CB2 agonist	Phase II plus preclinical	Reduced visceral hypersensitivity in models and abdominal pain in an IBS trial.	Not geriatric-specific; confirmatory efficacy and long-term safety are needed.	[180,181]
GI motility and inflammatory bowel disease	Dronabinol, THC-rich cannabis, CBD-containing regimens	CB1/CB2 and noncanonical targets	Mixed clinical and preclinical	Can reduce motility; symptom benefit reported in selected IBD studies, whereas CBD trials were inconsistent.	May worsen constipation or delayed gastric emptying, both common with aging.	[167,168,176,178]
Liver and metabolic disease	Peripheral CB1 inhibition; context-specific CB2 activation	CB1 ↓; CB2 ↑	Predominantly preclinical; observational human data	Reduced steatosis, insulin resistance, inflammation, and fibrosis in experimental models.	Central CB1 inverse agonists caused psychiatric adverse effects; observational cannabis associations are not causal.	[183,184]
Kidney disease	CB1 blockade; cell-specific CB2 modulation	CB1/CB2	Preclinical	CB1 blockade reduced albuminuria and tubular injury in diabetic models; CB2 findings vary by model.	Aging and diabetic nephropathy require separate evaluation; CB2 can be protective or profibrotic.	[145,146,150]
Muscle and insulin resistance	Genetic or pharmacological CB1 inhibition	Peripheral CB1	Preclinical	Improved insulin sensitivity, myogenesis, mitochondrial function, and endurance in aged or obese mice.	Clinical validation in older adults is lacking; systemic effects may not be muscle-autonomous.	[127,129]

Table 2. Continued.

Indication/system	Strategy or agent	Primary target	Evidence level	Reported outcome	Age-specific relevance and limitations	Representative references
Skin inflammation and repair	Topical PEA, CBD, or THC-containing formulations	PPARα and multiple cannabinoid targets	Preclinical and small clinical studies	Reduced pruritus and inflammation; improved wound healing in selected reports.	Formulations and doses vary; evidence for prevention of normal skin aging is limited.	[198,200,201]
Lifestyle/healthy aging	Mediterranean diet, caloric restriction, fasting, endurance and resistance exercise	Endogenous ligand production; PPARα; CB1/CB2 plasticity	Human interventions plus preclinical studies	Modulates circulating eCBs/NAEs, stress resilience, metabolism, and neural plasticity.	Responses vary by sex, metabolic state, intensity, and diet; mediation by the ECS is not always established.	[113,204,205]

Summary of pharmacological, cannabinoid-based, receptor-selective, topical, dietary, and exercise-related approaches that modify ECS activity in neurological, gastrointestinal, metabolic, renal, musculoskeletal, and dermatological conditions relevant to aging. Evidence ranges from cell and animal models to clinical trials and approved therapeutic applications; however, most interventions have not been evaluated specifically in geriatric populations. Reported benefits should be interpreted in relation to dose, receptor selectivity, tissue distribution, disease stage, adverse-effect profile, polypharmacy, and age-related pharmacokinetic changes. Experimental findings should not be interpreted as general recommendations for cannabinoid use in older adults.

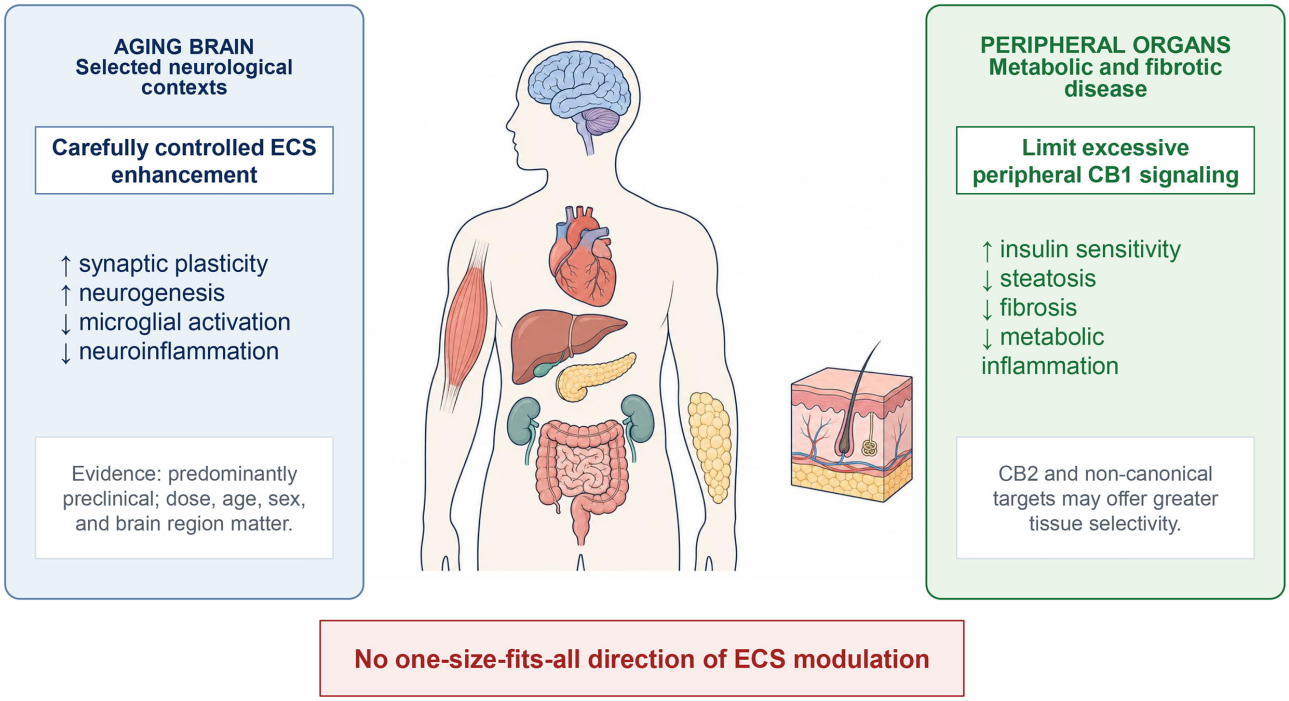


Fig. 5. Tissue-specific therapeutic modulation of the endocannabinoid system in aging and age-associated disease. The potential consequences of ECS modulation differ between the central nervous system and peripheral organs and depend on receptor subtype, tissue, and pathological context. Left: In selected preclinical models of brain aging and neurological dysfunction, carefully controlled enhancement of cannabinoid signaling, particularly through CB1-dependent mechanisms, has been associated with improvements in synaptic plasticity and cognitive function and, in some models, neurogenesis, together with reduced microglial activation and neuroinflammation. These findings do not establish that generalized ECS activation is beneficial during brain aging. Right: In experimental models of metabolic dysfunction, excessive peripheral CB1 signaling contributes to insulin resistance, hepatic lipid accumulation, and inflammatory or fibrotic responses. Accordingly, pharmacological inhibition or genetic deletion of peripheral CB1 can improve selected metabolic and tissue outcomes, although the magnitude and direction of these effects vary among organs and disease models. CB2 and other ECS-related molecular targets represent additional potential therapeutic pathways, but their effects are context-dependent and do not necessarily confer tissue specificity. The schematic illustrates the rationale for tissue- and receptor-selective approaches rather than a universally beneficial direction of ECS modulation. Most supporting evidence is preclinical, and clinical efficacy for promoting healthy aging remains unestablished.

acylethanolamine concentrations and showed smaller reductions in body weight and these lipids than men. A subsequent analysis reported greater improvements in memory and cardiovascular risk markers in men [209]. These findings indicate sex-specific metabolic responses but do not establish that reduced endocannabinoid concentrations mediate the clinical benefits.

Caloric restriction and fasting may represent additional non-pharmacological strategies for restoring age-related alterations in ECS signaling. Whereas obesity is associated with elevated endocannabinoid tone, physiological aging is characterized by a decline in several endocannabinoids, suggesting that nutritional interventions may normalize ECS activity in opposite directions depending on the metabolic state. Caloric restriction in obese T2D patients lowers endocannabinoid tone and improves cardiac function in T2D [210]. In contrast, in healthy individuals, calorie restriction partially reverses *PPARα* downregulation in rats [211] and mice [43]. Similarly, fasting was shown to increase 2-AG production in the intestine [212]. Also, endocannabinoid levels increase significantly within the hypothalamus and accumbens in response to fasting [213]. Collectively, these findings suggest that some of the beneficial effects of fasting on healthy aging and longevity may be mediated, at least in part, through normalization of endocannabinoid signaling [214].

Other dietary patterns remain insufficiently studied. Diet-induced changes in microbial diversity and taxa such as *Bacteroides* and *Akkermansia* may alter endocannabinoid metabolism and ECS responsiveness [215]. Conversely, ECS modulation can itself alter microbial composition, indicating a bidirectional relationship. The mechanisms and their relevance to healthy human aging remain to be established.

Notably, many dietary interventions that promote healthy aging—including the Mediterranean diet, caloric

restriction, intermittent fasting, and microbiome-targeted approaches—appear to converge on modulation of ECS activity, suggesting that the ECS may represent one of the common molecular mediators linking nutrition to longevity.

Exercise is a potent physiological modulator of endocannabinoid signaling and may partially reverse age-associated alterations in the ECS. Experimental studies indicate that exercise partially restores age-related alterations in ECS signaling, including reversal of *PPARα* downregulation in the hearts of aged rats [41].

Endurance exercise consistently increases circulating AEA concentrations, although the magnitude of the response depends on exercise intensity, with the greatest effects observed at approximately 70–80% of the age-adjusted maximal heart rate [216,217,218]. Those who experience positive effects of exercise show increases in pain tolerance and reduction of anxiety, leading to increased stress resilience [219].

The "runner's high" is largely mediated by increased circulating endocannabinoids and activation of CB1 receptors on GABAergic neurons together with peripheral CB1/CB2 signaling [220]. Voluntary exercise also enhances hippocampal endocannabinoid signaling and stimulates neural progenitor cell proliferation, providing a mechanistic explanation for exercise-induced improvements in learning and memory [221]. Physical activity is associated with increased circulating endocannabinoid concentrations and enhanced CB1 receptor expression in the brain [222]. These changes are accompanied by improved memory, enhanced neuroplasticity, antidepressant effects, and reduced neuroinflammation. Interestingly, exercise-induced modulation of the ECS may be even more pronounced in older adults. Resistance training increases CB1 receptor expression in human skeletal muscle to a greater extent in individuals older than 65 years than in younger adults, suggesting that aging muscle retains substantial ECS plasticity [113].

Collectively, diet and exercise can modulate ECS activity and may contribute to improvements in cognition, metabolic function, pain tolerance, and stress resilience. Direct comparisons with pharmacological cannabinoids are lacking; therefore, lifestyle interventions should not be described as equally potent. Their broader safety profile and systemic benefits nevertheless make them attractive strategies for supporting physiological ECS regulation.

Unlike exogenous cannabinoids, diet and exercise influence the ECS through endogenous physiological pathways and simultaneously affect multiple aging mechanisms. These interventions may therefore provide a safer and more sustainable means of supporting ECS homeostasis, although their cannabinoid-specific contribution to clinical outcomes remains difficult to isolate.

5. Conclusions and Future Directions

Age-associated ECS remodeling affects processes relevant to healthy aging, including mood, sleep, pain perception, inflammation, and metabolic regulation. In one recent study, adults aged 55–71 years had lower circulating AEA and DEA concentrations than adults aged 21–24 years. Acute cannabis administration increased several endocannabinoids and related lipids across age groups, with the largest AEA and DEA responses in older participants [35]. These acute biochemical responses do not yet establish sustained clinical benefit.

The available evidence identifies the ECS as an important regulator of aging-related physiology and a potential therapeutic target. However, age does not produce a single, uniform ECS phenotype, and the direction of beneficial modulation is strongly dependent on tissue, receptor, disease state, sex, dose, and timing.

A central conclusion of this review is that optimal ECS modulation differs among organ systems. Carefully controlled enhancement of cannabinoid signaling may support synaptic plasticity and limit neuroinflammation in selected neurological contexts, whereas inhibition of excessive peripheral CB1 signaling may improve insulin sensitivity and protect metabolic organs. CB2 and noncanonical ECS targets may offer additional tissue-selective strategies with fewer central adverse effects.

Because older adults commonly have multimorbidity, polypharmacy, chronic inflammation, and substantial inter-individual variability, cannabinoid-based interventions are unlikely to follow a one-size-fits-all model. Therapeutic selection should consider molecular target, compound composition, dose, route of administration, treatment duration, age, sex, metabolic status, and comorbidities. Biomarkers of ECS state may eventually support precision treatment, but circulating ligand concentrations, receptor abundance, and enzyme activity are not yet validated for routine clinical decision-making.

Clinical evidence in older adults remains limited. Future studies should prioritize adequately powered, age-stratified trials; pharmacokinetic and drug-interaction analyses; sex-specific outcomes; tissue-selective compounds; and long-term assessment of cognition, falls, cardiovascular events, metabolic health, and functional independence. Precision modulation of ECS signaling may ultimately complement lifestyle and disease-specific therapies, but translation should proceed cautiously.

Author Contributions

IK is the sole author, with contributions to all the manuscript work: the design, the literature collection, the literature analysis, manuscript drafting, editing, and submission. IK has prepared, read and approved the final manuscript, and agrees to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the writing of this article, the author used ChatGPT (OpenAI, GPT-6 model) for image creation. After using this tool, the author reviewed and edited the content as needed and assumes full responsibility for the final published content.

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