Adrenic acid: A promising biomarker and therapeutic target (Review)

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Abstract. Adrenic acid is a 22-carbon unsaturated fatty acid that is widely present in the adrenal gland, liver, brain, kidney and vascular system that plays a regulatory role in various pathophysiological processes, such as inflammatory reactions, lipid metabolism, oxidative stress, vascular function, and cell death. Adrenic acid is a potential biomarker for various ailments, including metabolic, neurodegenerative and cardiovascular diseases and cancer. In addition, adrenic acid is influenced by the pharmacological properties of several natural products, such as astragaloside IV, evodiamine, quercetin, kaempferol, Berberine-baicalin and prebiotics, so it is a promising new target for clinical treatment and drug development. However, the molecular mechanisms by which adrenic acid exerts are unclear. The present study systematically reviewed the biosynthesis and metabolism of adrenic acid, focusing on intrinsic mechanisms that influence the progression of metabolic, cardiovascular and neurological disease. These mechanisms regulate several key processes, including immuno-inflammatory response, oxidative stress, vascular function and cell death. In addition, the present study explored the potential clinical translational value of adrenic acid as a biomarker and therapeutic target. To the best of our knowledge, the present study is first systematic summary of the mechanisms of action of adrenic acid across a range of diseases. The present study provides understanding of the wide range of metabolic activities of adrenic acid and a basis for further exploring the pathogenesis and therapeutic targets of various diseases.

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Contents

1. Introduction

Adrenic acid (AdA), also known as cis-7,10,13,16-didodecatetraenoic acid, is an endogenous, 22-carbon long-chain polyunsaturated fatty acid (PUFA) with the molecular formula $C_{22}H_{36}O_2$ and a molecular weight of 332.52 g/mol (Fig. 1). The primary distinction between AdA and other PUFAs is its distinct carbon chain length and double bond configuration. AdA structure encompasses 22 carbon atoms and four double bonds at carbon atoms at positions 7, 10, 13 and 16. This configuration renders AdA unique in its physiological functions and metabolic pathways. AdA is formed via the extension of the 2-carbon chain of arachidonic acid (AA) (1,2). As a constituent of cell membrane phospholipids, AdA is predominantly located in the adrenal gland, liver, brain, kidneys and vascular system and it is classified under the n-6 family of fatty acids (2).

Although the metabolic pathway of AdA is similar to that of AA, its unique functional lipid derivatives and metabolites yield unique biological effects (3). AdA serves a role in several biological processes beyond its involvement in β-oxidation and the formation of cell membranes (2,4-9). It is a biologically active metabolite that participates in cell signalling and plays an important role in regulating physiological functions, including the immune response and metabolic homeostasis (2,4-9). AdA has been demonstrated to induce inflammatory responses in the liver and coronary arteries (4-6). *In vitro* studies have

demonstrated that AdA increases triglyceride (TG) and cholesteryl ester accumulation in fibroblasts, thereby serving an important role in regulation of lipid metabolism (7,8). Furthermore, AdA acts as an endogenous regulator to maintain vascular function by affecting ion channels and modulating vasoconstrictors and dilators (2,9). As a FA, AdA is susceptible to free radical attack, leading to redox imbalance and generation of lipid peroxidation products that cause cell membrane damage and cell death (10). Furthermore, AdA can be converted into other bioactive molecules via enzymatic and non-enzymatic reactions. These molecules participate in pathological processes, including oxidative stress, inflammation and cell death. They also play an important role in the progression of many diseases, including epilepsy, Alzheimer's disease (AD) (1,6,11). The application of technologies such as untargeted metabolomics has led to confirmation of a significant association between AdA levels in peripheral blood and several disease states, including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), type 2 diabetes mellitus (T2DM), AD, acute kidney injury (AKI) and pancreatic ductal adenocarcinoma (PDAC) (12-17). Certain natural products and synthetic drugs, such as astragaloside IV (AS IV), evodiamine (EVO), quercetin, kaempferol, Berberine-baicalin (RA) and prebiotics, have been demonstrated to regulate the metabolism of AdA, thereby exerting a therapeutic effect in treatment of disease (18-21). These findings indicate that AdA may serve as a potential biomarker in metabolic, neurodegenerative and cardiovascular disease and novel target for clinical therapy and drug development. Thus, the mechanism of action of AdA in disease and its potential clinical applications must be investigated. Although AdA plays an important role as a highly sensitive metabolite in a wide range of diseases, its precise mode of action remains unclear (22). Nevertheless, numerous challenges remain to be addressed before AdA-targeted therapies can be translated into clinical practice. To the best of our knowledge, there is a lack of clinical studies on AdA, highlighting the need for further research. Additionally, translating AdA quantification into clinical practice is challenging due to measurement complexity, lack of standardization, and individual metabolic differences.

The present study conducted a comprehensive search of major databases PubMed (https://pubmed.ncbi.nlm.nih.gov), Google Scholar (/scholar.google.com), Web of Science (https://www.webofscience.com) and China National Knowledge Infrastructure (https://www.cnki.net), up to October 2024 using search terms 'adrenic acid', '7,10,13,16-docosatetraenoic acid', 'adrenic acid AND metabolic diseases', 'adrenic acid AND cardiovascular diseases', and 'adrenic acid AND neurological diseases'. Previous studies have shown that there is a potential relationship between AdA and metabolic, cardiovascular and neurological diseases (12-17). The present study focused on research on the mechanism of action of AdA in these diseases. Literature from the past 5-10 years was included. A total of 201 papers were included. The present review summarizes the biosynthesis and metabolic pathways of AdA, AdA mediation of metabolic, cardiovascular and neurological disease by regulating immuno-inflammatory responses, oxidative stress, vascular function and cell death and its molecular mechanisms. Furthermore, the regulatory methods of AdA were outlined from the perspectives of exercise, natural products, dietary nutrition and endocrinology and the clinical translational role of AdA as a biomarker and therapeutic target was discussed to provide a new perspective for further exploring clinical therapeutic targets of common diseases.

2. Metabolism of AdA

Synthesis. AdA synthesis process primarily depends on the n-6 FA metabolic pathway. The process commences with ingestion of linoleic acid (LA) and culminates in the production of AA through a series of chemical reactions. These include dehydrogenation and carbon chain extension, which are catalysed by Δ6-desaturase (D6D), extra-long-chain FA elongase 5 (ELOVL5) and D5D (23). AA serves as the immediate precursor to AdA, which is catalysed by ELOVL2 and ELOVL5 (2). The carbon chain is extended further to generate AdA (2). AA, the direct precursor of AdA, can be obtained directly from food sources, in addition to being synthesized primarily through the LA metabolic pathway (24).

Catabolism. AdA is primarily metabolized by the lipoxygenase (LOX), cyclooxygenase (COX), and cytochrome P450 (CYP450) pathways, resulting in production of bioactive lipids that play a pivotal role in the inflammatory response, immunomodulation and vascular function (4). Furthermore, AdA can elicit biological effects via non-enzymatic oxidative metabolic reactions (25). AdA is also metabolized via the peroxisomal β-oxidation pathway, resulting in production of ATP for energy (26). In addition to undergoing metabolic processes, AdA is incorporated into cell membranes for storage. Upon stimulation of the cell, AdA can be released from the cell membrane via calcium-independent VIA phospholipase A_2 ($iPLA_2\beta$), which participates in the metabolic generation of various active molecules (27).

Enzymatic oxidative metabolic reaction. AdA is metabolized in platelets via the LOX pathway to dihomo (DH)-hydroxyeicosatetraenoic acid (28). AdA is metabolized by COX in human vascular endothelial cells to DH-prostaglandin I_2 (DH-PGI_2) and DH-thromboxane A_2, which inhibit thrombin-induced platelet aggregation (9). CYP450 mediates oxidative metabolism of AdA to generate epoxy FAs, particularly DH-16,17-epoxyeicosatrienoic acids (DH-16,17-EETs). These are involved in regulation of vascular tone in multiple vascular beds. DH-16,17-EETs induce concentration-dependent vasodilation via the activation of coronary vascular smooth muscle K^+ channels and hyperpolarisation responses (29). Additionally, they have been observed to cause the activation of large-conductance calcium-activated potassium channel (BKCa) in adrenocortical endothelial and globular zone cells, which mediate adrenocortical arteriolar diastole and regulate adrenal blood flow (2). Additionally, Singh *et al* (30) discovered that *in vitro*, the methyl ester regional isomers of DH-EETs markedly enhances cell viability and diminishes the phosphorylation/total protein ratios of the unfolded protein response markers, binding immunoglobulin protein and inositol-requiring enzyme 1α, as well as the levels of X-box binding protein 1, spliced form in human embryonic

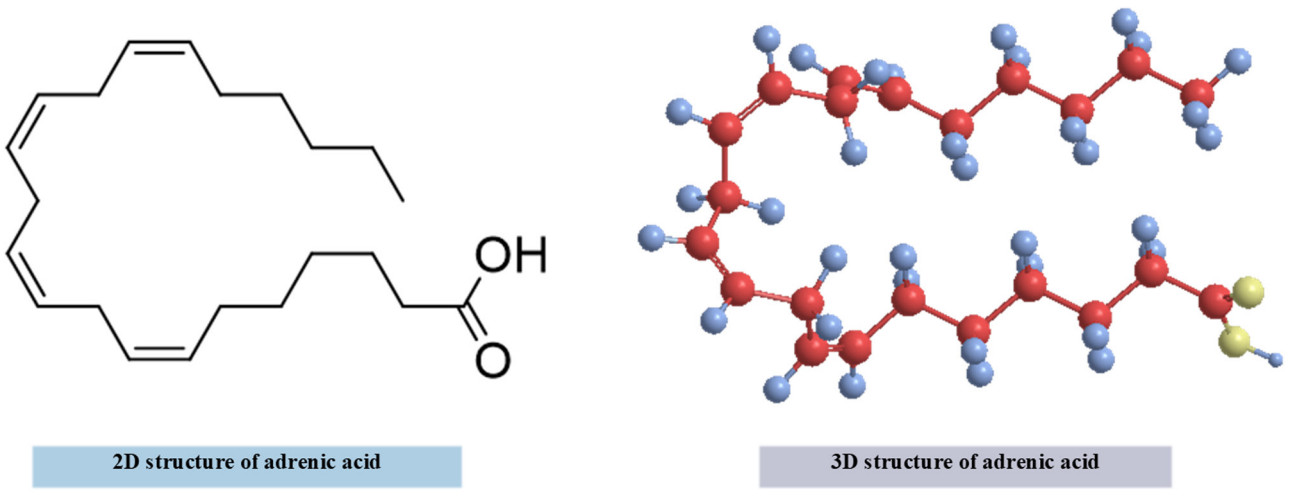

Figure 1. Chemical structure of adrenic acid.

kidney cells that had been subjected to prolonged clindamycin exposure. This resulted in alleviation of endoplasmic reticulum stress. *In vivo*, methyl ester regional isomers of DH-EETs alleviate carrageenan-induced inflammatory pain in rats (30).

Non-enzymatic oxidative metabolic reaction. Non-enzymatic oxidative metabolic reactions are non-selective and non-specific. F2-DH-isoprostane (IsoPs) and isofurans are biomarkers of oxidative stress produced via free radical-driven peroxidation of AdA (25). These markers are used to evaluate the extent and status of oxidative stress in a range of pathological conditions, including epilepsy, AD and cerebral white matter injury (14,15). This approach can potentially facilitate the early diagnosis and treatment. Furthermore, F2-dihomo-IsoPs are utilized to evaluate allograft function throughout the kidney transplantation process (16).

Peroxisome β-oxidation. AdA is β-oxidised, and the carbon chain is shortened in peroxisomes and translocated to mitochondria, where it participates in the tricarboxylic acid (TCA) cycle and produces ATP as an energy source. In peroxisomes, β-oxidation reaction involves oxidation, hydration, dehydrogenation and thiolysis. This process results in production of a molecule of acyl-coenzyme A (CoA) that is shortened by two carbon chains and a molecule of acetyl-CoA. The shortened acyl-CoA is transferred out of peroxisomes via the carnitine shuttle system and enters mitochondria to undergo β-oxidation. Repeated oxidation yields several acetyl CoA molecules, which participate in the TCA cycle in the mitochondrial matrix (31). This generates ATP, which provides energy to the cell (26). A study conducted on isolated hepatocytes revealed that AdA is β-oxidized by peroxisomes at a rate 2-3 times faster than that observed for oleic acid, AA and docosahexaenoic acid (DHA) (32). Furthermore, AdA is reverse-converted to AA by peroxisomal β-oxidation. This establishes a dynamic equilibrium between the two, whereby they act as metabolic precursors for each other. The initial step involves activation of AdA, which then forms its CoA derivative (AdA-CoA). In the peroxisome, AdA-CoA undergoes a series of β-oxidation reactions, in which two carbon atoms are removed, resulting in formation of a shorter-chain acyl-CoA. Following several β-oxidation cycles, AdA-CoA is converted to AA-CoA, and AA is released (33) (Table I; Fig. 2).

3. Mechanisms of AdA in metabolic disease

Metabolic diseases are a group of conditions resulting from the interaction of genetic, environmental and lifestyle factors that cause abnormal metabolic function in the body. This involves dysregulation of glucose homeostasis, lipid metabolism, immune cells and cytokines (34). Metabolic diseases encompass a range of conditions, such as diabetes mellitus, NAFLD, obesity and insulin resistance (IR). The prevalence of metabolic diseases has been increasing in recent years, leading to an increase in mortality rates and affecting the quality of life of nearly 2 billion people around the world (35). This has become a notable global health issue, placing a burden on public health and medical resources (36). Metabolic diseases have multifactorial pathological mechanisms that cause a series of metabolic disorders. These disorders damage tissues and organs, leading to acute or chronic complications and increasing risk of cardiovascular and cerebral vascular diseases, cancer and neurodegenerative disease (37-39). Therefore, the prevention and treatment of metabolic diseases are key.

AdA and NAFLD. NAFLD is characterized by abnormal fat accumulation in the liver and hepatic steatosis. The severity of the disease can range from simple steatosis to steatohepatitis; in certain cases, it can progress to advanced hepatic fibrosis, cirrhosis and liver failure (40,41). Patients with advanced liver disease and cirrhosis often require liver transplantation, which places a burden on society and the healthcare system. Approximately 30% of the global population is estimated to suffer from NAFLD, and this percentage is increasing (42). The onset and progression of NAFLD are typically associated with steatosis (43), IR (44), iron overload (45), oxidative stress (46) and mitochondrial dysfunction (47). Numerous studies have demonstrated that AdA is involved in these mechanisms and can induce

Table I. Enzymes and regulatory mechanisms of AdA biosynthesis and metabolism.

Metabolic process		Substrate	Enzyme	Catalytic mechanism	Product
Biosynthesis		LA	Δ6-desaturase	Dehydrogenation	GLA
		GLA	ELOVL5	Carbon chain extension	DGLA
		DGLA	Δ5-desaturase	Dehydrogenation	AA
		AA	ELOVL2 and 5	Carbon chain extension	AdA
Cell membrane storage		AdA	$iPLA_2\beta$	Hydrolysis	AdA
Metabolism	Enzymatic oxidative metabolism	AdA	LOX	Insertion of molecular oxygen into carbon-carbon double bonds to form hydroperoxides	DH-HETEs
			COX	Conversion to cyclic endoperoxide by two-step oxidation	DH-PGH_2 DH-TxA_2
			CYP450	Hydroxylation or epoxidation at numerous carbon positions by binding oxygen atoms in a mono-oxygenase reaction	DH-EETs
	Non-enzymatic oxidative metabolic reaction	AdA	-	Radical-driven	F2-dihomo-IsoPs, isofurans
	Peroxisome β-oxidation	AdA	ACS	Activation	Acyl-CoA
		Acyl-CoA	ACOX	Oxidation	2-Transenoyl-CoA
		2-Transenoyl-CoA	DBP, LBP	Hydration	3-Hydroxyacyl-CoA
		3-Hydroxyacyl-CoA	DBP, LBP	Dehydrogenation	3-Ketoacyl-CoA
		3-Ketoacyl-CoA	Thiolyase	Thiolation	Acyl-CoA, Acetyl-CoA

DGLA, dihomo-γ-linolenic acid; AA, arachidonic acid; AdA, adrenic acid; ELOVL, extra-long-chain fatty acid elongase; $iPLA_2\beta$, calcium-independent VIA phospholipase A_2; LOX, lipoxygenase; COX, cyclooxygenase; CYP450, cytochrome P450; DH-HETE, dihomo-hydroxyeicosatetraenoic; DH-PGH_2, dihomo-prostaglandin H_2; DH-TxA_2, dihomo-thromboxane A_2; DH-EET, dihomo-epoxyeicosatrienoic acid; F2-dihomo-IsoP, F2-dihomoisoprostane; ACS, acyl-CoA synthetase; ACOX, acyl-CoA oxidase; BP, bifunctional protein.

oxidative stress, exacerbate inflammatory responses and cause cellular damage, thereby accelerating the pathological process of NAFLD (1,5,48,49).

AdA induces hepatocyte injury via oxidative stress. Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) and antioxidant defences, contributes to hepatocyte injury in NAFLD (50). *In vitro* assay using HepG2 cells has demonstrated that AdA increases intracellular ROS production, leading to oxidative stress, decreased cell viability and a dose-dependent increase in cell death (1). Superoxide dismutase (SOD), glutathione peroxidase (Gpx) and haem oxygenase-1 (HO-1) are intracellular antioxidant defence enzymes (51). In cells treated with 500 μM AdA, SOD2 and HO-1 mRNA expression increases, while Gpx1 mRNA expression decreases. These findings suggest activation of the antioxidant defence mechanism in response to ROS generation, which compensates for the increase in SOD2 and HO-1 expression (1). However, AdA-induced ROS over-accumulation exceeds the antioxidant defence capacity and decreases expression of Gpx1, leading to oxidative stress (1). In conclusion, AdA induces cell oxidative stress injury by increasing the production of ROS and downregulating expression of Gpx1 (1). Other studies have shown that in a male Sprague-Dawley rat model of NAFLD induced by intraperitoneal injection of 0.01, 0.05 and 0.20 μmol/kg 3,3',4,4',5-pentachlorobiphenyl for 3 months, the levels of AdA increase in a dose-dependent manner (52), which results in a decrease in the hepatic glucose levels and peroxisomal oxidation levels of FAs, leading to hepatic steatosis and disturbing intrahepatic redox homeostasis and antioxidant enzyme levels (53-55).

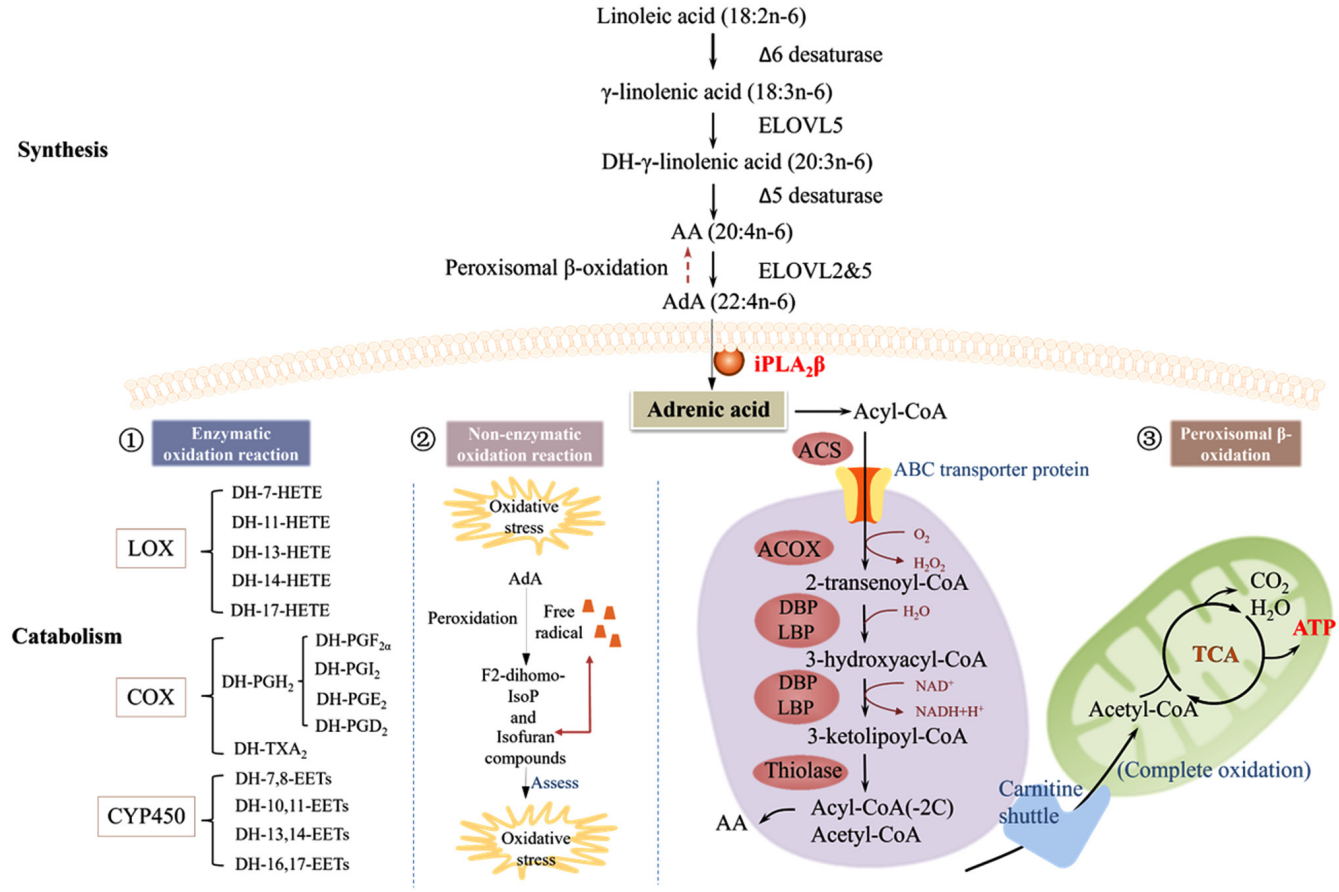

Figure 2. Metabolism of AdA. AdA synthesis process primarily depends on the n-6 fatty acid metabolic pathway. AdA is incorporated into the cell membrane for storage; upon stimulation of the cell, AdA is released from the cell membrane via iPLA$_2$β, thereby participating in metabolic generation of various active molecules. (1) AdA is primarily metabolized by the LOX, COX and CYP450 pathways to produce various bioactive lipids. (2) Non-enzymatic oxidation reaction of F2-DH-IsoPs and isofurans is produced by free radical-driven non-enzymatic peroxidation of AdA in the presence of oxidative stress. (3) Peroxisomes β-oxidise AdA and shorten the carbon chain, which is transferred to the mitochondria to participate in the TCA cycle and produce ATP as an energy source. AdA can be reverse-converted by peroxisomal β-oxidation to AA. AdA, adrenic acid; AA, arachidonic acid; iPLA$_2$β, calcium-independent VIA phospholipase A$_2$; LOX, lipoxygenase; COX, cyclooxygenase; CYP, cytochrome P; F2-DH-IsoP, F2-dihomo-isoprostane; TCA, tricarboxylic acid; ELOVL, extra-long-chain fatty acid elongase; HETE, hydroxyeicosatetraenoic acid; PG, prostaglandin; TXA, thromboxane A; EET, epoxyeicosatrienoic; ACS, acyl-CoA synthase; ABC, ATP-binding cassette; ACOX, acyl-coenzyme A oxidase; DBP, D-bifunctional protein.

AdA promotes NAFLD progression through an immune-inflammatory response. The progression of NAFLD to severe stages is driven by hepatocyte injury and inflammation. Lipotoxic effects occur due to excessive accumulation of harmful lipids in subcellular structures, such as cell membranes, endoplasmic reticulum and mitochondria (56). This leads to hepatocyte injury and the release of inflammatory cytokines (57). Injured hepatocytes release intracellular lipids and harmful molecules from intracellular organs, contributing to the inflammatory response, which activates and infiltrates immune cells, exacerbating the degree of hepatocyte injury and increasing the intensity and persistence of the immune response. This aggravates pathological damage to the liver, which may lead to severe consequences such as cirrhosis and hepatocellular carcinoma (58).

TCRαβ double-negative T (DNT) cells are a distinctive subset of T cell populations, predominantly present in the liver. These cells serve as immunomodulatory agents via the secretion of cytotoxic molecules, including granzyme B (GZMB) and perforin (59,60). It has been demonstrated that the apoptosis of TCRαβ DNT cells is markedly enhanced in patients with NAFLD. The adoptive transfer of DNT cells has been shown to inhibit accumulation of hepatic fat, reduce inflammation and hepatic fibrosis and consequently inhibit progression of NAFLD and NASH (61). AdA has been linked to the apoptosis of hepatic DNT cells in mice with NAFLD (49). *In vitro*, AdA induces apoptosis of TCRαβ DNT cells via downregulation of the PI3K/AKT signalling pathway and mRNA expression of downstream molecule c-Myc. Additionally, AdA decreases GZMB secretion, increases levels of pro-inflammatory CD4 and CD8 cells and decreases levels of anti-inflammatory CD8$^+$ regulatory T cells (49). This, in turn, has been shown to reduce the immunosuppressive function of TCRαβ DNT cells and promote progression of NAFLD (49).

AdA markedly elevates the levels of pro-inflammatory cytokines and triggers an inflammatory response in hepatocytes. *In vitro,* 0.5 mM AdA pretreatment increases the levels of autocrine tumour necrosis factor-α (TNFα) in HepG2 cells (5). Additionally, AdA pretreatment enhances TNFα-induced inflammatory response in HepG2 cells, as evidenced by increased mRNA levels of various pro-inflammatory cytokines, including IL-8, macrophage inflammatory protein 1β (MIP1β) and monocyte chemoattractant protein 1 (MCP1) (5). This indicates that AdA not only stimulates

inflammatory pathways directly in hepatocytes but also significantly enhances TNFα-mediated inflammatory signalling, thereby potentially contributing to a broader pro-inflammatory environment in liver pathology.

AdA promotes fibrosis by upregulating pro-fibrotic chemokine expression. Hepatic fibrosis is the accumulation of collagen fibres in liver tissue, resulting in the formation of excessive connective tissue. This can lead to impaired liver function, cirrhosis and liver failure (62). It is a key predictor of mortality in patients with NAFLD (63). The activation, proliferation and transformation of hepatic stellate cells (HSCs), the principal cell type responsible for synthesizing the extracellular matrix in the liver, are key steps in the process of liver fibrosis (64). Chemokines have pro-fibrotic effects (64). IL-8 activation stimulates stellate cell activation, whereas MCP1 and MIP1β can direct stellate cell migration (65,66). HSCs express C-C chemokine receptor 2 and 5 receptors for MCP1 and MIP1β (67). Horas *et al* (5) showed that 0.5 mM AdA treatment increases mRNA expression levels of the chemokines IL-8, MIP1β and MCP1 and fibroblast cytokine TGFβ1 in HepG2 cells and enhances activation of hepatic stellate cells, leading to extracellular matrix synthesis and liver fibrosis. These findings suggested that AdA promotes fibrotic progression by upregulating hepatocyte chemokine expression.

AdA may also contribute to progression of NAFLD through other pathways. Studies have shown that peroxisomal β-oxidation, the first step catalysed by acyl-coenzyme A oxidase 1 (ACOX1), may be impaired during progression from NAFLD to NASH and ACOX1 levels are decreased in NASH mice (5,68). Mice lacking the ACOX1 gene develop severe hepatic steatosis at a young age. By 5 months of age, hepatocytes begin to undergo apoptosis and form steatogranulomas that progress to hepatocellular carcinoma (69). Additionally, expression of ACOX1 in patients with NASH decreases with disease progression (70). Thus, impaired catabolism of AdA may mediate the progression of NAFLD. However, additional direct evidence is needed.

AdA can serve as a biomarker for liver injury. An increasing number of studies have shown a positive association between peripheral blood levels of AdA and liver injury (1,5). In patients with drug-induced liver injury (DILI), the ratio of serum ω-6/3 PUFA is significantly elevated (71). AdA may serve as an ideal predictive model for chronic risk in the acute phase of DILI (12). Studies have shown that esterified and unesterified free AdA is elevated in patients with NASH (72) and patients with NASH-associated hepatocellular carcinoma have higher plasma AdA concentrations than healthy controls (49,73). Furthermore, compared with healthy children, children with severe steatosis show a trend toward increased plasma AdA (74). Mice with NASH induced by high-fat diet (HFD) deficient in choline and amino acids exhibit significantly greater levels of free AdA and AdA-containing phospholipid species in the liver and plasma than mice fed a normal diet (5). Additional studies have shown the notable increase in free AdA levels in plasma and liver of NASH mice may be attributed to an increase in endogenous synthesis and decrease in AdA catabolism in hepatic peroxisomes (5,20). Furthermore, plasma AdA levels in patients with NAFLD are positively associated with serum alanine aminotransferase levels (5,75). Although the aforementioned studies indicate that AdA levels may be indicative of the extent of hepatocellular damage, other studies have proposed an alternative perspective (20,76). In patients with hepatitis B virus (HBV)-associated cirrhosis, a positive association is observed between serum AdA levels and expression of peroxisome proliferator-activated receptor γ (PPARγ) in HSCs, indicating AdA may play a pivotal role in regulating lipid metabolism. Following 48 weeks of entecavir treatment, a significant restoration of PPARγ expression is observed in HSCs of patients with HBV-associated cirrhosis, accompanied by an increase in AdA levels (76). Thus, AdA may affect lipid metabolism by regulating PPARγ expression, thereby contributing to the pathological state of cirrhosis.

Taken together, the aforementioned findings indicated that AdA accumulation mediates disease progression in NAFLD by inducing oxidative stress, activating the immune-inflammatory response and promoting the expression of hepatic fibrosis chemokines. Additionally, AdA serves as a biomarker of liver injury, reflecting the extent of damage to hepatocytes. However, in certain diseases such as HBV-associated cirrhosis, AdA may also promote liver repair (Fig. 3).

AdA and obesity. There may be a link between obesity and plasma AdA levels. Studies in humans have shown that the percentage of plasma AdA is significantly greater in overweight/obese children than in normal-weight children (74,77). Similarly, an animal study has shown that rats fed HFD have enlarged adipocytes and significantly greater plasma AdA levels than rats fed high-fructose diet (78). These findings suggested that obesity is associated with elevated plasma AdA levels. Untargeted metabolomics have shown that AdA is a common metabolite in IR and obese patients (79) but to the best of our knowledge, direct evidence linking AdA to obesity and adipocyte dysfunction is limited (18).

Phospholipases responsible for releasing AdA from membrane phospholipids may serve a role in obesity-related processes. Monge *et al* (27) demonstrated $iPLA_2\beta$ regulates the mobilization and release of AdA from membrane phospholipids of innate immune and inflammatory cells. Studies have shown that $iPLA_2\beta$ is associated with an increased percentage of body fat and risk of T2DM (80,81). Mice lacking $iPLA_2\beta$ are at decreased risk of obesity, IR, dyslipidaemia and fatty liver (82). Additionally, knocking down $iPLA_2\beta$ in 3T3-L1 inhibits the differentiation of 3T3-L1 cells into adipocytes induced by hormones (83). In conclusion, population studies, animal models and cellular experiments have shown that $iPLA_2\beta$, which mobilizes and releases AdA, promotes development of obesity.

In conclusion, an association exists between plasma AdA levels and obesity, indicating that AdA may serve a key role in the development of obesity and its associated metabolic disorders. In particular, the role of $iPLA_2\beta$ as a key enzyme for AdA release in the development of obesity offers novel insight into the molecular mechanism of obesity. Further research on the association between AdA and obesity should investigate its impact on adipocyte differentiation through animal models and 3T3-L1 cell experiments, examine obesity phenotypes alongside metabolomics and establish clinical trials to evaluate the effectiveness of supplements that decrease AdA levels for obese patients.

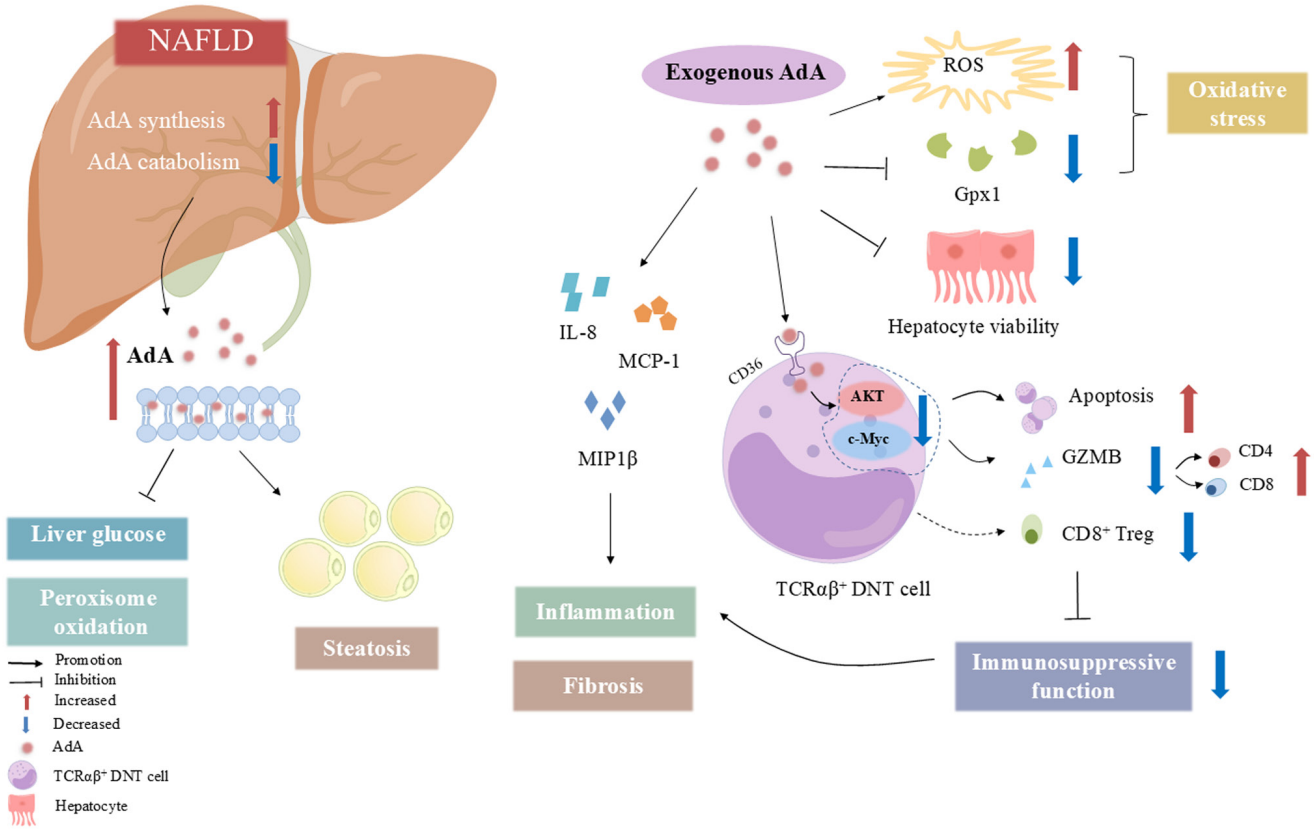

Figure 3. Mechanism of action of AdA in NAFLD. Enhancing endogenous synthesis and decreasing catabolism of AdA in hepatic peroxisomes notably increases levels of AdA-free and AdA-containing phospholipids in the liver and plasma. This can lower hepatic glucose levels and decrease peroxisomal oxidation, contributing to liver steatosis. Exogenous AdA treatment elevates cellular ROS, decreases the expression of the antioxidant enzyme Gpx1, causes oxidative stress damage and impairs cell viability. AdA also raises mRNA levels of chemokines IL-8, MIP1β and MCP1, which promote inflammation and fibrosis. *In vitro*, exogenous AdA stimulation of TCR DNT cells induces apoptosis by downregulating the PI3K/AKT signalling pathway and its downstream molecule, c-Myc. This reduces GZMB secretion, increases pro-inflammatory $CD4^+$ and $CD8^+$ T cells and decreases anti-inflammatory $CD8^+$ Treg levels, thereby diminishing the immunosuppressive function of TCRαβ DNT cells and advancing NAFLD progression. AdA, adrenic acid; NAFLD, non-alcoholic fatty liver disease; ROS, reactive oxygen species; Gpx, glutathione peroxidase; MIP, macrophage inflammatory protein; MCP, chemoattractant protein; TCR, T cell receptor; DNT, double-negative T; GZMB, granzyme B; Treg, regulatory T cell.

AdA decreases insulin sensitivity by modulating the insulin signalling pathway. Insulin signalling refers to transmission of specific biological effects within a cell by insulin through binding to its receptor and triggering signalling processes. Insulin activates the phosphatidylinositol 3-kinase (PI3K)/Akt pathway by binding to the insulin receptor on the cell surface and phosphorylating insulin receptor substrate 1 (IRS1). This pathway promotes translocation of glucose transporter 4 to the cell membrane of adipocytes and muscle cells, allowing glucose uptake and lowering blood glucose concentrations (84). The catalytic subunit of PI3K, p110β, is highly sensitive to insulin signalling (84). Additionally, expression levels of p110 and IRS1 are reduced in the muscle tissue of patients with IR (85). Studies report increased levels of AdA in liver of diabetic rats (86,87). Huang *et al* (78) established a rat model of HFD-induced IR and found that plasma AdA levels are significantly elevated. In addition, a human study has reported a negative association between expression of IRS1 and p110β in the visceral adipose tissue of obese patients and AdA levels (11). The aforementioned studies indicate that AdA may impair the IRS1/PI3K signalling pathway, resulting in decreased insulin sensitivity in various tissues and organs, including the liver and visceral adipose tissue. This may contribute to development of IR in the body. However, further direct evidence is required to validate this hypothesis.

In conclusion, the metabolism of AdA is associated with insulin sensitivity. Furthermore, elevated levels of AdA worsen metabolic disturbances in the IR state, highlighting the potential role of AdA in regulating insulin signalling and maintaining metabolic homeostasis.

AdA indirectly mediates T2DM and its complications via ACSL4 in the ferroptosis pathway. T2DM is a syndrome caused by a combination of etiological factors, including genetic and environmental factors. Pathophysiological disorders resulting from obesity, high-calorie diet and sedentary lifestyles impair glucose homeostasis and predispose individuals to T2DM (88). Forouhi *et al* (89) found high plasma levels of AdA are positively associated with the risk of developing T2DM. Therefore, inhibiting AdA may be a promising treatment for T2DM.

Ferroptosis is a type of programmed cell death caused by iron-dependent lipid peroxidation and is associated with development of diabetes and its complications (90). The onset of ferroptosis requires intracellular free iron, which catalyses the peroxidation of PUFAs in the lipid bilayer, producing highly reactive lipid peroxides that disrupt the integrity and stability of the cell membrane. Multiple metabolic pathways

regulate this process, including redox homeostasis, iron and lipid metabolism and mitochondrial activity (91).

AdA-containing phosphatidylethanolamines (PE-AdA) and PE-AA, key phospholipids in initiation of ferroptosis, can be oxidized by LOX, producing toxic lipid peroxides and inducing ferroptosis (92,93). Specifically, acyl-CoA synthase long-chain family member 4 (ACSL4), one of the genes responsible for initiation of ferroptosis, can selectively catalyse the binding of AdA and AA to CoA to form AdA-CoA and AA-CoA, which promotes esterification and activation of AdA and AA; therefore, ACSL4 may be a potential target or regulator of ferroptosis (94). In addition to its direct involvement in ferroptosis, AdA indirectly exacerbates lipid peroxidation and ferroptosis susceptibility in adrenocortical cells by promoting steroid synthesis (95,96). According to Doll *et al* (97), knockdown of ACSL4 in pituitary fibroblast α (Pfa)1 cells decreases levels of PE-AdA and PE-AA, thereby inhibiting ferroptosis. Conversely, exogenous supplementation of AdA/AA renders ACSL4 knockout Pfa1 cells susceptible to ferroptosis. Furthermore, ferroptosis is associated with IR and insulin secretion disorder in DM (98). Research has shown that antihyperglycemic agents, particularly thiazolidinediones, inhibit ACSL4 expression and decrease ferroptosis, thereby ameliorating metabolic disorder in diabetes (97). Therefore, ACSL4, AdA and AA may be potential targets for diabetes treatment.

AdA is associated with diabetic complications. AdA not only serves as a substrate promoting ferroptosis but also serves as an important biomarker. As one of the most abundant FAs in the retina, AdA can undergo lipid peroxidation induced by pathological conditions such as hyperglycaemia, resulting in accumulation of ROS and oxidative stress damage. Studies have demonstrated that serum AdA and its metabolite, DH-IsoP, can be used to assess the severity of a range of retinopathies, including diabetic retinopathy (99-101). Systemic chronic inflammation represents a key pathological feature of T2DM and is a major contributor to multiorgan complications (102). AdA may function as an epigenetic regulator of production and secretion of inflammatory cytokines. A significant positive association has been shown between the circulating blood levels of AdA and methylation levels of the pro-inflammatory cytokine TNF (103). This indicates AdA serves as an intermediate in the alleviation of inflammation by promoting methylation of TNF-encoding genes (103). This phenomenon is exclusively observed in the female population, suggesting that sex differences may influence the epigenetic regulatory effects of AdA (103).

AdA and ACSL4 are potential mediators and therapeutic targets for T2DM complications. Furthermore, diabetes can lead to complications including diabetic cardiomyopathy and neuropathy, vascular injury and pancreatic dysfunction (104). To the best of our knowledge, there are no population studies or animal experiments on the association and mechanism of action between these diabetic complications and AdA, however, several studies have confirmed associations and potential mechanisms of action of AdA with chronic kidney disease and vascular endothelial function (105,106). Therefore, AdA is a promising therapeutic target for research. Future studies should explore the potential of AdA as a biomarker for monitoring risk and extent of diabetes and its complications to facilitate development of individualized preventive and therapeutic programs.

4. Mechanism of AdA in atherosclerosis (AS)

AS is a chronic inflammatory disease that affects the arterial wall. Its occurrence is associated with multiple factors: One of the early pathological processes of AS is the accumulation of lipids in the intima-media layer. Low-density lipoprotein is a plasma lipid that is deposited in the arterial intima, causing inflammation and oxidative stress, which can cause endothelial dysfunction. A damaged arterial wall triggers an inflammatory and fibroproliferative response (107). Leukocytes and monocytes migrate into the vessel wall, releasing inflammatory mediators such as cytokines and chemokines that exacerbate the inflammatory response. The body responds to repair damaged arterial walls via the proliferation of smooth muscle cells and the synthesis of collagen fibres, leading to a fibroproliferative response (108). The combination of lipid accumulation, endothelial dysfunction, inflammatory response and fibroproliferation leads to vascular smooth muscle cell proliferation and extracellular matrix changes, forming AS plaques and thickening of the arterial wall (109).

AdA and its metabolites serve a role in regulation of vascular tone and function in several vascular beds, triggering physiological responses. The production of DH-PGI_2 and DH-16,17-EET by AdA via the COX and CYP450 metabolic pathways activates K^+ channels in vascular smooth muscle cells (29). This results in increased K^+ efflux, leading to hyperpolarisation and vasodilation in bovine coronary vascular smooth muscle cells (29). This concentration-dependent relaxation is blocked by COX and CYP450 inhibitors and potassium channel blockers (110). Endothelial and glomerular zone cell-derived DH-16,17-EET from the bovine adrenal cortex activates BKCa channels and exerts a hyperpolarising effect, which is instrumental in maintaining normal adrenal function and ensuring appropriate blood flow supply. The regulatory mechanism is reversed by EET antagonism, hyperkalaemia and CYP450 inhibitors (2). By contrast, inhibition of COX has no effect on vasorelaxation in the adrenal vascular system (2). Campbell *et al* (9) demonstrated that AdA is rapidly metabolized by COX to 1α,1β-dihyperprostaglandin E_2 (DH-PGE_2) and DH-$PGF_{2\alpha}$ in human umbilical vein endothelial cells, thereby inhibiting platelet aggregation. AdA has also been shown to compete with AA for the conversion of COX, inhibit oxidation of AA and reduce the synthesis of vasodilator and vasoconstrictor PGs, thereby modulating the vascular effects of PGs (111). The aforementioned studies demonstrate the role of AdA and its metabolites in physiological regulation of vascular function and blood flow supply. Furthermore, AdA has been found to modulate pathological processes in vascular disease (9).

AdA may serve as a marker for the risk of developing cardiovascular disease. A cohort study of patients at high risk of coronary artery disease found a positive association between AdA and expression levels of inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP), IL-6, fibrinogen and vascular cell adhesion molecule 1 (6). This association directly contributes to the increased risk of death from

coronary artery disease, with a mortality rate 10% higher than that observed in healthy controls (6); this was confirmed by meta-analysis examining the association between n-6 FAs and the likelihood of cardiovascular disease (112). A study discovered that individuals with elevated serum AdA levels are at increased risk of coronary heart disease, myocardial infarction and aortic stroke (113). Additionally, these patients demonstrate higher levels of fasting glucose, LDL-cholesterol and high-DL-cholesterol (113). Furthermore, excessive consumption of dietary oat bran leads to increased levels of AdA and its oxidized products F2-DH-IsoPs and DH-isofuran compounds in the cardiac tissue of apolipoprotein E-knockout mice, which is a model of AS (114); additionally, pro-inflammatory products HETE and $PGF_{2\alpha}$ increase, whereas hydroxy DHA, an oxidized product of PUFA with anti-inflammatory properties, decreases (114). This imbalance in pro- and anti-inflammatory mediators contributes to disruption in cardiovascular function and increases susceptibility to inflammation-driven vascular damage (115), linking high AdA levels with cardiovascular pathology and systemic inflammation.

AdA contributes to plaque formation by enhancing tissue factor (TF) activity. TF, which initiates the coagulation process, is expressed by thrombin-stimulated endothelial cells (116). Tardy *et al* (106) enriched human endothelial cell culture medium with FAs (eicosapentaenoic and docosapentaenoic acid and AdA) and found that only AdA significantly enhanced TF activity of thrombin-stimulated endothelial cells following 4 h thrombin stimulation. TF activation initiates a coagulation cascade leading to thrombus formation. These thrombi obstruct arterial flow, leading to cardiovascular events. Additionally, they cause release of pro-inflammatory factors and oxidative stressors from platelets and inflammatory cells, which worsen endothelial inflammatory responses and vessel wall damage, thereby contributing to plaque formation (117,118). TF expression in monocytes, platelets and platelet-leukocyte aggregates is pro-thrombotic in patients with acute coronary syndrome (119). In mice, pharmacological inhibition of TF activity decreases AS plaque formation (120). Consequently, AdA may mediate formation of thrombotic plaques in AS by activating endothelial cell TF activity.

AdA mediates AS by modulating AS risk factors. Hypertension, elevated plasma homocysteine (Hcy) levels, excessive alcohol consumption and dyslipidaemia are risk factors for the development of AS (121). Studies have shown that serum AdA levels are associated with these risk factors and contribute to development of AS (122-126).

Chronic hypertension causes damage to the endothelium and triggers inflammatory responses in blood vessels. This promotes plaque formation and thickening of arterial walls. Hypertension increases mechanical stress on the vessel wall, increasing the susceptibility of arteries to structural and functional abnormality (127). In spontaneously hypertensive rats (SHRs), a high-DHA diet reduces AdA levels. This may be attributed to the competitive inhibition of D5D activity by DHA, which subsequently leads to a decrease in AdA synthesis and a subsequent decrease in blood pressure (122). Additionally, untargeted serum metabolomic analysis shows that egg white peptides administered to SHRs at a dose of 50 mg/kg body weight for 4 weeks is associated with reduced AdA levels and antihypertensive effects (123). The application of metabolomic techniques in observational studies has enabled identification of key metabolic signatures associated with coronary artery disease (128,129). These signatures have the potential to facilitate more accurate disease diagnosis and predict patient prognosis and mortality (130).

Elevated plasma Hcy levels are an independent risk factor for cardiovascular disease. A study on middle-aged and elderly hyperlipidaemic patients found a significant positive association between plasma Hcy and AdA (124). AdA may regulate gene expression of enzymes that synthesize and metabolize plasma Hcy (124). However, the association between Hcy and AdA and the molecular mechanisms by which AdA regulates Hcy require further investigation.

Excessive alcohol consumption is a risk factor for AS; as alcohol consumption increases in male patients, so do serum levels of AdA (125). Excessive alcohol consumption may interfere with absorption, synthesis or metabolic processes of serum AdA (125).

Additionally, AdA can contribute to accumulation of TG and cholesteryl esters, leading to lipid deposition and abnormal distribution (8). By contrast, decreasing levels of n-6 PUFAs such as AdA *in vivo* and lowering the n-6/n-3 PUFA ratio can notably improve lipid metabolism (126). A recent study indicated that AdA may facilitate regression of cirrhosis by regulating lipid metabolism (76). In patients with HBV-associated cirrhosis, serum AdA is positively associated with PPARγ in HSCs (76). Furthermore, serum AdA levels and PPARγ expression in HSCs are significantly elevated following 48 weeks of entecavir treatment (76). PPARγ may be a key metabolic regulator of hepatic lipid metabolism and inflammation (131). AdA may confer benefits for improvement of liver cirrhosis via this signalling pathway.

Notably, a study examining FA composition of breast milk has demonstrated a positive association between AdA and the incidence of perinatal and persistent maternal cardiometabolic disorder (132). Therefore, regulating AdA activity may be a promising therapeutic approach for improving AS pathology and clinical outcomes. However, the precise mechanism of action of AdA in modulating AS risk factors remains unclear. Further experimental and clinical studies are necessary to explore this phenomenon.

In conclusion, AdA and its metabolites not only regulate physiological processes within blood vessels and blood flow but also regulate pathological processes associated with vascular disease. AdA contributes to AS plaque aggregation and thickening of the arterial wall by increasing production of inflammatory mediators, enhancing the activity of TF, leading to thrombosis, and modulating the risk factors for AS (high blood pressure, elevated Hcy levels, excessive alcohol abuse and dyslipidaemia) to drive the onset and progression AS (Fig. 4).

5. Mechanisms of AdA in neurological disorder

AdA is the third most prevalent PUFA in grey matter glycerophospholipids of the brain and is the most abundant PUFA in white matter ethanolamine phosphoglycerides (133). AdA is key for neuronal growth and myelin lipid enrichment and

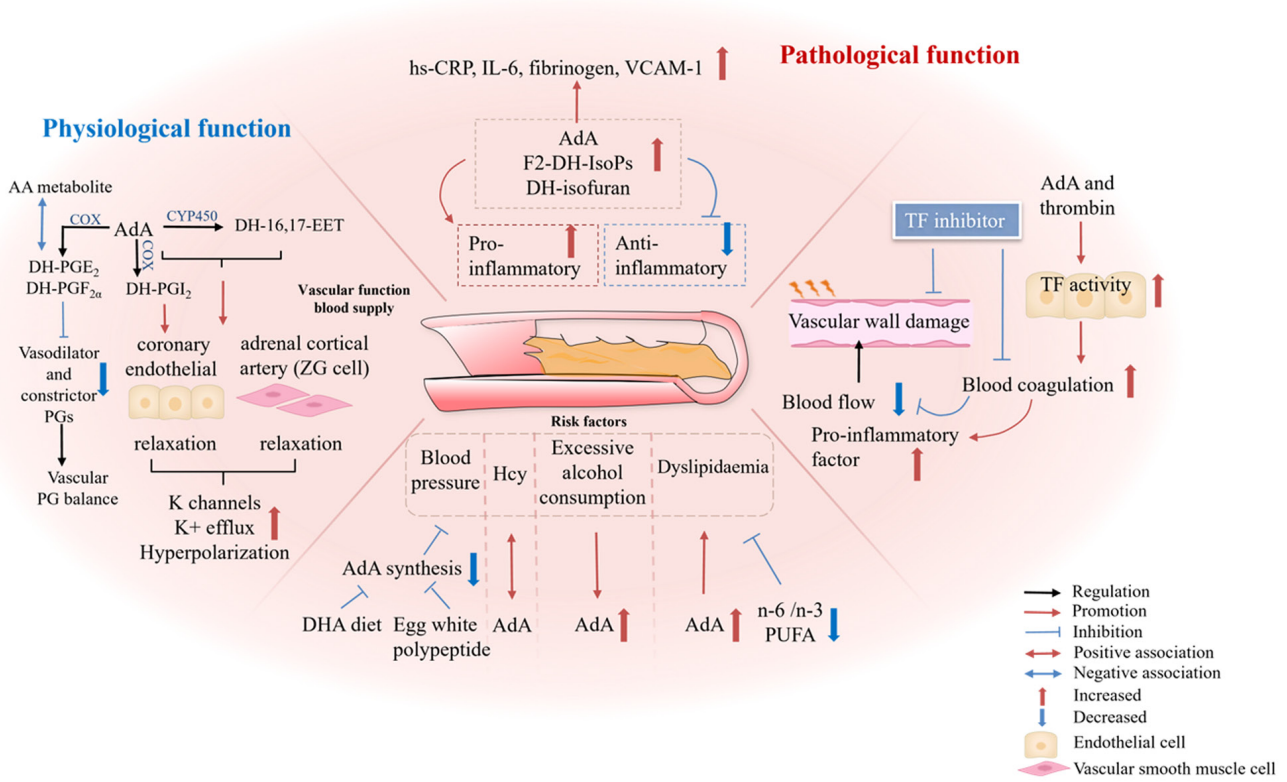

Figure 4. Mechanism of AdA in AS. AdA and its metabolites regulate physiological vascular function and blood flow supply. Additionally, AdA modulates pathological processes in vascular disease. AdA contributes to an elevated risk of coronary artery disease by increasing levels of inflammatory mediators, including hs-CRP, IL-6 and VCAM-1. Elevated levels of AdA and its oxidative products increase pro-inflammatory compounds and decrease anti-inflammatory hydroxy DHA, which impairs cardiovascular function. Stimulation of endothelial cells by AdA and thrombin increases TF activity, which initiates the coagulation cascade and may lead to thrombosis and obstruction of arterial flow. AdA affects other risk factors for AS, including high blood pressure, plasma Hcy levels, excessive alcohol intake and dyslipidaemia. A diet rich in DHA and egg white peptides inhibits the production of AdA, thereby lowering blood pressure. There is a positive association between plasma Hcy levels and AdA. Furthermore, heavy alcohol consumption increases serum AdA levels. AdA contributes to TG and cholesterol accumulation, promoting dyslipidaemia. AdA, adrenic acid; hs-CRP, high-sensitivity C-reactive protein; VCAM, vascular cell adhesion molecule; DHA, docosahexaenoic acid; TF, tissue factor; AS, atherosclerosis; Hcy, homocysteine; TG, triglyceride; IsoP, isoprostane; ZG, zona glomerulosa; CYP, cytochrome P; DH, dihomo; EET, epoxyeicosatrienoic; PG, prostaglandin; COX, cyclooxygenase; PUFA, polyunsaturated fatty acid; AA, arachidonic acid.

is implicated in modulation of physiological and pathological responses in the nervous system (134). Wijendran *et al* (135) demonstrated that dietary intake of AA can extend the carbon chain *in vivo* to produce AdA, which accumulates in the brain, suggesting that the extended action of AA can produce AdA in the brain. Nevertheless, levels of FAs in the brain largely depend on availability of the peripheral FA pool due to the markedly low activity of enzymes involved in FA metabolism in the brain (136). Orally ingested AdA can cross the blood-brain barrier (BBB) as an ethyl ester after metabolic conversion and accumulates in the brain, indicating AdA exerts biological activity within the central nervous system (CNS) (137). AdA has been found to play a significant role in neurodevelopmental disorder and neurodegenerative pathologies, mediating key pathophysiological processes (138,139). The levels of AdA and its oxidized products in the body may serve as biomarkers in pathological conditions such as AD, Rett syndrome (RTT), Parkinson's disease (PD) and epilepsy (15,17,105,140,141). Furthermore, in rats exposed to heavy metal mixture, serum metabolomic analysis reveals notable abnormalities in the biosynthetic pathways of unsaturated FAs, as well as significantly elevated levels of AA and AdA (142). These metabolic changes may be associated with heavy metal-induced neurological dysfunction (142).

AdA and neurodevelopmental disorder. Neurodevelopmental disorders are a group of genetic or environmental conditions that affect brain development and function. These include attention deficit hyperactivity disorder (ADHD) and RTT (143). Several studies have revealed that AdA serves a critical regulatory role in neurodevelopmental disorder (144-146).

ADHD is a prevalent neurodevelopmental disorder that impairs capacity to concentrate, consequently influencing academic, social, and daily living functions. A study has shown a negative association between AdA and personality stability traits, including emotional stability, responsibility and agreeableness (144). Personality traits in adolescent males with ADHD may be associated with FA composition of erythrocyte membranes. Therefore, modifying FA content may affect personality traits and behaviours of adolescent males with ADHD. Wu *et al* (145) combined lipidomics with psychological Bayley-III scale screening and found that the AdA content in human breast milk lipids is significantly negatively associated with infant adaptive behaviour development. The aforementioned study involved supplementing

Caenorhabditis elegans L1-L4 larvae with AdA to simulate AdA uptake of infants through breast milk: AdA uptake at concentrations >1 μM during the larval stage of *C. elegans* negatively impacts development of locomotive behaviours, foraging ability, chemotaxis and aggregation behaviours. AdA supplementation during larval stages impairs neurobehavioral development by upregulating intracellular ROS levels, blocking 5-hydroxytryptaminergic synthesis and fragmenting 5-hydroxytryptaminergic neurons (145). Additionally, AdA inhibits expression of dauer formation abnormal 16 (DAF-16) and DAF-16-regulated genes metallothionein-like protein 1 (MTL-1) and -2 and SOD-1 and -3 in the ROS quenching system, leading to the shortened lifespan of *C. elegans*. Increased intracellular ROS damages DNA and the DNA repair system, leading to accumulated DNA damage and cell death (145). RTT is also a neurodevelopmental disorder caused by a genetic mutation that predominantly affects females. Its first stage is most severe and is characterized by notable loss of neurological function and white matter atrophy (140). During this stage, patients exhibit significantly elevated plasma levels of F2-DH-IsoPs. These levels are positively associated with disease duration and symptom intensity and negatively associated with brain white matter score (146). F2-DH-IsoPs serve as early biomarkers of RTT, reflecting oxidative damage and dysfunction of brain white matter (146).

In summary, there is a negative association between AdA and ADHD, which may affect personality traits and behaviour. In addition, excessively high levels of AdA impair neurobehavioral development and increase intracellular ROS levels.

AdA and AD. AD is a prevalent neurodegenerative condition that results in the deterioration of memory and cognitive and behavioural abilities (147). Ageing is the most notable risk factor for developing AD. The hippocampus is one of the first areas to experience atrophy in AD and is also where neurofibrillary tangles develop initially (148). Phospholipid changes serve a critical role in the pathogenesis of AD (149). AdA-containing phospholipids in the hippocampus and other brain regions decline with age. This phenomenon has been observed in normal ageing and neurodegenerative diseases such as AD (150,151). Another study identified a reduction in AdA in the membrane phospholipid components PE and phosphatidylserin in the parahippocampal cortex of patients with AD (152). This remodelling of membrane lipids may be associated with development of neurological dysfunction. Amyloid β (Aβ) is a marker of neurodegeneration associated with AD (153,154). A cross-sectional study has shown that high serum levels of AdA in older adults with cognitive impairment are associated with low levels of Aβ aggregation in the brain (138), indicating that AdA may exert a protective effect on neurocognitive function. Furthermore, a study of total lipid fractions from disparate regions of the brain has demonstrated that AdA levels are markedly diminished in white matter of the frontal, parietal and parahippocampal regions of the brain in patients with AD, whereas they are 3-4 times higher than normal in grey matter (155). This may indicate varying metabolic and lipid processing patterns in different brain regions.

Neurodegenerative diseases involve lipid peroxidation, which is notable due to the high lipid content and oxygen consumption of brain tissue. The brain is particularly vulnerable to oxidative damage due to low levels of antioxidant enzymes, including catalase and glutathione peroxidase (156). Roberts and Milne (157) demonstrated that levels of the AdA peroxidation products F2-DH-IsoPs are markedly elevated in patients with AD and brain white matter undergoing oxidative damage. This suggests that AdA is rapidly peroxidised when white matter is subjected to oxidative damage, which generates a high quantity of peroxidation products. This partly explains the aforementioned reduction in brain tissue and serum AdA levels in patients with AD.

In conclusion, decreased levels of serum AdA and AdA-containing phospholipids in brain regions in patients with AD may indicate that AdA exerts a neuroprotective effect on cognitive function. However, AdA levels demonstrate contrasting trends in different brain regions, with elevated levels in grey and decreased levels in white matter. Thus, metabolic processes and lipid processing between these regions differ. Further research should determine the mechanisms through which AdA regulates inflammation, neuroprotection and lipid metabolism, as well as its potential as a therapeutic target.

AdA and PD. The primary biochemical characteristic of PD is the aggregation of aberrant α-synuclein (α-SYN) assemblies in neurons, which is mediated by misfolded conformational isoforms of the protein (158). α-SYN is capable of binding to PUFA, which induces the oligomerization of α-SYN and subsequently results in neurotoxicity (159). *In vitro* experiments by Xylaki *et al* (160) utilizing a human neuroblastoma cell line demonstrated that free cytoplasmic AA and AdA are key factors influencing the type of intracellular α-SYN oligomerization. Application of cytosolic phospholipase A_2 ($cPLA_2$) inhibitor GK200 results in a 26% decrease in free AA and a 72% decrease in AdA levels. This regulates the conformational changes of α-SYN, with a decrease in α-helical multimers and the formation of β-sheet oligomers (160). This contributes to the degradation of the α-SYN proteasome and significantly decreases the intracellular α-SYN levels. Decreased levels of free AA and AdA results in diminished cell membrane fluidity and a weakened membrane-binding capacity of α-SYN (160). This enhances cell survival and contributes to the alleviation of the pathological process of PD (160).

In conclusion, AdA and AA serve a key role in PD, influencing α-SYN aggregation and cytotoxicity. This indicates that modulating metabolic levels of AdA and AA may represent a promising therapeutic avenue.

AdA and depression. Depression is a prevalent disorder of the CNS that notably impacts psychosocial functioning and decreases quality of life. Its pathogenesis involves alterations in specific neurotransmitters, dysfunction of the endocrine system and inflammatory responses (161,162). AdA plays a dual role in depression risk. A study using Mendelian randomization to investigate the causal association between FAs and risk of depression found that high levels of AdA are associated with low risk of depression (163). Conversely, a prospective cohort study showed that high serum levels of AdA may be a risk factor for suicide and major depressive episodes in

early pregnancy (164). The aforementioned study evaluated the psychiatric state of pregnant patients and their serum FA composition between the 6 and 13th weeks of gestation. The results showed that high serum AdA levels are associated with a high likelihood of suicidality and major depressive episodes in early pregnancy (164). This contradicts previous studies and suggests the physiological and psychological state of pregnant patients may influence the role of AdA in depression (163,164). Two studies have investigated the association between serum FA patterns and depression in adults: Heightened levels of AdA are associated with increased risk of depression, whereas low levels of ω-6 FAs, including AdA, may protect against depression (165,166). A cross-sectional study revealed that levels of AA, AdA and oleic acid are strongly associated with severity of depressive symptoms as determined by subject work characteristic curve analysis (167). This suggests they may serve as biomarkers for the assessment of depression (167).

Furthermore, studies have demonstrated the potential of AdA to interact with neuroinflammatory processes (15,168). Alterations in gut microbiota and its metabolites may influence onset and progression of depression by regulating the gut-brain axis (169). The active ingredient in the drug Lily Dihuang Tang is metabolised by intestinal flora into FAs, including AdA, after intestinal absorption. Network pharmacological analyses and molecular docking simulations suggest FA metabolism may be one of the potential therapeutic targets of the aforementioned drug (168). Furthermore, the key target gene for depression, FA amide hydrolase (FAAH), demonstrates the strongest binding affinity with AdA (168). FAAH is associated with neuroinflammatory and neurodegenerative disease and FAAH inhibitors may serve as antidepressant drugs (170,171). Thus, AdA may participate in FAAH-mediated neuroinflammatory processes by binding with high affinity to FAAH, influencing development of depression. Furthermore, AdA levels are markedly altered during bacterial lipopolysaccharide (LPS)-mediated neuroinflammation and microglia activation in C57BL/6 mice, serving as a potential biomarker for differentiating between control and LPS-treated groups (172). This indicates that AdA may be associated with LPS-induced neuroinflammatory responses and may regulate inflammatory processes or microglia activation, but the precise mechanisms have yet to be determined. These findings underscore the role of AdA in the study of biomarkers associated with neuroinflammation.

The aforementioned findings demonstrate potential pathogenesis of depression and its causal association with AdA, thereby revealing a role for AdA in the risk of depression. Although certain studies indicate that elevated AdA levels may provide a preventive effect, they may also increase risk of depression in pregnant patients and adults (163). Furthermore, AdA may interact with neuroinflammatory processes. A large-scale longitudinal cohort study is required to compare the relationship between AdA levels and incidence of depression in different populations to elucidate the role of AdA in depression. Furthermore, animal models should be used to examine the effects of AdA on depressive symptoms and its underlying mechanisms, particularly for key target genes associated with depression, such as FAAH. The effect of intestinal flora on AdA production and its role in depression should be investigated, as well as the underlying mechanisms of the gut-brain axis.

Hence, AdA is a risk factor for neurodevelopmental disorder and PD. However, AD may exert a protective effect on neurocognitive function, with a dual role in risk of depression. Its peroxidation product, F2-DH-IsoPs, induces oxidative stress in the CNS and mediates neurological pathology (Fig. 5; Tables II and III).

6. Methods of regulating AdA

Exercise. Exercise has a wide range of physiological effects on the human body, and research supports the benefits of exercise in treating metabolic disorders, improving brain function and preventing cardiovascular disease and cancer (173-175). Exercise can reduce hepatic lipid deposition in T2DM mice by decreasing hepatic AdA concentration, improving IR and lipid metabolism signalling pathways and decreasing inflammation levels (176). Further *ex vivo* experiments have investigated the effects of exogenous AdA treatment on AML12 hepatocytes: Inflammatory factors such as IL-6, Il-1β, TNF-α and MIP1β are activated in the cells following AdA treatment, whereas AdA significantly increases the glucose content in supernatant and decreases expression levels of IRS1, Akt and glucose transporter 2 (176). Furthermore, AdA treatment significantly increases the expression levels of the lipid metabolism-related genes COX1, medium-chain acyl-CoA dehydrogenase and FA transport protein 2 but decreases the expression level of FA transporter molecule microsomal triglyceride transfer protein. Thus, AdA may be key for improving hepatic IR and lipid metabolism and decreasing inflammation in T2DM mice via exercise (176). Furthermore, a randomized controlled trial demonstrated that long-term moderate-intensity exercise training significantly decreases plasma levels of ω-6 FA oxides, such as AdA, and improves overall metabolic health and cardiovascular function in young, sedentary adults (177).

In conclusion, the aforementioned findings underscore the pivotal role of AdA in exercise-induced physiological adaptations and offer novel avenues for further investigation into the association between exercise and lipid metabolism.

Natural products. Several studies have used metabolomic approaches to investigate the metabolic processes and protective mechanisms of natural products and synthetic drugs affecting AdA (18-21,178). Oral administration of AS IV has been demonstrated to decrease serum AdA levels in rats by influencing the unsaturated FA metabolic pathway (21). Moreover, the effects of AS IV involve amelioration of inflammatory response and oxidative stress, alleviating cisplatin-induced AKI. Hence, serum AdA has been reported as a highly sensitive biomarker for the identification of AKI (21). EVO alleviates hyperglycaemia, hyperlipidaemia and IR, whilst also improving oxidative stress and inflammatory response in rats with T2DM. Untargeted metabolomic analysis revealed that EVO treatment affects the levels of 26 metabolites, including AdA (18). Although the precise regulatory mechanisms remain to be elucidated, the metabolic modulatory effects of EVO in T2DM rats may include metabolic pathways associated with AdA (18). Similarly, quercetin exhibits hepatoprotective effects on NAFLD rats by regulating levels of FAs such as AdA and metabolites related to inflammation and oxidative stress (20). According

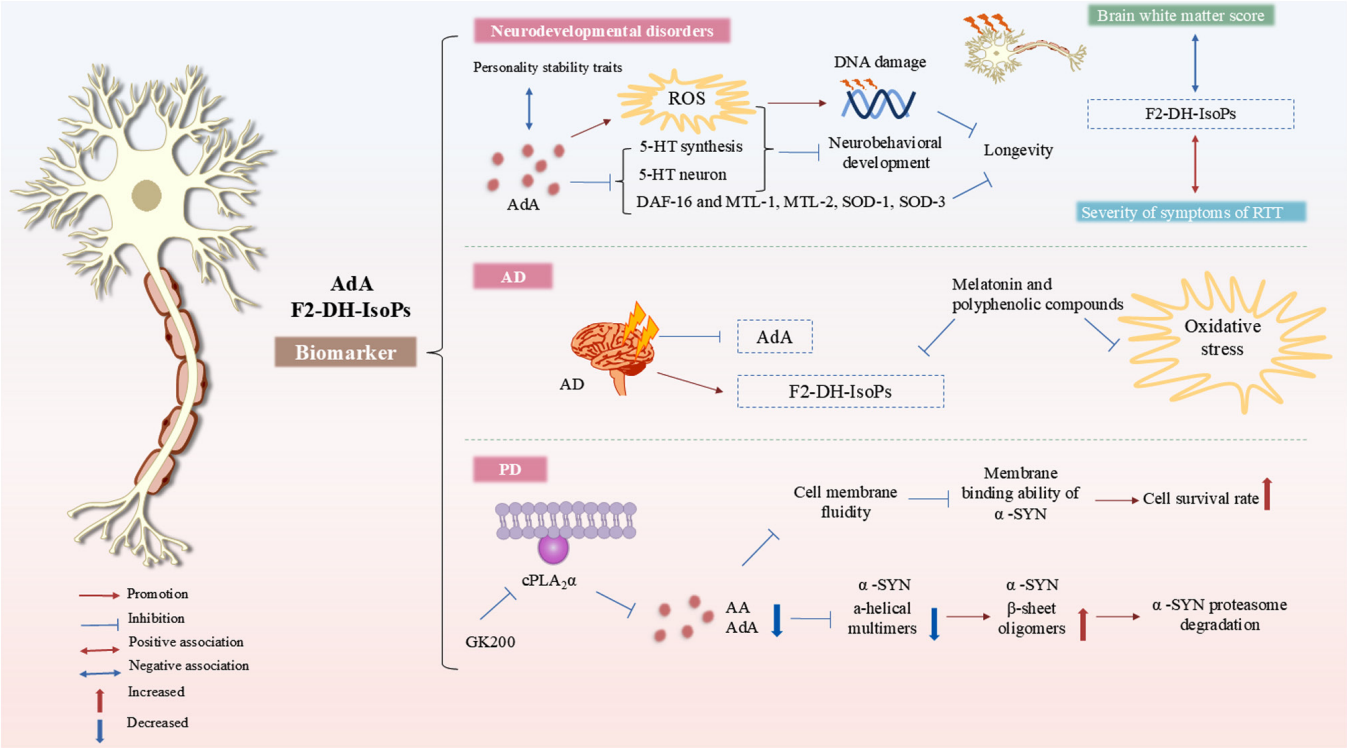

Figure 5. Mechanism of action of AdA in neurological disease. AdA and its oxidation products are potential biomarkers for neurodevelopmental and neurodegenerative diseases. Exogenous AdA increases ROS levels, damages DNA and inhibits 5-HT synthesis, impairing neurobehavioral development. AdA decreases lifespan of *Caenorhabditis elegans* by downregulating expression of ROS-quenching genes such as DAF-16, MTL-1 and -2 and SOD-1 and -3. In RTT, elevated plasma F2-dihomo-IsoPs levels are associated with disease severity. AdA negatively affects traits such as emotional stability. In AD, AdA levels fluctuate, but F2-dihomo-IsoPs remain elevated. Melatonin and polyphenolic compounds mitigate oxidative stress by decreasing F2-dihomo-IsoP levels in the central nervous system. The cPLA$_2$ inhibitor GK200 decreases free AA and AdA levels, causing conformational changes in α-SYN. This leads to fewer α-helical multimers, more β-sheet oligomers and enhanced α-SYN degradation, lowering its intracellular levels. Decreased levels of free AA and AdA also decrease membrane fluidity and weaken α-SYN membrane-binding, improving cell survival and mitigating Parkinson's disease pathology. AdA, adrenic acid; ROS, reactive oxygen species; 5-HT, 5-hydroxytryptaminergic; DAF, dauer formation abnormal; MTL, metallothionein-like protein; SOD, superoxide dismutase; DH, dihomo; RTT, Rett syndrome; IsoP, isoprostane; AD, Alzheimer's disease; cPLA$_2$, cytosolic phospholipase A$_2$; AA, arachidonic acid; SYN, synuclein.

to a previous report, kaempferol regulates the expression of genes associated with FA degradation and metabolic pathways, including CYP2b9 and CYP4a12b (19). This regulation affects nine serum and three liver metabolites, including AA, and improves pathophysiological processes such as energy and lipid metabolism, inflammation and oxidative stress in NASH mice (19). RA improves lipid levels in hyperlipidaemic mice. The underlying mechanism may pertain to RA regulation of the metabolic levels of FAs, including AdA, in the cecum of mice by modulating expression of CYP4a family genes (CYP4a10, 12b, 31 and 32) associated with FA degradation in the liver (178). In addition to its association with metabolic disorder, AdA is associated with inflammatory disease. The administration of prebiotics significantly restores faecal metabolite AdA levels in patients with post-traumatic osteoarthritis (179). Furthermore, there is an association between AdA and development of post-traumatic osteoarthritis (179).

The effects of the aforementioned drugs on AdA metabolism are mediated by common mechanisms and involve cross-talk. AS IV, EVO, quercetin and prebiotics may affect levels of AdA by modulating the unsaturated FA metabolic pathway. Additionally, kaempferol and RA modulate expression of key enzymes for FA degradation, such as the CYP4a family of genes. Moreover, these drugs improve metabolism-associated pathophysiological states by modulating inflammatory responses and oxidative stress. Notably, metabolomic analyses have identified AdA as a potential biomarker in diverse experimental models, demonstrating its role in metabolic regulation (20,123). These shared mechanisms and cross-talk indicate that distinct pharmacological agents may interact via analogous metabolic pathways and biomarkers to regulate AdA levels, improving the pathophysiological process of associated diseases.

In conclusion, alterations in serum AdA metabolism are associated with several pharmacological interventions and influence pathogenesis of numerous pathological conditions, including T2DM, AKI, NASH and NAFLD, indicating the potential value of AdA as a biomarker and therapeutic target.

Dietary nutrition. In a study involving healthy volunteers, the daily consumption of 20 capsules of fish oil concentrate MaxEPA (3.6 eicosapentaenoic acid + 2.4 g DHA) results in a significant decrease in AdA levels in platelet phospholipids from 7.9 to 3.1 mol% (180). Supplementation with 30 mg/day of elemental zinc for 24 months increases the abundance of PUFAs, including AdA, in the erythrocyte membranes of patients with T2DM and improves membrane flexibility (181). A nutritional supplement enriched with polyphenolic compounds

Table II. AdA levels in different disease states.

Disease	Experimental model		Clinical research	Results	(Refs.)
	In vivo	*In vitro*			
NAFLD	PCB126-induced SD male rats			Increased AdA levels	(52)
	Mice induced by MCD diet			AdA is positively associated with apoptosis of DNT cells	(49)
			Patients	AdA is positively associated with ALT	(5,75)
NASH			Patients	Increased levels of esterified and unesterified free AdA in plasma	(72)
	Mice induced by HFD lacking choline and restricted amino acids			Increased levels of free AdA and phospholipids containing AdA in liver and plasma and endogenous synthesis of AdA in liver peroxisome; decreased AdA catabolism	(5)
NASH-associated hepatocellular carcinoma			Patients	Increased plasma AdA concentration	(49,73)
Steatosis			Children with severe steatosis	Increased plasma AdA concentration	(74)
Cirrhosis			Patients with HBV-associated cirrhosis	AdA is positively associated with PPARγ in HSCs	(76)
Obesity			Children	Increased plasma AdA levels	(74,77)
	HFD-fed rats			Increased plasma AdA levels	(78)
IR	Diabetic rats			Increased AdA level in liver	(86,87)
			Obese patients	Increased AdA levels	(11)
T2DM			Patients	Increased AdA levels in plasma	(89)
AS			Patients with high risk of coronary heart disease	Increased AdA level	(113)
	Apo E knockout mice			Increased levels of AdA and its oxidation products in the heart	(114)
	SHRs fed high DHA diet			Decreased AdA synthesis	(122)
	SHRs fed egg white peptides			Decreased AdA level	(123)
			Elderly patients with hyperlipidemia	Plasma Hcy is positively associated with AdA	(124)
			Alcoholic patients	Increased serum AdA levels	(125)
	Rats exposed to heavy metals			Increased AdA level	(142)

Table II. Continued.

Disease	Experimental model		Clinical research	Results	(Refs.)
	In vivo	*In vitro*			
Neurodevelopmental disorder			Adolescent males with ADHD	AdA is negatively associated with personality stability traits	(144)
AD			Healthy elderly adults	Decreased AdA-containing phospholipids	(150, 151)
			Patients	Decreased PE-AdA and PS-AdA; increased F2-dihomo-IsoP levels	(152, 157)
			Elderly patients with cognitive impairment	Decreased serum AdA	(138)
PD		Human neuroblastoma cells treated with GK200		Decreased AdA, α-helix polymer and α-SYN levels; increased β-sheet levels	(160)
Depression			Pregnant patients	Increased serum AdA levels	(164)
			Adults	Elevated AdA levels are associated with higher risk of depression	(165, 166)
	LPS-treated C57BL/6 mice				(172)

AdA, adrenic acid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MCD, methionine-choline deficient diet; HFD, high-fat diet; IR, insulin resistance; T2DM, type 2 diabetes mellitus; AS, atherosclerosis; SHR, spontaneous hypertensive rat; Hcy, homocysteine; ADHD, attention deficit hyperactivity disorder; AD, Alzheimer's disease; PE, phosphatidylethanolamine; PS, phosphatidylserine; PD, Parkinson's disease; LPS, lipopolysaccharide.

inhibits oxidative stress in the CNS by attenuating urinary levels of F2-DH-IsoPs (182). Furthermore, a study analysed the FA content and oxidized lipids in rainbow trout fillets via gas chromatography-mass spectrometry: Using high-oleic sunflower oil for frying reduces AdA levels in fillets, and cooking decreases levels of oxidized n-6 PUFA-derived lipids in the diet (183).

In addition, animal studies have demonstrated that diet can modulate AdA levels *in vivo* (122,123). Consumption of a high-DHA diet results in reduced levels of AdA in SHRs *in vivo*, potentially due to the competitive inhibition of D5D activity by DHA, which reduces AdA synthesis (122). Similarly, in an SHR model, administration of 50 mg/kg body weight of egg white peptides for 4 weeks results in a significant decrease in serum AdA levels (123). Zhou *et al* (184) randomly assigned male Wistar rats to be fed either vitamin A-deficient or an adequate diet for 7 weeks. The vitamin A-deficient rats had elevated levels of AdA in the colonic and hepatic tissue, whereas supplementation with vitamin A decreased the AdA ratio. Feeding Yorkshire sows a diet containing flaxseed decreases AdA levels in the loin and abdomen (185). By contrast, concentrate-fed yak calves experience increased AdA levels in the pancreas, which result in anti-inflammatory and antibacterial effects (186). Previous studies have shown lead poisoning can cause carbon chain elongation of FAs and induce lipid peroxidation, leading to dysregulation of the intracellular antioxidant/pro-oxidant balance system (187,188). In mallards fed a diet containing 200 g/kg lead, plasma cholesterol levels increase, whereas TG levels decrease (189). A notable decrease in pituitary cell membrane lipids, particularly membrane phosphoglycerides, AA and AdA, is observed in young rats that were fed a diet lacking essential fats for 6 weeks following weaning (190).

In conclusion, metabolic levels of AdA are regulated by a variety of dietary nutrients. Changes in AdA levels are associated with physiological and pathological states, both in healthy individuals and in animal models.

Endocrinology. The metabolism of cholesterol esters in the adrenal gland is notably influenced by gonadal and sex hormones in C57BL/10J and DBA/2J mice, and AdA esters are more sensitive to this hormone-regulated response than

Table III. Mechanisms underlying effects of exogenous AdA treatment on different diseases.

Disease	Experimental model		Upregulation/activation	Downregulation/inhibition	(Refs.)
	In vivo	*In vitro*			
NAFLD		500 μM AdA-induced HepG-2 cells	ROS production, oxidative stress	Cell viability, expression of antioxidant enzyme Gpx1	(1)
		50 μM AdA-stimulated TCRαβ and TCRγδ DNT cells	Apoptosis	PI3K/AKT signaling pathway and its downstream molecule c-Myc mRNA expression, GZMB secretion, immunosuppressive function	(49)
		0.5 mM AdA + TNFα-treated HepG2 cells	Autologous TNFα levels, IL-8, MIP1β and MCP1 mRNA expression, inflammation, fibrosis		(5)
AS		$1x10^{-9}$-$1x10^{-5}$ M AdA/ DH-16,17-EET- induced bovine coronary arteries	Concentration-dependent relaxation of bovine coronary endothelial cells, K^+ channels in vascular smooth muscle cells, K^+ efflux, hyperpolarization of vascular smooth muscle cells, vasodilation		(29)
		10^{-8}-10^{-4} M AdA-induced bovine adrenal cortical arteries, zona glomerulosa cells	Concentration-dependent relaxation of adrenal cortical artery and K^+ channels and efflux, endothelial cell hyperpolarization, vasodilation		(2)
		Human umbilical vein endothelial cells treated with AdA and AA	Regulation of homeostasis of vascular PGs	Platelet aggregation, production of PGI_2	(9)
		AdA-enriched human EC cells stimulated with thrombin for 4 h	TF activity, blood clot formation, inflammatory reaction of the blood vessel lining, damage to the blood vessel wall	Arterial blood flow	(106, 117, 118)
Neurodevelopmental disorder	Supplementation of AdA in *Hidradenitis elegans* cryptic rodentia larvae			Neurobehavioral development, 5-hydroxytryptamine synthesis, 5-hydroxytryptaminergic neuron, expression of DAF-16 and its regulatory genes MTL-1 and -2 and SOD-1-3, longevity	(145)

AdA, adrenic acid; NAFLD, non-alcoholic fatty liver disease; ROS, reactive oxygen species; Gpx1, glutathione peroxidase 1; PI3K, phosphatidylinositol 3-kinase; DNT, Double-negative T; GZMB, granzyme B; AS, atherosclerosis; TNF-α, tumor necrosis factor-α; MIP1β, macrophage inflammatory protein 1β; MCP1, monocyte chemoattractant protein 1; TF, tissue factor; DH-16, 17-EET, dihomo-16, 17-epoxyeicosatrienoic acid; AA, arachidonic acid; MTL, metallothionein-like protein; SOD, superoxide dismutase.

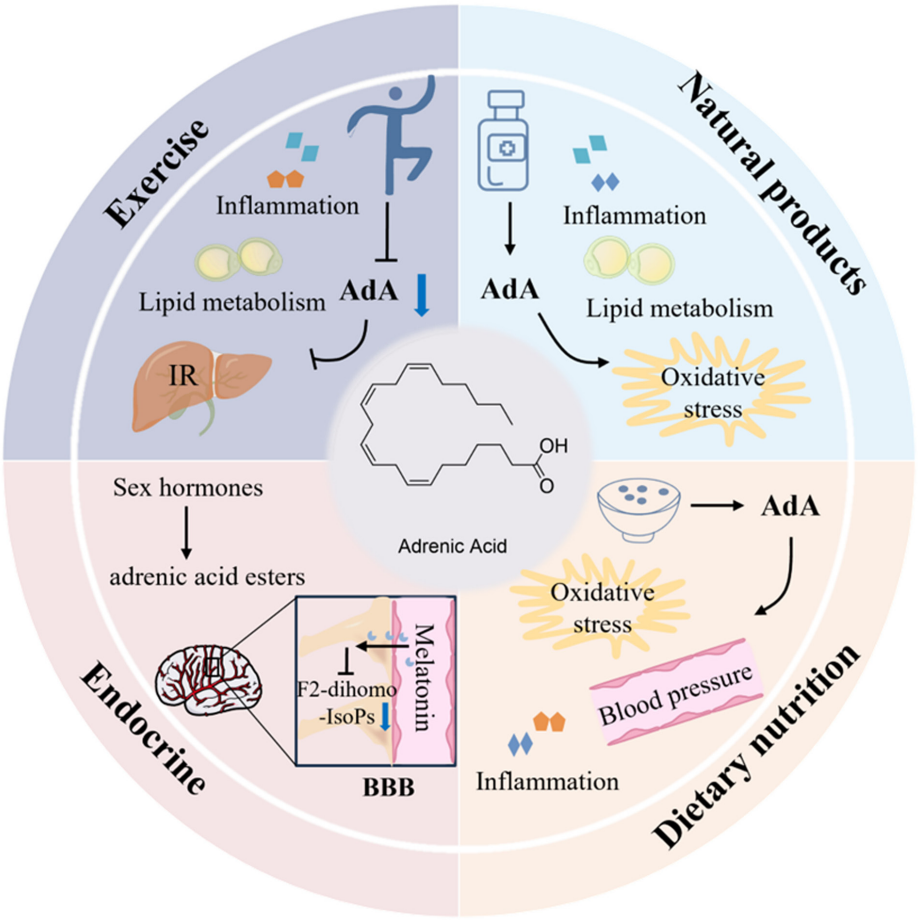

Figure 6. Methods for regulating AdA. The regulation of AdA through various pathways, including exercise, natural products, dietary nutrition and endocrinology, can effectively improve the pathological state of disease, mitigate the associated inflammatory response and promote the metabolic health. AdA, adrenic acid; BBB, blood-brain barrier; F2-dihomo-IsoP, F2-dihomo-isoprostane; IR, insulin resistance.

other adrenal cholesterol esters (191). Melatonin serves as an antioxidant across the BBB, exerting a neuroprotective effect by decreasing levels of F2-DH-IsoPs to protect AdA from oxidative attack without significant changes in AdA levels (192).

In conclusion, the regulation of AdA through various pathways, including exercise, natural products, dietary nutrition and endocrinology, can effectively improve the pathological state of disease, mitigate the associated inflammatory response and promote metabolic health. Therefore, regulation of AdA not only offers new potential targets for clinical intervention but also provides an important basis for understanding the interaction between exercise and nutrition in health management (Fig. 6)

7. Clinical applications

Recent clinical studies have demonstrated the potential utility of peripheral AdA levels as a biomarker for disease diagnosis (138,193). Firstly, AdA is considered a predictive model for chronic risk in patients with acute-phase DILI (12) and serves as a non-invasive biomarker for liver fibrosis in patients with NASH, as well as for early detection of stage I PDAC (13,17). Furthermore, AdA is used to evaluate the extent of oxidative stress in neurological disorder, including epilepsy, AD and cerebral white matter injury, via the non-enzymatic peroxidation reaction that generates F2-DH-IsoPs and isofurans (14,15). Additionally, AdA has demonstrated potential in assessing renal transplantation function (16). Nevertheless, there is a lack of research examining the clinical applications of targeted AdA therapy, which represents a key research area for future work.

Dayaker *et al* (194) found that AdA synthesises a neuroprotective D1 (NPD1) analogue. Research on NPD1 in animal models of AD, patients with stroke and human retinal pigment epithelial cells have confirmed that NPD1 suppresses activation of the inflammatory factor IL-1β (195,196). NPD1 upregulates the expression of the anti-apoptotic genes Bcl-2, Bcl-xl and Bfl-1/A1 but decreases expression of the proapoptotic genes Bax and Bad. These changes result in anti-inflammatory, anti-apoptotic and neuroprotective effects (195,196). To the best of our knowledge, however, the role of NPD1 analogues has not been reported. NPD1 analogues may act similarly to NPD1 by inhibiting inflammatory and apoptotic signalling, thereby preventing cell degeneration (197).

In clinical applications, the levels or activity of AdA are generally measured through analysis of blood or tissue samples. Commonly employed techniques include gas chromatography-mass spectrometry and high-performance liquid chromatography, which are effective for assessment of FA composition and concentration. Furthermore, ELISA is used for the identification of bioactive metabolites associated

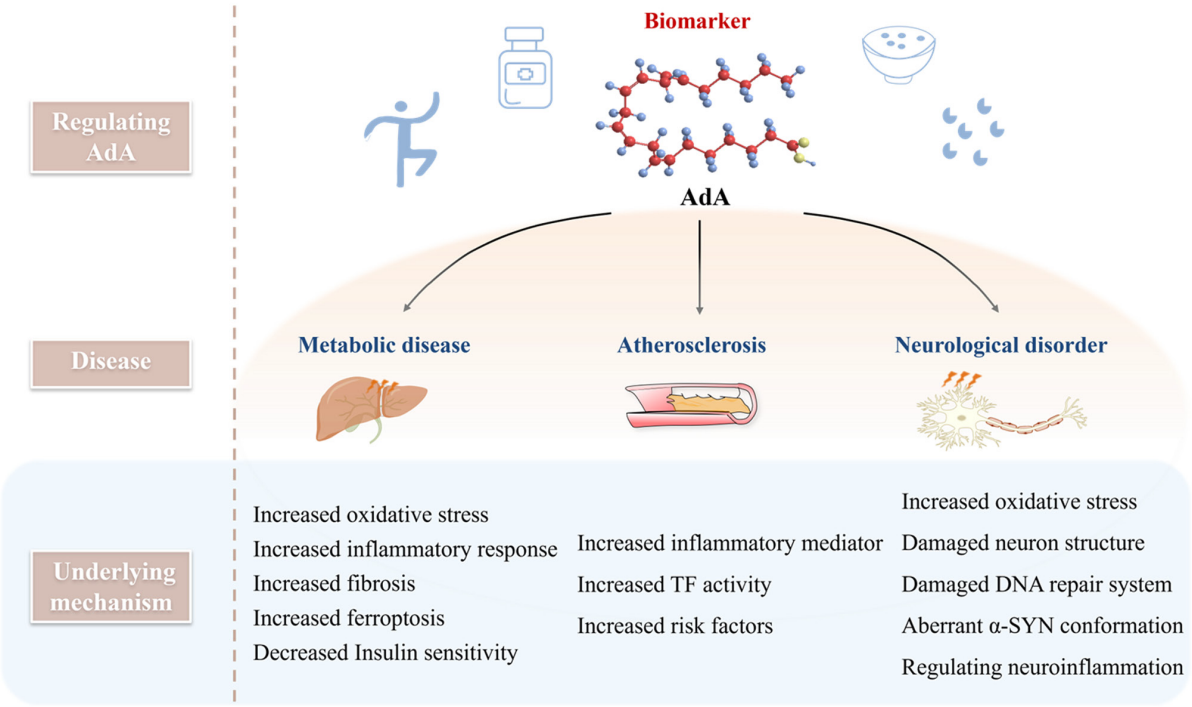

Figure 7. Potential mechanism of AdA in metabolic and neurological disease and atherosclerosis. TF, tissue factor; AdA, adrenic acid; SYN, synuclein.

with AdA. These methods provide quantitative data regarding AdA, facilitating the assessment of its role in various diseases (76,198). Nevertheless, numerous challenges are associated with the translation of these techniques into clinical practice, including complexity of the measurement process, lack of standardisation of methods and individual metabolic differences. For example, the variation in AdA concentrations across different physiological states and metabolic differences amongst patient populations are crucial factors influencing the clinical application of AdA (163,164). The interplay between AdA and physiological and pathological processes complicates its interpretation as a biomarker, thereby limiting its effectiveness in disease diagnosis and treatment monitoring. Further research and standardisation of measurement methods are essential to address these issues.

8. Conclusion

AdA is a crucial metabolite implicated in critical pathophysiological processes across several diseases. AdA is directly involved in various pathophysiological processes. AdA promotes oxidative stress by upregulating intracellular ROS levels and decreasing the expression of antioxidant enzymes, thereby disrupting redox homeostasis and inducing metabolic and neurological disorder (1,146). Furthermore, AdA enhances secretion of inflammatory mediators, promotes local inflammatory responses and decreases the immunosuppressive function of TCRαβ DNT cells, contributing to the immune inflammatory response of AS and metabolic disease (5,6,49,114). Furthermore, AdA enhances the activity of TF in endothelial cells, increasing risk of thrombosis (106). Additionally, it facilitates intra-arterial lipid deposition by modulating risk factors such as high blood pressure, elevated Hcy levels, extreme alcohol abuse and dyslipidaemia (122-126). In neurological disorder, AdA damages DNA and DNA repair system, impairs neuronal structure and modulates aberrant α-SYN conformation, which is associated with promotion of neurodegenerative pathology (145,160). The dual roles of AdA in different neurological diseases require further study (163,164). Furthermore, PE-AdA, a key phospholipid that induces ferroptosis, is susceptible to the lipid peroxidation-induced ferroptosis pathway (92,93). This suggests that AdA is a key initiator of iron-dependent cell death in tissue cells. On the other hand, AdA levels in the periphery are positively associated with the progression and severity of a range of diseases and organ damage, including NAFLD, NASH, T2DM, AD, epilepsy, cerebral white matter injury, DILI, AKI and PDAC (12-17,105,140,141). This emphasises the potential of AdA as a diagnostic biomarker (Fig. 7).

However, research on AdA is lacking. There is a lack of direct research and the mechanism of action of AdA requires further investigation. For example, AA and its metabolites are typically regarded as proinflammatory and AdA has been shown to elicit inflammatory responses (5). However, the anti-inflammatory effects of AdA via inhibition of chemokine leukotriene B4 production have also been documented (199). Further research is required to clarify the roles of n-6 PUFA. Adipose tissue is essential for overall metabolic homeostasis as an endocrine organ and energy reservoir (200,201). However, the association between AdA and adipocyte differentiation, obesity-associated inflammatory responses, energy metabolic processes and other obesity-associated metabolic abnormalities has been rarely investigated (77,79). Consequently, future studies should investigate the precise mechanisms of action. AdA has been identified as a highly sensitive marker for several types of disease, including NAFLD, NASH, T2DM, AD, epilepsy, cerebral white matter injury, DILI, AKI and PDAC, but the specific molecular mechanisms underlying its

role remain to be elucidated. A comprehensive investigation of molecular targets and signalling pathways regulated by AdA, coupled with the identification of biomarkers, is crucial for enhancing the precision of early diagnosis and efficacy monitoring. The development of animal models to mimic the role of AdA in disease is also essential. A second shortcoming is the lack of clinical studies. At present, most research on AdA remains at the *in vitro* and animal experimentation stage, with a lack of clinical studies. Further human experimentation and clinical studies are required to substantiate the efficacy of AdA as a biomarker and therapeutic target and translate these findings into clinical practice, facilitating the development of efficacious therapeutic strategies. Finally, novel therapeutic strategies need to be explored. AdA metabolism is influenced by lifestyle factors, including exercise and diet. Therefore, non-pharmacological therapeutic strategies for AdA should be explored to target its metabolic pathways or modulate its signalling and to understand the interaction between exercise and nutrition in health management. The potential of exercise therapy in addressing health concerns has interest because of its unique benefits in safety and cost-effectiveness. Nevertheless, literature examining the association between exercise and AdA is scarce (176), highlighting the need for further investigation into the potential of exercise to improve disease outcomes via AdA. This may provide a theoretical and practical foundation for prevention and treatment of diseases through exercise.

In conclusion, AdA is a highly sensitive metabolite in various types of disease and has broad potential applications. Although there are currently no clinically applicable drugs specifically targeting AdA, further studies and technological developments may allow AdA to serve a promising biomarker and therapeutic target for many diseases.

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Availability of data and materials

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Authors' contributions

ZW conceived the study, performed the literature review, constructed figures and wrote the manuscript. HG performed the literature review and wrote the manuscript. XM and DZ edited the manuscript and constructed figures. LZ conceived the study, edited the manuscript and constructed figures. WX supervised the study and constructed figures. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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