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REVIEW

# AKR1B1 as A Metabolic Enzyme and Pleiotropic Signaling Hub

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**ABSTRACT:** Aldo-keto reductase family 1 member B1 (AKR1B1) was historically characterized as the first and generally rate-limiting enzyme of the polyol pathway and, consequently, was primarily implicated in the pathogenesis of diabetic complications. Recent advances, however, have repositioned AKR1B1 as a pleiotropic signaling hub whose biological functions extend far beyond glucose metabolism. This review systematically integrates the complex regulatory network governing AKR1B1, including transcriptional control by tumor protein p53 (p53) and nuclear factor erythroid 2-related factor 2 (Nrf2), and its dual functionality as both a metabolic enzyme and a non-catalytic signaling scaffold. We elucidate its role in orchestrating cell fate by bi-directionally regulating apoptosis and ferroptosis, driving epithelial-mesenchymal transition (EMT), and fueling metabolic reprogramming via endogenous fructose production. Furthermore, we highlight its pathological significance in human diseases, ranging from gastric cancer and glioblastoma to aortic valve calcification. Finally, we evaluate the therapeutic prospect of targeting AKR1B1, emphasizing the need for novel strategies that address both its enzymatic activity and protein-protein interactions.

**KEYWORDS:** Aldo-keto reductase family 1 member B1; aldo-keto reductase; polyol pathway; ferroptosis

## 1 Introduction

For decades, Aldo-keto reductase family 1 member B1 (AKR1B1), traditionally known as aldose reductase (AR), has been implicated in diabetic cardiovascular complications [1–3]. As the first and generally rate-limiting enzyme of the polyol pathway, it catalyzes the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction of glucose to sorbitol [1,2]. Under hyperglycemic conditions, enhanced polyol flux leads to sorbitol accumulation, osmotic stress, and NADPH depletion, driving the pathogenesis of diabetic neuropathy, retinopathy, and nephropathy [1,2].

However, accumulating studies have revealed AKR1B1 as a pleiotropic regulatory hub. Beyond glucose, AKR1B1 catalyzes the reduction of diverse aldehydes and ketones, implicating it in lipid homeostasis, retinoid metabolism, prostaglandin synthesis, and the detoxification of both endogenous and exogenous carbonyl compounds [4,5].

Furthermore, AKR1B1's expression and activity are controlled by a sophisticated, multi-layered network. At the transcriptional level, it is a direct target of master-regulator transcription factors, including p53 (which acts as a repressor), nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor

kappa-light-chain-enhancer of activated B cells (NF-κB), and Twist-related protein 2 (Twist2), placing it at the nexus of tumor suppression, oxidative stress, and inflammatory responses [6–8]. At the post-transcriptional level, non-coding RNAs, such as long intergenic non-protein coding RNA 978 (LINC00978) and EPS15 antisense RNA 1 (EPS15-AS1), and promoter methylation finely tune their expression [9,10].

Most importantly, AKR1B1 functions not only as a classic enzyme but also as a signal-scaffolding protein. In this non-catalytic capacity, it physically interacts with key signaling molecules, such as signal transducer and activator of transcription 3 (STAT3) and the β2-adrenergic receptor (β2-AR), to directly modulate downstream pathways [11,12]. This functional duality allows it to mediate profound cellular effects, including the dual regulation of apoptosis and ferroptosis, the promotion of malignant phenotypes like the epithelial-mesenchymal transition (EMT), and the metabolic reprogramming of cancer cells via endogenous fructose production [8,13].

This review aims to systematically integrate the current understanding of the complex molecular networks that regulate AKR1B1 and the associated downstream effects of its activity. We will analyze its roles as an oxidoreductase, its function as a master regulator of core cellular processes, and its emerging role as a non-canonical signaling scaffold. By placing these mechanisms in special human diseases such as gastric cancer, breast cancer, glioblastoma, and aortic valve calcification, this review elucidates how AKR1B1 functions as a central, "druggable" nexus.

## 2 Physiological Functions of AKR1B1

### *2.1 Genetic and Structural Characteristics*

The human AKR1B1 gene is located on chromosome 7q33 and consists of 10 exons. The encoded protein is a monomeric enzyme of approximately 36 kDa that adopts a classic (α/β)8-barrel (TIM-barrel) fold, forming a highly conserved catalytic core [14]. Unlike many other oxidoreductases, AKR1B1 lacks a canonical Rossmann fold; instead, its cofactor NADPH binds in an extended conformation across the barrel's C-terminal face.

Although the catalytic pocket itself is relatively rigid, substrate specificity is strictly determined by the conformational flexibility of three variable loops (Loops A, B, and C) positioned near the active site at the C-terminus of the barrel. These dynamic loops undergo substantial conformational rearrangements upon ligand binding, thereby gating substrate access to the active site. This plasticity allows AKR1B1 to accommodate a diverse range of hydrophobic and hydrophilic carbonyl substrates, underpinning its pleiotropic physiological roles [15].

Beyond regulating enzymatic specificity, the flexible A-, B-, and C-loops can generate transient hydrophobic interfaces that facilitate protein–protein interactions (PPIs). Such loop-mediated adaptability provides a structural basis for AKR1B1 to act as a "moonlighting" protein, supporting non-catalytic scaffolding functions in addition to its canonical reductase activity.

### *2.2 Distinct Roles of AKR1B1 and AKR1A1*

AKR1B1 shares several functional overlaps with AKR1A1 (aldehyde reductase), particularly in the detoxification of lipid peroxidation–derived aldehydes such as 4-hydroxynonenal (4-HNE) [4]. Both enzymes adopt a conserved $(\alpha/\beta)_8$ TIM-barrel fold; however, subtle differences in their active-site architectures dictate substrate preference and catalytic efficiency [14,15]. AKR1A1 generally exhibits higher catalytic efficiency toward a broad spectrum of aldehydes, whereas AKR1B1 serves as the predominant physiological enzyme mediating glucose reduction in the polyol pathway [16,17]. Unlike the inducible AKR1B1, AKR1A1 exhibits a constitutive expression profile with marked enrichment in the liver and kidney, where it is essential for

aldehyde detoxification [18,19]. Importantly, although classical aldose reductase inhibitors (ARIs), such as epalrestat, were developed to selectively target AKR1B1, accumulating evidence indicates that their isoform selectivity is limited. Partial cross-inhibition of other AKR family members, particularly AKR1A1, has been reported, raising concerns that such off-target effects may interfere with physiological aldehyde detoxification and cytoprotective mechanisms in the liver and kidney. A key pathological distinction lies in their non-enzymatic functions: AKR1B1 has been identified as a critical signaling scaffold, for example, through direct interaction with STAT3 in cancer, whereas comparable scaffold functions have not yet been reported for AKR1A1 [11].

### *2.3 The Polyol Pathway and Metabolic Reprogramming*

AKR1B1 is the first rate-limiting enzyme of the polyol pathway. In mammalian cells under normoglycemia, hexokinase phosphorylates most glucose for glycolysis. A minor fraction (approx. 3%) is shunted into the polyol pathway, where AKR1B1 uses NADPH to reduce glucose to sorbitol. Sorbitol dehydrogenase (SDH) then oxidizes sorbitol to fructose, using nicotinamide adenine dinucleotide ($NAD^+$) [1]. This two-step process is the only known physiological pathway for the endogenous conversion of glucose to fructose, which implicates it in metabolic reprogramming, particularly in cancer [13]. This constitutes a critical energy reprogramming mechanism, where AKR1B1-driven endogenous fructose production fuels glycolysis and the pentose phosphate pathway, bypassing normal glycolytic checkpoints and exemplifying the emerging concept of carbon flux plasticity [1,2,20].

### *2.4 Lipid Metabolism and Detoxification*

AKR1B1 is a highly efficient reductase of lipid aldehydes, which are toxic byproducts of lipid peroxidation generated during oxidative stress. Its substrates include free aldehydes, such as 4-HNE and 4-oxononenal (4-ONE), as well as "core" aldehydes that remain esterified to phospholipids, such as 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine (POVPC) [4]. This detoxification function is not shared by all AKR families; AKR1C, AKR6, and AKR7, for instance, are relatively ineffective against these substrates [4].

Furthermore, AKR1B1 is a critical enzyme in metabolizing precursors of Advanced Glycation End-products (AGEs), such as methylglyoxal, glyoxal, and 3-deoxyglucosone [21]. By reducing these reactive dicarbonyls, AKR1B1 prevents their accumulation. In diabetic models, genetic deletion of AKR1B1 leads to increased accumulation of AGEs and exacerbates atherosclerotic lesion formation, demonstrating a protective role for AKR1B1 against AGE-mediated vascular damage.

### *2.5 Retinoid Metabolism and Prostaglandin Synthesis*

AKR1B1 exhibits retinaldehyde reductase activity and participates in retinoid metabolism. The conversion of retinol to retinoic acid (RA), the active signaling molecule, involves a rate-limiting reversible oxidation of retinol to retinaldehyde. While other enzymes, alcohol dehydrogenases (ADHs) and retinol dehydrogenases (RDHs), perform the oxidative step, NADP-dependent reductases, including AKR1B1, can catalyze the reverse reaction, reducing retinaldehyde back to retinol. Although its activity with this substrate is relatively low compared to AKR1B10, this provides a mechanism for regulating the bioavailability of retinaldehyde for RA synthesis [5]. AKR1B1 plays a dual, environment-dependent role in prostaglandin (PG) synthesis, acting on the precursor prostaglandin H2 (PGH2) as PG F synthase (PGFS) and PG D synthase (PGDS). In an NADPH-rich environment, AKR1B1 functions as the primary PGF2$\alpha$ synthase in tissues like the endometrium and fetal membranes. It catalyzes the NADPH-dependent reduction of PGH2 to

PGF2$\alpha$ [22]. This activity is essential for regulating the menstrual cycle and is a core component in the initiation of human labor [23,24]. In the absence of NADPH or $NADP^+$, AKR1B1 acts as an isomerase, converting PGH2 to PGD2. This reaction is mediated by a key histidine residue (His110) acting as a proton acceptor, demonstrating a distinct catalytic mechanism independent of the enzyme's reductase function [25].

### *2.6 Osmoregulation and Renal Function*

AKR1B1 is abundantly expressed in the renal medulla, particularly in collecting duct cells, where it serves a critical osmoregulatory function. By catalyzing the reduction of glucose to sorbitol, it generates an essential intracellular organic osmolyte that balances the high extracellular tonicity of the renal medulla, preventing cellular dehydration [26]. Research using Akr1b1-deficient mice has demonstrated that loss of this enzyme leads to a defect in urinary concentrating ability [26]. Furthermore, these mice exhibit hypercalciuria and hypermagnesemia, indicating that AKR1B1 is also essential for maintaining divalent cation homeostasis in the kidney.

### *2.7 Reproductive Function*

Reflecting its role in prostaglandin (PG), particularly PGF2$\alpha$, synthesis, AKR1B1 is abundantly expressed throughout the reproductive system. In females, it is detected in the endometrial epithelium and stroma as well as fetal membranes, consistent with its involvement in uterine receptivity, implantation and parturition [23,27]. In mammalian models such as swine, AKR1B1 is expressed in the testis, epididymis, prostate, and seminal vesicles, but is absent from the bulbourethral glands. The enzyme is also present in ejaculated sperm, highlighting a direct role in sperm physiology [28,29].

Proteomic and functional studies suggest that AKR1B1 exerts context-dependent effects on male fertility. In porcine models, higher levels of the AKR1B1 in sperm are negatively correlated with sperm motility and intracellular calcium levels. Accordingly, lower levels of sperm AKR1B1 are associated with better *in vitro* fertilization rates and embryo development. By contrast, the concentration of AKR1B1 in seminal plasma shows no significant association with conventional sperm quality parameters, such as motility or viability, indicating a cell-intrinsic rather than extracellular regulatory role [28].

#### *2.7.1 Sperm Capacitation and Metabolism*

Beyond its inhibitory associations in some species, AKR1B1 also functions as a dynamic regulator of sperm metabolism and stress adaptation. In yak (*Bos grunniens*), metabolomic screening identified AKR1B1 as a key determinant of sperm cryoresistance. By catalyzing the reduction of galactose to galactitol, AKR1B1 supports osmotic balance and energy metabolism, positively correlating with sperm motility and ATP content and partially restoring sperm activity following freeze–thaw cycles [30]. Similarly, in alpaca (*Vicugna pacos*) sperm, exposure to follicular fluid induces an AKR1B1-dependent proteomic shift toward glycolytic and gluconeogenic pathways. This metabolic reprogramming facilitates cytoskeletal remodeling and membrane dynamics required for capacitation and fertilization, underscoring the role of AKR1B1 in coupling carbohydrate metabolism to functional sperm maturation [31].

#### *2.7.2 Ovarian Function and Ovulation*

AKR1B1 also contributes to female reproductive physiology, particularly ovulation and endometrial preparation. In rabbits, transcriptomic analyses have identified AKR1B1 as a differentially expressed gene associated with the Hippo signaling pathway during ovulation. Its upregulation coincides with the luteinizing hormone (LH) surge and increased progesterone levels, suggesting that AKR1B1 acts as a

downstream effector in the ovulatory cascade, potentially integrating mechanical and hormonal cues [32]. Furthermore, in Holstein heifers, pre-estrus estradiol concentrations modulate AKR1B1 expression in the endometrium, linking steroid hormone profiles to the prostaglandin synthesis machinery required for uterine receptivity and early pregnancy establishment [33].

#### *2.7.3 Placental Biology and Pregnancy Complications*

AKR1B1 is critical for pregnancy maintenance and the timing of parturition. Proteomic analyses reveal that although placental AKR1B1 levels physiologically decline during term labor, they are aberrantly elevated in placentas associated with spontaneous preterm birth (PTB). This dysregulation drives excessive PGF2$\alpha$ production, thereby accelerating cervical ripening and premature uterine contractions [34]. Mechanistically, inflammatory stimuli such as interleukin-1$\beta$ (IL-1$\beta$) induce AKR1B1 expression in myometrial cells through activation of the Nrf2 signaling pathway. This newly identified Nrf2–AKR1B1 axis provides a molecular link between oxidative stress and inflammation-driven prostaglandin overproduction, offering insight into the pathogenesis of preterm labor [35].

### ***2.8 Other Metabolic Roles***

AKR1B1 is implicated in other niche metabolic pathways. Emerging and less well-characterized metabolic roles of AKR1B1 include pyridoxal reductase and tetrahydrobiopterin (BH4) salvage. It is believed to function as a human pyridoxal reductase, an enzyme involved in vitamin B6 metabolism, converting pyridoxal to pyridoxine [36]. It also participates in a novel "salvage pathway II" for tetrahydrobiopterin (BH4) synthesis, where it reduces the intermediate 1′-hydroxy-2′-oxopropyl-tetrahydropterin (2′-OXPH4) to biologically active BH4, a critical cofactor for nitric oxide synthases and aromatic amino acid hydroxylases [37]. These findings further expand the metabolic repertoire of AKR1B1 beyond canonical polyol pathway activity.

### ***2.9 Immune and Inflammatory Regulation***

Accumulating evidence implicates AKR1B1 as a modulator of immune and inflammatory responses across diverse pathological contexts.

#### *2.9.1 Macrophage Polarization*

Within the tumor microenvironment (TME), AKR1B1 influences immune cell infiltration and macrophage phenotype. In colorectal cancer, AKR1B1 colocalizes with $CD163^+$ M2-like macrophages in the stromal compartment. Intriguingly, its expression correlates with improved survival in specific patient cohorts, suggesting a context-dependent immunomodulatory function rather than a uniformly pro-tumorigenic role [38].

#### *2.9.2 The NLRP3 Axis*

AKR1B1 serves as a metabolic regulator of inflammasome-driven pathology. A direct mechanistic link between AKR1B1 and innate immunity has been established in ulcerative colitis. AKR1B1 facilitates the assembly and activation of the NLRP3 inflammasome. Pharmacological inhibition of this axis—using bioactive compounds such as ellagic acid—disrupts NLRP3–ASC oligomerization and subsequent IL-1$\beta$ maturation, thereby attenuating colonic inflammation [39].

### *2.10 Dermatological and Hair Follicle Physiology*

Recent studies have expanded the functional landscape of AKR1B1 to dermatology and hair follicle biology. In alopecia areata (AA), metabolomic profiling of lesional scalp tissue reveals marked metabolic disturbances accompanied by upregulation of AKR1B1 [40]. Enhanced polyol pathway flux driven by AKR1B1 activity increases fructose production, which is subsequently metabolized to uric acid. Elevated uric acid levels activate vascular endothelial cells, as evidenced by increased ICAM-1 expression, and promote immune cell infiltration. This process contributes to the autoimmune-mediated destruction of hair follicles, defining a previously unrecognized AKR1B1–fructose–uric acid axis in the pathogenesis of autoimmune hair loss.

## 3 The AKR1B1 Regulatory Network

AKR1B1 is not a statically expressed enzyme but a dynamic component of the cellular stress response. Its expression and activity are governed by a multi-layered network involving transcriptional, epigenetic, and post-translational mechanisms (Fig. 1A).

### *3.1 Transcriptional Regulation*

A Convergence of Master Regulators AKR1B1 transcription serves as a nexus for competing cellular signals.

#### *3.1.1 The p53 Repression*

The tumor suppressor p53 exerts context-dependent regulation over cell fate, utilizing distinct mechanisms in different malignancies. In breast cancer, wild-type p53 functions as a direct transcriptional repressor of *AKR1B1*. It binds directly to the *AKR1B1* promoter to reduce its expression. Consequently, the loss of functional p53—a hallmark of many cancers—relieves this repression, leading to AKR1B1 overexpression and the promotion of metastatic phenotypes via EMT [6].

Distinct from this direct regulation of *AKR1B1*, p53 utilizes a different mechanism in gastric cancer to exert its tumor-suppressive effects. In this context, p53 promotes ferroptosis primarily by transcriptionally repressing the cystine/glutamate antiporter solute carrier family 7 member 11 (SLC7A11), rather than targeting *AKR1B1* directly [41]. This downregulation of SLC7A11 depletes intracellular glutathione (GSH) and sensitizes cells to lipid peroxidation [11]. Therefore, while AKR1B1 and p53 are both critical players in these cancers, their interplay varies: p53 directly targets the AKR1B1 gene in breast cancer to block metastasis, whereas in gastric cancer, p53 targets the redox regulator SLC7A11 to induce ferroptosis.

#### *3.1.2 Nrf2-Mediated Activation*

As a central effector of the antioxidant response, Nrf2 (NFE2L2) directly activates AKR1B1 transcription by binding to Antioxidant Response Elements (AREs) in its promoter, thereby positioning AKR1B1 within a broader Nrf2-driven transcriptional program that coordinates metabolic adaptation, redox homeostasis, and resistance to ferroptotic lipid peroxidation [42]. This induction enhances the cell's capacity to detoxify reactive aldehydes generated by oxidative stress, a mechanism frequently co-opted by cancer cells to evade ferroptosis. In malignancies such as gastric cancer, this Nrf2-AKR1B1 axis serves as a key mechanism for inhibiting ferroptosis [11]. In glioblastoma, this regulation can also be indirect, where NFE2L2 promotes the expression of LINC00978, which in turn upregulates AKR1B1, further reinforcing redox and metabolic resilience [9].

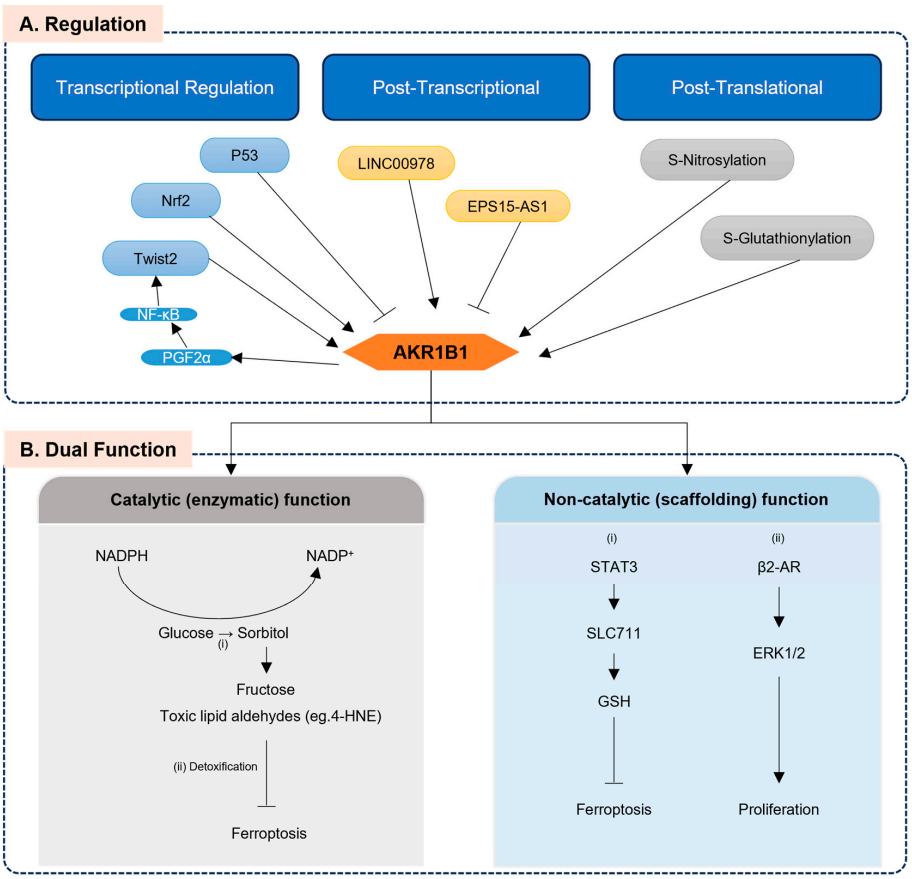


**Figure 1:** The AKR1B1 Dual-Function Signaling Hub. AKR1B1 is a central signaling node that integrates complex transcriptional inputs and mediates downstream pathological effects through two distinct functional branches. (**A**) Transcriptional Regulation (Inputs): In the nucleus, the AKR1B1 gene is a convergence point for opposing master regulators. Its transcription is activated (+) by the oxidative stress sensor Nrf2 and by the epithelial-mesenchymal transition (EMT)-driving Twist2/NF-κB positive feedback loop. Conversely, its expression is repressed (–) by the wild-type tumor suppressor p53. (**B**) Dual Function (Output): The AKR1B1 protein produced by translation exerts its effects through two parallel mechanisms. Catalytic (Enzymatic) Function: This pathway utilizes NADPH as a cofactor, primarily performing two roles: (i) Achieving metabolic reprogramming via the polyol pathway (glucose → sorbitol → fructose) to provide an endogenous fructose source for tumor cell metabolism; (ii) Suppresses ferroptosis by directly detoxifying toxic lipid aldehydes (e.g., 4-HNE), secondary cytotoxic byproducts of ferroptotic lipid peroxidation, thereby attenuating ferroptosis-associated cell injury (enzymatic action). Non-catalytic (scaffolding) function: AKR1B1 utilizes its protein structure to construct critical protein-protein interaction scaffolds independently of its active site. (i) Inhibits ferroptosis by physically binding STAT3 (scaffolding), thereby activating transcription of the SLC7A11 antiporter and establishing a GSH-based antioxidant defense system. (ii) Drives cell proliferation through interaction with the β2-adrenergic receptor (β2-AR), which synergistically activates the pro-survival ERK1/2 pathway.

### *3.1.3 The Twist2/NF-κB Positive Feedback Loop*

In aggressive basal-like breast cancer, the EMT-inducing transcription factor Twist2 directly upregulates AKR1B1. The resulting increase in AKR1B1 activity stimulates the NF-κB signaling pathway, which in turn promotes Twist2 expression. This malignant positive feedback loop locks cells into an invasive, mesenchymal state [8].

#### *3.1.4 Chromatin Remodeling and Epigenetic Control*

Beyond classical transcription factor–mediated regulation, chromatin accessibility constitutes an important upstream determinant of *AKR1B1* expression. In acute leukemia, SMARCA5—the ATPase core of the ISWI chromatin remodeling complex—acts as a critical positive regulator of AKR1B1 transcription. SMARCA5 maintains an open chromatin configuration at the *AKR1B1* locus and facilitates the recruitment of the transcriptional cofactors DDX5 and SP1 to its promoter. Through this SMARCA5–AKR1B1 axis, leukemic cells reprogram endogenous fructose metabolism to support proliferation and survival, directly linking epigenetic remodeling to metabolic enzyme expression and leukemogenesis [43].

#### *3.1.5 Regulation by Claudin-1*

Cell–cell junction components can also influence AKR1B1 transcriptional output. In pancreatic ductal adenocarcinoma (PDAC), the tight junction protein Claudin-1 markedly upregulates AKR1B1 expression. This regulation enhances metabolic flexibility through activation of the polyol pathway, thereby promoting tumor cell proliferation, migration, and chemoresistance. Conversely, depletion of Claudin-1 results in coordinated downregulation of AKR1B1 and related family members, including AKR1C2 and AKR1C3, underscoring a broader junction–metabolism regulatory axis in PDAC progression [44].

### *3.2 Post-Transcriptional and Epigenetic Control*

#### *3.2.1 Non-Coding RNAs*

Long non-coding RNAs (lncRNAs) provide fine-tuned regulation. For instance, LINC00978 has been shown to upregulate AKR1B1 in glioblastoma to drive metabolic rewiring and proliferation [9]. Conversely, in hepatocellular carcinoma (HCC), the lncRNA *EPS15-AS1* suppresses AKR1B1 expression, thereby sensitizing cells to ferroptosis [10].

#### *3.2.2 Epigenetic Regulation*

The methylation status of the AKR1B1 promoter is a critical determinant of its expression. Hypomethylation of the promoter region is frequently observed in tumors with high AKR1B1 levels, contributing to its aberrant upregulation [6].

### *3.3 Post-Translational Modification of Activity*

The enzymatic activity of AKR1B1 is rapidly modulated by the cellular redox environment. Nitric oxide (NO) can induce S-nitrosylation of Cys-298 near the active site, enhancing enzymatic activity. This modification is reversible; the S-nitrosylated enzyme can be converted to an S-glutathionylated intermediate and subsequently reduced back to the basal state by glutathione (GSH). This “molecular switch” allows AKR1B1 to respond instantly to acute oxidative or nitrosative stress signals [45,46].

## 4 The Dual Nature: Enzyme and Scaffold

A paradigm shift in our understanding of AKR1B1 biology is the recognition that, beyond its canonical oxidoreductase activity, AKR1B1 functions as a non-catalytic scaffold (Fig. 1B). Through distinct surface-exposed domains, AKR1B1 physically associates with multiple signaling proteins, thereby promoting pathway activation independently of its enzymatic catalytic cycle. This dual functionality positions AKR1B1 as both a metabolic enzyme and a structural signaling hub.

While the enzymatic role of AKR1B1 in detoxifying aldehydes is well documented, growing evidence indicates that catalytic functions alone cannot explain the full breadth of AKR1B1-dependent phenotypes observed in cancer and complex diseases. This has prompted a reassessment of the protein, leading to the identification of "moonlighting" roles where AKR1B1 coordinates signaling and transcriptional programs via direct protein–protein interactions (PPIs), as detailed below.

### *4.1 Canonical Catalytic Functions of AKR1B1*

AKR1B1 is classically characterized as a cytosolic, NADPH-dependent oxidoreductase that catalyzes the reduction of a broad spectrum of aldehydes and ketones generated during cellular metabolism and oxidative stress [1,47,48]. Through this activity, AKR1B1 plays a central role in maintaining redox homeostasis by detoxifying reactive carbonyl species, including lipid peroxidation–derived aldehydes such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). These reactions are critical for limiting carbonyl-induced protein modification, membrane damage, and DNA instability under conditions of metabolic and inflammatory stress [1,48].

Beyond detoxification, the enzymatic activity of AKR1B1 drives key metabolic pathways implicated in disease progression. Most notably, AKR1B1 is the first and generally rate-limiting enzyme of the polyol pathway, catalyzing the reduction of glucose to sorbitol. This process influences cellular osmotic balance, NADPH consumption, and redox signaling [1,16]. Dysregulation of the polyol pathway is linked to chronic inflammation, amplification of oxidative stress, and tissue injury in diabetes, cardiovascular disease, and cancer. In tumor cells, elevated AKR1B1 activity supports survival by buffering oxidative stress and sustaining NADPH-dependent antioxidant defenses, thereby shaping the cellular response to hypoxia and metabolic reprogramming [47,49].

### *4.2 Non-Catalytic Scaffolding Functions of AKR1B1*

Although traditionally defined by its reductase activity, AKR1B1 acts as a critical protein interaction partner independent of its enzymatic cycle. This scaffolding capability expands its functional repertoire, allowing it to directly modulate signal transduction and gene transcription.

#### *4.2.1 Interference with Epigenetic Repression Complexes*

A newly characterized non-canonical function of AKR1B1 involves its direct interaction with the deacetylase activation domain (DAD) of nuclear receptor corepressors (NCOR1/SMRT). Structural modeling and molecular dynamics simulations reveal that AKR1B1 acts as a "molecular wedge," competing with histone deacetylase 3 (HDAC3) for binding to the DAD region. Notably, the leucine residue at position 289 (L289) of AKR1B1 is critical for this hydrophobic interaction [50]. By physically displacing HDAC3 from the corepressor complex, AKR1B1 inhibits histone deacetylation, thereby relieving transcriptional repression of specific target genes. Importantly, this interaction occurs on a protein surface distal to the $NADP^+$-binding catalytic pocket, confirming that this transcriptional co-regulatory function is mechanistically distinct from its reductase activity [50].

#### *4.2.2 Scaffolding for Oncogenic Kinase Signaling*

AKR1B1 serves as a molecular platform that facilitates the activation of oncogenic kinase signaling pathways, particularly in tumor progression and metastasis.

**SMAD2/3 Complex Assembly and EMT:** During epithelial-mesenchymal transition (EMT), AKR1B1 physically interacts with SMAD2. This interaction promotes Transforming Growth Factor β

(TGF-β)–dependent phosphorylation and the subsequent nuclear translocation of the SMAD2/3 complex. This scaffolding effect drives the transcription of mesenchymal markers, including N-cadherin and Vimentin, reinforcing the mesenchymal phenotype [51]. Additionally, in breast cancer, AKR1B1 has been shown to promote EMT and metastasis through interactions with NF-κB and Twist2 [8].

**AKT1–STAT3 Signaling Hub:** AKR1B1 binds directly to AKT1 and STAT3, stabilizing their phosphorylated (active) states without enzymatically modifying them [52]. In gastric and lung cancers, the AKR1B1–STAT3 interaction is essential for the transcriptional activation of *SLC7A11*, a key component of the cystine/glutamate antiporter [11]. This upregulation increases cystine uptake and glutathione synthesis, thereby conferring resistance to ferroptosis.

**β2-Adrenergic Receptor Signaling:** In pancreatic cancer, AKR1B1 directly binds to the β2-adrenergic receptor (β2-AR). This complex synergistically activates the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway, promoting cell proliferation and inhibiting apoptosis [12].

Collectively, these findings highlight the therapeutic potential of targeting the scaffolding interfaces of AKR1B1—using interface-targeting peptides or structure-specific inhibitors—rather than relying solely on catalytic inhibitors.

## 5 AKR1B1 as a Pleiotropic Disease Mediator

The integration of AKR1B1's enzymatic functions with its complex regulation and non-canonical scaffolding roles places it at the center of multiple disease pathologies, particularly in cancer and cardiovascular disease (Fig. 2).

### *5.1 Role in Tumor Progression*

#### *5.1.1 Apoptosis/Ferroptosis Modulation*

AKR1B1 demonstrates a dual role in regulating programmed cell death, inducing apoptosis in some contexts and inhibiting ferroptosis in others.

Apoptosis: In pancreatic cancer, the non-catalytic AKR1B1/β2-AR complex inhibits apoptosis by activating ERK1/2 signaling [12]. Conversely, in glioma, AKR1B1 levels are often low, and its re-expression acts as a tumor suppressor by inducing apoptosis. This mechanism involves the activation of the p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway, which subsequently modulates the B-cell lymphoma 2 (Bcl-2)-family proteins (downregulating anti-apoptotic Bcl-2, upregulating pro-apoptotic Bcl-2-associated X protein (BAX)) to activate effector caspases 3 and 7 [53].

Ferroptosis: A primary oncogenic role for AKR1B1 in many malignancies (e.g., gastric cancer, HCC, colorectal cancer) is its function as a potent inhibitor of ferroptosis—an iron-dependent cell death driven by lipid peroxidation [51,54]. Recent studies have highlighted that ferroptosis sensitivity is determined by the coordinated activity of multiple metabolic and redox defense systems that limit lipid peroxide accumulation, providing a functional framework for understanding the anti-ferroptotic role of AKR1B1 [20]. This inhibition is mediated by at least two distinct and parallel pathways: (1) Non-Catalytic Scaffolding: In its non-enzymatic capacity, AKR1B1 physically interacts with the STAT3 protein. AKR1B1 serves as a critical facilitating scaffold for activating the cystine/glutamate antiporter SLC7A11, which promotes GSH synthesis and thus neutralizes the ferroptotic cascade [11]. (2) Enzymatic Detoxification: In its classic catalytic role, AKR1B1's NADPH-dependent reductase activity directly neutralizes the toxic lipid aldehydes (e.g., 4-HNE) that are the ultimate executioners of ferroptotic cell death [55]. These parallel mechanisms are consistent with the emerging concept that ferroptosis defense relies on both enzymatic detoxification of lipid aldehydes and transcriptionally controlled antioxidant systems [42].

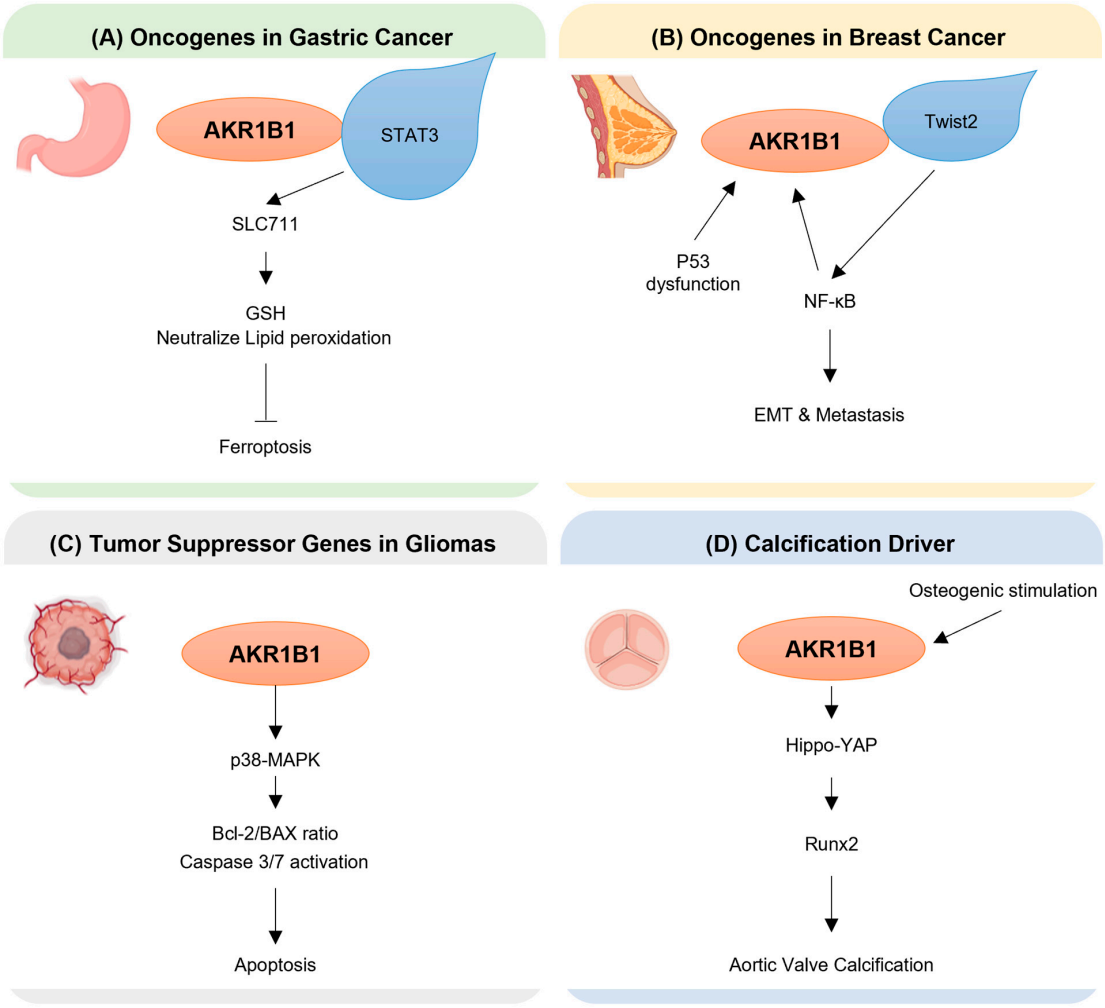


**Figure 2:** Context-Dependent Pathologies of AKR1B1. It functions as a potent oncogene, a tumor suppressor, or a driver of cardiovascular disease, depending on the specific cellular context and activated signaling pathway. (**A**) Oncogene in Gastric Cancer: AKR1B1 promotes malignancy by acting as a context-dependent inhibitor of ferroptosis. It executes its non-catalytic scaffold function by binding to STAT3. This interaction is required to activate the transcription of SLC7A11, thereby increasing intracellular GSH synthesis and neutralizing ferroptotic lipid peroxidation. (**B**) Oncogenes in Breast Cancer: In basal-like breast cancer, AKR1B1 is a key component of a malignant positive feedback loop driving epithelial-mesenchymal transition (EMT). p53 suppresses AKR1B1 expression by binding to its promoter, whereas p53 dysfunction leads to AKR1B1 overexpression. The EMT master regulator Twist2 induces AKR1B1 expression, which in turn activates the NF-κB pathway. This pathway then transcribes Twist2, locking cells into a metastatic mesenchymal state. (**C**) Tumor Suppressor in Glioma: In a stark functional reversal, AKR1B1 expression in glioma acts as a tumor suppressor. Its presence induces apoptosis by activating the p38-MAPK signaling pathway. This cascade modulates the Bcl-2/BAX ratio and activates effector caspases 3 and 7, leading to programmed cell death. (**D**) Driver of Cardiovascular Disease (Aortic Valve Calcification): AKR1B1 drives pathology by promoting the osteogenic differentiation of valvular interstitial cells (VICs). It activates the Hippo-YAP signaling pathway, leading to Yes-associated protein (YAP) dephosphorylation and nuclear translocation. In the nucleus, YAP complexes with the transcription factor TEA domain family member (TEAD1) to drive the expression of the master osteogenic factor Runx2, causing VICs transformation and leading to valve calcification.

#### *5.1.2 Driving EMT and Metabolic Reprogramming*

AKR1B1 actively promotes several "hallmarks of cancer." It is a potent inducer of EMT, the process by which cancer cells gain invasive and metastatic properties. It functions as a core component of the Twist2/NF-κB positive feedback loop and acts as a downstream effector of the classic EMT-inducer, transforming growth factor beta (TGF-β) [8].

By driving the polyol pathway (glucose → sorbitol → fructose), AKR1B1 provides cancer cells with an endogenous source of fructose [13]. This internal fructose production grants cancer cells a "metabolic autonomy" and a significant malignant advantage. Fructose metabolism can enhance glycolysis, promote proliferation, inhibit apoptosis, and fuel the cell cycle, allowing cancer cells to thrive [13,56].

#### *5.1.3 Context-Dependent Roles in Specific Malignancies*

In non–small cell lung cancer (NSCLC), AKR1B1-driven activation of the polyol pathway sustains glycolysis and bypasses metabolic checkpoints. Silencing AKR1B1 induces energetic collapse, DNA damage, and subsequent JNK-mediated apoptosis [57]. AKR1B1 is also implicated in arsenic-induced lung squamous cell carcinoma, where it is inhibited by the diphtheria toxin mutant CRM197 [58]. Moreover, the phytochemical trans-(±)-kusunokinin suppresses the AKR1B1/SORD axis, reducing intracellular sorbitol and fructose levels, reversing EMT, and inhibiting metastatic potential [59]. Given the central role of EMT in both metastasis and fibrosis, these findings underscore AKR1B1 as a key metabolic regulator of phenotypic plasticity [60].

In gastric cancer, hyperglycemia-induced AKR1B1 activity generates fructose that activates nuclear ketohexokinase-A (KHK-A) signaling. This pathway represses *E-cadherin* (*CDH1*) expression, thereby strongly inducing EMT and metastatic dissemination [61].

In HCC, AKR1B1 contributes to metabolic reprogramming in drug-resistant tumor cells [62]. Given its high expression in activated tumor stroma, the AKR1B1 inhibitors, such as epalrestat or natural products targeting AKR1B1 signaling, such as *Senecio scandens* extracts have been proposed to overcome resistance in HCC treatment [62,63].

In ovarian cancer, tiliroside directly binds to and destabilizes AKR1B1, resulting in intracellular accumulation of ferrous ions ($Fe^{2+}$) and lipid peroxides, ultimately triggering ferroptosis [64]. In leukemia, AKR1B1 is closely linked to stemness. Hydrogel-based culture systems reveal marked upregulation of AKR1B1 alongside stemness markers Oct4 and Nanog in leukemia stem cells, indicating a role in maintaining self-renewal and therapeutic resistance [65].

### *5.2 Role in Cardiovascular Pathology*

#### *5.2.1 Cardiovascular Injury*

In the cardiovascular system, AKR1B1 exhibits context-dependent roles. In the context of doxorubicin-induced cardiotoxicity, the aldose reductase inhibitor epalrestat confers protection by suppressing AGE–RAGE signaling and downstream NF-κB activation, thereby limiting inflammatory injury [66]. Conversely, in abdominal aortic aneurysm (AAA), metformin enhanced translocation of pNRF2 to the nucleus and AKR1B1 expression in vascular smooth muscle cells, enhancing redox homeostasis and cellular resilience [67].

#### *5.2.2 Aortic Valve Calcification*

Calcific aortic valve disease (CAVD) is now recognized as an actively regulated fibro-osteogenic disorder rather than a passive degenerative process. The disease is driven by maladaptive activation

of valvular interstitial cells (VICs), extracellular matrix remodeling, and pathological mineralization, orchestrated through the integration of mechanotransductive cues, metabolic reprogramming, redox imbalance, and endothelial–interstitial crosstalk [68–70]. Increasing evidence indicates that VIC osteogenic differentiation requires the integration of mechanical signaling with metabolic adaptation to sustain runt-related transcription factor 2 (Runx2)-driven transcriptional programs [71–73].

Recent studies have identified AKR1B1 as a critical mediator of VIC osteogenic conversion. AKR1B1 expression is markedly upregulated in calcified human aortic valves and in osteogenically stimulated VICs. Mechanistically, AKR1B1 promotes VIC calcification by activating the Hippo–YAP signaling pathway, facilitating Yes-associated protein (YAP) dephosphorylation, nuclear translocation, and TEA domain family member 1 (TEAD1)-dependent induction of the osteogenic master regulator Runx2 [74]. Pharmacological inhibition of AKR1B1 using epalrestat significantly attenuates VIC calcification *in vitro* and reduces valve mineralization *in vivo*, highlighting its translational relevance [74]. Beyond direct YAP activation, AKR1B1 may further amplify calcification by coordinating redox homeostasis and metabolic reprogramming. By detoxifying lipid peroxidation–derived aldehydes and maintaining NADPH-dependent redox balance, AKR1B1 may relieve oxidative constraints on mechanosensitive YAP signaling [69]. In parallel, metabolic rewiring toward a glycolytic phenotype has been shown to be essential for VIC osteogenic differentiation, linking cellular energetics to Runx2 activation via Ras homolog family member A (RhoA)/Rho-associated protein kinase (ROCK) and AMP-activated protein kinase (AMPK)-dependent pathways [71]. Collectively, these findings support a multi-signal coupling model in which AKR1B1 integrates mechanical, metabolic, and redox inputs to drive VIC osteogenic differentiation and CAVD progression.

#### *5.2.3 Myocardial Ischemia/Reperfusion (I/R) Injury*

The role of AKR1B1 in I/R injury is complex. Its enzymatic activity is protective during the acute oxidative burst of reperfusion by detoxifying the surge of lipid aldehydes such as 4-HNE [75]. This protective function can be rapidly "switched on" via S-nitrosylation of Cys-298 in response to nitric oxide signals during ischemic preconditioning. However, other studies suggest it may protect against I/R injury through other signaling pathways, such as suppression of acute activation of β-catenin [76].

### *5.3 Neurological and Psychiatric Disorders*

Accumulating evidence implicates AKR1B1 in the regulation of neural metabolism, neuroinflammation, and synaptic signaling, linking its dysregulation to a spectrum of neurological and psychiatric disorders.

In experimental models of diabetic neuropathic pain, metabolic reprogramming of microglia toward aerobic glycolysis drives sustained neuroinflammation. Pharmacological inhibition of AKR1B1 with aucubin reverses this metabolic shift, restoring oxidative phosphorylation and alleviating pain hypersensitivity [77]. Consistently, mangiferin reduces lipid droplet accumulation in neuronal cells through AKR1B1 inhibition, suggesting that suppression of aberrant polyol pathway flux mitigates neuroinflammatory stress.

AKR1B1 has been identified as a diagnostic, exosome-associated gene capable of distinguishing high-risk postpartum depression patients, potentially through disruption of synaptic signaling networks [78]. Given the emerging role of exosomes as vectors of pathological signaling—illustrated in models of pulmonary fibrosis [79]—the possibility that AKR1B1 is transported via exosomes in the central nervous system warrants further investigation as both a biomarker and a mechanistic mediator.

In cerebral ischemia–reperfusion injury, the traditional medicine borneol (Aipian) confers neuroprotection by modulating fructose and mannose metabolism. Network pharmacology and target identification studies

implicate AKR1B1 as a key molecular target in this metabolic reprogramming, linking polyol pathway regulation to ischemic tolerance [80].

### *5.4 Inflammatory and Autoimmune Diseases*

AKR1B1 drives chronic inflammatory and autoimmune conditions by regulating metabolic and redox landscapes. In autosomal dominant polycystic kidney disease (ADPKD), AKR1B1 acts within the senescence-associated secretory phenotype (SASP) to promote cyst expansion and disease progression [81]. Similarly, in diabetic acute kidney injury, the renoprotective effects of agents such as esculetin and phloretin are mediated partially through AKR1B1 inhibition, which reduces oxidative stress and inflammation [82].

## 6 Therapeutic Perspectives

This review has repositioned Aldo-keto reductase 1 member B1 (AKR1B1) from its traditional role as a metabolic enzyme in the polyol pathway to a multifunctional signaling hub that integrates metabolic, redox, and transcriptional networks. This expanded understanding reveals significant therapeutic opportunities, but also major challenges arising from the pleiotropic and context-dependent nature of AKR1B1 function.

### *6.1 Targeting Enzymatic Activity: Aldose Reductase Inhibitors (ARIs)*

One of the most immediately actionable strategies is the "repurposing" of classical aldose reductase inhibitors (ARIs), such as epalrestat and sorbinil [83]. Originally developed for diabetic complications, these drugs effectively suppress AKR1B1 catalytic activity, thereby limiting endogenous fructose production and detoxifying reactive lipid aldehydes. Importantly, emerging evidence supports their utility beyond metabolic disease. For example, epalrestat has been shown to reverse chemotherapy resistance in HCC [62] and to attenuate experimental aortic valve calcification [74], highlighting the therapeutic relevance of enzymatic inhibition in select pathological contexts. However, the clinical potential of ARIs is constrained by their inability to interfere with AKR1B1's non-catalytic functions. In particular, ARIs do not disrupt critical protein–protein interactions, such as AKR1B1–STAT3 or AKR1B1–$\beta_2$-adrenergic receptor complexes, which are central drivers of ferroptosis resistance, oncogenic signaling, and tumor progression. This limitation underscores the need for complementary strategies.

### *6.2 Targeting Scaffold Function: Protein–Protein Interaction (PPI) Inhibitors*

Targeting the scaffolding function of AKR1B1 represents a critical but currently unmet therapeutic need. As discussed above, AKR1B1 promotes malignancy through direct protein–protein interactions that stabilize oncogenic signaling nodes, independent of its enzymatic activity. Disrupting these structural interfaces—rather than the catalytic pocket—offers a conceptual framework for selectively blocking pro-tumorigenic signaling while sparing physiological metabolic functions.

The development of protein–protein interaction (PPI) inhibitors against AKR1B1 remains technically challenging, but recent advances in interface mapping, peptide mimetics, and structure-guided drug design provide a feasible path forward. Importantly, preclinical studies demonstrate that disrupting AKR1B1-mediated PPIs can impair cancer cell survival more effectively than catalytic inhibition alone, highlighting the therapeutic value of this approach.

### *6.3 Context-Dependent Challenges and the Need for Precision Targeting*

Despite these opportunities, several major hurdles complicate AKR1B1-targeted therapy. The primary challenge is the context-dependent, pleiotropic nature of AKR1B1's function. As this review demonstrates,

its role is dictated by the cellular context: (1) Tissue-Specific Duality: It acts as a tumor suppressor in some contexts (e.g., glioma, where its re-expression induces p38 MAPK-mediated apoptosis) and as a potent oncogene in others (e.g., gastric cancer, breast cancer, and HCC, where it blocks ferroptosis and drives EMT). (2) Pathway-Specific Duality: Its expression is the result of a "push-pull" dynamic between competing master regulators. It is repressed by the tumor suppressor p53 but simultaneously activated by oncogenic transcription factors, including Nrf2 and the Twist2/NF-κB feedback loop. This "push–pull" regulatory architecture means that AKR1B1 inhibition may have divergent consequences depending on the dominant signaling context. (3) Functional Duality: It promotes malignancy via two distinct mechanisms that may not be co-dependent: (1) its enzymatic function (driving endogenous fructose production and detoxifying lipid aldehydes) and (2) its non-catalytic scaffolding function (e.g., the AKR1B1-STAT3 interaction that drives the GSH-axis). This complex landscape explains the limitations of existing ARIs (which only block enzymatic activity) and complicates the development of new inhibitors. A "one-size-fits-all" inhibitor is likely to fail and could have unpredictable, potentially detrimental effects. This underscores the critical need for robust, pathway-specific biomarkers (e.g., p53, Nrf2, and STAT3 activation status) to guide therapeutic strategies and stratify patient populations.

### *6.4 Emerging Inhibitors and Drug Repurposing*

The expanding understanding of AKR1B1 biology has reinvigorated efforts to identify novel inhibitors beyond traditional ARIs.

Natural products represent a rich source of AKR1B1 modulators with pleiotropic effects. Kusunokinin, derived from *Piper nigrum*, suppresses EMT markers in lung cancer more effectively than epalrestat [59], while tiliroside functions as a ferroptosis inducer in ovarian cancer [64]. Additional natural inhibitors include mangiferin, aucubin, and extracts from *Orthosiphon stamineus* containing rosmarinic acid. Marine sponge–derived tagpyrrollins have also demonstrated inhibitory potential, further expanding the chemical diversity of AKR1B1-targeting compounds.

Synthetic agents have yielded highly potent inhibitors. N-substituted phthalimide derivatives, such as compound 5f, exhibit nanomolar inhibitory activity and selective cytotoxicity toward cancer cells [84]. Another compound, 5N-D, not only inhibits AKR1B1 but also modulates the PI3K–Akt–Nrf2 axis, producing anti-aging effects in model organisms.

Drug repurposing strategies have further broadened the therapeutic landscape. Computational docking analyses identify the alkaloid strychnine as a high-affinity AKR1B1 ligand, suggesting potential anticancer applications [85]. In addition, the lipid-lowering drug ezetimibe exhibits binding affinity toward AKR1B family members, hinting at unanticipated metabolic and oncologic indications.

## 7 Conclusion

In conclusion, AKR1B1 stands as a master regulator at the intersection of metabolism and signaling. A deepened understanding of its functional duality and complex regulatory networks has illuminated novel mechanisms in oncology and cardiovascular disease, providing a scientific foundation for the development of innovative, targeted therapies.

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## Abbreviations

| | |
|---|---|
| 4-HNE | 4-hydroxynonenal |
| 4-ONE | 4-oxononenal |
| ADHs | Alcohol dehydrogenases |
| AGEs | Advanced Glycation End-products |
| AKR1A1 | Aldo-keto reductase family 1 member A1 |
| AKR1B1 | Aldo-keto reductase family 1 member B1 |
| AMPK | AMP-activated protein kinase |
| AR | Aldose reductase |
| AREs | Antioxidant Response Elements |
| ARIs | Aldose reductase inhibitors |
| BAX | Bcl-2-associated X protein |
| Bcl-2 | B-cell lymphoma 2 |
| BH4 | Tetrahydrobiopterin |
| CAVD | Calcific aortic valve disease |
| EMT | Epithelial-mesenchymal transition |
| EPS15-AS1 | EPS15 antisense RNA 1 |
| GSH | Glutathione |
| HCC | Hepatocellular carcinoma |
| I/R | Ischemia/Reperfusion |
| LINC00978 | Long Intergenic Non-Protein Coding RNA 978 |
| NAD+ | Nicotinamide adenine dinucleotide |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NO | Nitric oxide |
| Nrf2 (NFE2L2) | Nuclear factor erythroid 2-related factor 2 |
| p38 MAPK | p38 mitogen-activated protein kinase |
| p53 | Tumor protein p53 |
| PG | Prostaglandin |
| PGDS | Prostaglandin D synthase |
| PGFS | Prostaglandin F synthase |
| PGH2 | Prostaglandin H2 |
| POVPC | 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine |
| PPI | Protein-protein interaction |
| RA | Retinoic acid |
| RDHs | Retinol dehydrogenases |
| RhoA | Ras homolog family member A |
| ROCK | Rho-associated protein kinase |
| Runx2 | Runt-related transcription factor 2 |
| SDH | Sorbitol dehydrogenase |
| SLC7A11 | Solute carrier family 7 member 11 |
| STAT3 | Signal Transducer and Activator of Transcription 3 |

| | |
|---|---|
| TEAD1 | TEA domain family member 1 |
| TGF-β | Transforming growth factor beta |
| TIM | Triosephosphate isomerase |
| Twist2 | Twist-related protein 2 |
| VICs | Valvular interstitial cells |
| YAP | Yes-associated protein |
| β2-AR | β2-adrenergic receptor |

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