



## Review Article

# Noncoding RNA Roles in Pharmacogenomic Responses to Aspirin: New Molecular Mechanisms for an Old Drug

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Aspirin, as one of the most frequently prescribed drugs, can have therapeutic effects on different conditions such as cardiovascular and metabolic disorders and malignancies. The effects of this common cardiovascular drug are exerted through different molecular and cellular pathways. Altered noncoding RNA (ncRNA) expression profiles during aspirin treatments indicate a close relationship between these regulatory molecules and aspirin effects through regulating gene expressions. A better understanding of the molecular networks contributing to aspirin efficacy would help optimize efficient therapies for this very popular drug. This review is aimed at discussing and highlighting the identified interactions between aspirin and ncRNAs and their targeting pathways and better understanding pharmacogenetic responses to aspirin.

## 1. Introduction

Acetylsalicylic acid (ASA), generally known as aspirin, is mostly prescribed for treating patients with cardiovascular diseases [1]; besides, it can also have therapeutic effects on the different types of cancers and metabolic diseases [2, 3] by modulating different molecules and cellular signaling pathways [4].

Noncoding RNAs (ncRNAs) are regulatory RNAs that could modulate different steps in the transcription and translation processes [5–7]. ncRNAs are powerful, flexible, and pervasive cellular regulators. They are among the most critical molecules that aspirin can affect and subsequently cause many changes in the cellular signaling pathways [8,

9]. ncRNAs have different classifications, but so far, the effects of aspirin have been reported just on the microRNAs (miRNAs, miRs) and long noncoding RNAs (lncRNAs) [9, 10].

The discovery of ncRNAs has changed our understanding of the biology of diseases. A better knowledge of the interactions between ncRNAs and drugs can help clarify the molecular mechanisms by which drugs exert their effects. Some previous review studies clarified the effects of aspirin on miRNAs in cardiovascular diseases [11] and cancer [12]; however, none investigated the effects of aspirin on ncRNAs in different diseases. This review intends to discuss aspirin effects on ncRNAs to identify their impacts in detail and elucidate potential therapeutic approaches.

**1.1. Aspirin: Sources, Bioavailability, and Mechanism of Action.** Aspirin is a nonsteroidal anti-inflammatory drug (NSAID), which is mostly used against platelet aggregation and pain, which has inhibitory activities in various disorders such as cancers and cardiovascular and central nervous system (CNS) disorders [13, 14]. Aspirin's molecular formula is  $C_9H_8O_4$ , and its IUPAC name is "2-acetoxybenzoic acid" [15].

It is believed that aspirin naturally originated from willow bark. Willow species have small amounts of salicin, which would be turned into salicylate fractions. Salicylic consistency is higher in aspirin pills than willow bark, and willow bark cannot be a suitable source for analgesia alone [14, 16]. Prescription and dose of aspirin can vary among different diseases, from 50 mg to 6000 mg daily. Most of its side effects, such as gastrointestinal bleeding, are dose-dependent [17]. An investigation indicated that after administering a 100 mg dose of aspirin, the average  $C_{max}$  was 0.94 mg/L and 2 mg/L in patients with myocardial infarction and healthy people, respectively [18].

It is believed that aspirin's analgesic and antiplatelet activity is due to the ability of this drug to lower prostaglandins and thromboxane A2 [19]. Aspirin can inhibit prostaglandins and thromboxane due to its ability to suppress cyclooxygenase (COX). COX is needed to produce prostaglandins and thromboxane. Aspirin is an acetylating compound that can bind to the serine residue of COX. Thus, aspirin inhibits the enzyme irreversibly, which is different from the other NSAIDs that are reversible inhibitors. COX-1 suppression leads to thromboxane repression and vasoconstriction. COX-2 suppression also causes prostaglandin inhibition and, consequently, inflammation prevention [16, 20]. Aspirin can also be involved in uncoupling oxidative phosphorylation in mitochondria resulting in a higher respiration rate and diminished respiratory control ratio and signaling modulation through preventing NF- $\kappa$ B in neoplastic cells [21, 22].

**1.2. ncRNAs.** Most of the mammalian transcriptomes are noncoding [23]. ncRNAs are divided into two categories, regulators and housekeepers [24]. So far, different classes of regulatory ncRNAs have been found in mammals that have significant roles in most cellular signaling pathways [25, 26] (Table 1).

Regulatory ncRNAs are involved in gene expression regulation under physiological and pathophysiological conditions [27, 28]. So far, the effects of aspirin alone or with others on the two classes of ncRNAs, including lncRNAs and miRNAs, have been reported (Figures 1 and 2). lncRNAs have regulatory effects on the transcriptional and posttranscriptional stages [29]. They play essential roles in biological activities and participate in many disorders, especially in cancer and chronic diseases [30–34]. Apart from the gene expression's effect, lncRNAs can also stick to proteins and modulate their necessary functions for signaling pathways [35]. Among ncRNAs, miRNAs are the main agents for gene silencing and posttranscriptional regulation. These molecules affect gene expression by attaching to specific areas in the UTRs or coding regions of the targets and impressing RNA expression or function [36–38].

## 2. Effects of Aspirin on ncRNAs in Different Conditions

The effects of aspirin on ncRNAs in various conditions are demonstrated as follows and briefly in Table 2.

**2.1. Osteosarcoma.** miR-34a expression is related to p53 status [39]. Tan et al. compared the expression of miR-34a in osteosarcoma cell lines p53 wild-type U2OS and p53-deficient Saos2, and the results showed significantly lower expression of miR-34a in Saos2 cells. It was demonstrated that restoration of miR-34a in Saos2 cells would not increase apoptosis. miR-34a downregulates SIRT1 by elevation of NF- $\kappa$ B levels. Adding aspirin (2 mM) to miR-34a restored Saos2 cells leading to decreased NF- $\kappa$ B amounts and elevated apoptosis in Saos2 cells. To conclude, combination therapy with aspirin and miR-34a increased cell apoptosis in Saos2 cells [40].

**2.2. Colorectal Cancer.** Transcription factor 7 like 2 (TF7L2 or TCF4) is a transcription factor in the Wnt/ $\beta$ -catenin/TCF signaling pathway that participated in regulating several target genes [41]. Lan et al. elucidated that miR-21 has a differential expression between normal and colon cancer tissues [10]. miR-21 is a TCF4 target, and its expression is increased in various tumors [42]. Blocking the Wnt/ $\beta$ -catenin/TCF signaling pathway by aspirin (10 mM) resulted in the downregulation of miR-21 and confirmed that TCF4 could control miR-21 expression in colon carcinogenesis [10].

In a similar study on colorectal cancer, after treating the cells with aspirin (100  $\mu$ M), 28 lncRNAs increased that the most considerable change among them belonged to lncRNA OLA1P2. It was found that aspirin promotes the transcription of OLA1P2 by upregulating FOXD3. OLA1P2 could block phosphorylated STAT3 homodimer formation and activate the STAT3 signaling pathway, inhibiting colorectal cancer cell growth and metastasis [9].

**2.3. Breast Cancer.** Glycolysis is a critical process in cancer stem cell pathogenesis [43]. Progressive cancer cells use aerobic glycolysis rather than oxidative phosphorylation [44]. Glycolysis produces molecules, such as acetyl-CoA, to accelerate DNA replication that induces cell proliferation [45]. It has been shown that pyruvate dehydrogenase kinase 1 (PDK1) is abundant in breast cancer stem cells. Reducing PDK1 significantly diminished the ALDH<sup>+</sup> subpopulation and decreased stemness-related transcriptional factor expression, sphere formation, and tumor growth. It was demonstrated that lncRNA H19 contributed to glycolysis and maintenance of breast cancer stem cells, with a trial on hypoxia-related lncRNAs [46]. H19, an endogenous RNA, could upregulate hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ) expression by sponging let-7, which subsequently upregulates PDK1 expression. It was demonstrated that aspirin (5 mM) reduced glycolysis, glucose uptake, lactate production, ATP levels, and stem-like cancer feature by inhibiting both H19 and PDK1 in MDA-MB-231 and MCF-7 cells [46].

TABLE 1: Classification of ncRNAs.

ncRNA type	Abbreviation	Full name	Function	Nucleotides	References
Housekeeping	rRNAs	Ribosomal RNAs	Ribosomal component during translation	7216	[24]
	tRNAs	Transfer RNAs	Adaptor in translation	76-90	[24]
	snRNAs	Small nuclear RNAs	RNA splicing	60-300	[114, 115]
	tel-sRNAs	Telomere small RNAs	Telomere maintenance	24	[24, 116]
	snoRNAs	Small nucleolar RNAs	Chemical modifications (methylation and pseudouridylation) of other ncRNAs (rRNA, tRNA, snRNA); alternative splicing; cis- and trans-gene regulation; may also function as miRNA	70-200	[24]
	miRNAs	MicroRNAs	Gene silencing: translational repression or RNA degradation	18-15	[117, 118]
	siRNAs	Small interfering RNAs	Gene regulation, transposon control, and viral defense	21-23	[118, 119]
	piRNAs	PiwiRNAs	Transposon repression, chromatin modification	24-30	[118, 120, 121]
	eRNAs	Enhancer derived RNAs	Regulation of gene expression	50-2000	[24]
	LncRNAs	Long noncoding RNAs	Gene regulatory processes: promoter-specific repression, activation of epigenetic gene regulation	200-100,000	[117, 122, 123]
	CircRNAs	Circular RNAs	Serving as RNA sponges (ceRNAs) to bind miRNAs and modulate miRNA-targeted gene expression	>200	[124]
	xiRNAs	X-inactivation RNAs	X-chromosome inactivation in placental mammals	>200	[125, 126]
Regulatory	gRNAs	Guide RNAs	RNA editing	100	[24]
	Promoter-associated RNAs (PARs)		A general term encompassing a suite of long and short RNAs, including promoter-associated RNAs (PASRs) and transcription initiation RNAs (tiRNAs) that overlap promoters and TSSs. These transcripts may regulate gene expression	20-200	[127, 128]
	Sno-derived RNAs	sdRNAs	Small RNAs, some of which are Dicer-dependent, which are processed from small nucleolar RNAs (snoRNAs). Some sdRNAs have been shown to function as miRNA-like regulators of translation	20-24	[129, 130]
	MicroRNA-offset RNAs	moRNAs	Small RNAs, derived from the regions adjacent to pre-miRNAs. Their function is unknown	20	[131, 132]
	tRNA-derived RNAs		tRNAs can be processed into small RNA species by a conserved RNase (angiogenin). They are able to induce translational repression	73-90	[133]
	MSY2-associated RNAs	MSY-RNAs	MSY-RNAs are associated with the germ cell-specific DNA/RNA binding protein MSY2. Like piRNAs, they are largely restricted to the germline. Their function is unknown	26-30	[134]
	Centrosome-associated RNAs	crasiRNAs	Derived from centrosomes for local chromatin modification	34-42	[135]

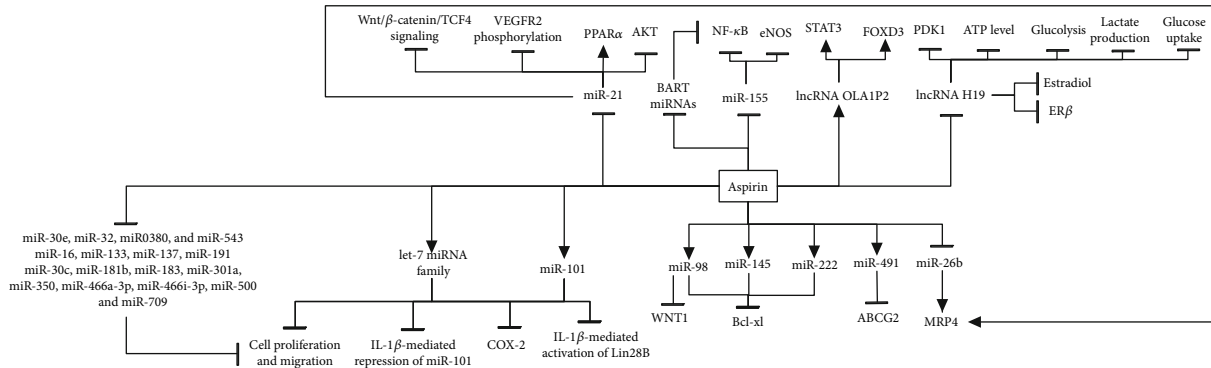


FIGURE 1: Identified effects of aspirin on ncRNAs. Aspirin alters the expression of miRNAs and lncRNAs and subsequently their targets.

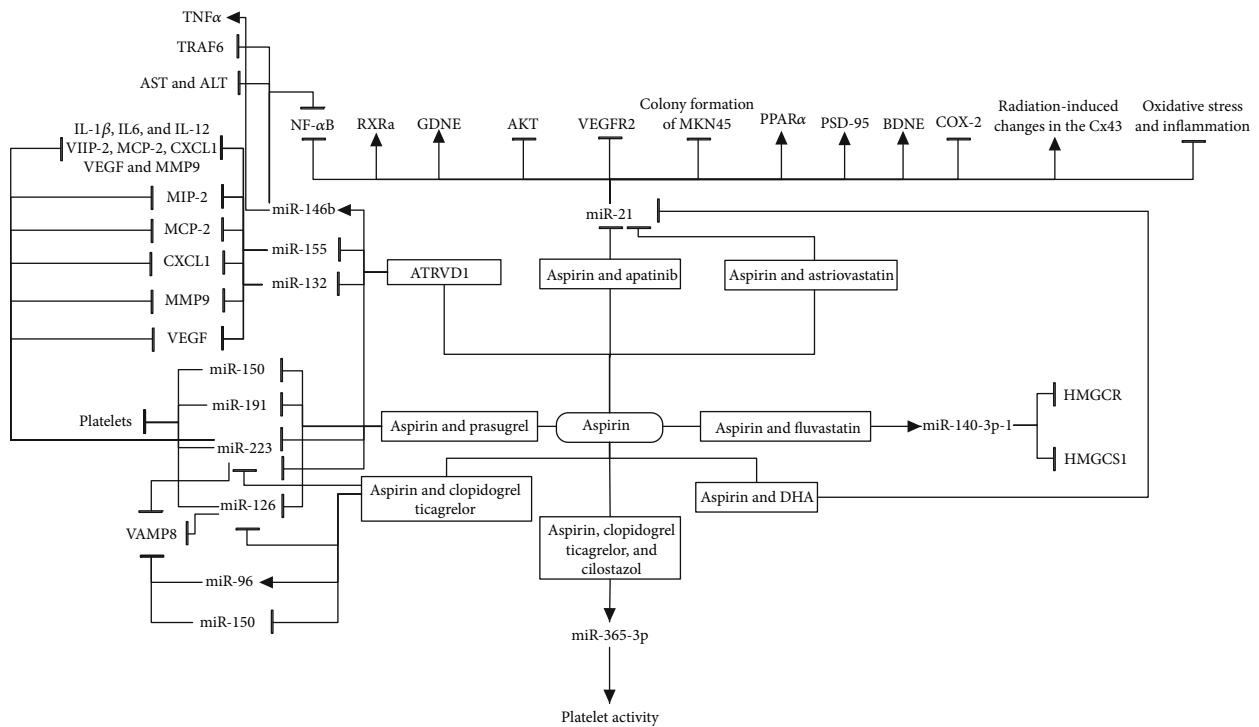


FIGURE 2: Effects of aspirin combined with other drugs on ncRNAs. Aspirin combined with other drugs alters the expression of miRNAs and lncRNAs and consequently their targets.

Bhardwaj and colleagues stated that 5' isomiRNA from miR-140-3p (miR-140-3p-1) and its direct targets, HMG-CoA reductase (HMGCR) and HMG-CoA synthase 1 (HMGCS1), critical enzymes for the biosynthesis of cholesterol, were negatively regulated in the conversion of normal cells to preneoplastic cells [47]. It was shown that miR-140-3p-1 downregulation diminished cell growth, and this miRNA was directly linked to HMGCR and HMGCS. According to this supposition, researchers found that targeting miR-140-3p-1 and its reduction with fluvastatin (5 μM) limits the preneoplastic growth of MCF10.AT1 cells and reduces the colony formation by MCF10.AT1 and MCF10.DCIS cells. They found that inhibition of cholesterol leads to the elimination of tumorigenesis. To inhibit the response of HMGCR to statins, they treated the fluvastatin-resistant preneoplastic cells with an AMP-

activated protein kinase activator (AMPK) to prevent the cholesterol feedback pathway. The initiation of AMPK by aspirin (0.5 mM and one mM) strongly reduces the high-level HMGCR-induced statin. Therefore, combination therapy with fluvastatin and aspirin can prevent triple-negative breast cancer (TNBC) [47].

According to the studies, COX inhibitors can decrease the probability of breast malignancy [48]. Wong and his collaborators indicated that miR-98 and miR-222 expression was reduced in mouse breast tumor tissues after treatment with aspirin (200 ppm) and celecoxib (1500 ppm), and malignant cell growth was prevented [49].

2.4. Gastric Cancer. Mikami and colleagues treated tumor-bearing mice orally with 100 μL aspirin (20 mg/kg of body weight) daily. The aspirin administered to the mice was

TABLE 2: Effects and consequences of aspirin on ncRNAs in different conditions.

Treatment	Cell type	Effects on ncRNAs	Outcomes	References
Aspirin (5 mM)	Human umbilical vein endothelial cells) HUVECs(	Downregulation of miR-155	Downregulation of eNOS and NF- $\kappa$ B	[3]
Aspirin (1 mM)	MKN-45 cells (gastric cancer cell line)	Downregulation of miR-21	Upregulation of PPAR $\alpha$ , downregulation of VEGFR2 phosphorylation and AKT	[8]
Aspirin (1 mM)+apatinib (0.1 mM)	MKN-45 cells (gastric cancer cell line)	Downregulation of miR-21	Upregulation of PPAR $\alpha$ , downregulation of VEGFR2 phosphorylation, AKT, migration and colony formation	[8]
Aspirin (100 $\mu$ M)	Colorectal cancer cells (primary and cell lines)	Upregulation of lncRNA OLA1P2	Upregulation of FOXD3, activating STAT3 pathway	[9]
Aspirin (10 mM)	LS174T cells (colorectal cancer cell line)	Downregulation of miR-21	Downregulation of Wnt/ $\beta$ -catenin/TCF4 signaling	[10]
Aspirin (5 mM)	MDA-MB-231, MCF-7, SK-BR-3, and HEK293T cells (breast cancer cell lines)	Downregulation of lncRNA H19	Downregulation of PDK1, glycolysis, glucose uptake, lactate production, ATP levels and stem-like cancer characteristics	[46]
Aspirin (0.5 and 1 mM)+fluvastatin (5 $\mu$ M)	MCF10.AT1 and MCF10.DCIS cells (MCF10A-based model for breast cancer)	Upregulation of miR-140-3p-1	Downregulation of HMGCR and HMGCS1	[47]
Aspirin (200 ppm)	MCF-7 (breast cancer cells)	Upregulation of miR-222, miR-98, and miR-145	Downregulation of Bcl-xl	[49]
Aspirin (100 $\mu$ L)	MKN-45 cells (gastric cancer cell line)	Downregulation of miR-4670-5P	—	[50]
Aspirin (1600 mg/kg)	Lung of mice	Downregulation of miR-30e, miR-32, miR-380, and miR-543	Downregulation of proliferation by non-prostaglandin-dependent pathways	[52]
Aspirin (1600 mg/kg)	Serum of mice	Downregulation of miR-16, miR-133, miR-137, and miR-191	Downregulation of proliferation affects non-prostaglandin-dependent pathways	[52]
Aspirin (1600 mg/kg)	Lung and serum of mice	Downregulation of miR-30c, miR-181b, miR-183, miR-301a, miR-350, miR-466a-3p, miR-466i-3p, miR-500, and miR-709	Downregulation of proliferation by non-prostaglandin-dependent pathways	[52]
Aspirin (1 mM)	Human NSCLC cell lines H460 and H1299 cell line	Upregulation of miR-101 and let-7 miRNA family	COX-2, IL-1 $\beta$ -mediated repression of miR-101, IL-1 $\beta$ -mediated activation of Lin28B, cell proliferation, and migration	[55]
Aspirin (2.5 mM and 5 mM)	A549 and H1299 lung cancer cell lines	Upregulation of miR-98	Downregulation of WNT1	[56]
Aspirin (5 mM)	Human thyroid cancer cell lines (TPC-1 and K-1)	Downregulation of lncRNA H19	Downregulation of estradiol and ER $\beta$	[58]
Aspirin (2.5 $\mu$ mol/mL)	Non-SP and SP cells isolated from MHCC-97L cell line	Upregulation of miR-491	Downregulation of ABCG2 protein expression	[59]
Aspirin (4 mM)	C666-1 cell line (nasopharyngeal carcinoma cells)	Downregulation of BART miRNAs	Downregulation of NF- $\kappa$ B activity	[61]

TABLE 2: Continued.

Treatment	Cell type	Effects on ncRNAs	Outcomes	References
Aspirin (300 mg and 100 mg)+clopidogrel (300 mg and 75 mg) Aspirin+ticagrelor (180 mg and 90 mg) Aspirin+clopidogrel+cilostazol (100 mg)	Platelet-rich plasma of CAD patients	Upregulation of miR-365-3p	Upregulation of platelet activity	[62]
Aspirin (100 mg)+clopidogrel (300 mg)	Blood samples of CAD patients	Upregulation of miR-126, miR-130a, miR-142, and miR-27	—	[63]
Aspirin low dose (75-100 mg)+clopidogrel (300–600 and 75 mg)	Plasma CAD patients	Downregulation of miR-223	—	[65]
Aspirin (75 and 300 mg)+prasugrel (10 mg)	Platelets of patients	Downregulation of miR-223, miR-191, miR-126, and miR-150	Downregulation of platelet	[68]
Aspirin (100 mg)+indomethacin (200 $\mu$ mol/L)	Platelets of healthy males	Downregulation of miR-19b-1-5p	—	[70]
Aspirin (100 mg/day)+clopidogrel (75 mg/day)+ticagrelor (90 mg/BD)	Plasma of patients	Downregulation of miR-126, miR-150, and miR-223, upregulation of and miR-96	—	[71]
Aspirin (330 $\mu$ mol/L)	Plasma or platelet of healthy volunteers	Downregulation of miR-126	—	[72]
Aspirin (100 and 300 mg/day, 50 $\mu$ mol/L)	Human platelets and DAMI cells (human megakaryoblastic)	Downregulation of miR-21	Upregulation of MRP4 and PPAR $\alpha$	[74]
Aspirin (100 mg/day)	Platelets of atherothrombotic patients	Downregulation of miR-135a-5p and miR-204-5p	—	[76]
Aspirin (100 mg/day)	Platelets of patients	Downregulation of miR-26b	Upregulation of MRP4	[78]
Aspirin (75 and 100 mg, 150 mg/day)	Plasma of patients	Downregulation of miR-92a	Aspirin resistance	[80]
Aspirin (1000 mM)+DHA (1000 mM)	SH-Y5Y cell line	Downregulation of miR-21	Upregulation of PPAR $\alpha$ and RXRa, PSD-95, BDNF, GDNF, downregulation of NF- $\kappa$ B and COX-2	[83]
AT-RvD1 (150 ng/eye; 5 $\mu$ L drop)	Corneal cells of mice	Downregulation of miR-223, miR-155, and miR-132	Downregulation of proinflammatory mediators such as IL1 $\beta$ , IL6, and IL-12, as well as MIP-2, MCP-2, CXCL1, VEGF, and MMP9	[91]
AT-RvD1 (5 $\mu$ g/kg)	Liver of rats	Upregulation of miR-146b	Downregulation of TRAF6 and NF- $\kappa$ B, ALT, AST, and liver tissue damage, amelioration of TNF $\alpha$ and myeloperoxidase	[110]
Aspirin (3 mg/day)+atorvastatin (0.25 mg/day)	Myocardial cells of rats	Downregulation of miR-21	Improvement of radiation-induced changes in the Cx43, improvement of oxidative stress and inflammation	[112]

similar to a human dosage of about 80–110 mg/day, showing a more remarkable decrease in microvessel density (MVD) (an indicator of tumor-associated neovascularization) than the control group. Based on the *in vitro* experiments, gastric cancer cell line, MKN-45, NUGC-3, and AGS, proliferation was increased after coinubation with platelets, suppressed by aspirin (1 mM). The findings demonstrated different

expressions of miR-4670-5p in response to incubation with platelet aggregation or the addition of aspirin. Aspirin could diminish platelet-induced cancer cell proliferation, and miR-4670-5p may be an essential player in these responses [50].

miR-21 and VEGF expression was upregulated in gastric cancer *in vivo* and *in vitro*, while PPAR $\alpha$  was downregulated; expression of VEGF and PPAR $\alpha$  was correlated with

miR-21 levels. Aspirin (1 mM) and apatinib (0.1 mM) for 24 hours, respectively, accelerate PPAR $\alpha$  expression and inhibit VEGFR2 phosphorylation. The activation of PPAR $\alpha$  down-regulated the levels of AKT and miR-21 in GC cells. All in all, aspirin and apatinib inhibited cell proliferation and decreased migration, viability, and MKN-45 cell colony growth [8].

**2.5. Lung Cancer.** Recent research has identified that NSAIDs have suppressing effects on cigarette smoke-induced lung tumors, either mainstream (MCS) or environmental (ECS) in mice [51]. Izzotti and colleagues analyzed 1135 miRNAs in the lung and serum of mice subjected to smoke and/or oral usage of either aspirin (1600 mg/kg) or naproxen (320 mg/kg). Aspirin could regulate some miRNAs out of 1135 pulmonary miRNAs, including miR-16 in apoptosis, miR-133 in inflammation, miR-137 in cell proliferation and negative regulation of COX-2, miR-191 in COX regulation and cell proliferation, miR-199b in COX activation, miR-223 in stress response and protein repair and k-Ras regulation, and miR-543 in stress response and inflammation in pulmonary cancer [52]. Inflammatory stimulators can help lung cancer development [53]. miRNAs are new classes of inflammatory mediators that interact with inflammation and tumorigenesis [54]. Wang and coworkers found that IL-1 $\beta$  is abundant in non-small-cell lung cancer (NSCLC) patients. *In vitro* investigations demonstrated that IL-1 $\beta$  increases the growth and migration of NSCLC cell lines H460 and H1299 by downregulating miR-101, a miRNA with a tumor suppressive property, through the COX-2-HIF1 $\alpha$  pathway. Lin28B, a target of miR-101, has been shown to have tumor-suppressive effects. miR-101 also upregulates the let-7 family by regulating Lin28B. IL-1 $\beta$  increases Lin28B through miR-101 downregulation. Interestingly, inhibition of COX-2 using aspirin (1 mM) and celecoxib (25  $\mu$ M), IL-1 $\beta$ -mediated suppression of miR-101, and IL-1 $\beta$ -mediated activation of Lin28B inhibited NSCLC cell proliferation and migration. These data show that aspirin can reverse the IL-1 $\beta$  effect on the miR-101-Lin28B-let-7 regulatory axis and antagonizes the IL-1 $\beta$  effect on NSCLC cells [55]. In a similar study, it was shown that aspirin (5 mM) significantly suppressed NSCLC cancer cell stability (A549 and H1299 cell lines) and decreased cancer cell concentration by upregulating miR-98 as a tumor suppressor and downregulating its target gene, WNT1, in lung cancer cells [56].

**2.6. Papillary Thyroid Carcinoma.** Estrogen receptor  $\beta$  (ER $\beta$ ), a key factor in thyroid malignancies [57], is upregulated in papillary thyroid carcinoma stem cells (PTCSCs), and its degradation reduces the expression of stemness-related factor ALDH<sup>+</sup> cell concentrations, sphere formation, and tumor growth. lncRNA H19 was overexpressed in PTCSCs and PTC tissues by estradiol (E2) via ER $\beta$ . The silencing of H19 can inhibit E2-induced stem-like traits. It was demonstrated that aspirin (5 mM) treatment regulates E2-induced cancer stem-like by downregulation of H19 and ER $\beta$  expression in mice [58].

**2.7. Hepatocellular Carcinoma.** An experimental study demonstrated that treatment with doxorubicin reduced the ability to form colonies by hepatocellular side population (SP) and non-SP cells. However, the doxorubicin effect on SP cells has been more than non-SP cells. Doxorubicin inhibited SP stability, but by adding aspirin (2.5  $\mu$ mol/mL), the inhibitory effect of doxorubicin (500 ng/mL) significantly increased. Compared to non-SP cells, miR-491 expression in SP cells was reduced more in which aspirin had a significant effect. miR-491 directly controls ABCG2 expression. In the existence of doxorubicin and miR-491 inhibitors, aspirin's inhibition decreases the stability of SP cells, but the suppression of ABCG2 reverses it. Moreover, it was indicated that miR-130b, miR-491, miR-612, miR-3650, and miR-7-5p expressions were negatively regulated in SP cells, but aspirin only reverses the expression of miR-491. Aspirin treatment could inhibit ABCG2 expression in SP cells, which is much higher than non-SP cells. Therefore, aspirin increases SP cells' sensitivity to doxorubicin by regulating the miR-491/ABCG2 signaling pathway [59].

**2.8. Nasopharyngeal Carcinoma.** Epstein-Barr virus (EBV) expresses viral proteins in nasopharyngeal carcinoma (NPC) and large amounts of BamHI-A rightward transcripts (BARTs) that contain lncRNAs and BART miRNAs [60]. It was shown that NF- $\kappa$ B activates BART promoters in infected cells with EBV in NPC. BART miRNAs and lncRNAs are associated with NF- $\kappa$ B activity in infected epithelial cells during EBV harboring. NPC C666-1 cells treated with aspirin (4 mM) and NF- $\kappa$ B kinase inhibitor, PS-1145 (0.2 mM), suppressed NF- $\kappa$ B activity leading to a decrease in BART expression [61].

**2.9. Coronary Artery Disease.** miRNAs are responsible for the pathogenesis of several cardiovascular diseases [62]. Tang and colleagues showed that high levels of miR-142 were detected in plasma samples related to adverse cardiovascular events in coronary artery disease (CAD) patients who had undergone percutaneous coronary intervention (PCI) and administration of aspirin (200 mg) and clopidogrel (300 mg). The researchers reported that miR-142 could be a biomarker for MACE prediction in CAD patients. Additionally, miR-126, miR-130a, and miR-27 expressions increased in aspirin-sensitive and clopidogrel-resistant patients. Besides, miR-21 has downregulated in clopidogrel-resistant patients. Accordingly, these miRNAs are associated with antiplatelet therapy efficiency [63]. In another study, the correlation between miR-96-5p, miR-495-3p, miR-107, miR-223-3p, miR-15a-5p, miR-365-3p, and miR-339-3p and platelet response was investigated in 155 patients with CAD. Patients had anticoagulant therapy with aspirin (loading 300 mg, then 100 mg once daily) and clopidogrel (standard dose: loading 300 mg, then 75 mg once daily), aspirin and ticagrelor (loading 180 mg, then 90 mg twice daily), and aspirin and cilostazol (100 mg twice daily). The findings demonstrated that seven miRNAs are affected by the platelet activity level; however, the expression of miR-365-3p elucidated the most remarkable association

with platelet activity, with higher expression levels correlated with higher platelet activity [62].

It was suggested that a reduction in the plasma level of miR-223, mainly from the platelet source, is an indicator of the effectiveness of antithrombotic therapy [64]. However, the platelet response was correlated with a reduction in the expression of miR-223 in the plasma of CAD patients and dual antiplatelet therapy (DAPT) treatment, including low-dose aspirin (75-100 mg) and low-dose clopidogrel (300-600 mg and 75 mg). Based on the results, it was proposed that low levels of miR-223 could be considered a biomarker for platelet response to DAPT [65].

**2.10. Platelet-Associated Cardiovascular Disease.** Platelets are the main sources of circulatory miRNAs [66]. miRNAs are attractive biomarkers for monitoring multiple cardiovascular disease progression [67]. Interestingly, the levels of certain miRNAs correlate with platelet activation levels [68]. Aspirin is one of the most important antiplatelet drugs used as secondary prevention in cardiovascular disease progression [54]. However, aspirin's effectiveness can be limited since 10 to 20 percent of patients with aspirin-treated arterial thrombosis encounter a recurring vascular disorder during long-term follow-up [69].

A study on 15, 35-60-year-old healthy male volunteers without a family history of cardiovascular disease with no medication history demonstrated altered expression of six miRNAs after aspirin treatment (100 mg once daily, for two weeks), which include miR-1225-3p, miR-1271, miR1537-5p, miR-19b-1-5p, miR-548e, and miR-587. These changes were related to decreased platelet aggregation. Also, it was shown that downregulation of miR-19b-1-5p after treatment with aspirin was along with the accumulation of stable platelets in the presence of indomethacin (200  $\mu$ mol/L), indicating insensitivity to aspirin. Therefore, miR-19b-1-5p can be an appropriate indicator of aspirin insensitivity in patients with cardiovascular diseases [70].

Carino et al. demonstrated that the circulating levels of miR-126, miR-223, and miR-150 were remarkably decreased, while the level of miR-96 was increased after switching from aspirin (100 mg/day) and clopidogrel (75 mg/day) to ticagrelor (90 mg BD) [71]. miR-126 is associated with endothelial cell function, and angiogenesis and recent research show that this miRNA could be regarded as a biomarker in vascular disease. According to de Boer and colleagues, in pathophysiological conditions related to platelets' activation, such as type 2 diabetes, treatment with aspirin (330  $\mu$ mol/L) might decrease circulating miR-126 levels [72]. Overexpression of multidrug resistance protein 4 (MRP4) causes increased platelet reactivity in aspirin treatment [73]. It was demonstrated that MRP4 inhibition downregulated platelet function and increased thrombosis. There is a negative association between miR-21 and MRP4-PPAR $\alpha$  in the presence of aspirin. In megakaryoblastic cell line (DAMI), miR-21 mimic transfection decreased MRP4 and PPAR $\alpha$  mRNA expression, even if transfected cells would not be treated with aspirin. Aspirin (50  $\mu$ mol/L) therapy in human mega-

karyocytes reduced miR-21 and upregulated MRP4. miR-21 inhibited MRP4 and PPAR $\alpha$  transcription, and aspirin prevented these events [74].

Platelet reactivity is different among cardiovascular patients and has variable clinical outcomes in the patients treated with antiplatelet drugs [75]. It was shown that downregulated miR-135a-5p and miR-204-5p are related to platelet reactivity, and these miRNAs were suggested as regulatory candidates in patients with cardiovascular diseases treated with aspirin (100 mg/day). These miRNAs can have synergistic effects on seven overlapping genes (THBS1, CDC42, CORO1C, SPTBN1, TPM3, GTPBP2, and MAPRE2) [76].

MRP4 overexpression has been recently reported as a factor in reducing aspirin efficacy after bypass surgery [77]. In patients treated with aspirin (100 mg), MRP4 protein expression was upregulated, and miR-26b was decreased. Moreover, the results showed that transfecting DAMI cells with miR-26b reduced MRP4 expression in aspirin-treated cells. miR-26b has an essential effect on MRP4 modulation, and it was revealed that the incubation of platelets with this miRNA could downregulate MRP4, but it will be inhibited by aspirin treatment [78].

About 25% of cardiovascular patients deal with inadequate platelet inhibition following treatment with aspirin [79]. Aspirin resistance can be figured out using miR-92 profiling and platelet distribution width. miR-92a levels in the aspirin responders, aspirin-resistant, and control groups were investigated, and all groups showed a miR-92a downregulation after aspirin therapy (75, 100, and 150 mg per day). The findings showed that plasma miR-92a could potentially contribute to identifying aspirin resistance [80]. It was also observed that plasma levels of miR-223, miR-191, miR-126, and miR-150 decreased during platelet inhibition. These miRNAs were used as biomarkers to detect antiplatelet therapy effectiveness, which included prasugrel (10 mg), followed by a low dose of aspirin (75 mg in the second week) and higher doses of aspirin (300 mg in the third week). The results indicated that the increased aspirin dose combined with prasugrel led to increased platelet inhibition [68].

**2.11. Parkinson's Disease.** Parkinson's disease (PD) is a fatal neurologic disease with few effective treatments [81]. It was shown that miR-21, which plays a preservative role in Alzheimer's disease [82], was associated with PPAR $\alpha$  in PD. In PD patients, the level of miR-21 was increased, and PPAR $\alpha$  was reduced. DHA (1000 mM) and aspirin (1000 mM) could activate RXR $\alpha$  and PPAR $\alpha$ . Besides, DHA could increase the expression of PPAR $\alpha$  by suppressing miR-21 in SH-Y5Y cells. Combining DHA and aspirin effectively increased the heterodimer formations of PPAR $\alpha$  and RXR $\alpha$  and expression of the postsynaptic density protein 95 (PSD-95), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF), whereas inhibited NF- $\kappa$ B and COX-2. In general, the synergism of DHA and aspirin can exert neuroprotective effects through the suppression of miR-21 and activation of RXR $\alpha$  and PPAR $\alpha$  [83].



**2.12. Preeclampsia.** Preeclampsia, a disease followed by inflammation and endothelial cell disorder, is correlated with a decreased activity of endothelial nitric oxide synthase/nitric oxide (eNOS/NO) [84]. Circulating levels of proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are increased in maternal and cord blood in patients with preeclampsia [85], leading to endothelial dysfunction via various mechanisms such as reactive oxygen species- (ROS-) mediated oxidative stress [86], which results in the progression of hypertension and proteinuria [87]. TNF- $\alpha$  and ROS activate NF- $\kappa$ B that participated in expressing various genes associated with the pathogenesis of inflammatory diseases, including preeclampsia [88]. It was demonstrated that aspirin (5 mM) could prevent endothelial cell dysfunction and preeclampsia by preventing NF- $\kappa$ B-dependent miR-155 and decreasing eNOS expression in human umbilical vein endothelial cells (HUVECs) [3].

**2.13. Herpes Simplex Virus-Induced Corneal Immunopathology.** Stromal keratitis (SK) is a chronic ocular lesion affected by Herpes simplex virus 1 (HSV1) infection, which is a regular etiology of vision impairment in humans [89]. Ulcers in the cornea are initially caused by neutrophils and CD4<sup>+</sup> T cells in acute participation [90]. After aspirin-triggered resolvin D1 (AT-RvD1) (150 ng/eye; 5  $\mu$ L drop) therapy, the degree of neovascularization and stromal keratitis injuries in mice with ocular infection of HSV-1 was reduced. AT-RvD1 acts by multiple mechanisms, including suppressing proinflammatory mediators including IL1 $\beta$ , IL6, IL-12, MIP-2, MCP-2, CXCL1, VEGF, and MMP9, and also, proinflammatory miRNAs such as miR-223, miR-155, and miR-132 participated in SK and corneal neovascularization pathogenesis. Thus, AT-RvD1 treatment could be a useful strategy for managing virus-related immunopathology [91].

**2.14. Hepatic Ischemia.** Liver ischemia/reperfusion (I/R) is a critical morbidity factor associated with several clinical outcomes, such as hepatectomy, liver transplantation, and trauma. In such situations, the accumulation of inflammatory cells and mediators, ROS, and further biochemical imbalance in intracellular homeostasis lead to hepatocellular damage after I/R [92]. Inflammation has an essential role in tissue damage throughout liver ischemia [93]. Resolvin D1 (RvD1) is a pivotal factor in reducing liver damage by inhibiting inflammatory responses [94].

AT-RvD1 is a member of specialized proresolving lipid mediators (SPMs) and is biosynthesized by an omega-3 fatty acid (DHA) and has been shown to promote resolution in many inflammatory diseases [95, 96]. AT-RvD1, the 17R epimer of RvD1, is more durable and resistant to catalysis than RvD1 [97]. AT-RvD1 begins resolution pathways by attaching to the high-affinity G protein-coupled receptors (GPCRs), containing the LXA4 receptor (ALX/FPR2) and GPR32 [96], and downregulation of TNF- $\alpha$  stimulated NF- $\kappa$ B [98]. Both RvD1 and AT-RvD1 are potential compounds for treating several human inflammation diseases, including inflammatory pain [99, 100], arthritis [101], peritonitis [102], kidney ischemia/reperfusion injury [103], and sepsis

[104]. It was indicated that the usage of RvD1 before hepatic I/R alleviates hepatic damage through suppression of inflammatory responses [105]. Besides, it was shown that during self-limited acute inflammatory, RvD1 upregulated miRNA-146b [106], which inhibited the expression of TNF receptor-associated factor 6 (TRAF6) in human umbilical vein endothelial cells [107].

TRAF6, as a target of miR-146b, involves NF- $\kappa$ B activation [108, 109]. Treatment with AT-RvD1 (5  $\mu$ g/kg) in an animal model of liver ischemia remarkably downregulated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and liver tissue damage. Additionally, AT-RvD1 considerably suppressed inflammatory responses, as demonstrated by ameliorating TNF $\alpha$  and myeloperoxidase and apoptosis inhibition. Moreover, AT-RvD1 pretreatment upregulated the expression of miR-146b in the liver of the rats with hepatic impairment. Downregulation of miR-146b suppressed TRAF6 and NF- $\kappa$ B expression in the liver. Therefore, AT-RvD1 treatment alleviates hepatic injury by modulating miR-146b [110].

**2.15. Radiation Therapy.** Radiation harms the heart during cancer therapy, mainly due to oxidation and inflammation [111]. Viczenczova and coworkers showed that a separate dose of radiation could increase connexin 43 (Cx43) in the myocardium, activate protein kinase C (PKC) signaling through miR-1 downregulation, and miR-21 (with a role in myocardial remodeling and apoptosis) upregulation in the left ventricle of male rats. Also, it was demonstrated that antioxidant and anti-inflammatory drugs with vasodilating properties such as aspirin (3 mg/day) and atorvastatin (0.25 mg/day) could increase myocardial response in the left and right ventricles during radiation. Aspirin treatment prevented the upregulation of Cx43 (allows electrical connection and intercellular interconnection) and PKC $\epsilon$  expression with no changes in miR-1 levels. Also, this treatment prevented miR-21 upregulation in the left ventricle, which was associated with improved radiation-induced changes in the Cx43 myocardium protein and miR-21, possibly due to the improvement of oxidative stress and inflammation [112].

### 3. Conclusion and Perspectives

Aspirin is one of the most famous ancient drugs that has been used in human and nonhuman studies as a therapeutic agent in various diseases. On the other hand, numerous studies have shown the role of different ncRNAs as diagnostic, prognostic, and therapeutic molecules. Because of the importance of both, we conducted a study to evaluate the effects of aspirin on the expression of ncRNAs through a mechanistic approach.

Effects of aspirin alone or in combination with other medications such as statins, P2Y2 antagonists, and tyrosine kinase inhibitors on ncRNAs affect different cellular and molecular pathways. In different disease models, various ncRNAs and their effects on cellular pathways were affected by aspirin, of which miRNAs including miR-155, miR-21, miR-98, miR-191, miR-126, miR-223, and miR-150 and

lncRNA H19 were the most common. Elucidating the molecular networks of the ncRNAs related to aspirin and their impacts on cellular functions will help better understand its mechanistic diversity as one of the most widely used drugs. The effects of aspirin on the expression of different ncRNAs in various diseases are more investigated than the other NSAIDs including celecoxib [37] and ibuprofen [113]; however, further investigations are recommended to evaluate aspirin effects on diseases through the expression of ncRNAs.

## Conflicts of Interest

All the authors declare that they have no competing interests.

## Authors' Contributions

Mohammad Amin Khazeei Tabari and Mohammad Amir Mishan contributed equally to this manuscript. Abdolkarim Mahrooz is the co-corresponding author.

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