Review

The Role of the Renin-Angiotensin-Aldosterone System in Cancer and the Potential of Sartans in Oncology Treatment

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Abstract:

The Renin-Angiotensin-Aldosterone System (RAAS) is essential for blood pressure regulation and the body's homeostasis, with Angiotensin II (Ang II) playing a key role in vasoconstriction, sodium reabsorption, and cellular growth. Recent studies suggest that RAAS, particularly through the classical axis (renin → Ang I → ACE → Ang II → AT1 receptor), may contribute to cancer development by promoting cell migration, angiogenesis, and metastasis. Ang II, through AT1 receptors, activates pathways such as PI3K/AKT/mTOR and Ras/Raf/MEK/ERK, which enhance tumor progression. In contrast, the alternative RAAS axis (ACE2 → Ang-(1-7) → Mas receptor and AT2 receptors) shows potential anti-cancer effects. Angiotensin II receptor blockers (ARBs), such as candesartan, losartan, valsartan, and telmisartan, which inhibit the AT1 receptor, may reduce the pro-tumorigenic effects of RAAS. This suggests that the ARBs could be explored as a potential adjunctive in cancer therapy. However, further research is needed to fully understand their role in oncology considering that there are studies which paradoxically suggest that these compounds could induce carcinogenesis

Keywords: Angiotensin II; AT1 receptors; Angiotensin 1-7; Cancer; Sartans

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1. Introduction

The Renin-Angiotensin-Aldosterone System (RAAS) is a hormonal cascade that has a crucial role in maintaining the body`s homeostasis and the blood pressure regulation [1]. Signals including reduced renal perfusion, low tubular sodium content, or nervous sympathetic stimulation cause RAAS activation, which determines the release of renin from the kidney's juxtaglomerular cells, initiating the RAAS pathway. The renin, when is released,

converts Angiotensinogen into Angiotensin I (Ang I), which is converted by the Angiotensin-Converting-Enzyme (ACE) into Angiotensin II (Ang II), the main effector of RAAS via Angiotensin II receptors AT1 and AT2. Angiotensin II has critical implications in the vasoconstriction processes, vasopressin releasing (ADH), aldosterone secretion, and the increasing of sodium and water reabsorption [1,2].

Once angiotensin II and aldosterone are secreted into the systemic circulation, negative consequences may arise, such as hypertensive effects, induction of myocardial fibrosis, proarrhythmic effects, vascular endothelial dysfunction, increased reactive oxygen species (ROS), disruption of water and electrolyte balance, proteinuria, and vasoconstriction of the afferent and efferent renal arteries [3]. In recent years, the RAAS system has been viewed as a dual-axis system with opposite actions. Thus the "classical" axis (renin → Ang I → ACE → Ang II → AT1 receptor) is considered responsible for unfavorable outcomes of the RAAS activation, in contrast, an "alternative" axis (ACE2 → Ang-(1-7) → Mas receptor, and the AT2 receptors) can counteract these unfavorable effects exhibiting vasodilatory, antiproliferative, and antioxidant effects [4]. ACE2 is a membrane-associated enzyme that converts Ang I to Ang 1–9 and Ang II to Ang 1–7. Via stimulating the Mas-related G protein-coupled receptor D known as (MrgD) by Ang 1-7, subsequently the phosphatidylinositol 3-kinase/AKT (PI3K /AKT) pathway is activated, leading to the induction of NO synthase, arising the NO generation, and suppressing the progression toward cardiac hypertrophy and remodeling [5].

Evidences from literature indicate that a tissue Renin-Angiotensin-System (tRAS) is implicated in the evolution of many diseases being present in tissues such as skeletal myocytes, bone, cardiovascular, and intervertertebral discs. This system appears to be independent of the circulating RAAS, participating in many key intracellular processes [6]. Additionally, it seems to exist another 2 pathways known as non-renin pathways involved in Ang II forming, where the substrates are Ang-(1-25) and Ang-(1-12) [7]. Figure 1 represents a graphical illustration of the classical and alternative RAAS pathways.

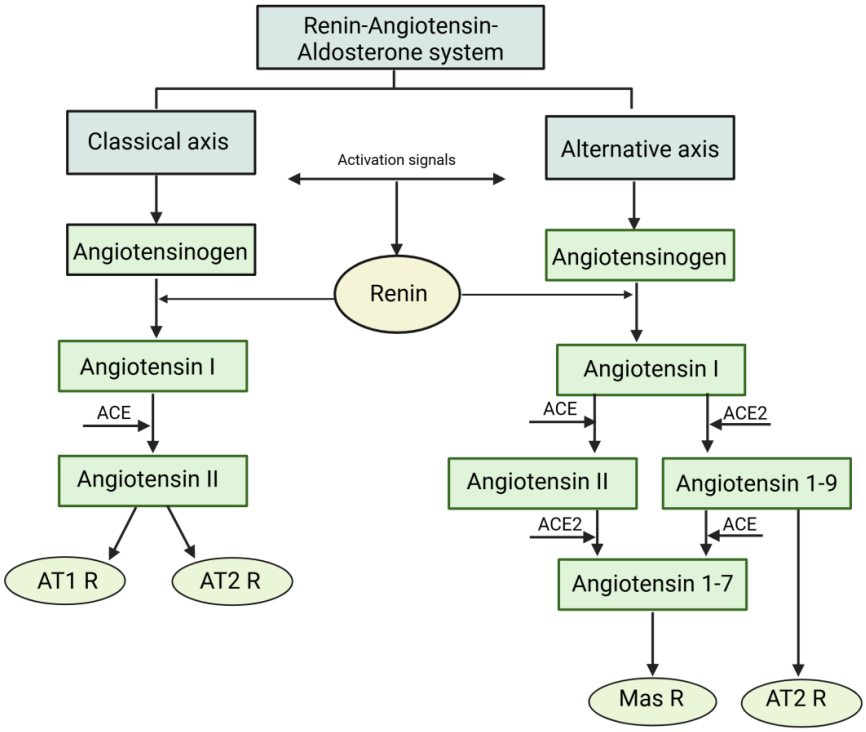


Figure 1. The classical and alternative Renin-Angiotensin-Aldosterone pathways. Created in https://BioRender.com.

Due to the complexity and significant implications of this system in various essential processes within the cardiovascular, renal, and other tissues, numerous classes of drugs have been developed to specifically target it. The main mechanisms of action of the RAAS blockers are the inhibition of ACE, the blockade of Ang II and neprilysin receptors, the antagonism of aldosterone receptors, and the suppression of angiotensin by the inhibition of angiotensinogen synthesis [1]. The pharmacological effects of RAAS inhibitors on the cardiovascular system have been relatively well-documented over time; nevertheless, these medications also offer multiple benefits in conditions beyond the cardiovascular sphere.

Therefore, this review aims to explore the involvement of the RAAS system in carcinogenesis and to evaluate the therapeutic potential of four angiotensin AT1 receptor blockers (losartan, valsartan, telmisartan, and candesartan) in cancer treatment, which remains one of the greatest challenges in the medical field. Cancer is characterized by uncontrolled cell growth and division and continues to be a leading cause of death worldwide, making it a significant global health concern [8].

2. The RAAS implications in cancer pathogenesis

Beyond the cardiovascular effects of the circulating RAAS, the local RAS (tRAS) is expressed in various tissues and primarily acts at cellular level, mediating cell growth, metabolism, and proliferation. In this way, it plays a significant role in cancer development and progression [9]. The RAAS pathway can have dual effects on carcinogenesis, with the balance between the classical axis (ACE/Ang II/AT1R) and the alternative axis (ACE2/Ang 1–7/Mas receptor) significantly influencing cell proliferation processes. While the

interactions of Ang I/AT2R, Ang1-7/Mas, and alamandine/MrgD may exert anticancer effects, Ang II/AT1R interactions are more likely to contribute to cancer development [10].

The mechanisms by which Ang II/AT1R exerts a pro-tumorigenic effect are complex. For instance, Ang II can trigger the phosphorylation of PI3K/Akt and promote cellular migration. By activating the AT1R/PI3K/AKT pathway, it enhances the activity of NF-κB (Nuclear Factor Kappa B) and IKKα/β (IkappaB kinase α/β). This leads to an increase in the expression of matrix metalloproteinases, such as MMP2 and MMP9, which enables cell migration [11]. Ang II can modulate the TGF-β (transforming growth factor β) signaling as well. This leads to the upregulation of TGF-β receptors, amplifying its activity. Ang II also activates thrombospondin-1 via p38-MAPK (P38-Mitogen-Activated-Protein-Kinase) and c-jun N-terminal kinase pathways, facilitating the release of active TGF-β1. The TGF-β signaling pathway, which involves Ras/Raf/MEK/ERK and Smad pathways, affects tumor response and suppresses apoptosis by modulating PI3K signaling. TGF-β1 through the PI3K/AKT/mTOR pathway also inhibits PTEN (Phosphatase and tensin homolog) expression. Consequently, the cell migration and the level of PD-L1 (Programmed Death-Ligand 1) are increased. Additionally, PD-L1 can activate the PD-1 receptors on T-cells, thus weakening the cellular immune response [12,13].

The role of AT1R in tumor development can be understood as part of a complex interaction of multiple cellular signaling pathways within endothelial cells, including those involving EGFR (Epidermal Growth Factor Receptor), and MAPK/ERK1/2. Ang II triggers the expression of VEGF-A (Vascular Endothelial Growth Factor A) in endothelial cells via the AT1R and ERK1/2 pathways, both of which are crucial for the processes of neovascularization and tumor progression. This mechanism contributes to the formation of new blood vessels in various types of cancer [14,15]. In addition to supporting angiogenesis, Ang II via AT1R may also contribute to cancer development through EGFR transactivation. This interaction can interfere with key signaling pathways linked to malignant transformation, triggering molecular processes that drive the proliferation of cancer [16]. Figure 2 represents a graphical illustration of the main mechanisms and pathways by which Angiotensin II can be involved in the carcinogenesis processes.

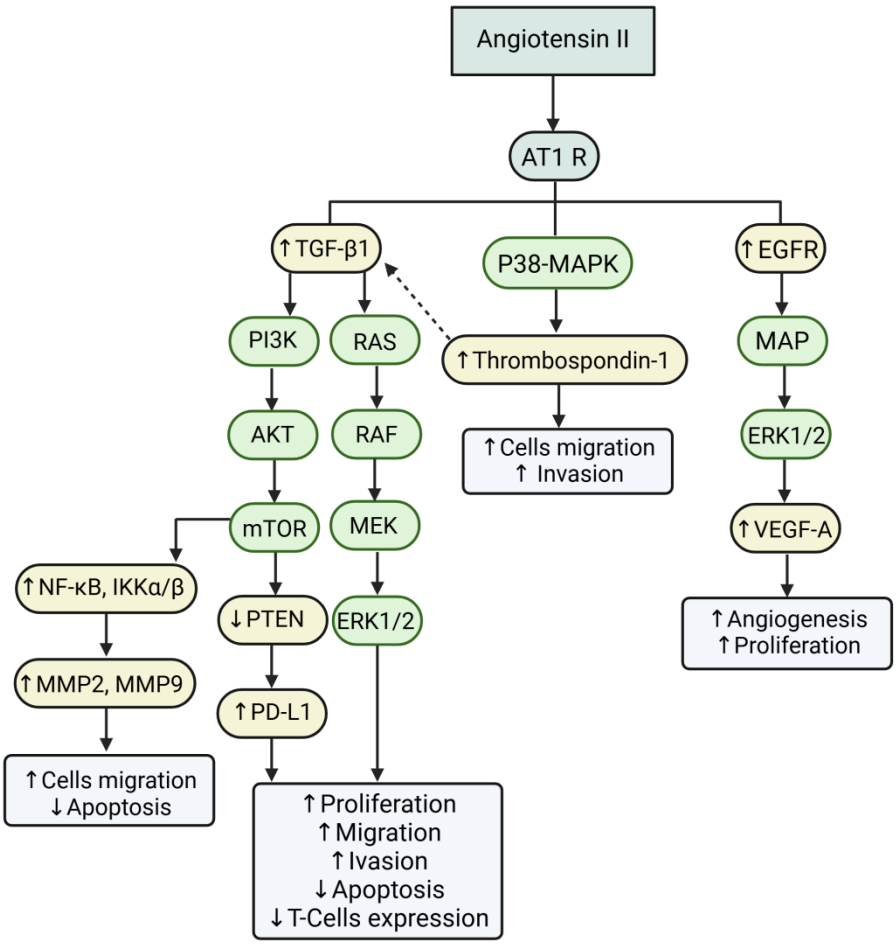


Figure 2. The main pathways modulated by Angiotensin in cancer (↑: increase, ↓: decrease). Created using https://BioRender.com

3. Angiotensin II receptors blockers (ARBs)

Angiotensin II receptor blockers (ARBs), also known as sartans, selectively target and inhibit the angiotensin II type 1 (AT1) receptors. This inhibition leads to a reduction in vasoconstriction, aldosterone secretion, and sodium reabsorption. Medications such as candesartan, losartan, valsartan, irbesartan, telmisartan, olmesartan, eprosartan, and azilsartan are all classified as ARBs [17]. The following section will provide a brief overview of studies of four angiotensin AT1 receptor blockers (losartan, valsartan, telmisartan, and candesartan) aimed at exploring the potential benefits of sartans in the context of cancer treatment. In Table 1 are presented in vitro, in vivo, and clinical trial studies regarding the role of sartans in cancer.

Table 1. *In vitro, in vivo*, and clinical trial studies regarding the ARBs activity in cancer (↑: increase, ↓ decrease).

AT1 Receptors Blocker	Anti-cancer mechanism of action	Cell line	Animal model	Clinical trial	References

Losartan	Antifibrotic effect, ↓ TGF-β1 activators, thrombospondin-1, synthesis of collagen.	Mammary carcinoma-associated fibroblasts (CAFs), human soft-tissue sarcoma (HSTS26T), human melanoma (Mu89), human pancreatic adenocarcinoma cells (L3.6pl)	FVB/N-Tg (MMTV-PyVT) 634MU1/J mice	-	[18]
	↓ The expression of PI3K, AKT (protein kinase B), and cyclin D1, ↑ the expression of Bax and p53, ↓ MMP-2 and -9,	colon cancer cell line (CT-26)	BALB/c mice nu/nu mice	-	[19]
	↓IL-6, pSTAT3(Phosphorylated Signal Tranducer and Activator of Transcription 3), TNFα	-	FVB/n mice (as a model for breast cancer)	-	[20]
	↓ PD-L1	Human normal glial cells (SVG p12), human glioblastoma cell lines (U-87 MG, T98G), and cervical carcinoma cell line(HeLa)	Athymic nude mice		[21]
Valsartan /losartan	↓ PI3K/AKT, ↑ cleaved caspese-3, and -9, cytochrome C, caspase-3 activity	Nasopharyngeal carcinoma cell(TW01)	-	927 patients with nasopharyngeal carcinoma and hypertension, among which 272 received losartan. The results of the study indicated that losartan improved the level of overall survival rate (87.8% under losartan/valsartan treatment vs. 75.1% without	[22]

				losartan/valsartan treatment).	
Valsartan	↑ BAX, BCL2, and P53 expression, ↓MMP2/9, intestinal tissue fibrosis	Colorectal cancer cell line (CT-26)	BALB/c- nu/nu mice	-	23]
	↓ PI3K/Akt , IL-6/STAT3 , VEGF, N-cadherin, NANOG gene expression	-	Sprague Dawley rats (as a model for breast cancer)	-	[24]
Telmisartan	↓ cyclin D1, cyclin E, ↓phosphorylation EGFR, and AMP-activated protein kinase (AMPK)	human esophageal adenocarcinoma cell lines (OE19, OE33, and SKGT-4)	BALB/c -nu/nu mice	-	[25]
	↓ cyclin D1, catalytic subunit of cyclin dependent kinase 4 (CDK4), ↓ phosphorylation of (EGFR),↑ angiogenesis-related protein tissue inhibitor of metalloproteinase-1 (TIMP-1)	gastric cancer cell lines (MKN74, MKN1, MKN45)	BALB/c -nu/nu mice	-	[26]
	↓AKT-1, N-cadherin	prostate cancer cell lines (PC3, DU145), breast cancer (MDA-MB-468)	-	-	[27]
Candesartan	↓ Cyclin D1, MMP3/9, and E-cadherin	colorectal cancer cell lines (CT-26 and SW-480)	BALB/c mice nu/nu mice	-	[28]
	↓ TGF-β1, ↓stromal fibrosis	Gastric Cancer (MKN45)	-	-	[29]
	↑ apotosis mediated by TRAIL (Tumor necrosis factor-Related Apoptosis-Inducing Ligand) via DR5 and DR4(Death receptors 4,5), ↓c-Flip (Cellular FLICE-like inhibitory protein), ↓AMPK phosphorylation	Lung cancer cells ((A549, HCC-15)	-	-	[30]
Candesartan, losartan,	-	-	-	138769 patients with cardiac	[31]

valsartan, telmisartan				diseases treated with candesartan, losartan, valsartan, and telmisartan in 15 clinical trials were monitored for 23-60 months for increased risk of cancer associated with these drugs. Results indicate that these drugs do not increase the risk of breast, prostate, or lung cancer or the risk of cancer-related death.	

3.1. Losartan

Losartan was the first angiotensin II receptor blocker (ARB) introduced into clinical practice for the management of cardiovascular disease. Notably, losartan demonstrates significant antifibrotic effects reducing the occurrence of renal and cardiac fibrosis. These effects can be attributed to the downregulation of TGF-β1 activators, such as thrombospondin-1 (TSP-1). Given these properties, Diop-Frimpong et al. assessed the in vitro antifibrotic impact of losartan on mammary carcinoma-associated fibroblasts (CAFs). The findings revealed that losartan markedly reduced active TGF-β1 levels by 90% and decreased the in vitro synthesis of collagen I by 27% [18]. Another study conducted by Hashemzehi et al. evaluated the in vitro, in vivo, and in silico effects of losartan at concentrations ranging from 0 to 1000 μM on the CT-26 colon cancer cell line and a 3D spheroid cell culture model. The MTT assay demonstrated a dose-dependent decrease in cell viability (IC50 = 300 μM). In silico findings indicated that losartan increased the expression of pro-apoptotic genes, such as P53 and BAX. The in vivo assays showed that losartan reduced angiogenesis and metastasis in treated mice by inhibiting matrix metalloproteinases-2 and -9 activities and reducing tumor vasculature [19].

3.2. Valsartan

Valsartan is currently used for the treatment of hypertension, heart failure, and diabetic nephropathy. In vitro evidence suggests that valsartan may exhibit antitumor activity by inducing apoptosis and affecting angiogenesis and metastasis. A study conducted by Lin *et al.* evaluated the anticancer activity of valsartan on the TW01 nasopharyngeal carcinoma cell line. The 48-hour MTT assay showed a dose-dependent decrease in cell viability (IC50 = 17.2 μM). The in vitro assays also indicated that valsartan can induce apoptosis by increasing the levels of cleaved caspase-3, cleaved caspase-9, and cytochrome C [22]. In a study by Asgharzadeh et al., the anticancer effects of valsartan were demonstrated in vitro on CT-26 cells. The findings showed that valsartan inhibited cell proliferation and, more importantly, exhibited a synergistic anti-tumor effect when

combined with fluorouracil. This synergy was linked to the induction of apoptosis through the modulation of BAX, BCL2, and P53, as well as alterations in the cell cycle. Moreover, valsartan demonstrated antimigratory properties by inhibiting matrix metalloproteinases-2 and -9 [23].

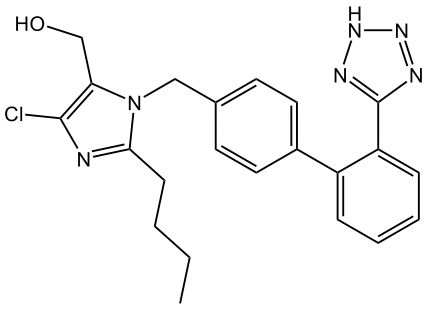
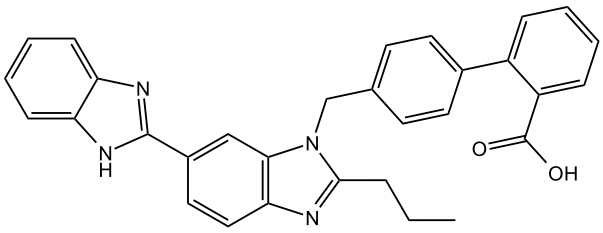
3.3. Telmisartan

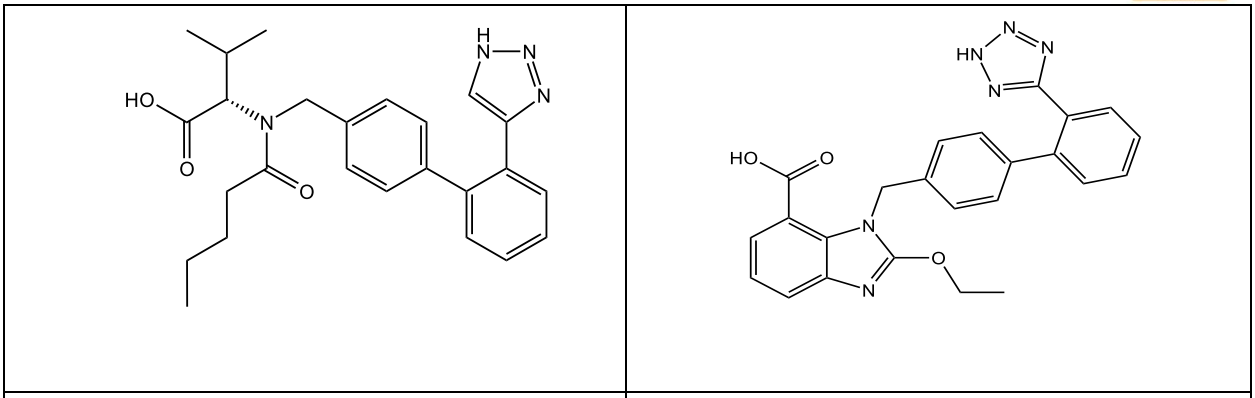
In addition to its AT1 receptor blockade, telmisartan can also be described as a partial PPAR-γ (peroxisome proliferator-activated receptor-gamma) agonist, thus exerting a dual inhibitory effect on cell proliferation in multiple types of cancer. Evidence from the literature indicates that telmisartan activates AMP-activated protein kinase (AMPK), which regulates cell proliferation via the mammalian target of rapamycin (mTOR). Fujihara et al. assessed the impact of telmisartan (1, 10, and 100 μM) on three human esophageal adenocarcinoma cell lines (OE19, OE33, and SKGT-4). The findings from this assay indicate that telmisartan effectively inhibits cell proliferation in a dose-dependent manner. Flow cytometry analysis showed that it triggers cell cycle arrest in the G0/G1 phase and modulates cell cycle-related proteins in esophageal adenocarcinoma cell lines [25].

3.4. Candesartan

Candesartan is a potent AT1 receptor inhibitor. It has also been demonstrated to be effective in decreasing tumor progression in multiple types of cancer, such as renal, bladder, colon, prostate, and breast cancer, in addition to boosting sensitivity to chemotherapy. Tabatabai et al. evaluated the cytotoxic activity of candesartan (0-1000 μM) on two colorectal cancer cell lines (CT-26 and SW-480). Candesartan decreased cell viability in a dose-dependent manner and demonstrated pro-apoptotic and antimigratory effects via modulation of Cyclin D1, MMP3/9, and E-cadherin [28][23]. Okazaki et al. evaluated the in vitro effect of candesartan on the MKN45 cancer cell line, where antiproliferative activity was also demonstrated [29].

The chemical structures of losartan, valsartan, telmisartan and candesartan are illustrated in Figure 3.

	
Losartan	Telmisartan



Valsartan	Candesartan

Figure 3. Chemical structures of losartan, valsartan, telmisartan and candesartan. The chemical structures were performed with KingDraw V.3.6.1.

4. The risk of cancer associated with Angiotensin II receptors blockers (ARBs)

Paradoxically, evidence from the literature suggests a potential role of ARBs in cancer induction following long-term exposure to the maximum daily dose of these agents. However, data from various clinical trials investigating the role of ARBs in increasing the risk of malignancies are contradictory [32]. One of the possible explanations for ARBs exerting a pro-carcinogenic effect is the presence of nitrosamine impurities, such as N-nitrosodimethylamine (NDMA), which is classified by the IARC (International Agency for Research on Cancer) as a potential carcinogenic agent (Group 2A) [33]. In 2018, traces of NDMA impurities, resulting from manufacturing processes, were discovered in various formulations of valsartan, leading to the withdrawal of these formulations [34]. This discovery prompted testing of other ARBs for the potential presence of additional carcinogenic nitrosamine compounds. As a result, other nitrosamine impurities, such as N-nitroso-N-methyl-4-aminobutyric acid (NMBA) and N-nitrosodiethylamine (NDEA), were found in several pharmaceutical formulations of sartans, including valsartan, irbesartan, and losartan, which led to further recalls of contaminated products [35-38]. However, the precise mechanism behind this potential pro-tumorigenic effect of ARBs remains unclear. For example, Walther et al. reported a paradoxical induction of angiogenesis in vivo after treatment with losartan, which appears to be mediated by AT2 receptors [39]. One possible mechanism by which AT2 receptors stimulate angiogenesis is through the production of proangiogenic factors, such as VEGF [40].

5. Conclusions

The renin-angiotensin-aldosterone system (RAAS) plays a significant role in cancer progression by influencing angiogenesis, inflammation, and tumor microenvironment remodeling. Angiotensin II receptor blockers (ARBs), such as losartan, valsartan, telmisartan, and candesartan, show potential anticancer effects by modulating tumor perfusion, inhibiting proliferation, and enhancing the response to chemotherapy. However, some studies also suggest a possible role of these drugs in increasing cancer risk. Targeting the RAAS may offer a novel therapeutic strategy for cancer treatment, but this dual aspect warrants further investigation of sartans as adjuvant agents.

Author Contributions:

Conceptualization, [D.H.A. and C.A.D.]; Software, [D.H.A.]; Validation, [C.D.], Writing—Original Draft Preparation, [D.H.A and C.D.] Writing—Review & Editing, [C.A.D.]; Visualization, [C.D.]; Supervision, [C.A.D.]. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest:

The authors declare no conflict of interest.

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