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Review Article

Insights into repurposing telmisartan beyond its cardiovascular applications: Emphasis on the metabolic, neuroprotective, nephroprotective, and anticancer potential

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ABSTRACT

Telmisartan, a long-acting angiotensin II type 1 (AT1) receptor blocker (ARB), is widely used in the management of hypertension and cardiovascular diseases. Its primary pharmacodynamic action involves selective inhibition of the renin-angiotensin-aldosterone system (RAAS), resulting in vasodilation, reduced blood pressure, and attenuation of cardiac afterload. Beyond its antihypertensive properties, telmisartan exhibits a unique pharmacological profile due to its partial agonistic activity on peroxisome proliferator-activated receptor-gamma (PPAR-γ), contributing to metabolic regulation and organ protection. Clinically, telmisartan plays a pivotal role in preventing cardiac hypertrophy and remodelling by reducing myocardial fibrosis and improving ventricular compliance. It also exerts neuroprotective effects, potentially beneficial in mitigating neurodegenerative conditions, through anti-inflammatory and antioxidative mechanisms. Renal protection is another critical benefit, as telmisartan reduces proteinuria and glomerular injury, making it effective in managing diabetic and non-diabetic nephropathies. Recent studies have revealed an anticancer potential for telmisartan across various malignancies, including glioblastoma, osteosarcoma, endometrial, and renal cancers. It induces apoptosis, inhibits cell proliferation, modulates the mTOR signalling pathway, and promotes DNA damage in tumor cells. The multifaceted pharmacological actions of telmisartan position it as a promising agent to be repurposed beyond the cardiovascular applications.

Keywords: *Cardiovascular effects; Telmisartan; Neuroprotection; Anticancer effects.*

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1. Introduction

Telmisartan (TLM) is an angiotensin II receptor blocker (ARB) commonly used to treat hypertension. It binds with high affinity to angiotensin II type 1 (AT1) receptors, effectively blocking the vasoconstrictive and pro-hypertensive effects of angiotensin II on vascular smooth muscle. This inhibition results in vasodilation and a subsequent reduction in arterial blood pressure **[1]**. Beyond its role as an AT1 receptor antagonist, telmisartan also acts as a partial agonist of peroxisome proliferator-activated receptor gamma (PPAR-γ). This dual mechanism enhances its pleiotropic effects, including anti-inflammatory, antiproliferative, and antioxidant properties, which may provide additional benefits beyond blood pressure

regulation **[2]**.

Telmisartan's primary pharmacodynamic effect is its ability to lower blood pressure. Telmisartan provides superior blood pressure control compared to other antihypertensive agents such as losartan, valsartan, and atenolol, particularly at the end of the dosing interval, ensuring sustained efficacy throughout the day **[3]**. It mitigates cardiac hypertrophy by inhibiting the nuclear translocation of nuclear factor of activated T-cells (NFAT) and downregulating the expression of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). This effect is dose-dependent and plays a crucial role in reducing cardiac remodeling, a key factor in preventing heart failure progression **[4]**. In this mini review, we highlight the potential for repurposing telmisartan beyond the cardiovascular applications, including metabolic, neuroprotective, nephroprotective, and anti-cancer benefits.

2. Metabolic Effects

2.1. Insulin Sensitivity

It has been reported that TLM enhances insulin sensitivity, making it particularly beneficial for patients with type 2 diabetes. Interestingly, this effect is independent of its AT1 receptor antagonism and PPAR-γ activation, suggesting the involvement of alternative mechanisms, such as the modulation of ion channels. It directly blocks the Kv2.1 channel, a type of voltage-gated potassium channel crucial for regulating insulin release in pancreatic β-cells. By inhibiting Kv2.1, TLM extends the duration of action potentials, leading to increased calcium entry into the cells and thereby boosting insulin secretion. TLM also influences L-type voltage-gated calcium channels (VGCCs), enhancing the influx of extracellular calcium. This action is a key in amplifying insulin secretion, specifically in response to elevated glucose levels **[5]**. TLM was reported to increase insulin sensitivity by promoting glucose uptake and insulin signalling independently of PPAR-γ. Through the activation of the AMPK/SIRT1 pathway in skeletal muscle, the upregulation of Sirt1 mRNA, the enhancement of AMPK phosphorylation, and the elevation of the NAD+/NADH ratio **[6]**.

2.2. Lipid Metabolism

Several studies showed that TLM affects adipokine regulation through its PPAR-γ agonist activity, leading to improved lipid metabolism. This modulation may help lower the risk of hyperlipidaemia, contributing to better cardiovascular and metabolic health **[3, 7]**. Furthermore, TLM has been reported to decrease lipid accumulation and enhance ^{18}F-FDG uptake in differentiated 3T3-L1 adipocytes. Additionally, it upregulates the expression of endothelial nitric oxide synthase (eNOS) and carnitine palmitoyl transferase 1α (CPT1α), while downregulating proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), thereby promoting improved metabolic outcomes **[8]**.

3. Neuroprotective Effects

Reports indicated that TLM enhances hippocampal neuronal excitability by increasing the peak amplitude of voltage-gated sodium currents (I_Na). This neurophysiological effect suggests potential therapeutic benefits in neurological conditions such as cognitive disorders **[9]**. TLM exerts neuroprotective effects in the LPS-induced rat model of Parkinson's disease by reducing apomorphine-induced rotations, increasing striatal dopamine concentrations, and decreasing levels of inflammatory markers such as TNF-α and BDNF. These effects contribute to the protection of dopaminergic neurons and the attenuation of neuroinflammation **[10]**. TLM demonstrates

superior cell viability compared to perindopril and nebivolol, through ameliorating LPS-induced injury and neuroinflammation, preserving acetylcholine levels, and reducing the expression of inflammatory markers TNF-α, IL-1β, and NFκB in neuron-like cells **[11]**. TLM also showed significant results in the cuprizone-induced demyelination model by improving locomotor activity, restoring myelin basic protein expression, reducing oxidative stress and apoptosis, and modulating inflammatory responses via the NF-κB and Nrf2 signaling pathways, thereby promoting overall brain health **[12]**. TLM also exerts neuroprotective effects in neural stem cells by inhibiting the NLRP3 inflammasome and activating the PI3K signaling pathway. These actions enhance cell viability and proliferation, upregulate survival-related proteins, and downregulate death-related proteins in response to oxygen-glucose deprivation **[13]**. TLM shows neuroprotective effects in Huntington's disease model by attenuating oxidative stress, neuroinflammation, and apoptosis; modulating the PI3K/Akt/GSK-3β and ERK1/2 signaling pathways; and inducing PPAR-γ expression. These mechanisms collectively enhance muscle strength and improve motor functions **[14]**.

4. Nephroprotective Effects

A multitude of studies supported that TLM exerts nephroprotective effects by reducing aldosterone production and modulating sympathetic tone, which helps preserve kidney function. These properties make it particularly beneficial for patients with renal diseases, including hypertension-induced nephropathy **[2]**. TLM also provides kidney protection in diabetic rats by regulating blood glucose, decreasing oxidative stress and inflammation, inhibiting NF-κB p65 and TNF-α activity, boosting antioxidant defense mechanisms, and activating the Nrf2/HO-1 signaling pathway, thereby preventing renal damage **[15]**. TLM shows nephroprotection in metabolic syndrome rats by reducing leptin secretion from perirenal adipose tissue, reestablishing the equilibrium between the angiotensin II-AT1R and ACE2-angiotensin (1-7)-Mas receptor pathways, and suppressing the activation of the p38 MAPK signaling cascade, thereby enhancing renal function **[16]**. Another pathway is to activate the PPARγ/HGF signaling pathway, independently of angiotensin II type 1 receptor inhibition. By upregulating hepatocyte growth factor expression, it attenuates renal fibrosis and inflammation, ultimately preventing kidney injury and atrophy **[17]**. By blocking angiotensin II receptors, TLM halts the progression of renal injury. It reduces proteinuria and albuminuria, ameliorates histopathological damage, and stabilizes plasma lipid levels, collectively counteracting the detrimental impact of type 2 diabetes on renal function **[18]**.

5. Anticancer activity

Studies demonstrated that TLM has promising anticancer properties by modulating key signalling pathways involved in cancer cell proliferation, survival, and metastasis. Its partial agonist activity on peroxisome proliferator-activated receptor gamma (PPAR-γ) contributes to its anti-inflammatory and antiproliferative effects, making it a potential therapeutic option in cancer treatment **[2]**. Preclinical studies support the potential anti-cancer activity of telmisartan through a variety of mechanisms as follows:

5.1. Inhibition of Angiotensin II Receptor

Previous data indicated that TLM disrupts pathways that promote cancer cell proliferation and metastasis by blocking the angiotensin II receptor. This inhibition enhances tumor microenvironment fluidity, facilitating improved drug delivery and increasing the efficacy of chemotherapy **[19]**.

5.2. N-Cadherin Antagonism

TLM functions as an N-cadherin antagonist, similar to ADH-1, reducing cancer cell attachment and migration. It shows a significant decrease in cell migration and proliferation in various cancer cell lines, including PC3 and MDA-MB-468, through targeting the N-cadherin signalling pathway **[20]**.

5.3. Chemo-sensitization and Cancer Stem Cells (CSCs)

TLM derivatives have been designed to target therapy-resistant CSCs, which are responsible for tumor recurrence and resistance. These derivatives disrupt CSCs' persistence mechanisms, such as hyperactivated STAT5 signalling, thereby enhancing the effectiveness of chemotherapy **[21]**.

5.4. Apoptosis Induction

TLM has demonstrated pro-apoptotic effects across various cancer models. It inhibits tumor cell proliferation and activates apoptotic pathways in cancers such as glioblastoma, osteosarcoma, endometrial cancer, and renal cell carcinoma. TLM induces arrest in the G0/G1 phase in glioblastoma and gastric cancer cells, thereby suppressing proliferation and promoting apoptosis **[22, 23]**. In osteosarcoma and renal cell carcinoma, TLM inhibits the mTOR signalling pathway—critical for cell growth and survival—leading to reduced phosphorylation of mTOR and AKT, and suppression of downstream molecules like Cyclin D1 and p-P70S6K, which are involved in cell growth and apoptosis, leading to apoptotic cell death **[24, 25]**. Treatment with TLM induces DNA double-strand breaks in endometrial cancer cells, a key initiator of apoptosis **[26]**. TLM modulates the expression of apoptosis-related proteins, notably increasing pro-apoptotic Bax and decreasing anti-apoptotic Bcl-2, thus tipping the balance toward cell death **[24, 25]**.

TLM can act as both a proapoptotic and anti-apoptotic agent depending on the cell type and pathological context. Its dual action is mediated through modulation of oxidative stress, inflammatory pathways, and specific signaling cascades that regulate cell survival and death **[27]**. The proapoptotic effect is more pronounced in cancerous or proliferative cells, through distinct molecular pathways, while normal or injured non-cancerous cells are protected from apoptosis and inflammation. This dual action underlies its therapeutic versatility in both organ protection and cancer treatment.

In conclusion, cumulative evidence from preclinical studies supports a diversity of potential applications for the repurposing of telmisartan. Those include cardiovascular, metabolic, neuroprotective, nephroprotective, and anti-cancer effects of telmisartan as depicted in **Fig.1 and Table 1**.

Table 1. Summary of studies investigating telmisartan monotherapy or combinations in different disease models

Effect	Animal species	Disease model	Combined drugs	Dose used	Targets affected	Study Reference
Cardiac hypertrophy.	male C57/BL6 mice.	abdominal aortic banding (AB) model, which simulates cardiac hypertrophy due to increased	None	50 mg/kg/day for 4 weeks.	NFAT ANP BNP	**[4]**

		afterload.				
Insulin Sensitivity	Adult male Wistar rats and db/db mice.	Diabetic db/db mouse.	Compared to valsartan and irbesartan.	8.2-16.4 mg/kg for 3 weeks.	Kv2.1 channel. L-type Voltage-Gated Calcium Channels (VGCCs)	**[5]**
Lipid metabolism	guinea pigs	high-fat diet-induced hyperlipidemic guinea pig model	pitavastatin	3 mg/kg/day for 8 weeks.	Angiotensin II receptor has partial agonistic effects on PPARγ, PPARα, and PPARδ receptors. Adipose tissue and adipocytes reduction.	**[7]**
Neurologic effect	Sprague Dawley (SD) rats.	Lithium-pilocarpine-induced seizure model.	Pioglitazone	TEL used in the study ranged from 0.1 µM to 100 µM, with specific attention to the effective concentration of 0.94 µM for stimulating I Na. Dpse was administered twice daily for 7 consecutive days.	Voltage-Gated Sodium Channels (NaV channels) Hippocampal Neuronal Excitability	**[9]**
N-Cadherin Antagonism	PCa PC3, DU145, MDA-MB-468 cell lines.	prostate cancer (PCa PC3, DU145,) cell lines breast cancer cell lines: MDA-MB-468	Docetaxel	0.1 µM	The N-cadherin signaling pathway, which is crucial for regulating epithelial-mesenchymal transition (EMT) in various cancers	**[20]**
Chemosensitization and Cancer Stem Cells (CSCs)	NOD/SCID mice	imatinib-resistant leukemia xenografts	Imatinib Telmi-amide	10 mg/kg once daily for 30 consecutive days	hyperactivated STAT5 signaling and increased drug transporter activity	**[21]**
Apoptosis induction	human osteosarcoma cell lines (U2OS)	human osteosarcoma cell lines (U2OS)	None.	TLM induced cell death in a dose-dependent manner, indicating that varying concentrations were likely tested. It was added to the culture media for varying durations of 24 hours, 48 hours, and 72 h.	mTOR signaling pathway. Cyclin D1 and p-P70S6K.	**[24]**

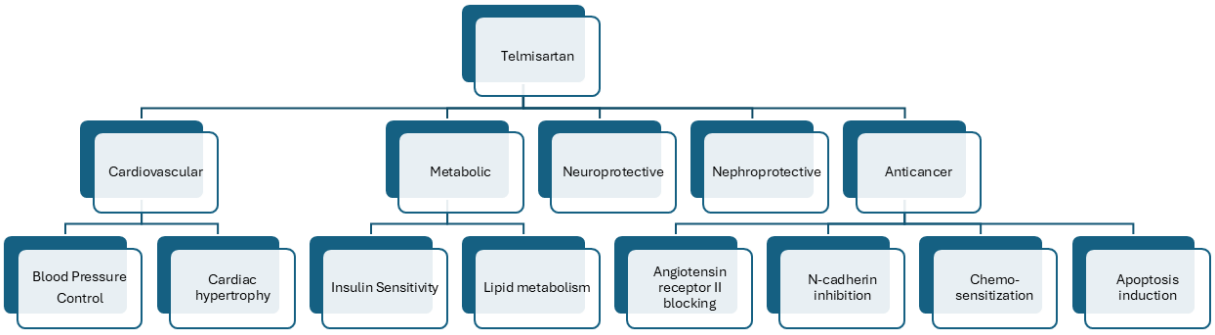

Fig.1. Diagram depicting the wide scope of effects of telmisartan

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Participate

Not applicable.

Consent for publication

Not applicable.

Availability of the data and Material

Data will be made available on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MFT contributed to the review idea and outline. The first draft of the manuscript was written by HN. The table and figure were prepared by HN. MFT revised and edited the manuscript. All authors have read and approved the final manuscript.

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