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PRACA POGLĄDOWA
REVIEW

The potential anticancer activities of telmisartan – a literature review

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ABSTRACT

In the field of pharmacological therapy, due to the high costs and other obstacles encountered in developing novel drugs, a variety of studies have recently focused on repositioning existing pharmaceutical agents. Regarding the pharmacotherapy of cancer, many possible drugs may exhibit anticancer effects owing to the vast number of biological mechanisms involved in the proliferation and survival of malignant cells. Telmisartan, a well-known inhibitor of the angiotensin II receptor used clinically as an antihypertensive, has been shown to target various signaling pathways in cancer cells, therefore exhibiting anti-proliferative, anti-apoptotic and anti-metastatic effects. Moreover, inhibitors of the angiotensin II receptor have been shown to increase the fluidity of the tumor microenvironment, thus increasing the efficacy of chemotherapy as drug delivery to the tumor is enhanced. The present review provides an insight into the different anticancer mechanisms of telmisartan, as well as recent and past studies which have tested the drug in vitro and in vivo on different types of cancers. This may provide a perspective for future clinical trials on repositioning telmisartan as an anti-cancer agent.

KEYWORDS

cancer chemotherapy, antihypertensives, telmisartan

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Introduction

Despite the continuous discovery of novel therapeutic approaches, cancer remains one of the leading causes of mortality globally, indicating the need for further research to be undertaken in the field of anticancer therapies [1]. Nonetheless, in the field of pharmacological therapy, the development of a new drug has been estimated to cost approximately 2.5 billion US dollars and may require more than a decade to receive approval and reach the pharmaceutical market [2,3]. For this reason, many recent studies, especially in the field of oncology, have been focused on drug repurposing, in other words, the use of existing drugs in the therapeutic regimen of other diseases [4,5,6].

In the past, many studies and trials were undertaken to investigate the possibility of repurposing antihypertensive drugs as anti-cancer agents and administering them simultaneously with chemotherapeutic drugs [7]. Angiotensin II receptor blockers (ARBs) comprise a category of drugs used to regulate blood pressure in people with chronic hypertension and metabolic syndrome

as well as have shown to exhibit anti-cancer effects [7,8]. However, it is worth mentioning that a meta--analysis conducted in 2010, reported an 8% increase in cancer risk in people using ARBs, indicating that they may also have a slight procarcinogen effect [9]. Later on, a study was conducted reporting that compared to other ARBs, the use of telmisartan was not associated with an increased risk of cancer [10].

Moreover, it has been shown that telmisartan does not alter uric acid levels in patients in contrast to other ARBs such as valsartan and losartan [11,12]. This indicates that its use in cancer patients is safer compared with other ARBs since many cancer patients may present hypouricemia and hyperuricemia, either as a result of the cancer or a side effect of chemotherapeutics [13,14]. Hence, in this mini-review, we aimed to synthesize the existing evidence on the anti-cancer effects of telmisartan and explore the effects of this drug on different types of cancer, providing possible future insights for researchers to conduct more studies on the effects of this drug.

The rationale for using telmisartan as an anticancer agent

Clinically, telmisartan is used to regulate blood pressure by inhibiting the angiotensin II transmembrane receptor AT1R, and consequently disturbing the renin--angiotensin-aldosterone system [15]. Simultaneously, the renin-angiotensin-aldosterone system has been studied as a potential target in cancer as it is one of the essential mechanisms of cancerous cell survival [16]. Firstly, several studies have shown that stimulation of the AT1R receptor induces angiogenesis by enhancing the secretion of the vascular endothelial growth factor (VEGF), and thus enhances vascular growth in tumors, assisting their survival [17,18,19]. In this manner, telmisartan as an antagonist of the receptor can exhibit an anti-angiogenic effect, and therefore suppress tumor growth, resulting in better prognosis and possible therapy.

Moreover, the renin-angiotensin system has been shown to affect the texture of a tumor's microenvironment, including the structure of the extracellular matrix [16,20,21]. One of the novel therapeutic approaches being studied in solid tumors is to reengineer the tumor's microenvironment for better treatment response [22]. Indeed, increasing the fluidity of the tumor microenvironment, which in turn, results in decompression of the surrounding blood vessels, can augment anticancer drug delivery to the malignant cells, increasing the efficacy of chemotherapy [23,24]. Inhibiting the angiotensin II receptor has been shown to trigger inhibition of the transforming growth factor beta (TGF-β) signaling pathway, which is responsible for structuring the microenvironment [25]. Specifically, inhibition of the TGF-β signaling pathway down-regulates the expression of collagen fibers and cancer--associated fibroblasts (CAFs) in tissues, consequently increasing the fluidity of the tumor microenvironment [26,27]. Also, a study by Chauhan et al. [28] suggested that inhibiting the angiotensin II receptors and the TGF-β pathway results in decompression of the blood vessels in a tumor's environment. This implies that administering telmisartan as co-adjuvant therapy can increase the efficacy of chemotherapy as drug delivery to the tumor is enhanced.

On the other hand, Khorsand et al. [29] revealed in a study that telmisartan is a potent inhibitor of N--cadherin in cancerous tissue. N-cadherin is a connective protein that has been shown to assist malignant cells to form aggregates, and thereby invade the extracellular matrix to migrate to other sites [30]. Moreover, it has been shown that N-cadherin can polarize and activate the Rho-family GTPase signaling pathway in cells and promote their migration [31]. The activation of the latter pathway assists the regulation of actin dynamics, the rearrangement of the cytoskeleton and the deadhesion of cells from the basal lamina, supporting the process of metastasis [32,33]. This indicates that telmisartan can exhibit anti-metastatic effects and can also be effectively used as co-adjuvant therapy in patients receiving maintenance or palliative chemotherapy.

Another known effect of telmisartan is its potential to act as an agonist of the peroxisome proliferator--activated receptor gamma (PPAR-γ) [34,35]. The activation of PPAR-γ has been shown to inhibit cell proliferation, trigger several apoptotic pathways and simultaneously sensitize cells to radiation therapy, indicating that telmisartan can induce anti-proliferative and pro-apoptotic effects [36,37,38]. It is worth mentioning that one of the main pro-apoptotic mechanisms of the latter pathway, which also sensitizes malignant cells to chemotherapy and radiation therapy, is by upregulating the expression of death receptors on the cellular surface [39]. In fact, numerous recent studies have suggested that telmisartan can either inhibit cellular growth in tumors or induce their apoptosis in vitro and in vivo, validating this scientific rationale [40,41,42,43].

Overall, the available evidence suggests that telmisartan can be used as a potential anticancer agent and possibly be administered as coadjutant therapy alongside chemotherapy in patients with malignant neoplasms, given that it does not affect uric acid levels and bears a low risk of complications compared to other ARBs [10,12]. All the potential activities of telmisartan on tumors are summarized in Figure 1.

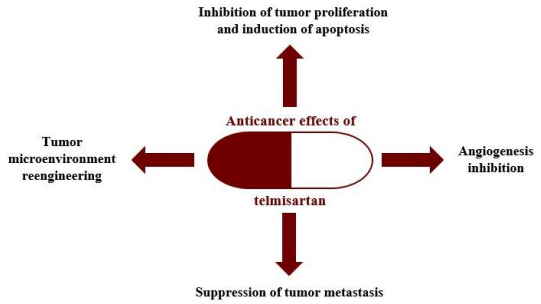

Fig. 1. Summary of potential anticancer mechanisms of telmisartan.

The anticancer effects of telmisartan

During recent years, several studies have been conducted to assess the effects of telmisartan on different types of cancer cells in vitro and in vivo. Indeed, its antihypertensive action has been found to be effective as an anticancer drug through a variety of different mechanisms. In Table I, the anticancer effects of telmisartan in different types of malignancies are reported.

Table I. Effects of telmisartan on different types of cancer. (↑): upregulation, (↓): downregulation

Type of cancer	Dosage and time of administration	Mode of anticancer activity	Molecular mechanism of action	Tested in vitro	Tested in vivo	References
Breast cancer	10 μm (0–24 h)	anti-proliferative and anti-metastatic	expression levels of IL-6 (↓)	✓	×	[40]
Bile duct cancer	0–100 μm (0–48 h)	anti-proliferative	blocker of G0 to G1 cell cycle transition	✓	✓	[41]
Colorectal cancer	0.2–5 μm (0–24 h)	anti-proliferative and pro-apoptotic	PPARγ activation; expression levels of cystatin A (↑)	✓	×	[42,43]
Endometrial cancer	0–100 μm (0–48 h)	anti-proliferative and pro-apoptotic	PPARγ activation; inhibitor of estradiol and angiotensin II induced proliferation	✓	✓	[44]
Gastric cancer	0–100 μm (0–48 h)	anti-proliferative	inhibitor of EGFR; expression levels of cyclin D1 (↑)	✓	✓	[45]
Hepatocellular cancer	0–100 μm (0–48 h)	anti-proliferative and pro-apoptotic	inhibitor of mTOR signaling pathway; inhibitor of ERBB3 phosphorylation; expression levels of caspase--cleaved cytokeratin 18 (↑)	✓	×	[46]
Melanoma	0–100 μm (0–72 h)	anti-proliferative and pro-apoptotic	PPARγ activation	✓	×	[47]
Non-small cell lung cancer	0–20 μm (in vivo for 8 mos.)	anti-proliferative, pro-apoptotic and anti-metastatic	expression levels of EGFR (↓), MET (↓), hNanog (↓), SOX2 (↓), Oct-4 (↓), TGF-β (↓), MMP-9 (↓) and E-cadherin (↑)	✓	✓	[48,49,50]
Osteosarcoma	0–50 μm (0–72 h)	anti-proliferative, pro-apoptotic and anti-metastatic	inhibitor of mTOR signaling pathway; expression levels of Bax (↑), caspase-3 (↑) and Bcl-2 (↓)	✓	×	[51]
Ovarian cancer	0–100 μm (0–72 h)	anti-proliferative, pro-apoptotic and anti-metastatic	expression levels of PPARγ (↑), caspase-3 (↑) and MMP-9 (↓)	✓	×	[52]
Pancreatic duct cancer	–	anti-proliferative and autophagy inducer	accumulation of signal adaptor protein p62; expression levels of LC3A/B antibodies (↓)	✓	✓	[53]
Prostate cancer	0–100 μm (0–72 h)	anti-proliferative	PPARγ activation	✓	×	[54]
Renal cancer	0–400 μm (0–48 h)	anti-proliferative and pro-apoptotic	expression levels of Bcl-2 (↓) and caspase-3 (↑)	✓	×	[55]
T-cell leukemia	0–100 μm (0–48 h)	anti-proliferative, pro-apoptotic and autophagy inducer	increase in LC3B enriched protein fraction and caspase-3 (↑)	✓	×	[56]
Testicular cancer	0–100 μm (0–72 h)	anti-proliferative	PPARγ activation	✓	×	[57]

IL-6 – interleukin 6; PPARγ – peroxisome proliferator-activated receptor gamma; EGFR – epidermal growth factor receptor; mTOR – mammalian target of rapamycin; ERBB3 – human epidermal growth factor receptor 3; MET – mesenchymal epithelial transition receptor; hNanog – homeobox protein NANOG; SOX2 – sex determining region Y-box 2; Oct-4 – octamer-binding transcription factor 4; TGF-β – transforming growth factor beta; MMP-9 – matrix metalloproteinase 9; LC3A/B – light-chain 3 autophagosome antibodies A and B; Bcl-2 – B-cell lymphoma-2 protein.

As seen in most studies, telmisartan has an outstanding effect on angiogenesis inhibition and tumor development reduction due to its molecular mode of action. Furthermore, it has been demonstrated that telmisartan plays a key function in the suppression of proliferation. Approximately a maximum dose of 100 μm of telmisartan can exhibit anti-proliferative and pro-apoptotic effects over a period of 2−3 days. The only exception was in the case of renal carcinoma cells, where a dose of 400 μm of the drug was required to exert its anticancer effects [55]. In many cases, one of the responses to telmisartan was an increase in the expression levels of caspase-3. The enzyme caspase-3 is a proteinase capable of degrading many structures, which is activated in many apoptotic signaling pathways, and its expression can be used as an accurate marker of apoptosis [58]. At the same time, the activation of PPARγ has been observed in many studies, validating the hypothesis that telmisartan can exhibit anticancer effects though the latter mechanism. Another observed effect of telmisartan on malignant cells, was the induction of autophagy, another mechanism which can suppress both tumor growth and tumorigenesis [59]. An antimetastatic effect was observed in the case of osteosarcoma and ovarian cancer, by inhibiting the mammalian target of the rapamycin (mTOR) signaling pathway and reducing expression of the matrix metalloproteinase 9 (MMP-9) enzyme (which can assist in degradation of the extracellular matrix), respectively [51,52,60]. The mTOR signaling pathway is one of the major pathways that promotes cell metastasis through different mechanisms, and therefore its inhibition can result in better prognosis in patients [61]. Overall, there is substantial evidence that telmisartan may be used as an anti-cancer medicine as animal in vivo studies have already been conducted.

Conclusions and future perspectives

Nowadays, various studies are undertaken to explore possible candidates for drug repositioning in the field of medical oncology [62,63]. One of the dilemmas that medical oncologists may encounter is the fact that a wide combination of drugs is the optimal regimen for chemotherapy, but amongst such regimens, many drugs such as platin salts are highly toxic and bear numerous unwanted side-effects, owing to which, patients may not fully comply with their treatment [64,65,66]. Nonetheless, this dilemma is not encountered when it comes to using drugs with a low risk of side effects, such as telmisartan [67].

As discussed in this review, there is plenty of evidence indicating that telmisartan can be used as an anti-cancer agent and already studies have been conducted on animals [45,49]. However, clinical trials need to be conducted in order to gain approval for repositioning the drug [68]. A search conducted from October 2022 until inception on the Clinicaltrials.gov website using the keywords “cancers” and “telmisartan” did not retrieve any registered clinical trial on using telmisartan in cases of malignancies. This clearly indicates the need to conduct such studies in the near future by researchers and clinicians, using the available evidence as an insight.

On the other hand, further studies have been conducted on the ARB drug losartan regarding its effect on a tumor’s stiffness and its role in reengineering the microenvironment [69]. As known from other conducted research, the microenvironment plays a significant role in the oxygenation and proliferation of a tumor and can increase chemotherapy delivery [70]. Nonetheless, the literature search conducted by the authors did not retrieve any in vivo study on the effects of telmisartan on the microenvironment. Thus, more studies can be conducted in this direction to validate the rationale reported in this review.

It is also worth mentioning that telmisartan can be used as a protective agent alongside chemotherapy to reduce adverse effects and toxicities [71]. For example, studies have revealed that telmisartan can protect patients from cardiotoxicity and oxidative stress induced by anthracycline drugs such as doxorubicin and epirubicin [72,73]. Another study by Kelleni et al. [74] concluded that the administration of telmisartan reduced hepatoxicity amongst rats that were treated with methotrexat. Overall, with all its varying effects, one can conclude that telmisartan can be used a multi-edged sword for combating various types of cancer, in combination with other therapies.

Author’s contribution

Study design – A. Hadjiyianni, D. Kalali
Data collection – A. Hadjiyianni, D. Kalali
Manuscript preparation – A. Hadjiyianni, D. Kalali
Literature research – A. Hadjiyianni, D. Kalali
Final approval of the version to be published – A. Hadjiyianni, D. Kalali

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