Research in Molecular Medicine

Apatinib as a Potential Therapeutic Agent in Breast Cancer Treatment With a Focus on Clinical Trials: A State-of-the-art Study

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ABSTRACT

Breast cancer is the most common cancer in females. The treatment of this cancer is one of the challenges facing the world's health system. Metastasis and cancer cell invasion are the reasons for the difficulty in treating this cancer. Also, the formation of new blood vessels, or angiogenesis, facilitates metastasis in cancer patients. Therefore, researchers are seeking new therapeutic drugs. One of the important factors in the processes of angiogenesis and metastasis is vascular endothelial growth factor and its receptor. Agents that can inhibit this molecule and its receptor will have helpful therapeutic potential for treating breast cancer. Apatinib is a drug that has drawn the attention of cancer researchers in the last decade, and many studies have been conducted on its effectiveness in cancer treatment, especially breast cancer. In this review article, we aimed to summarize the therapeutic potential of apatinib in vivo and animal models, with a focus on clinical trials.

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Research in Molecular Medicine

Introduction

Cancer remains a significant concern in any healthcare system [1, 2]. Breast cancer is the second most common cancer globally, particularly affecting women, with statistics indicating that one in eight women will be diagnosed with this disease in their lifetime. The high mortality rate associated with breast cancer has prompted scientists to investigate new agents with the potential to suppress metastasis and invasion in patients [3]. Apatinib, also known as Aitan in China, is a novel small-molecule tyrosine kinase inhibitor that selectively suppresses vascular endothelial growth factor receptor-2 (VEGFR-2). Since VEGFR-2 plays a crucial role in angiogenesis, introducing this antiangiogenic drug could potentially help overcome metastasis and angiogenesis [4]. Documents have shown apatinib's efficacy through molecular and cellular mechanisms, including cell cycle arrest, inhibition of cell proliferation, suppression of metastasis, and down-regulation of key genes associated with metastasis and the poor prognosis of breast cancer patients [5]. Apatinib, when combined with other chemotherapy agents, shows promising efficacy in breast cancer treatment, demonstrated by favorable disease control rates, prolonged progression-free survival, and improved overall survival (OS) in patients who have failed systemic therapies, including radiotherapy and surgery [6, 7]. Another important benefit of apatinib, a new anticancer drug, is its ability to overcome multidrug resistance (MDR), which reduces chemotherapy efficacy by increasing the efflux of chemotherapeutic drugs [8, 9]. This review article aims to comprehensively examine the potential of apatinib as a therapeutic option for breast cancer (Figure 1), with a specific focus on its role in clinical trials.

Properties of apatinib

Apatinib (YN968D1) is a newly approved, orally administered small-molecule antitumor drug derived from valatinib and produced in China, a highly potent VEGFR-selective inhibitor that binds VEGFR2 and exerts antiangiogenic effects [8]. Apatinib mesylate (MW:493.178 g/mol and molecular formula of C25H27N5O4S) or N-[4-(1-cyanocyclopentyl) phenyl]-2-(4-pyridylmethyl) amino-3-pyridine carboxamide [9], first produced by Advanchen Laboratories in California, USA, and then by Jiangsu Hengrui Medicine (China), LSK BioPartners (US), and Bukwang Pharmaceutical Company (Korea) [8]. In vitro, apatinib showed selective inhibition of VEGFR2 and inhibited the activities of specific receptor tyrosine kinases (RTKs), including RET, c-kit, and c-src [10]. Apatinib stimulation of related ligands causes inhibition of the phosphorylation of c-kit and PDGFR-β (PDGF receptor beta) in different cells. Several agents, especially VEGFR inhibitors such as apatinib, have been developed to target intracellular ATP-binding sites of RTKs, preventing phosphorylation and downstream signaling [11]. CYP3A4/5 (cytochrome P450 3A4/5), CYP2D6, CYP2C9, and CYP2E1 have a main role in the metabolism of apatinib [12]. Apatinib, with a half-life of 9 hours and taken once daily, can effectively reduce VEGFR2 levels by maintaining steady-state concentrations [13]. The Cmax of apatinib is reached in patients within 2.9 to 4.7 hours after drug administration. Nearly 76.8% of the administered dose is recovered, with the majority (69.8%) excreted in the feces. A small amount is excreted in the urine (7.02% of the dose). Additionally, about 59% of the dose taken is excreted unchanged in feces, and only very small amounts of unmetabolized apatinib are found in urine, suggesting that apatinib undergoes extensive metabolism in the bio-system [13]. Song et al. introduced 57.8 L/h as the absolute clearance (CL/F) of apatinib and its occupied volume at steady state was 112.5 L. The pharmacokinetics of apatinib are primarily influenced by the drug dosage and cancer condition [14].

Antiproliferative effect of apatinib

Apatinib has been shown to induce cell death and inhibit tumor formation in many cancers. Based on studies, apatinib has shown a positive effect in both clinical and preclinical trials for treating various types of solid tumors, including breast cancer, hepatocellular carcinoma (HCC) [15], non-small-cell lung cancer [14], liver cancer [16], gastric cancer, and several other cancers. In breast cancer, Zhang et al. reported that apatinib treatment decreased cell proliferation and induced cell cycle arrest in a dose-dependent manner. Further investigation into the molecular mechanisms revealed reduced angiomotin (AMOT) expression, along with decreased LATS1/2, YAP, ERK1/2 phosphorylation, and cyclin D1. Apatinib's beneficial effects are attenuated by AMOT overexpression; thus, apatinib inhibits MCF-7 and BT-474 cell proliferation and invasion via the AMOT/VEGFR-2 pathway [17]. Moreover, our previous study showed that apatinib decreased cell viability, inhibited tumor spheroid formation, altered cell morphology, regulated the cell cycle, and induced apoptosis in MDA-MB-231 cells. In a mechanistic view, apatinib treatment reduces the expression of p-p65 and p65 in NF-κB (nuclear factor kappa B) signaling pathways, and increases the expression of p38, p-p38, JNK, and p-JNK in MAPK (mitogen-activated protein kinase) signaling pathways [18].

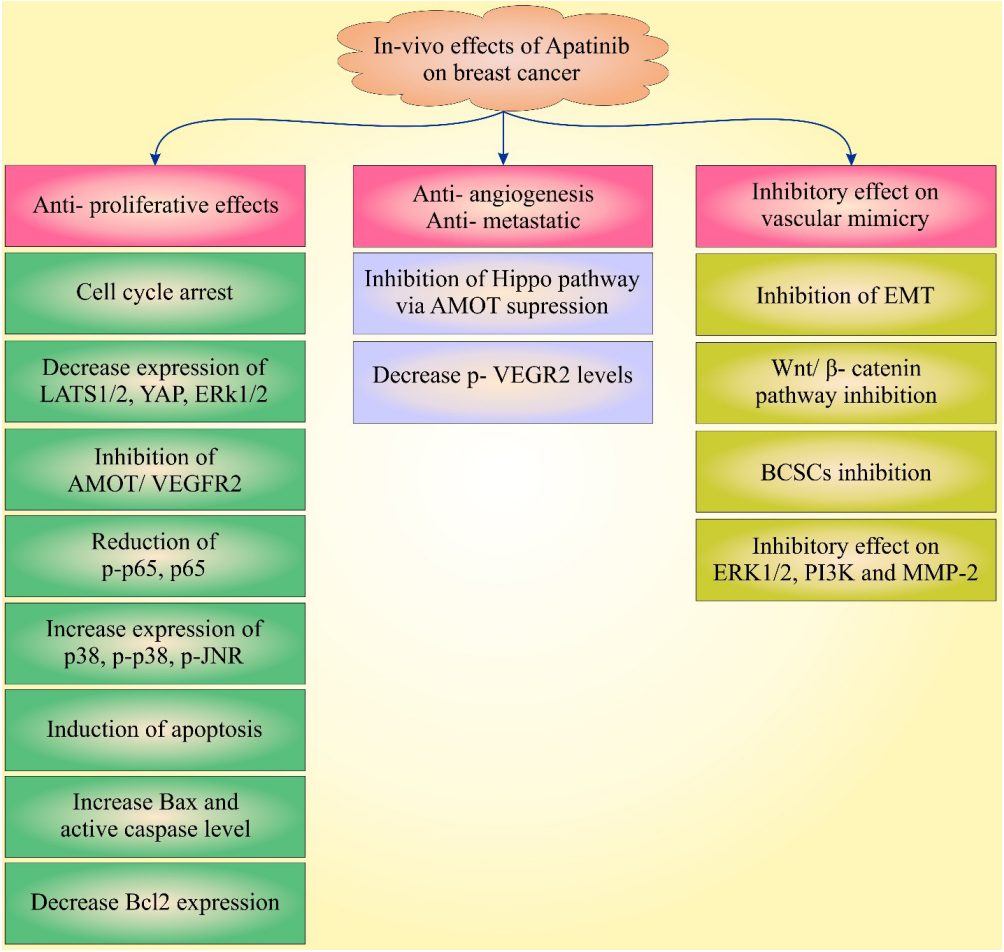

Figure 1. In vivo effects of apatinib on breast cancer

Combination therapy is an alternative method in cancer treatment that is progressively drawing attention because of the assimilation of several drug benefits [19]. Moreover, the role of the VEGF-VEGFR axis in reducing the efficacy of chemotherapy and radiotherapy has been previously confirmed. So, due to apatinib's inhibitory effect on VEGF/VEGFR signaling, its combination with other therapeutic agents and or radiotherapy can improve the efficacy of cancer treatment. In this regard, Zhenyuan Gao et al. aimed to investigate the combination of cisplatin and apatinib on the proliferation of the MDA-MB-231 breast cancer cell line. The study reported that the inhibitory effects of cisplatin on the proliferation and induction of apoptosis in MDA-MB-231 cells were enhanced by apatinib. Molecular investigation showed that increasing Bax and active caspase 3 levels and decreasing Bcl-2 expression are involved in the aforementioned effects in a breast cancer cell line [20]. The synergistic effect of apatinib with paclitaxel on triple-negative breast cancer (TNBC) in vivo and in vitro has been previously reported, with suppression of cell viability and promotion of apoptosis, and inhibition of tumor size and weight through reduced expression of p-PI3K, p65, and Bcl-xl proteins [21]. As it is known, TNBC is a kind of breast cancer that determines a poor prognosis, challenging management and treatment, reduced long-term effectiveness, which leads to poor life quality of patients [22]. Further investigations reported that apatinib, Curcumin, and their combinations could significantly decrease the viability and proliferation of breast cancer cells (MCF-7) in a concentration- and time-dependent manner by affecting the expression levels of apoptosis-related genes (*BAX, SMAC, BCL2,* and *SURVIVIN*) [23]. Another report also reported the promising synergic effect of apatinib+doxorubicin on MDA-MB-231 breast cancer cells through decreased proliferation and significantly increased apoptosis percentage due to modification of apoptosis-related gene expression (at mRNA and protein level) [24]. Further investigations showed that apatinib, via reactive oxygen species (ROS), increases apoptosis and inhibits NF-κB signaling pathways, sensitizing DOX-resistant breast

cancer cells to DOX. Moreover, in vivo results indicate that combining DOX with apatinib enhances antitumor effects in TNBC cell xenograft models [7].

An immune checkpoint inhibitor, the programmed cell death-1 receptor (PD-1) and its ligand, play an important role in cancer cell immune escape mechanisms. PD-1 is expressed on the surface of immune effector cells that are predominantly activated by PD-L1, which can be expressed by all human cells [25]. Many reports have shown that blocking PD-1 or PD-L1 is an effective alternative in cancer treatment. In metastatic TNBCs, potential therapeutic effects of PD-1 have been suggested [26]. According to studies on non-invasive (MCF-7) and invasive (MDA-MB-231) breast cancer models, apatinib may prevent the progression of benign cancers and, in malignant cancers, may be effective in combination with other chemotherapies and natural factors. However, this claim is confirmed when positive results from clinical trials are reported, which will be discussed in coming section of this article.

Antiangiogenesis and antimetastatic effects of apatinib

Angiogenesis is the growth of new blood vessels and can occur in physiological and pathological situations, and plays a major role in tumor development and evolution [27]. Compared with normal tissues, tumor tissues require abundant new blood vessels to meet their growth and metastasis requirements [28]. The receptor tyrosine kinase-mediated signaling includes (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and angiogenin (ANG), which play important roles in angiogenesis [29]. Therefore, targeting receptor tyrosine kinases might be a potential anti-angiogenic approach [29]. Although VEGFR-2 is linked to endothelial cells via various pathways, these connections have distinct activities, including activating 4 important pathways [30]. The pathways involved in angiogenesis include the MAPK [31], phosphoinositide 3-kinase (PI3K) [32], protein kinase C (PKC) [33], and signal transducer and activator of transcription 3 (STAT3) [34]. These activities lead to the production, proliferation, migration of tumor cells, and tube formation [29]. Activation of the PI3K/Akt pathway leads to the production of PIP3 from PIP2. PIP3 acts like a signal beacon, drawing Akt to the cell membrane. At the membrane, Akt is activated by phosphorylation, enabling it to regulate downstream molecules that drive cell survival and growth [32]. Another significant pathway activated by VEGFR-2 is the MAPK pathway. On this pathway, when VEGFR-2 is active, it recruits and activates certain proteins, leading to Ras activation and, subsequently, the MAPK signaling pathway. This pathway is one of the major regulatory pathways that regulate gene expression and cell growth [31]. Another pathway involved in VEGFR-2 activation is the PKC pathway, which binds to specific receptors and phosphorylates downstream targets involved in the proliferation of new blood vessels after activation [33]. As the STAT3 pathway is another pathway activated by VEGFR-2, its activation involves VEGFR-2 binding its specific ligand, with STAT3 translocating into the cell nucleus and inducing gene expression, particularly genes involved in angiogenesis, growth, and survival, leaving a positive impact [34]. To inhibit these pathways for an antiangiogenic effect, apatinib is used as an effective drug, either alone or in combination [35]. In addition, the effect of apatinib on glycogen synthase kinase 3 beta (GSK3β) and AKT, both of which modulate HIF-1α and, consequently, angiogenesis, has been demonstrated previously [36, 37]. In breast cancer, transduction and participation in angiogenesis, tumorigenesis, and metastasis of VEGFR-2 signaling can be initiated via the Hippo pathway. AMOT is a newly identified member of the Hippo pathway that is aberrantly expressed in a variety of cancers, including breast cancer. Reduction in invasion has been reported previously, and, along with AMOT inhibition via Apatinib treatment, was observed [17]. Another report shows that, although cisplatin does not affect p-VEGFR2 expression, the combination of cisplatin with apatinib decreased p-VEGFR2 expression, suggesting that Apatinib enhances the antitumor effect of cisplatin via VEGFR2. Moreover, Apatinib decreased the VEGF-mediated Akt/mTOR signaling activity. Suppression of angiogenesis via inhibition of the VEGFR2-Akt-mTOR signaling pathway has been proposed as a potential approach in antitumor therapy, so apatinib exerts antiangiogenic effects via this pathway and can be a potential agent in breast cancer treatment [20].

Inhibitory effect of apatinib on vascular mimicry (VM)

Solid tumors require a vascular network to receive blood, oxygen, and essential nutrients [38]. Until now, it was thought that the formation of new tumor vessels followed the same mechanisms as normal physiological processes, such as endothelial sprouting and proliferation, but today we know that tumors use different methods to produce new blood vessels. One of the most common methods is VM [39]. VM is the formation of new vascular structures to deliver blood and nutrients to tumor cells [40]. For the first time, VM was defined in melanoma cancer forms, and later it was discovered that many other tumors have these structures [41]. The

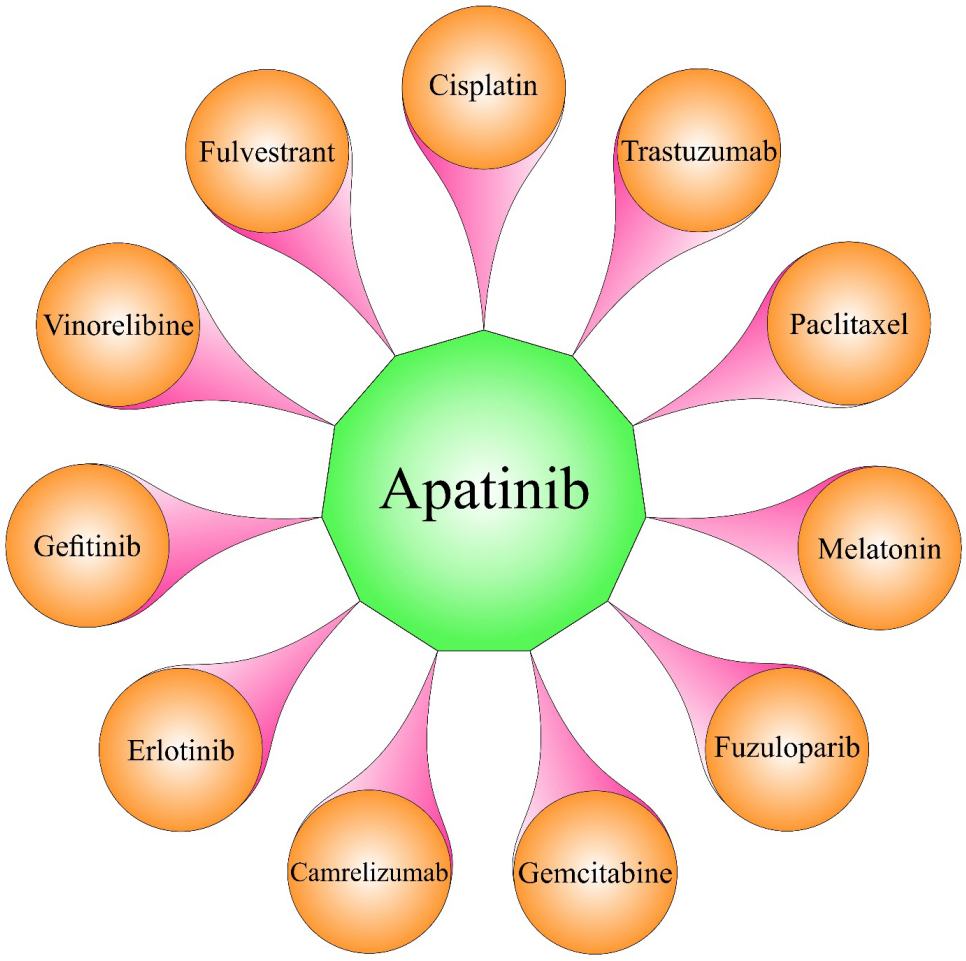

Figure 2. The drugs used in combination with apatinib in clinical trials

most common cancer types that have VM structures are breast [42], ovarian [43], prostate [44], HCC [31], colorectal [45], and lung [46] cancers. Different genes control the formation pathways of new blood vessels and VM, which play vital roles in the survival of cancer cells and in increasing metastasis [47]. Studies show that VM is necessary to provide blood and nutrients for tumor growth in the early stages of formation [48, 49]. Metastasis, tumor development, and a negative prognosis are due to the presence of VM [50]. Microarray analysis of tissues showing VM positivity indicates the involvement of cancer stem cells (CSCs), a subset of tumor cells that can self-renew, differentiate into multiple cell types, initiate tumor growth, and resist chemotherapy or radiotherapy [51]. Blood channels created by the VM process show positive results in periodic acid-Schiff (PAS) testing, but CD31 staining results are negative [52]. Unlike angiogenesis, which is performed by endothelial cells, VM is performed by cancer cells. Despite the blood flow, basement membrane, and tumor cells that cover the outer wall of the VM channels, there are no endothelial cells on the inner wall of the VM channels. Antiangiogenesis therapies are promising treatments for cancer patients; however, because VM channels form without endothelial cells, angiogenesis inhibitors have more limited effects on VM [53, 54]. Recent research has shown that tumors employ aggressive mechanisms of neovascularization, such as VM. Angiogenesis inhibitors can lead to hypoxia in tumor cells, which stimulates the formation of VM to supply blood to tumor cells [47].

Therefore, VM has been identified as a contributing factor to the failure of current antiangiogenesis therapies. These findings indicate that using only antiangiogenesis drugs is insufficient for treating cancer and may even contribute to its advancement [55]. To effectively treat cancer, both angiogenesis and VM inhibitors need to be used. Research has indicated that apatinib can effectively suppress angiogenesis and VM in both in vitro and in vivo cases of melanoma cancer [56, 57]. Apatinib binds to the ATP-binding site of VEGFR-2. This connection prevents its phosphorylation and limits its signaling

Table 1. Summary of apatinib clinical trial monotherapy or in combination with other chemotherapy agents

Drug Monotherapy or Drug Combination	Type of Breast Cancer	Results/Findings	Ref.
Apatinib+etoposid	Advanced TNBC	6.0 months for PFS and 24.5 months for OS 10% and 62.5%, respectively, reported for objective response and disease control rate	[74]
Camrelizumab+apatinib	Advanced TNBC	Favorable therapeutic mixture via the median 8.3 months PFS and ORR of 43.3%	[76]
Apatinib+chemotherapy	Advanced TNBC	Median PFS was 6.0 months, while OS was 10.0 months	[77]
Apatinib+chemotherapy	Advanced TNBC	CBR with 4.4 months PFS and 11.3 months OS	[78]
Camrelizumab+apatinib+ eribulin	Advanced TNBC	Significant ORR (37% vs 0% placebo) and DCR (87% vs 33.3% placebo) with combination therapy - Longer median PFS (8.1 months vs 4.6 months placebo).	[72]
Camrelizumab + apatinib+ fuzuloparib	Recurrent TNBC	Favorable tolerability with combination therapy - objective responses observed in two patients-reductions in tumor sizes (79% and 39%).	[79]
Apatinib + oral vinorelbine	Metastatic HER-2-negative BC	Median PFS of 5.2 months with combination therapy-ORR of 17.1% and CBR of 45.7%-Patients without baseline ctDNA had extended PFS.	[80]
Apatinib	Metastatic breast cancer	Overall response rate and CBR were 10.7 and 25%, respectively. Median PFS and OS were 3.3 and 10.6 months, respectively.	[68]
Apatinib	Metastatic breast cancer	PFS was 4 months and 15 days	[70]
Apatinib+chemotherapy	HER-2-negative breast cancer	The PFS and OS were 4.7 months and 15.3 months, respectively. DCR were 80.5%	[71]
Apatinib+chemotherapy	HER-2-negative breast cancer with chest wall metastasis	The mean PFS and OS were 4.9 months and 18 months, respectively. DCR were 76.9 %	[73]
Apatinib+docetaxel+ epirubicin plus cyclophosphamide	Early-stage TNBC	Objective responses were achieved in all patients (100%), and disease control was achieved in all patients (100%). The 2-year PFS and 2-year OS were 90.9% and 94.4%, respectively.	[67]
Apatinib+chemotherapy	Advanced breast cancer	PFS and OS were 4.8 and 15.4 months, respectively, and DCR was 86.5%	[82]

Abbreviations: PFS: Progression-free survival; OS: Overall survival; DCR: Disease control rate; TNBC: Triple-negative breast cancer; HER-2: Human epidermal growth factor receptor 2; ORR: Objective response rate.

pathways [58]. According to the results, the presence of VEGFR-2 on tumor cell surfaces is associated with the formation and progression of VM.

Furthermore, VEGFR-2 stimulates enhanced cell proliferation by activating ERK signaling pathways [59, 60]. The activation of ERK1/2 induces downstream signaling, including PI3K/MMP-2, which increases VM channel development and formation by remodeling the tumor extracellular matrix (ECM) [61]. In breast cancer, after using apatinib, the expression of VEGFR-2 is reduced, leading to the suppression of relevant signaling molecules such as ERK1/2, PI3K, and MMP-2 in the apatinib-treated groups [20, 56, 62]. These molecules lead to VM formation via the ERK1/2 signaling pathway. Thus, the inhibitory effect of apatinib on ERK1/2, PI3K, and MMP-2 can be attributed to its impact on VM [56]. Moreover, it has been reported that apatinib treatment reduces breast cancer stem cell (BCSC) viability, colony formation, and sphere numbers, suppresses migration, invasion, stem properties, and the EMT process, and induces apoptosis in a concentration-dependent manner. So it seems that apatinib, via BCSC inhibition, might suppress VM formation in breast cancer [63]. In other studies, the researchers delved into the effects of apatinib, melatonin, and their combined application on VM-induced BCSCs. The study findings highlight that apatinib, melatonin, and the apatinib/melatonin combination effectively inhibit VM initiation by CSCs by decreasing the expression of genes associated with VM [56]. Thus, it can be concluded that apatinib can be used as an effective treatment to inhibit VM in the treatment of breast cancer. However, more studies are needed to provide more accurate evidence.

Application of apatinib in clinical trials

While apatinib has shown promise as monotherapy in certain cases, researchers have also explored its potential in combination with other drugs to enhance its therapeutic effects, and apatinib combination therapy has shown promising results in the treatment of breast cancer [64, 6,

65] (Figure 2). Combining apatinib with chemotherapy or targeted therapies has been shown to result in higher response rates, longer progression-free survival, and increased OS in various clinical trials (Table 1, Figure 1). In this section, we will discuss the promising effects of apatinib in breast cancer clinical trials. Recently, apatinib has been used in a variety of clinical trials for TNBC and non-TNBC, either alone or in combination with other chemotherapies. This subtype of breast cancer poses challenges due to its lack of estrogen receptor, progesterone receptor, and HER2 expression [66]. In the treatment of early-stage TNBC, a single-arm, phase II study enrolled patients (N=31) with previously untreated stage IIA-IIIB TNBC who were treated with 250 mg of apatinib once daily plus docetaxel, epirubicin, and cyclophosphamide. The results of this study were very satisfying. Objective responses and disease control were achieved in all patients (100%). The 2-year EFS and 2-year OS were 90.9% and 94.4%, respectively. Fatigue, hypertension, anorexia, hand-foot syndrome, and diarrhea were reported as common side effects [67]. In the study with NCT01176669 ID, a prospective, open-label, phase II trial in metastatic TNBC (n=56, Chinese population), the apatinib dose was 500 mg/d. The toxic effects of apatinib included thrombocytopenia (13.6%), leukopenia (6.8%), neutropenia (3.4%), anemia (1.7%), hand-foot syndrome, proteinuria, hypertension, and increased ALT. Overall response rate and clinical benefit rate (CBR) were 10.7% and 25%, respectively. Median progression-free survival (PFS) and OS were 3.3 and 10.6 months, respectively. Because of limited treatment options for heavily pretreated patients with metastatic TNBC, the results of this study are promising [68].

In accordance with this, apatinib treatment in a non-clinical trial setting (N=45) showed median PFS, median OS, and median TTF of 4.90, 10.3, and 3.93 months, respectively. Also, this study confirmed that prior bevacizumab treatment did not affect the efficacy of apatinib [69]. Another clinical trial investigated the efficacy of apatinib in metastatic breast cancer patients (N=64) who were unresponsive to previous multifaceted chemotherapy. The results of this study showed that the median progression-free survival (PFS) was 4 months and 15 days. Moreover, the beneficial effects of apatinib in patients with intracranial metastases were found [70]. For further confirmation, another study investigates Apatinib treatment (250 mg orally once per day) on treatment of (HER2)-negative breast cancer patients. The PFS and OS were 4.7 months and 15.3 months, respectively, and the DCR was 80.5%. Moreover, in this study, combination immunotherapy or paclitaxel-platinum regimens showed improved response rates compared with other regimens [71]. Hypertension, anemia, and hand-foot syndrome were reported as the most common adverse effects [72]. In a similar study, the HER2-negative breast cancer patients with chest wall metastasis received apatinib treatment (500 mg orally once per day); the mean PFS and OS were 4.9 months and 18 months, respectively. DCR was 76.9 % [73]. The results of these two studies along with each other showed that apatinib may be helpful in the treatment and management of (HER2)-negative breast cancer. In a single-arm phase II trial, patients (N=40) with advanced TNBC were treated with a combination of apatinib (500 mg/d) and oral etoposide. The combination might have facilitated treatment because apatinib and etoposide are oral agents that patients can use at home without infusion devices. The side effects were reported as hypertension, fatigue, thrombocytopenia, nausea, and vomiting, and no treatment-related death was reported. The results reported PFS of 6.0 months and OS of 24.5 months. About 10 and 62.5%, respectively reported for objective response and disease control rate [74]. As mentioned in the previous section, targeting the PD-1/PD-L1 axis might be as potential treatment option. Camrelizumab is an immune checkpoint inhibitor designed to treat various cancers. It targets the PD-1 receptor on immune cells, preventing cancer cells from evading the immune system's detection and attack. This action helps activate the immune response against the cancer, potentially leading to tumor regression [75]. In this regard, Jieqiong Liu et al. investigated the combination of camrelizumab with apatinib efficacy in advanced TNBC as an open-label phase II trial (ID: NCT03394287, n=28). The Camrelizumab+apatinib combination might be a favorable therapeutic combination, with a median PFS of 8.3 months and an objective response rate (ORR) of 43.3% in patients with partial response, including 77 patients with advanced TNBC [76].

Moreover, biomarkers associated with antiangiogenesis drug outcomes in TNBC patients include higher baseline TILs, CD4+T cells, and B cells; increased tumor-infiltrating CD8+T cells; lower HGF/IL-8; reduced IL-8; and increased TIM-3/CD152 [75]. In the study by Zhaoyun Liu et al. and Zhu et al. as a retrospective study, the beneficial effects of apatinib were reported through an increase in PFS and OS, and the clinical beneficial rate was 40.9% with slight side effects such as hypertension, fatigue, and hand-foot syndrome [77, 78]. Moreover, apatinib in combination with chemotherapy agents has been confirmed in clinical trials. In this regard, the combination of camrelizumab, apatinib, and eribulin led to a substantial ORR of 37% in the combination therapy group, compared with 0% in the control group [72]. In another study, a combination of camrelizumab, apatinib,

and fuzuloparib in TNBC patients led to a reduction in tumor size [79]. Apatinib in combination with vinorelbine also increased median PFS by 5.2 months, an ORR of 17.1%, and a CBR of 45.7% in HER2-negative metastatic breast cancer [80]. Recently, Shen et al. (ID: NCT04722718) showed that adding apatinib to sintilimab and chemotherapy led to an increase in free survival responses (94.1%) in patients with early TNBC [81]. As it is obvious, apatinib shows potential treatment ability that investigated in clinical trials, however because of small population study and lack of a control, there is a high need to design more accurate studies.

Conclusion

In conclusion, apatinib emerges as a promising and potent therapeutic agent in the fight against breast cancer, specifically targeting the critical pathways of angiogenesis and metastasis. By selectively inhibiting VEGFR-2, it directly addresses a fundamental mechanism that suppresses tumor progression. The collective evidence from in vivo studies and animal models robustly demonstrates apatinib's efficacy in suppressing tumor growth, inhibiting metastasis, and VM. While clinical trials further substantiate its potential, particularly in advanced and treatment-resistant settings, they also underscore the need to manage its safety profile and optimize combination strategies.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

Conceptualization and writing the original draft: All authors; Funding acquisition, review and editing: Nazila Fathi Maroufi.

Conflict of interest

The authors declared no conflict of interest.

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