Stilbenes: A Promising Class for Triple Negative Breast Cancer Treatment

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1. Abstract

Triple Negative Breast Cancer (TNBC) is an aggressive subtype of breast cancer defined by the absence of hormone receptors, which presents significant therapeutic challenges. Constituting approximately 10-20% of breast cancer cases, particularly in younger women, TNBC is associated with rapid progression, elevated recurrence rates, and a heightened propensity for metastasis. Current treatment modalities, including chemotherapy, radiotherapy, and surgical interventions, often lead to substantial adverse effects, thereby necessitating the exploration of novel therapeutic strategies.

Stilbenes, a class of naturally occurring polyphenolic compounds, have garnered attention for their potential as therapeutic agents against TNBC due to their diverse biological activities, particularly their anticancer properties. Among these, resveratrol is the most extensively investigated, with notable concentrations found in grapes, berries, and red wine. This review comprehensively examines the chemical properties of stilbenes, their multifaceted mechanisms of action—including antioxidant activity, anti-inflammatory effects, and modulation of critical signaling pathways (NF-κB, PI3K/Akt, and Wnt/β-catenin)—and summarizes findings from preclinical studies. By juxtaposing stilbenes with existing treatment modalities, we elucidate their potential advantages and the obstacles to clinical implementation. Ultimately, this review aims to provide insights into the viability of stilbenes as innovative and effective therapeutic options for TNBC, thereby advancing the pursuit of improved patient outcomes.

Key Words: TNBC, Stilbenes, Polyphenols, Resveratrol, Anti-cancer activity

2. Introduction

TNBC (Triple Negative Breast Cancer) is an aggressive breast cancer subtype that lacks hormone receptors on its surface, such as Estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). Due to the absence of these hormone receptors, TNBC treatment is the greatest challenge nowadays. **[1]** Out of all breast cancer subtypes, TNBC accounts for approximately 10 to 20% of them in younger women. **[2]** It is a highly aggressive cancer due to its rapid progression, higher recurrence rate, and greater tendency to metastasize compared to other breast cancer subtypes. **[3]** Recently, TNBC Patients have been treated with standard treatment modalities such as Chemotherapy, Radiotherapy, and Surgery. But, these treatments may lead to certain co-morbid conditions and severe side effects. **[4]** So, there arises a need for novel therapeutic strategies that are more specific and less harmful.

In recent years, stilbenes—a class of naturally occurring polyphenolic compounds—have garnered considerable attention for their potential in cancer therapy, including their applicability in treating TNBC. **[5] [6] [7]** Stilbenes are found in various plants and are noted

for their diverse biological activities, including potent anticancer properties. Among the stilbenes, resveratrol is the most extensively studied and is known for its presence in high concentrations in grapes, berries, peanuts, and red wine. Resveratrol and other stilbenes have shown promise in preclinical studies due to their ability to modulate multiple cellular pathways in cancer progression. **[8] [9] [10] [11]**

This review aims to comprehensively explore the potential of stilbenes as therapeutic agents for TNBC. It will examine the chemical properties of stilbenes, their mechanisms of action, and the results from preclinical and clinical studies. Furthermore, the review will compare stilbenes to existing treatment modalities for TNBC, highlighting their advantages and addressing the challenges that need to be overcome to translate these findings into clinical practice. By evaluating the current state of research and future directions, this review seeks to provide insights into the viability of stilbenes as a novel and effective treatment option for TNBC.

3. Chemical Structure and Properties of Stilbenes

Stilbenes are compounds characterized by a backbone of 1,2-diphenylethylene, with two phenyl groups connected by an ethylene bridge. This simple yet versatile structure allows for various substitutions, leading to multiple derivatives with differing biological activities. **[12] [13]** The most extensively studied stilbene is resveratrol (3,5,4'-trihydroxy-trans-stilbene), found in high concentrations in grapes, berries, peanuts, and red wine. Resveratrol can exist in cis and trans isomeric forms, with the trans form being more stable and biologically active. **[14] [15]**

Natural sources of stilbenes include various plants. They are synthesized as phytoalexins in response to stress, injury, or fungal infection. Other notable natural stilbenes include pterostilbene (found in blueberries) and piceatannol (found in passion fruit), each with unique properties and potential health benefits. **[16] [17]**"Synthetic stilbene derivatives have been created to improve their stability, bioavailability, and therapeutic effectiveness." **[18]**

Stilbenes' anticancer properties are multifaceted, involving a combination of antioxidant, anti-inflammatory, and cell signalling modulation activities. **[19] [20] [21] [22]** These mechanisms work synergistically, with stilbenes playing a crucial role in inhibiting cancer cell proliferation, inducing apoptosis, and preventing metastasis. **[18] [24]** Below is a detailed exploration of these mechanisms.

4. Antioxidant Properties

Stilbenes are potent antioxidants that neutralize free radicals, reducing oxidative stress and preventing cellular damage. Oxidative stress, characterized by an imbalance between free radicals and antioxidants in the body, is a known contributor to cancer development and progression. Free radicals can cause DNA damage, promote mutations, and activate oncogenes, which can lead to the initiation and progression of cancer. **[19] [24] [25]**

Mechanism:

- **Neutralization of Free Radicals**: Stilbenes like resveratrol act as scavengers of free radicals, preventing them from causing cellular damage. By donating electrons,

stilbenes neutralize free radicals, thereby protecting cells from oxidative stress. **[26] [27] [28]**

- **Upregulation of Antioxidant Enzymes**: Resveratrol upregulates the expression of antioxidant enzymes such as superoxide dismutase (SOD) and catalase. These enzymes play crucial roles in detoxifying reactive oxygen species (ROS). SOD converts the superoxide radical into hydrogen peroxide, which is then broken down by catalase into water and oxygen, thus reducing oxidative damage. **[29] [30] [31]**
- **Enhancement of Cellular Defense Mechanisms**: By boosting the body's natural antioxidant defenses, stilbenes provide a robust protection against oxidative stress, which is pivotal in preventing cancer initiation and progression. **[14]**

5. Anti-inflammatory Effects

Chronic inflammation is a hallmark of cancer and plays a significant role in various stages of tumor development, including initiation, promotion, and metastasis. Inflammatory cells and cytokines present in the tumor microenvironment can promote tumor growth and metastasis. Stilbenes exhibit strong anti-inflammatory properties, which can help mitigate cancer progression. **[18]**

Mechanism:

- **Inhibition of Pro-Inflammatory Cytokines**: Stilbenes inhibit the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines are involved in promoting inflammation and are often elevated in cancerous tissues. **[22] [32] [33] [34]**
- **Suppression of Inflammatory Enzymes**: Stilbenes inhibit enzymes like cyclooxygenase-2 (COX-2) that are involved in the inflammatory process. COX-2 is often upregulated in tumors and contributes to the inflammatory microenvironment that supports cancer growth and survival. **[14] [22]**
- **Reduction of Inflammatory Signalling Pathways**: By inhibiting key inflammatory signalling pathways, stilbenes reduce the overall inflammatory response, which can impede cancer cell proliferation and survival. This anti-inflammatory action not only hampers cancer progression but also reduces the side effects associated with conventional cancer treatments. **[35]**

6. Modulation of Signalling Pathways

Stilbenes affect several key signalling pathways implicated in cancer cell proliferation, apoptosis, and metastasis. These pathways include the NF-κB, PI3K/Akt, and Wnt/β-catenin pathways.

6.1 NF- κB Pathway

Role in Cancer

The NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway is a critical regulator of immune response, cell survival, and proliferation. NF-κB proteins are transcription factors that, when activated, translocate to the nucleus and promote the expression of genes involved in inflammation, immune response, cell proliferation, and survival. In many cancers, NF-κB is constitutively active, meaning it is continuously active without the usual

regulatory controls. This persistent activation supports the survival, proliferation, and metastatic potential of cancer cells, contributing to tumor growth and resistance to apoptosis (programmed cell death). **[36] [37]**

Stilbene Action

Stilbenes, such as resveratrol, can inhibit the NF-κB pathway. Resveratrol prevents the activation of NF-κB by interfering with upstream signaling molecules that normally lead to NF-κB activation. This inhibition results in decreased expression of NF-κB target genes that are crucial for cell survival and proliferation. As a consequence, resveratrol can induce apoptosis in cancer cells, sensitizing them to chemotherapy and other treatments. By blocking NF-κB signaling, stilbenes can reduce tumor growth and enhance the efficacy of conventional cancer therapies. **[19] [20] [38]**

6.2 PI3K/Akt Pathway

Role in Cancer

The PI3K/Akt (phosphatidylinositol-3-kinase/Akt) pathway is essential for regulating cell growth, survival, and metabolism. Activation of this pathway promotes cell proliferation, inhibits apoptosis, and enhances cell survival under stress conditions. In many cancers, the PI3K/Akt pathway is hyper activated due to mutations or overexpression of its components, leading to uncontrolled cell growth and resistance to cell death mechanisms. **[36] [39] [40] [41]**

Stilbene Action

Stilbenes like pterostilbene inhibit the PI3K/Akt pathway. Pterostilbene blocks the activation of PI3K, which subsequently prevents the activation of Akt. By inhibiting this pathway, stilbenes reduce cell proliferation and promote apoptosis. This action helps to suppress tumor growth and makes cancer cells more susceptible to apoptosis-inducing agents, potentially enhancing the effectiveness of cancer treatments. **[20] [22] [32]**

6.3 Wnt/β-catenin Pathway

Role in Cancer

The Wnt/β-catenin signaling pathway plays a key role in regulating cell proliferation, differentiation, and migration. In many cancers, including triple-negative breast cancer (TNBC), the pathway is dysregulated, leading to excessive cell proliferation, inhibition of apoptosis, and increased metastatic potential. Dysregulation typically involves stabilization and accumulation of β-catenin in the nucleus, where it activates the transcription of target genes that promote tumor growth and metastasis. **[42] [43]**

Stilbene Action

Stilbenes have been shown to inhibit the Wnt/β-catenin pathway. They prevent the accumulation of β-catenin in the nucleus, thereby reducing the expression of genes involved in cell proliferation and survival. By blocking this signalling pathway, stilbenes can suppress tumor growth, reduce metastasis, and decrease tumor aggressiveness. This action helps in

preventing the spread of cancer and enhances the overall effectiveness of cancer therapies. **[20] [44]**

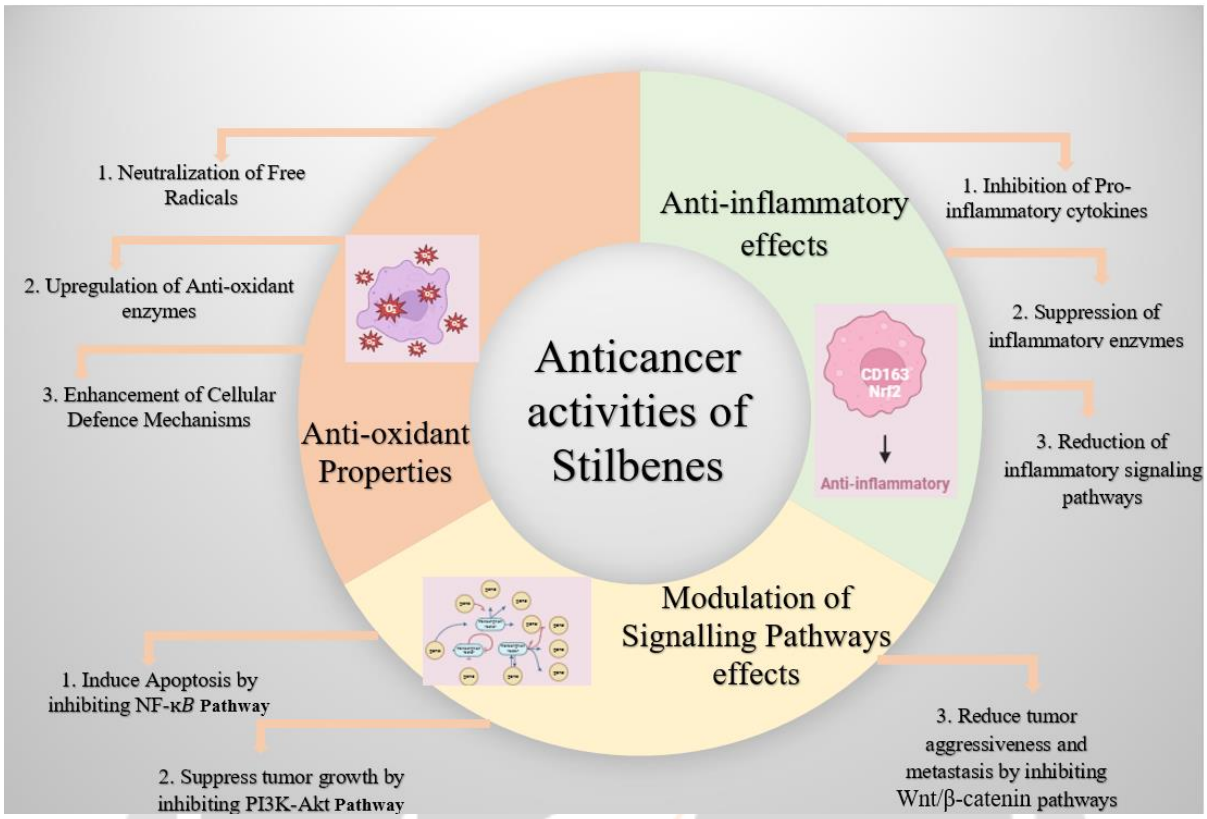

Figure: 1 Anti-cancer activities of Stilbenes and its derivatives

The multifaceted anticancer properties of stilbenes make them promising candidates for TNBC treatment. By acting as potent antioxidants, reducing inflammation, and modulating critical cell signalling pathways, stilbenes can inhibit cancer cell proliferation, induce apoptosis, and prevent metastasis. These mechanisms highlight the potential of stilbenes as effective therapeutic agents, offering a targeted approach with fewer side effects compared to conventional treatments. Further research and clinical trials are essential to fully understand the therapeutic potential of stilbenes and to integrate them into standard cancer treatment regimens.

7. Preclinical Studies

Preclinical studies provide essential insights into the efficacy and mechanisms of action of stilbenes in TNBC treatment. These studies involve both in vitro (cell culture) and in vivo (animal model) experiments.

1. **In Vitro Studies**: Research on TNBC cell lines has demonstrated that stilbenes can inhibit cell proliferation, induce apoptosis, and impair metastatic potential. For instance, resveratrol has been shown to reduce the viability of MDA-MB-231 and MDA-MB-468 TNBC cell lines by inducing cell cycle arrest at the G1 phase and promoting apoptosis through the activation of caspases. **[45] [46] [47]** Additionally, pterostilbene has been observed to inhibit TNBC cell migration and invasion by

downregulating matrix metalloproteinase (MMPs), which are enzymes involved in extracellular matrix degradation and metastasis. **[48]**

2. **In Vivo Studies**: Animal models of TNBC have further corroborated the anticancer effects of stilbenes. **[49]** In one study, mice xenografted with MDA-MB-231 cells and treated with resveratrol exhibited significant tumor growth inhibition compared to control groups. **[49] [50]** Histopathological analysis revealed increased apoptosis and reduced angiogenesis in resveratrol-treated tumors. Similarly, pterostilbene administration in TNBC-bearing mice resulted in reduced tumor volume and metastasis, with improved survival rates. **[49]**

These preclinical findings underscore the potential of stilbenes as effective anticancer agents against TNBC, warranting further investigation in clinical settings.

8. Clinical Studies

While preclinical studies are promising, translating these findings into clinical practice requires rigorous testing through clinical trials. Clinical studies on the use of stilbenes for TNBC are currently limited, but several trials have explored the effects of resveratrol and other stilbenes in cancer patients.

8.1 Safety and Efficacy Trials: Initial clinical trials have focused on evaluating the safety, tolerability, and preliminary efficacy of resveratrol in cancer patients. For example, a phase I clinical trial assessed the safety of resveratrol in patients with colorectal cancer, demonstrating that oral resveratrol was well-tolerated at doses up to 5 grams per day. **[51] [52]** Another study investigated the effects of resveratrol on biomarkers of breast cancer risk in postmenopausal women, showing a reduction in levels of IGF-1 and IGFBP-3, which are associated with cancer progression. **[53]**

8.2 Case Studies and Patient Outcomes: Case studies have provided anecdotal evidence supporting the potential benefits of stilbenes in cancer therapy. In one case report, a patient with metastatic breast cancer who received resveratrol supplementation in conjunction with standard chemotherapy experienced significant tumor regression and improved quality of life. While these individual cases are encouraging, they highlight the need for well-designed, large-scale clinical trials to validate the therapeutic potential of stilbenes in TNBC. **[54]**

9. Comparative Analysis with Other Treatments

To fully appreciate the potential of stilbenes in TNBC treatment, it is important to compare them with existing treatment modalities, particularly chemotherapy.

9.1 Efficacy: Chemotherapy remains the cornerstone of TNBC treatment, with drugs like doxorubicin, cyclophosphamide, and paclitaxel commonly used. While effective, chemotherapy is often associated with significant side effects, including myelosuppression, cardiotoxicity, and neurotoxicity. Stilbenes, with their ability to target multiple pathways involved in cancer progression, offer a more targeted approach with potentially fewer side effects. For instance, the ability of resveratrol to inhibit the NF-κB pathway and sensitize cancer cells to chemotherapy could enhance the efficacy of conventional treatments while reducing the required dosage and associated toxicity.

9.2 Safety Profile: One of the major advantages of stilbenes over chemotherapy is their favourable safety profile. Natural stilbenes like resveratrol and pterostilbene are generally well-tolerated, with few reported side effects at therapeutic doses. This contrasts sharply with the adverse effects commonly associated with chemotherapy, making stilbenes an attractive option for long-term use and for patients who cannot tolerate conventional treatments.

9.3 Additional Benefits: Beyond their direct anticancer effects, stilbenes offer additional health benefits due to their antioxidant and anti-inflammatory properties. These benefits can mitigate the side effects of chemotherapy, improve patient well-being, and enhance overall treatment outcomes. For example, the antioxidant activity of stilbenes can protect against chemotherapy-induced oxidative damage, while their anti-inflammatory effects can reduce treatment-related inflammation and improve patient quality of life.

10. Challenges and Future Directions

Despite the promising potential of stilbenes, several challenges must be addressed to fully realize their therapeutic potential in TNBC treatment.

10.1 Bioavailability: One of the major limitations of natural stilbenes, particularly resveratrol, is their poor bioavailability. Rapid metabolism and elimination result in low plasma concentrations, limiting their therapeutic efficacy. Strategies to overcome this challenge include the development of synthetic derivatives with improved pharmacokinetic properties, the use of nanoparticle-based delivery systems, and the combination of stilbenes with bioenhancers that inhibit their metabolism.

10.2 Standardization and Quality Control: The variability in stilbene content among natural sources can lead to inconsistencies in therapeutic outcomes. Standardization and quality control measures are essential to ensure the purity, potency, and reproducibility of stilbene-based therapies. This includes the use of standardized extraction methods, rigorous quality control testing, and the development of pharmaceutical-grade stilbene formulations.

10.3 Comprehensive Clinical Studies: While initial clinical studies are encouraging, more comprehensive, large-scale clinical trials are needed to fully understand the therapeutic potential and safety profile of stilbenes in TNBC. These trials should focus on optimizing dosing regimens, evaluating long-term safety, and assessing the efficacy of stilbenes in combination with conventional treatments. Additionally, studies should investigate the potential of stilbenes in different subtypes and stages of TNBC to identify the most responsive patient populations.

10.4 Mechanistic Studies: Further mechanistic studies are needed to elucidate the precise molecular mechanisms underlying the anticancer effects of stilbenes. Understanding these mechanisms will facilitate the development of more targeted and effective therapies and help identify biomarkers for predicting treatment response.

11. Conclusion

Stilbenes represent a promising class of compounds for the treatment of Triple Negative Breast Cancer. Their ability to modulate key signaling pathways, combined with their antioxidant and anti-inflammatory properties, make them attractive candidates for novel therapeutic approaches. While further research is needed to overcome current limitations and confirm their clinical efficacy, stilbenes hold great potential as a complementary treatment for TNBC, offering hope for improved patient outcomes.

The integration of stilbenes into TNBC treatment regimens could provide a multi-faceted approach to cancer therapy, enhancing the efficacy of existing treatments while reducing side effects and improving patient quality of life. As research continues to advance, stilbenes may emerge as a valuable addition to the arsenal of treatments for this challenging and aggressive form of breast cancer.

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