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Fungal-Derived Anti-Cancer Compounds: Innovative Strategies in Breast Cancer Management: A Review

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Abstract
Globally, breast cancer is a significant public health concern. It is the leading cause of death among women and the second most common type of cancer. Conventional therapies, such as radiation, chemotherapy, and surgery, are commonly used for breast cancer treatment. However, the high mortality rate among female patients suggests that traditional treatments are ineffective. These therapies have been associated with drug resistance, undesirable side effects, and cancer metastasis. Consequently, scientists are exploring the use of various medications to treat breast cancer. Natural compounds derived from organisms have shown promise in preventing metastasis and promoting apoptosis, making them potential options for breast cancer treatment. This review summarizes the literature on breast cancer, natural compounds from fungi, and their potential anticancer activity.

Keywords: Breast cancer, Conventional therapies, Natural compounds, anticancer activity, secondary metabolites.

1. Introduction

Breast cancer is the most common type of cancer diagnosed and a major cause of death for women (Islam *et al*., 2022) [1]. Although there is a slight probability that men could get breast cancer, women are more frequently affected by the illness (Tagde *et al*., 2022) [2]. According to global cancer (GLOBOCAN) data, breast cancer was the second most common cause of cancer worldwide in 2022. There were an estimated 2.3 million new cases, representing 11.6% of all cancer cases and 6.9% of all cancer deaths (Bray *et al*., 2024) [3]. Breast cancer is typically treated using conventional therapeutic approaches such as radiation, chemotherapy, and surgery. However, the significant death rate among women with this malignancy indicates that conventional treatment is inefficient (Tagde *et al*., 2022) [2].

The limits of existing chemotherapeutic medications present substantial obstacles in the treatment of breast cancer. These medications are associated with cancer metastasis, drug resistance, and undesirable side effects.

To overcome these challenges, researchers are investigating the use of different medicines to treat breast cancer. Natural substances derived from living organisms have shown potential in promoting apoptosis and preventing metastasis, making them viable options for treatment (Islam *et al*., 2022) [1]. A valuable resource for researchers in identifying new drugs is the abundance of natural bioactive compounds (Abdel-Razek *et al*., 2020) [4].

Chemical compounds or substances that are naturally produced by living organisms are known as natural products (Ouyang *et al*., 2014). Natural products have been widely employed as a source of medication due to their availability and affordability. They are also the most valuable resource for drug discovery and development, thanks to their unique bioactivities and chemical composition (Abdel-Razek *et al*., 2020) [4]. Fungi-derived secondary metabolites exhibit a wide range of pharmacological properties, including antifungal, antioxidant, antibacterial, and anticancer properties (Vallavan *et al*., 2020) [6]. These compounds hold promise for the development of new treatments for breast cancer.

2. The initiation of cancer cells

Cancer is a complex process in which a single cell develops mutant gene products that result in various pathophysiologic characteristics. These characteristics include uncontrolled growth, proliferation, blocked differentiation, inappropriate induction of angiogenesis, tissue invasion, and genomic instability (Felsher *et al*., 2016) [7].

Important gene alterations that affect normal cell development and differentiation are involved in the molecular processes that lead to the initiation of cancer cells. It has been demonstrated that these cells play a crucial role in tumor formation and possess the necessary mutations for tumor development (Tysnes & Bjerkvig, 2007) [8].

Malignant transformation occurs due to mutations in specific cellular genes that activate oncogenes and deactivate tumor suppressor genes (Grandér & Grandér, 1998) [9]. These genes are susceptible to mutations, amplifications, or deletions, which can disrupt the biological processes that regulate normal cell development and differentiation. Subsequently, clonal selection occurs, producing variant cells with progressively aggressive behaviors. These behaviors include the ability to infiltrate and destroy normal tissues, as well as the ability to proliferate despite normal growth-regulating mechanisms (Tysnes & Bjerkvig, 2007) [8].

3. Breast cancer metastasis

A tumor mass is considered malignant when tumor cells invade adjacent normal cells or spread to other body parts (Tagde *et al*., 2022) [2]. The primary cause of cancer-related mortality is the spread of malignant cells through metastases. The process of metastasis is intricate and associated with the development of distant secondary cancers.

The complex process of metastasis begins with local invasion, followed by the intravasation of cancer cells into adjacent blood and lymphatic vessels. Subsequently, cancer cells pass through the hematogenous and lymphatic systems and escape from the lumina of these vessels into the parenchyma of distant tissues. Cancer cells then form small nodules, known as micro-metastases, which eventually grow into macroscopic tumors (Hanahan & Weinberg, 2011; Meirson *et al*., 2020) [10].

4. Molecular subtypes of breast cancer

According to an analysis of gene expression data, breast cancer can be classified into different molecular subtypes, each with unique clinical characteristics (Yang *et al*., 2007) [12]. Currently, subtype determination can be achieved through gene-based assays and immunohistochemistry (IHC)-based markers (Gao & Swain, 2018) [13]. These subtypes are commonly categorized based on the immunohistochemical (IHC) expression of hormone receptors, namely estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2) (Orrantia-Borunda *et al*., 2022) [14]. Gene expression profiling has identified four main molecular subtypes of breast cancer: luminal A, luminal B, HER2-enriched, and basal-like. These subtypes differ significantly in terms of incidence, prognosis, treatment response, survival, and imaging characteristics (Johnson *et al*., 2021) [15].

4.1. luminal A subtype and luminal B subtype

The Luminal A subtype of breast cancer is characterized by the presence of hormone receptors (ER/PR), low HER2 expression, and low Ki-67 expression. Compared to the Luminal A subtype, the Luminal B subtype has a worse prognosis, a greater probability of local recurrence, and lower survival rates. Hormonal treatment in addition to chemotherapy may be beneficial for Luminal B carcinomas (Inic *et al*., 2014; Orrantia- Borunda *et al*., 2022) [17].

4.2. HER2-enriched subtype

The HER2-enriched subtype of breast cancer is characterized by high HER2 expression and the absence of hormone receptors (ER/PR) (Orrantia-Borunda *et al*., 2022) [14]. It is well-established that HER2 overexpression is associated with increased disease recurrence and mortality rates. Additionally, HER2+ breast tumors are more likely to develop brain metastases. In 1998, trastuzumab, also known as Herceptin, was approved as the first anti-HER2-directed treatment for metastatic HER2+ invasive breast cancer (Patel *et al*., 2020) [18]. HER2-targeting treatments, such as neoadjuvant trastuzumab, have shown more favorable results in HER2-positive patients compared to non-HER2-targeting treatments (Niikura *et al*., 2016) [19].

4.3. Basal-like breast cancer

Basal-like breast tumors are characterized by the absence of hormone receptor expression (progesterone (PR), estrogen (ER)) and human epidermal growth factor receptor-2 (HER2). This subtype is significant in breast cancer as it is associated with a high prevalence of distant metastases, particularly within the first five years of the disease. It has an aggressive clinical prognosis, limited response to therapy, and a relatively high death rate (Badowska-Kozakiewicz & Budzik, 2017; Milioli *et al*., 2017) [20]. The expression profile of the basal subtype, which accounts for 15–25% of cases, is comparable to that of myoepithelial normal mammary cells. Unlike other subtypes, basal-like tumors exhibit unique epidemiological characteristics. They are characterized by early and frequent relapses. Despite a relative sensitivity to chemotherapy treatment, the prognosis for basal-like breast cancer is poor (Bertucci *et al*., 2012) [22].

5. Treatment of breast cancer

The main objective of breast cancer treatment is to manage and control the illness to achieve recovery. Treatment aims to reduce the probability of local recurrence and
.(prevalence of metastases, relieve symptoms, and enhance survival (Rahman, 2011) [23]. The principal treatments for breast cancer include surgery, chemotherapy drugs, and radiation therapy (Akram *et al*., 2017) [24]. Surgery and radiation therapy are local treatments used to lower the risk of recurring cancer in the breast, chest wall, and regional lymph nodes. After local therapy, systemic treatments such as hormone therapy and cytotoxic chemotherapy are used to reduce the overall death rate from breast cancer and systemic recurrences (Shapiro & Recht, 2001) [25].

5.1. Surgery

Currently, the primary approach to treating breast cancer is surgery. This involves performing either a mastectomy or a breast-conserving procedure (Cipora *et al*., 2018) [26].

The amount of tissue removed along with the cancer varies depending on the type of breast cancer, its spread, and the patient's sentiments (Akram *et al*., 2017) [24].

Mastectomy has often been the recommended method of surgery for early-stage invasive breast cancer. However, breast-conserving surgery is now the most common surgical approach for treating breast cancer. It involves removing a malignant tumor from a portion of the breast, along with some healthy tissue and accompanying lymph nodes, while preserving the majority of the breast (Maughan *et al*., 2010) [27].

Approximately 70% of all surgical treatments performed for breast cancer involve this type of surgery. The therapeutic efficacy of breast-conserving surgery is just as successful as mastectomy. In recent years, surgical procedures have advanced significantly, allowing breast-conserving surgery to be successfully used even in cases of large tumors (Cipora *et al*., 2018) [26].

5.2. Radiation therapy

After primary surgery for invasive breast cancer, radiation therapy is the most successful approach to prevent recurrence. It is more successful than adjuvant chemotherapy following either mastectomy or breast-conserving surgery. Meta- analyses have shown that radiation therapy may reduce the probability of both cancer death and distant metastases. Patients who are incurable benefit greatly from radiotherapy in terms of palliative care (Rutqvist *et al*., 2003) [28].

While radiation therapy for early-stage breast cancer can reduce death from the disease, it can also increase death from other causes, particularly heart disease and lung cancer (Darby *et al*., 2005) [29]. Previous research has demonstrated significantly increased cardiac death rates after radiotherapy for breast cancer on the left side. Although there were other contributing factors to this excess mortality, individuals who had received radiation therapy had a greater probability of dying from cardiac disease (Brown *et al*., 2015) [30].

5.3. Hormonal therapy

For all patients with hormone-receptor-positive breast malignancies, hormonal therapy is required. Patients with breast cancer whose tumors express progesterone (PR), estrogens (ER), hormone receptors (HR), or both are eligible for hormonal treatment. Hormone therapy is beneficial for patients with low recurrence scores; however, chemotherapy is required for those with high recurrence scores. All hormone treatments appear to be equally effective in treating HR+ metastatic breast malignancies. Chemotherapy is advised if hormone treatment is not effective.

Approximately 50% of hormone receptor-positive breast neoplasms are or become resistant to hormone therapy. Some chemicals associated with certain pathways of tumor cell growth reverse the resistance to hormone therapy (Drăgănescu & Carmocan, 2017) [31].

5.4. Chemotherapy

In recent years, there have been significant advancements in the use of cytotoxic chemotherapy for both advanced and early-stage breast cancer (Hassan *et al*., 2010) [32]. Chemotherapy can reduce the recurrence risk in early-stage breast cancer by approximately 30% (Wang & Wu, 2023) [33]. The best chemotherapy strategy involves a combination or sequence of taxane and anthracycline. Although the use of anthracyclines is still debatable, it appears to be crucial for high-risk patients, including those with HER-2 positive and triple-negative subtypes (Wang & Wu, 2023) [33].

Chemotherapy was originally used to treat cancer in the 1940s, and since then, it has been a cornerstone of medical oncology, despite its often serious adverse effects. Although chemotherapy has advanced significantly in therapeutic approaches (Bagnyukova *et al*., 2010) [34], chemoresistance remains a common problem that explains most treatment failures in metastatic cancer patients (Toh *et al*., 2014) [35]. Resistance to chemotherapy restricts the efficacy of anti-cancer medication therapy. Chemotherapy- resistant tumors may form during treatment or may already be drug-resistant tumors. These tumors not only become resistant to the medications originally used to treat them, but they may also develop cross-resistance to other medications with different mechanisms of action. It is estimated that more than 90% of individuals with metastatic cancer have developed resistance to chemotherapy, and resistant micro-metastatic tumor cells can also decrease the efficacy of chemotherapy in adjuvant therapy (Longley & Johnston, 2005) [36].

6. Bioactive compounds of fungi and their anticancer activity

Natural products play a crucial role in chemistry, biology, and medicine due to their diverse structures and chemical properties, which surpass those of synthetic small molecules. They remain the primary sources of medications and drug leads, evolving to resemble pharmaceuticals (Shen, 2015) [37]. As a result, natural products are considered the foundation of medication research, providing valuable insights for the discovery of new drugs (Abdel-Razek *et al*., 2020) [4].

In recent years, fungi have emerged as a promising source of secondary metabolites with various beneficial properties for therapeutic and commercial applications. Fungal metabolites have garnered significant interest as a reliable source of valuable molecules that can serve as novel entities for medicinal techniques (Youssef & Singab, 2021) [38]. Endophytic fungi, in particular, possess bioactive chemicals that show potential in cancer treatment (Kumar *et al*., 2021) [39]. These chemicals inhibit cancer growth and promote apoptosis (Kousar *et al*., 2022) [40]. The ongoing efforts to derive pharmaceutical chemicals from endophytic fungi offer a potentially cost-effective, reliable, and environmentally friendly approach to producing such medications. Additionally, endophytic fungi employ alternative mechanisms for synthesizing bioactive anticancer drugs (Kumar *et al*., 2021) [39].

6.1. Rubrofusarin

Rubrofusarin is a derivative of naphthopyrone that is found in significant quantities in both terrestrial and marine environments (Megawati *et al*., 2017) [41]. It is an orange-brown pigment produced by various fungal species, including Aspergillus niger, Fusarium graminearum, Aspergillus parasiticus, and Ustilaginoidea virens (Rugbjerg *et al*., 2013) [42]. Previous studies have reported several biological properties of rubrofusarin, such as hepatoprotective and anti-inflammatory effects (Megawati *et al*., 2017) [41]. Additionally, it has been found to possess antioxidant, antimicrobial, and anticancer properties (Yi *et al*., 2020) [43]. Wang *et al*. (2018) [44] have shown that rubrofusarin may inhibit the activity of DNA topoisomerase II-α and exhibit anti-estrogenic properties.

Different cancer types have varying levels of expression of topoisomerase I and topoisomerase II. For example, colon cancer primarily expresses topoisomerase I, while breast and ovarian cancer primarily express topoisomerase II (Hu *et al*., 2018) [45]. Topoisomerases II α and β cause double-strand breaks on a single DNA molecule, allowing other DNA strands to pass through. Consequently, topoisomerases are desirable drug targets in cancer treatment (Xu & Her, 2015) [46].

There are two main groups of topoisomerase II inhibitors: topoisomerase II poisons and topoisomerase II catalytic inhibitors. Topoisomerase II poisons kill cancer cells by increasing the amount of covalent "topoisomerases II-DNA complexes" and preventing the cleaved DNA strand from religating. This leads to the accumulation of unwanted double-strand breaks, ultimately causing DNA strand breaks that induce apoptosis in tumor cells. On the other hand,

topoisomerase II catalytic inhibitors kill tumor cells by inhibiting the critical enzymatic activity of topoisomerase II (Hu *et al*., 2018) [45].

6.2. Podophyllotoxin

Podophyllotoxin is a significant natural compound that acts as a precursor to three anticancer medications: teniposide, etoposide phosphate, and etoposide (Eyberger *et al*., 2006) [47]. Some endophytic fungi, such as Dysosma veitchii and Sinopodophyllum hexandrum, can produce podophyllotoxin (Kousar *et al*., 2022) [40]. It has also been isolated from the endophytic fungus Phialocephala fortunii, which has demonstrated cytotoxic effects on cells (Kumar *et al*., 2021) [39]. Podophyllotoxin causes cell cycle arrest and mitotic failure by blocking microtubule polymerization (Chen *et al*., 2013). It exhibits its anti-tumor effects by preventing tubulin assembly into microtubules, leading to apoptosis and cell cycle arrest during mitosis. This interference with the development of mitotic spindle microtubules is achieved by preventing tubulin polymerization (Kumar *et al*., 2021) [39].
In addition to its impact on microtubules, podophyllotoxin also demonstrates cytotoxic effects by attaching to topoisomerase II and preventing DNA replication (Kousar *et al*., 2022) [40]. Topoisomerase inhibitors can increase the production of topoisomerase II or remove its catalytic activity. This accumulation of permanent DNA breaks ultimately leads to cell death (Uzma *et al*., 2018) [52].

6.3. Camptothecin

Camptothecin is a pentacyclic pyrroloquinoline alkaloid, extracted from plants, that serves as a significant cancer drug. It is utilized in the production of anti-cancer medications such as topotecan and irinotecan. Interestingly, endophytic fungi, which share the same metabolite as the host, have the potential to produce various bioactive anticancer chemicals, including camptothecin (Kumar *et al*., 2021) [39].

One such endophytic fungus, Entrophospora infrequens, isolated from Nothapodytes foetida, was initially identified as having the ability to produce camptothecin. Furthermore, camptothecin was also isolated from two strains of endophytic Fusarium solani. These findings highlight the potential of fungi as an alternative source for camptothecin production (Aswini & Soundhari, 2018) [49].

Camptothecin has demonstrated cytotoxic activity against various types of cancer cells, making it an extremely potent chemotherapeutic agent (Landgraf *et al*., 2020) [50]. It functions by poisoning DNA topoisomerase I, thereby inhibiting tumor growth (Beretta *et al*., 2013) [51]. Topoisomerase-I plays a crucial role in the supercoiling and relaxation of DNA during replication. Camptothecin binds to topoisomerase-I, inhibiting its catalytic activity. This binding triggers a sequence of apoptotic events, ultimately leading to cell death (Uzma *et al*., 2018) [52].

6.4. Vinblastine

Vinblastine is a naturally occurring Vinca alkaloid first discovered in *Catharanthus roseus* (Dhyani *et al*., 2022) [53]. According to reports, the endophytic fungus *Alternaria sp.*, which was isolated from the original plant from which vinblastine was extracted, also produces vinblastine (Lee & Shim, 2020) [43].
Vinblastine inhibits cell proliferation by binding to microtubules. It binds to tubulin and inhibits the formation of microtubules, disrupting the construction of the mitotic spindle and stopping tumor cells in the M phase of the cell cycle (Dhyani *et al*., 2022) [53]. The inadequate development of the mitotic spindle caused by vinblastine exposure prevents cells from proliferating during the mitotic phase, ultimately leading to cell death (Kumar *et al*., 2021) [39].

7. Conclusions

Breast cancer is a leading cause of death among women worldwide, emphasizing the urgent need for effective prevention and treatment strategies. Early detection plays a crucial role in improving survival rates and reducing the risk of metastasis, which is the spread of cancer to other parts of the body. The alarming mortality rate associated with breast cancer highlights the limitations of conventional treatment methods, necessitating exploration of alternative approaches. Fortunately, natural substances derived from living organisms have emerged as promising candidates for breast cancer treatment. These bioactive compounds have demonstrated the ability to induce apoptosis, a process of programmed cell death, and inhibit metastasis. Among the diverse array of natural chemicals, endophytic fungal natural products have garnered significant attention due to their consistent and abundant anticancer properties. These compounds have shown the ability to impede cancer growth and promote apoptosis, offering hope for improved treatment outcomes.
However, it is important to note that the potential of natural chemicals in breast cancer treatment extends beyond endophytic fungal products. A multitude of other compounds have also exhibited anticancer properties, further emphasizing the need for continued research in this field. By harnessing the power of natural chemical compounds produced by organisms, scientists can potentially unlock new treatment avenues for breast cancer.
In conclusion, the exploration of natural chemicals as potential treatments for breast cancer holds immense significance. The urgency to find effective alternatives to conventional therapies is evident, given the high mortality rate associated with this disease. Continued research and investigation into the anticancer properties of natural substances are paramount to improve patient outcomes and ultimately combat breast cancer on a global scale.

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