ISSN 2348-0319 International Journal of Innovative and Applied Research [2023]
(Volume 11, Issue 12)
01-09

Journal home page: http://www.journalijiar.com

INTERNATIONAL JOURNAL
OF INNOVATIVE AND APPLIED RESEARCH

REVIEW ARTICLE

Article DOI: 10.58538/IJIAR/2055
DOI URL: *http://dx.doi.org/10.58538/IJIAR/2055*

EXPLORING NATURAL PLANT PRODUCTS IN BREAST CANCER MANAGEMENT: A COMPREHENSIVE REVIEW AND FUTURE PROSPECTS

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Manuscript Info

Manuscript History
Received: 02 November 2023
Final Accepted: 06 December 2023
Published: December 2023

Keywords:
Breast Cancer, Tumor, Natural Plant Products, Metastasis, Anti-Cancer Drugs

Abstract

Breast cancer, characterized by uncontrollable growth of abnormal breast cells forming tumors, can be fatal if unchecked, spreading throughout the body. Originating in breast milk ducts or lobules, its early stages pose no immediate threat, but invasive forms can metastasize to other organs. Its prevalence has surpassed lung cancer globally. Projections suggest 28.4 million cases by 2040. Treatment varies based on the individual, cancer type, and its spread, involving surgery, radiation, and medication. Natural plant products show promise as antitumor and anti-cancer agents, exhibiting reduced toxicity and resistance to conventional drugs. These products leverage antioxidant, anti-inflammatory, and immunomodulatory properties, influencing cancer cell behavior. Some studies highlight herbs' potential in developing anti-cancer drugs. Notably, breast cancer's impact is significant in developing countries. Inadequate medical infrastructure and high treatment costs promote the use of natural products in these countries. Plant-based remedies offer a less toxic alternative, crucial in regions with limited access to conventional treatments. Understanding breast cancer and early diagnosis is critical in managing its impact. Therefore, this review delves into breast cancer intricacies and underscores natural plant products' potential in mitigating the projected increase in breast cancer-related deaths.

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Introduction:-

The most common cancer diagnosed in women is currently breast cancer, surpassing lung cancer in this regard. According to forecasts, there will be 28.4 million cases of cancer globally by 2040, a 47% rise from 2020. Although lung cancer remains the leading cause of cancer-related deaths worldwide, female breast cancer ranked second in 2022 [1, 2]. In the United States, breast cancer is the second most common cancer-related death cause for women

and the most common cancer type [3]. Treatment strategies are tailored to individuals, considering the cancer type and its extent, typically involving a combination of surgery, radiation therapy, and medications [4]. There's growing promise in natural plant products as effective antitumor and anti-cancer agents [5, 6]. Throughout history, plant-based alternatives for managing various diseases, including breast cancer, have been extensively documented. Plants have exhibited diverse pharmacological effects, such as anti-malarial [7, 8], antidiabetic [9-13], anticholesterolemic [14, 15], cardio-protective [16, 17], antiarthritic [18-21], antimicrobial [22], hypolipidemic [23-25], and organ-protective properties [26-29]. Numerous reports have highlighted plants with potential anticancer and antiprostate effects [30, 31], attributing these properties to the bioactive compounds they contain [32-35]. Over 80% of the global population relies on plant-based products for maintaining good health [36, 37]. Alarmingly, about 70% of breast cancer deaths occur in developing countries, predominantly in Africa [4]. These regions face challenges of limited healthcare resources, high treatment costs, and considerable distances to accessible healthcare facilities. Additionally, compared to conventional drugs, plant-based products tend to have lower toxicity and fewer adverse effects [38, 39]. Consequently, there's a growing inclination towards using plant products, especially in regions where healthcare resources are limited, to manage diseases like breast cancer. Given that many conventional anticancer medications originated from plants, there's an urgent need to explore more plants for their potential anticancer properties. Enhanced understanding, early diagnosis, and effective treatment methods are crucial for better breast cancer management outcomes. This article delves into breast cancer and underscores the potential of natural plant products with anticancer properties. The objective is to gain comprehensive knowledge about the disease and identify numerous natural plant products that could help mitigate the anticipated increase in breast cancer-related deaths.

Breast Cancer Prevalence

Globally, there were 2.3 million female cases of breast cancer in 2020, which resulted in 685,000 fatalities. Globally, breast cancer is the most frequent cancer type; by the end of 2020, 7.8 million women who were diagnosed with the disease during the preceding five years were still alive. It is noteworthy that breast cancer can occur in women of any age post-puberty, though its incidence rises in later stages of life [40].

Risk Factors for Breast Cancer

The risk of breast cancer is influenced by various factors. These encompass factors like age, obesity, excessive alcohol intake, family history of the disease, exposure to radiation, smoking, postmenopausal hormone therapy, reproductive patterns (such as age at first pregnancy and onset of menstrual periods), late first childbirth (after 30 years) or no pregnancies, and early onset of menstruation (before 13 years old). Interestingly, almost half of breast cancer instances arise in women without identifiable risk factors except for being female and over 40 years old [41]. While a family history increases the risk, it's crucial to note that most diagnosed women do not have a known familial susceptibility to the disease. Not having this history doesn't necessarily mean a reduced risk [42]. Specific inherited gene mutations, particularly in high-risk genes like BRCA1, BRCA2, and PALB-2, significantly increase the likelihood of developing breast cancer [43].

Breast Cancer Types

The immunohistochemical expression of hormone receptors—estrogen receptor-positive (ER+), progesterone receptor-positive (PR+), human epidermal growth factor receptor 2-positive (HER2+), and triple-negative (TNBC), which does not express these receptors—is the primary determinant of breast cancer classification. HER2-positive, triple-negative, luminal A, and luminal B are the four main subtypes identified by this approach [44].

The estrogen receptor (ER) is pivotal in diagnosis, with approximately 70–75% of invasive breast carcinomas exhibiting notably high ER expression [45]. Progesterone receptor (PR) expression, which is controlled by ER, is found in more than 50% of patients with ER-positive breast cancer but is infrequently seen in ER-negative instances. In breast cancer cells, ER and PR function as prognostic and diagnostic indicators, respectively [46]. While lower levels frequently signify a more aggressive disease trajectory and a worse prognosis, elevated PR levels are linked with improved general survival, longer period to recur, and less treatment failure [47, 48]. Treatment choices are greatly influenced by the expression of human epidermal growth factor receptor-2 (HER2), which is expressed in approximately 15–25% of breast cancer cases. In HER2+ situations, HER2 amplification results in increased proto-oncogenic signaling pathways, which in turn cause unchecked cancer cell proliferation and poorer clinical outcomes [49].

Subtypes and Characteristics of Breast Cancer

Luminal A:

Characterized by ER and/or PR presence, lackof HER2, and little Ki-67 (less than 20%) expression. These tumors have the greatest prognostic outcome with the fewest relapses since they are low-grade and slowly developing, and are highly responsive to hormone therapy, offering limited benefits from chemotherapy [50].

Luminal B:

Higher grade than Luminal A, ER-positive (potentially PR-negative), with elevated Ki-67 (greater than 20%) expression. These tumors grow faster than Luminal A and have a poorer prognostic outcome. In addition to chemotherapy, hormone treatment is more beneficial to them [51].

HER2-positive:

Constituting 10–15% of breast cancers, these tumors exhibit high HER2 expression, lacking ER and PR. They proliferate more quickly than luminal types, with a worse prognosis but high response rates to chemotherapy [53].

Triple-negative breast cancer (TNBC):

About twenty percent of breast tumors are TNBC, which are defined as having no expression of the ER, PR, or HER2 receptors. African-American women and women under 40 are more likely to have it. There are other subclassifications of TNBC as well, the most common being basal-like (BL1 and BL2), claudin-low, mesenchymal (MES), luminal androgen receptor (LAR), and immunomodulatory (IM) [54]. TNBC displays aggressive characteristics, with about 80% of these tumors associated with tumor suppressor genes BRCA1 and BRCA2 [55].

Breast Cancer Metastasis, Survival, and Relapse

Despite advancements in early detection and treatments, breast cancer mortality has decreased. However, distant metastases remain a possibility, with a median survival time of 2–3 years for women with advanced breast cancer [56]. Studies have shown a correlation between breast cancer subtypes, metastatic sites, and overall survival. For instance, the luminal B subtype is significantly associated with heightened bone metastasis risk compared to luminal A, while both luminal subtypes are linked to higher rates of liver, brain, and lung metastases. TNBC exhibits higher rates of brain, liver, and lung metastases but lower bone metastasis rates than luminal A. Survival rates vary with breast cancer subtypes, with luminal A demonstrating the highest survival rates (94.4%), followed by luminal B (90.7%), HER2 (84.8%), and TNBC (77.1%) [58].

Signs and Symptoms of Breast Cancer

Signs of breast cancer encompass a breast lump or thickening, changes in breast size, shape, or appearance, skin alterations (redness, pitting), changes in nipple appearance or surrounding skin, and abnormal or bloody nipple discharge. Early detection and treatment of small, non-metastatic lumps enhance successful treatment. As breast cancer progresses, symptoms may extend to other body parts, including the lungs, liver, brain, and bones [61].

Diagnosis of breast cancer

Initially, mammography and ultrasonography were used for imaging in breast cancer diagnosis. Magnetic resonance imaging (MRI) is employed selectively, particularly in cases involving dense breasts, a history of breast cancer, evaluation for contralateral disease, or in high-risk patients [62]. MRI is valuable for presurgical planning in cases of biopsy-confirmed breast cancer and for evaluating patients with dense breasts, contralateral disease, or those who have undergone prior breast surgery or radiation. In cases of invasive breast cancer, MRI often reveals irregular masses, pleomorphic microcalcifications, anatomical distortion, and posterior acoustic shadowing as typical imaging findings [63]. Confirmation of the disease requires a tissue biopsy, providing details on Tumor grade, Immunohistology, and the Oncotype DX Breast Recurrence Score, aiding in estimating neoadjuvant chemotherapy's potential utility and the chance of recurrence in people with initial stages of breast cancer [63].

Treatment of Cancer of the Breast

Treatment strategies for breast cancer depend on the cancer subtype, spread outside the breast (to lymph nodes or other body parts), hormone receptivity, histologic markers, patient age, and preference. A combination of treatments aims to reduce the risk of cancer recurrence. Options include surgery (lumpectomy or mastectomy), radiation therapy, and medications targeting cancer cells and preventing spread through hormonal therapies, chemotherapy, or targeted biological therapies [64]. Lumpectomy is often preferred for unilateral disease [65]. Radiation therapy reduces the possibility of a recurrence of chest wall cancer by treating any remaining microscopic tumors in breast

tissue or lymph nodes. Some cases might consider accelerated partial breast irradiation for specific patient profiles [66]. Medication choices vary based on multiple factors like hormone reception status, HER-2 status, and the existence of cancer disease. Neoadjuvant chemotherapy is frequently used before surgery for breast cancers that are triple-negative and locally progressed. Following surgery, different chemotherapeutic drugs and methods are used according to the histology of the tumor, the presence of HER-2, and the state of hormone receptors [67]. HER-2 blockers like trastuzumab and pertuzumab may be potent in treating HER-2-positive cancer of the breast. Hormone-positive breast cancer typically involves SERMs (selective estrogen receptor modulators) like tamoxifen [68].Natural plant-based anti-cancer compounds have been reported [69].

Natural plant products Use in the management of breast cancer

Natural plant products have emerged as promising agents in combating and preventing cancer. Their efficacy is attributed to reduced toxicity during use and a decreased tendency for resistance development against hormone-targeted anticancer medications [5]. Plants are rich sources of antioxidants and anti-inflammatory compounds [70, 71]. They combine these properties with immunomodulatory effects, exerting anti-metastatic and anti-apoptotic impacts on malignant cells. This multifaceted approach presents chemopreventive, prophylactic, and therapeutic benefits, promoting safe long-term use [69]. Metabolites like flavonoids, alkaloids, coumarins, and terpenoids (e.g., curcumin), possess antioxidant and anti-inflammatory properties alongside lymphocyte activation (e.g., ginseng, quinic acid, β-carotene, and epigallocatechin-3-gallate), crucial in suppressing or combating cancer cells [72].

Bioactive compounds such as phytoestrogens and isoflavonoids act as endocrine disruptors, impacting hormonal disorders underlying certain cancer types. Plants include flavonoids, which have estrogenic or anti-estrogenic qualities. They also cause oxidative stress, inhibit processes that are dependent on and independent of estrogen receptors, and influence the induction of cancer by estrogen receptor signaling [73, 74]. Research demonstrates the effectiveness of natural ingredients, such as herbs, in the development of anticancer medications. For instance, Asiimwe et al. [75] identified 121 plant species with anticancer properties, notably from families like Asteraceae, Euphorbiaceae, Fabaceae, and Apocynaceae. Commonly cited plants include Hoslundiaopposita Vahl, Aspiliaafricana, Spathodeanilotica, Annona muricata L., Prunus Africana, Kalkman, Acacia hockii, Bidens pilosa L., and Carica papaya. Preparation methods primarily involve decoction and oral administration. Similar studies in Ethiopia and Egypt support these findings, highlighting plants like Oxalis corniculata,Opuntia species, Albizia coriaria, Daucus carota, Cyperus alatus, and Markhamia lutea [76, 77]. Plants like Catharanthus roseus, Allium sativum, Moringa oleifera, and Opuntia species, have also been reported for their anticancer properties [78].

In developing regions, plant use for breast cancer treatment or symptom alleviation is more prevalent compared to other parts of the world [75]. Studies in Asia and Europe have showcased how herbal medicines improve cancer patients' quality of life, enhance survival rates, and exhibit chemo-preventive activities [79, 80]. Based on research by Ayaz et al. [81], certain medicinal herbs may be able to stop cancer from starting, spreading, and metastasizing.

By 2040, the Global Breast Cancer Initiative (GBCI) of the WHO hopes to save millions of lives by reducing the annual worldwide breast cancer deaths by 2.5 percent. Its main goals are to promote health through early identification, prompt diagnosis, and all-encompassing care [82]. Given the effectiveness of plants in managing breast cancer, it is crucial to protect their habitats, promote sustainable use, and conserve them to preserve their potential as alternative or complementary treatments. This becomes significant considering the high cost of conventional anticancer medicines, the comatose nature of the healthcare system in developing regions, and the numerous adverse effects of conventional drugs.

Conclusion and Future Prospects:-

The prevalence of breast cancer is increasing worldwide, necessitating innovative approaches to its management. This comprehensive review underscores the pivotal role of natural plant products as promising adjuncts in the multifaceted landscape of breast cancer treatment. With their proven anti-tumor, anti-cancer, antioxidant, and immunomodulatory properties, these plant-based remedies offer a beacon of hope, particularly in regions with limited access to conventional therapies. The disparity in healthcare resources globally, coupled with the rising costs of conventional treatments, accentuates the significance of exploring alternative remedies. Natural plant products, enriched with bioactive compounds, exhibit reduced toxicity and hold the potential tomitigate the adverse effects often associated with traditional medications. While this review has highlighted the vast spectrum of plant-derived compounds and their effects on breast cancer, there remains a need for further research. Specific studies focusing on the efficacy of individual compounds, their mechanisms of action, and standardized formulations are crucial to

validate and integrate these remedies into mainstream cancer care. Moreover, efforts toward conservation and sustainable utilization of these plant resources are paramount. Protecting natural habitats and promoting responsible use ensure the preservation of these valuable remedies for future generations. Ultimately, integrating natural plant products into breast cancer management represents a promising avenue, supplementing conventional therapies and potentially enhancing treatment outcomes. Embracing this natural synergy between traditional wisdom and modern medicine holds the key to addressing the escalating challenges posed by breast cancer on a global scale.

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