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Cancer Cell International (2025) 25:144
https://doi.org/10.1186/s12935-025-03767-1

Cancer Cell International

REVIEW

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Synergistic strength: unleashing exercise and polyphenols against breast cancer

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Abstract

Breast cancer remains a major global health challenge, necessitating innovative preventive and therapeutic strategies. Emerging evidence such as clinical trials suggests that the combination of exercise and polyphenol intake exerts synergistic effects in mitigating breast cancer progression by modulating key molecular pathways. Exercise enhances immune function, reduces inflammation, and regulates cellular metabolism, while polyphenols, natural compounds found in various plant-based foods, exhibit antioxidant, anti-inflammatory, and anti-carcinogenic properties. Together, these interventions influence apoptosis, oxidative stress, and ferroptosis which play crucial roles in breast cancer pathophysiology. This review explores the molecular mechanisms underlying the combined impact of exercise and polyphenols on breast cancer prevention and treatment. Understanding the interplay between exercise and polyphenols at the molecular level could pave the way for novel, non-invasive therapeutic strategies. Future research should focus on optimizing exercise regimens and dietary interventions to maximize their anti-cancer benefits. By bridging molecular insights with clinical applications, this review aims to provide a foundation for incorporating lifestyle-based interventions into breast cancer management. Our findings collectively highlight the promising potential of combining curcumin supplementation with exercise as a multifaceted approach to breast cancer treatment. The synergistic effects observed in various studies suggest that integrating lifestyle modifications with dietary interventions may enhance therapeutic efficacy and mitigate cancer progression. Further clinical investigations are warranted to validate these results and explore their applicability in human subjects. The evidence supports a holistic strategy for breast cancer management that could improve patient outcomes and quality of life during treatment.

Keywords Exercise training, Natural products, Polyphenols, Breast cancer, Signaling pathway

Introduction

Breast cancer represents the most prevalent malignant tumor among women globally. While the incidence of this malignancy is rising across all regions, industrialized nations exhibit the highest rates. Developed countries account for nearly half of all breast cancer cases worldwide [1]. According to WHO, between the 1980s and 2020, age-standardized breast cancer mortality rates in high-income countries decreased by 40% (1). Nations that have effectively lowered breast cancer mortality have managed to achieve a reduction of 2–4% in annual breast cancer deaths.

This trend is largely attributed to the adoption of a new lifestyle characterized by smoking, dietary deficiencies, limited physical activity, and elevated stress levels [1]. Mammography has emerged as the standard screening tool for breast cancer. Its effectiveness is particularly pronounced in women aged 50–69 years [1–3]. Tumors that lack increased expression of all three

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hormone receptors are categorized as triple-negative breast cancers (TNBC), which do not respond to hormonal treatment [4]. Standard management strategies for breast cancer often include chemotherapy, radiotherapy, and surgical procedures, all of which can lead to significant adverse effects [5]. Furthermore, the development of drug resistance poses an additional challenge to the efficacy of these treatments. Consequently, researchers are actively exploring innovative alternative approaches to manage breast cancer more effectively [6].

Natural products that are derived from plants, have been the subject of investigation for centuries due to their therapeutic efficacy in addressing a wide range of diseases [7]. In the realm of oncology, it is noteworthy that approximately 60% of the clinically utilized anticancer agents demonstrating notable efficacy are derivatives of natural products [8]. These substances also provide cost-effective options in contemporary drug development. The secondary metabolites found in plants, such as flavonoids, tannins, and alkaloids have shown great antitumor effects [9]. They can initiate, enhance, or modulate metabolic pathways that influence cell proliferation, migration, and apoptosis in cancerous cells through various mechanisms. Consequently, phytochemical constituents are central to the exploration of chemotherapeutic agents in both preclinical and clinical cancer research. A prime example is paclitaxel, a plant-derived alkaloid first identified in 1962 during the screening of natural products for cancer treatment which has emerged as one of the most effective therapies available for breast cancer [10–13]. Some other drugs which are approved by FDA for treating breast cancer include: 5-FU, Docetaxel, Gemcitabine Hydrochloride, Abemaciclib, Capivasertib, and Inavolisib [14].

The essence of exercise training is characterized by repeated sessions of physical activity that challenge the homeostatic balance of the entire body, resulting in significant adaptations across various organ systems [15, 16]. While extensive research has focused on changes within skeletal muscle, adipose tissue, and the vascular system, there remains a paucity of knowledge concerning other tissues, particularly tumors [17]. Nevertheless, exercise training is posited to target and enhance nearly every potential health outcome for cancer patients. Indeed, exercise is widely recognized as contributing to positive alterations in objective physiological indicators, such as body mass, function of an individual, and cardiopulmonary fitness. In addition, it affects patient-reported parameters, such as sleep quality and fatigue [18, 19]. Notably, novel studies have indicated a direct correlation between exercise training and the regulation of tumor biology, potentially enhancing clinical outcomes.

A study conducted in 2008 has demonstrated the relationship between physical activity and cancer prevention, attributing this association to exercise-induced decreases in various cancer risk factors, such as sex hormones, levels of insulin and Insulin-like growth factor 1 (IGF) levels and inflammatory markers [20]. Recent studies conducted on mice have also revealed that exercise training can affect progression of tumor by affecting intrinsic tumor characteristics, including growth, metastasis, metabolism, and immunogenicity. Furthermore, it interacts with systemic factors and may improve negative effects related to cancer and its treatments while enhancing the effectiveness of cancer therapies [21].

The primary aim of this manuscript is to explore the potential synergistic effects of polyphenols and exercise on breast cancer, with a focus on their impact on cancer cell metabolism, proliferation, and survival. By integrating findings from existing studies, we seek to provide insights into how these two factors may contribute to novel supportive strategies for breast cancer management.

Breast cancer: from epidemiology to treatment options

Epidemiology

According to the World Health Organization (WHO), malignant neoplasms represent the most significant global health burden for women, with an estimated 107.8 million Disability-Adjusted Life Years (DALYs) lost [22]. Breast cancer accounts for 19.6 million DALYs [23]. Breast cancer is the most commonly diagnosed malignancy in women all around the world and approximately 2.26 million new cases of breast cancer have been reported in 2020 [24]. In the United States, breast cancer is projected to constitute 29% of all newly diagnosed cancers in women [25]. In 2008, approximately 1.4 million women around the globe were diagnosed with breast cancer, resulting in about 459,000 deaths related to the disease. The incidence rates were significantly higher in more developed nations, at 71.7 cases per 100,000, compared to 29.3 cases per 100,000 in less developed countries. However, the mortality rates were 17.1 per 100,000 in developed countries and 11.8 per 100,000 in developing nations, suggesting that breast cancer deaths are nearly 17% more prevalent in less developed regions [26]. Consequently, the five-year relative survival rates vary widely, from 12% in Africa, where the incidence is lower, to nearly 90% in the United States, Australia, and Canada, where the incidence is considerably higher. It is projected that by 2050, the global incidence of female breast cancer could reach around 3.2 million new cases annually. Although the incidence of breast cancer has been rising globally, there are notable disparities between

affluent and impoverished nations. The rates of incidence are highest in more developed areas, whereas mortality rates are considerably greater in less developed countries [26].

In addition to being the most prevalent cancer among women, breast cancer is the leading cause of cancer-related mortality in this population globally. In 2020, breast cancer was responsible for approximately 684,996 deaths [24]. Although the highest incidence rates were observed in developed regions, countries in Asia and Africa accounted for 63% of total breast cancer deaths in that year [24]. Survival rates for women diagnosed with breast cancer are generally high in high-income countries, contrasting sharply with the outcomes for women in many low- and middle-income nations [27].

Risk factors and etiology

Breast cancer risk is primarily influenced by gender and age, with various factors contributing to its development. Hormonal exposure, particularly to estrogen and progesterone, plays a significant role in breast cancer risk. Risk factors can be categorized into modifiable and non-modifiable factors. Early menarche, positive family history of breast cancer, height, density in mammographic data, late menopause, race, and some gene alterations are considered as non-modifiable risk factors [28]. In contrast, some of breast cancer risk factors can be modified or prevented, such as use of exogenous hormones, age at first live birth, number of parities, breastfeeding, postmenopausal body mass index (BMI), level of physical activity, educational level, and alcohol consumption [28]. With regard to lifestyle factors after the age of 50, numerous studies have established a correlation between elevated BMI, limited physical activity, alcohol consumption, and the use of menopausal hormone therapy (HT) with an increased likelihood of developing breast cancer [29–37]. Furthermore, research indicates that tobacco smoking is also linked to a heightened risk of breast cancer; however, the relationship remains somewhat ambiguous [38]. The genetic and environmental risk factors associated with carcinoma in situ appear to be similar to those linked to invasive breast cancer [39, 40]. This finding implies that both premalignant lesions and invasive breast cancer may originate from the same underlying causes. In addition, many of the risk factors pertinent to invasive breast cancer are crucial for the initiation of tumors [41].

Classifications

Breast cancer can be categorized into various types based on factors such as etiology, anatomical location, and both clinical and molecular features. In terms of the levels of aggregation, breast cancer is typically classified into two categories: non-invasive and invasive. Non-invasive breast cancer remains contained within the lobules or ducts from which it originates, whereas invasive breast cancer extends into the surrounding mammary tissue beyond these structures [42]. Additionally, breast cancer can be divided into two primary groups based on estrogen receptor (ER) expression: ER-positive and ER-negative [43]. Other molecular traits, such as the presence of progesterone receptors (PR) and the human epidermal growth factor receptor 2 (HER2), also play a role in the classification of breast cancer [44, 45].

Global gene expression profiling research has categorized breast cancers into five intrinsic subtypes through hierarchical clustering. These subtypes include luminal A, luminal B, HER2-overexpressing, basal-like breast cancers (BLBC), and normal-like tumors. In this classification, the Luminal A and B subtypes are composed of ER-positive cancers, while the HER2-overexpressing, BLBC, and normal-like tumors are ER-negative [46–48].

The Luminal A and B subgroups are defined by gene expression profiles that are similar to those of normal luminal epithelial cells in the breast, along with other genes linked to ER activation. Luminal A is the most prevalent molecular subtype, accounting for 40 to 50% of invasive breast cancer cases. Generally, luminal A cancers are classified as low grade and have the most favorable prognosis among all intrinsic subtypes. In contrast, Luminal B cancers are usually of a higher grade and have a poorer prognosis compared. They exhibit lower levels of ER-related gene expression but show increased expression of genes associated with proliferation, as well as variable expression of HER2-related genes compared to Luminal A cancers [46–48].

The HER2-overexpressing subtype accounts for approximately 15% of all invasive breast cancers and is marked by the overproduction of HER2 and genes related to HER2 signaling, as well as genes found in the HER2 amplicon on chromosome 17q12. These tumors are typically high grade, negative for ER and progesterone receptor (PR), and tend to follow an aggressive clinical trajectory. However, they respond well to anti-HER2-targeted therapies, leading to significantly better outcomes [46–48]. Triple-negative breast cancer (TNBC) is characterized by the absence of hormone receptors (ER/PR) and the overexpression of human epidermal growth factor receptor 2 (HER2). This subtype represents 10–15% of all breast cancer cases. This type of BC typically manifests as high-grade invasive ductal carcinoma and is associated with a greater likelihood of early recurrences, frequently accompanied by distant metastases. It is also linked to a worse prognosis when compared to other breast cancer subtypes [49]. Treating triple-negative breast cancer can be difficult due to the presence of various molecular subtypes. There are multiple treatment options available,

including chemotherapy, immunotherapy, radiotherapy, and surgery, with chemotherapy being the most commonly used. TNBC is typically managed with systemic chemotherapy, employing drugs like anthracyclines and taxanes in either neoadjuvant or adjuvant contexts. The main challenges to effective chemotherapy for cancer include the development of resistance to anticancer drugs and off-target toxicity. It is crucial for researchers, clinicians, and pharmaceutical companies to collaborate in creating effective treatment strategies for TNBC. Several studies have indicated that nanotechnology may offer a promising approach to address the inadequacies in TNBC treatment [49].

BLBC are linked to the expression of genes found in normal mammary basal and myoepithelial cells, including basal cytokeratin. They exhibit an overexpression of genes related to proliferation but do not express ER, PR, or HER2-related genes. Histologically, BLBCs are typically high grade, characterized by a high proliferation index, and display a triple-negative phenotype. Patients with BLBC generally have a poor prognosis, with the possibility of relapses occurring within five years of diagnosis [46–48].

The normal-like cluster identified in the initial research was marked by the expression of genes akin to those found in normal breast epithelium. However, this subgroup is contentious and has since been regarded as an artifact resulting from contamination by genuine normal epithelial cells in tumors with low malignant cell content [46–48].

Pathophysiology

The specific processes involved in the progression of breast cancer remain incompletely understood. As previously mentioned, the causes of breast cancer involve a complex mix of genetic and environmental influences that lead to the malignant transformation of breast cells. Additionally, the tumor microenvironment, which includes interactions between tumor, stromal, and immune cells, plays a significant role in cancer development. Gaining insight into these mechanisms is essential for crafting preventive measures and targeted treatments.

Genetic mutations serve as the foundation for the development of cancer. When an individual carries a heterozygous mutation in BRCA1/2, the transformation of cells into fully malignant forms occurs following a significant external secondary event, leading to genome instability and cellular dysfunction [50]. This genetic instability subsequently results in alterations within the cells, including non-inherited somatic mutations in PIK3CA and TP53. Furthermore, chromosomal instability, a characteristic feature of cancer, contributes to somatic copy number variations and intratumor heterogeneity among subclones as cancer progresses [51].

Hormonal factors, such as menopausal hormone therapy, excessive estrogen intake from food, and various forms of endocrine instability, are significant contributors to sporadic breast cancer. In particular, the binding of estrogen to nuclear estrogen receptors (encoded by ESR1) plays a key role in the development of breast cancer. Disruptions in the balance between estrogen and progesterone can stimulate cell growth and lead to the accumulation of DNA damage. Excess estrogen further encourages the proliferation of malignant cells and increases the supportive stroma, aiding in cancer advancement [52]. When activated by a ligand, estrogen receptors influence gene transcription by attaching to estrogen response elements in the promoter regions, thus regulating gene expression. Furthermore, these receptors can interact directly with other proteins involved in growth signaling pathways, which enhances the transcription of genes essential for cell growth and resistance to programmed cell death. Overall, imbalances in estrogen regulation within breast tissue may facilitate the progression and spread of breast cancer [53, 54].

Ferroptosis is another important basis of BC pathophysiology. Ferroptosis satisfies the criteria for regulated cell death (RCD) as it is induced by harmful lipid peroxidation, which results from cellular metabolism and disrupted redox balance. In recent decades, various types of cell death have been identified and categorized into accidental or regulated cell deaths. Unlike accidental cell death, which is an uncontrolled and passive process, regulated cell death is an active process that can be influenced by a range of molecular mechanisms and signaling pathways [55–59]. Apoptosis, the most extensively studied form of regulated cell death, is primarily initiated by the activation of caspase family proteases. Recently, non-apoptotic cell death has gained significant attention in cancer treatment, as resistance to apoptosis is a common characteristic of cancer. One specific type of non-apoptotic cell death, known as ferroptosis, is characterized as an iron-dependent regulated necrosis resulting from extensive lipid peroxidation that leads to membrane damage [55–59].

This process can be inhibited by directly blocking lipid peroxidation or by reducing iron levels through pharmacological or genetic interventions. Notably, increasing evidence indicates that ferroptosis may play significant roles in tumor suppression and immune responses [55–59]. In this regard, numerous tumor suppressors have been identified as factors that increase cell sensitivity to ferroptosis. This leads to a plausible hypothesis that ferroptosis may play a role in the antitumor effects of these suppressors, suggesting that tumor suppression could be

a fundamental physiological role of ferroptosis. Among these tumor suppressors, the role of p53 in ferroptosis has been extensively studied. p53 enhances ferroptosis by inhibiting the transcription of the SLC7A11 subunit of the system. This mechanism may be linked to the tumor-suppressive properties of p53 [60]. Additionally, a cancer-associated single nucleotide polymorphism of p53, known as P47S, has been identified as being more prevalent in the African population and is associated with increased resistance of cancer cells to ferroptosis [61]. Although these results align with the idea that ferroptosis plays a role in p53's tumor-suppressing function, it remains uncertain whether the diminished ferroptosis-promoting activity of p53 is the sole effect of these particular mutations.

In breast cancer point of view, many studies have approved the association between this process and breast cancer progression. For instance, some ferroptosis-related genes including GPX4 have a reduced expression in BC cells and this expression is positively correlated with ER and PR labelling [62]. Importantly, the expression levels of ACSL4 in a subset of triple-negative breast cancer (TNBC) cell lines were found to be linked to their sensitivity to ferroptosis agents. This relationship seems to resemble the one seen in the treatment of resistant mesenchymal carcinoma cells and clear cell renal carcinoma cells. ACSL4 levels are higher in breast cancer tissues than in the healthy tissues surrounding the cancer, and there is a negative correlation between ACSL4 expression and estrogen receptor (ER) levels [63]. These results suggest that ferroptosis could be a crucial adaptive mechanism for eliminating cancer cells.

Diagnosis

Mammography remains the cornerstone of breast cancer screening and diagnosis [64]. Its sensitivity, however, is limited in certain patient populations, including those with dense breast tissue, younger individuals, and those unable to tolerate the required breast compression. Abnormal findings on mammograms, such as mass lesions, calcifications, or architectural distortions, prompt further investigation with diagnostic mammography, which employs higher-quality imaging and multiple views. Alternative imaging modalities, including breast ultrasound and magnetic resonance imaging (MRI) with contrast, are often employed in challenging cases [64]. While ultrasound offers sensitivity comparable to mammography and facilitates image-guided biopsy, MRI, despite its superior sensitivity, is often limited by factors such as cost, availability, and time constraints [65]. MRI is indicated in specific scenarios, such as axillary lymph node involvement, occult primary malignancy, Paget disease, multifocal or bilateral cancers, neoadjuvant chemotherapy response evaluation, and high-risk patient screening [66]. The Breast Imaging Reporting and Data System (BI-RADS) provides a standardized framework for classifying breast imaging findings, correlating them with the probability of malignancy and recommending appropriate management strategies. The BI-RADS categories, ranging from 0 to 6, serve as a guide for clinicians in determining the next steps [67]. Upon the identification of a suspicious lesion, it is crucial to perform a tissue biopsy to achieve a definitive diagnosis. The stereotactic core needle biopsy, guided by imaging techniques, is considered the preferred approach owing to its higher accuracy in comparison to fine needle aspiration [68]. For regional lymph nodes that are clinically positive, an ultrasound-guided core needle biopsy is advisable. Routine laboratory tests and systemic imaging are typically not recommended for operable breast cancer in the absence of any symptoms. However, if symptoms are present, imaging techniques such as MRI of the brain, chest CT scan, bone scan, or CT scans of the abdomen and pelvis may be warranted. In cases of advanced breast carcinoma, which may present with characteristics such as inflammatory breast cancer, involvement of the chest wall or skin, and significant axillary lymphadenopathy, a multi-modal diagnostic strategy that includes CT scans of the chest, abdomen, and pelvis, along with either a bone scan or an FDG-PET scan, is frequently utilized [69].

Molecular diagnostics analyzes genetic and molecular changes in breast cancer cells, enabling a more precise classification of tumors and guiding targeted therapies. Unlike conventional histopathology, which examines tissue morphology, molecular diagnostics identifies specific genetic mutations and biomarkers that influence treatment decisions. Liquid biopsy is a revolutionary technique that detects cancer-related genetic material, such as circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs), in blood samples. Unlike traditional tissue biopsies, which require surgical or needle procedures, liquid biopsy is minimally invasive and can be performed repeatedly to monitor disease progression. In breast cancer point of view, ctDNA analysis can detect tumor-specific mutations before conventional imaging methods, improving early diagnosis. Plus, MRD detection helps assess whether cancer cells remain after treatment, guiding decisions on adjuvant therapy. Liquid biopsy enables dynamic tracking of treatment response, identifying emerging resistance mutations (e.g., ESR1 mutations in ER-positive breast cancer resistant to hormone therapy). Interestingly, CTC analysis helps predict metastasis risk and guides systemic therapy choices for advanced-stage breast cancer. Taken together, Liquid biopsy offers a non-invasive, real-time window into

tumor biology, making it a powerful tool for early detection and treatment personalization [70, 71].

Artificial intelligence (AI) is transforming breast cancer imaging by improving the accuracy and efficiency of mammography, ultrasound, and MRI analysis. AI-powered algorithms can detect subtle abnormalities, reducing false positives and improving early diagnosis rates. AI-enhanced mammograms improve the detection of small or dense breast lesions that may be missed by human radiologists. Studies show that AI-assisted screening can reduce false positives, minimizing unnecessary biopsies. Furthermore, AI models help distinguish between benign and malignant breast lesions in ultrasound, reducing reliance on invasive biopsies. AI-driven breast MRI analysis aids in evaluating tumor size, spread, and response to neoadjuvant therapy.

Treatment

In the case of nonmetastatic breast cancer, the primary objectives of treatment involve eliminating the tumor from the breast and the associated regional lymph nodes, as well as preventing the recurrence of metastasis [72]. The local treatment for nonmetastatic breast cancer typically encompasses surgical excision along with the sampling or removal of axillary lymph nodes. In addition, postoperative radiation therapy may be applied. Systemic treatment can be administered preoperatively (neoadjuvant), postoperatively (adjuvant), or as a combination of both. The choice of standard systemic therapy is guided by the breast cancer subtype, including endocrine therapy for all hormone receptor-positive (HR+) tumors, with some patients necessitating chemotherapy. For all ERBB2-positive tumors, trastuzumab-based antibody therapy directed at ERBB2, alongside chemotherapy, is standard; endocrine therapy may also be provided if there is concurrent HR positivity. In the case of triple-negative breast cancer, chemotherapy is administered as a standalone treatment. For metastatic breast cancer, the treatment goals shift towards extending life and alleviating symptoms. Presently, metastatic breast cancer is deemed incurable for the vast majority of patients affected by it. The fundamental categories of systemic therapy utilized in metastatic breast cancer mirror those employed in the neoadjuvant and adjuvant treatments described earlier. Local treatment options, such as surgery and radiation, are generally limited to palliative care in the context of metastatic disease [72].

Is the combination of polyphenols and exercise effective on BC?

In this section we would discuss different polyphenols which their combination with exercise is examined on BC patients.

Saffron

Saffron and its applications

Saffron, derived from the stigmas of the *Crocus sativus* L. plant, has been extensively documented in traditional medicinal texts as an herbal remedy. In addition to its historical use, saffron is commonly employed as a food coloring and flavoring agent [73]. Interestingly, its significance in the food industry has not only been maintained but has also evolved over time [74]. The key components of saffron include crocin, safranal, crocetin, and picrocrocin [75]. Recent research has focused on saffron's effects on the central nervous system, particularly concerning mental health disorders, with a substantial body of data now available [76]. Various in vitro, in vivo, and animal studies have highlighted saffron's potential in addressing numerous age-related conditions, such as cardiovascular diseases, ocular disorders, neurodegenerative diseases, and type-2 diabetes [77–83]. Furthermore, numerous clinical studies have demonstrated the advantageous effects of saffron and its active constituents as either primary or adjunctive treatment options for these ailments [84–87].

Saffron in breast cancer

Superoxide dismutase (SOD) plays a crucial role within the antioxidant defense system of humans' body. This enzyme is considered as a potential therapeutic agent for diseases mediated by reactive oxygen species (ROS), as well as a proper candidate for cancer therapies. Carotenoids derived from saffron, specifically crocin (Cro) and crocetin (Crt), exhibit antioxidant properties alongside antitumor effects. Research has demonstrated that Cro and Crt possess significant radical scavenging capabilities. In the MCF-7 breast cancer cell line, both Crt and Cro inhibit SOD activity. The findings indicate that Cro inhibits SOD activity by neutralizing superoxide radicals. On the other hand, Crt exerts its inhibitory effect by interacting with the copper-binding site of the enzyme. However, contrary to the in vitro results, Cro and Crt were shown to significantly enhance the activity of SOD in breast tumors of BALB/c mice following a one-month treatment period. This mechanism appears to be critical for compensating the reduced SOD activity typically observed in the pathophysiology of cancer cells [88]. Another study on crocin has indicated that this compound effectively inhibits the activation of NF-κB, leading to a decrease in both cell viability and proliferation within breast cancer cells. Furthermore, crocin is able to suppress inflammation in breast cancer cells as evidenced by a notable reduction in the levels of tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) following treatment. Consequent to the inhibition of NF-κB, both proliferation and inflammation are reported to be

decreased within cancer cells. Treatment with crocin was shown to inhibit NF-κB activation in cancer cells by diminishing the expression of Protein kinase C theta (PRKCQ), which is a potential target for crocin based on the PharmMapper database. On the other hand, the activation of the NF-κB pathway, which is dependent on PRKCQ, counteracted the effects of crocin on proliferation and inflammation. Therefore, crocin is implied to inhibit inflammation and proliferation by NF-κB pathway through reducing the expression of PRKCQ [89]. Arzi et al. [90] has also conducted an in vitro study on the roles of crocetin and crocin in triple negative metastatic breast cancer cells (4T1) and their impact on the Wnt/β-catenin axis. They found that crocin and crocetin treatment led to a dose-dependent reduction in cell viability in 4T1 cells. Further analyses indicated that crocin and crocetin significantly inhibit invasion, migration, and cellular mobility. Also, they lead to a reduction of adhesion to the extracellular matrix. Notably, crocin was found to decrease the expression of FZD7, NEDD9, VIM, and VEGF-α genes at the mRNA level, while simultaneously upregulating the expression of E-CAD. Both crocin and crocetin demonstrated similar properties in reducing invasion in 4T1 cells. However, crocin was more effective at inhibiting migration, whereas crocetin displayed a stronger antiadhesion effect. Additionally, it is suggested that the antimetastatic properties of crocin may be mediated through the Wnt/β-catenin signaling [90]. Ghorbanzadeh and colleagues have also employed a TNBC cell line to examine the anti-metastatic properties of crocin in relation to the Wnt/β-catenin signaling pathway. The results indicated that crocin dose-dependently inhibits the proliferation and migration of tumor cells. Furthermore, the expression levels of β-catenin, Snail, Vimentin, and Zeb-1 was found to be reduced following crocin treatment. In MDA-MB-231 cell line, an increase in E-cadherin expression was observed following crocin treatment. Altogether, these findings suggest a correlation between crocin and the Wnt/β-catenin signaling pathway [91].

Combination of saffron and exercise training in breast cancer

An investigation has been done evaluate the impact of four weeks of high-intensity interval training (HIIT) and saffron aqueous extract (SAE) on the gene expression of Sirtuin-1 (SIRT1), human telomerase reverse transcriptase (hTERT), and p53 within breast tumor tissue of female mice. The findings indicated that compared to both the HIIT and control groups, the mRNA levels of SIRT1 significantly increased in the HIIT + SAE group. Additionally, there was a notable rise in p53 mRNA levels following the four-week HIIT regimen, particularly in relation to the control and HIIT + SAE groups within the tumor tissue. However, no significant differences were observed in the mRNA expression of hTERT across the various groups. Therefore, it is implied that HIIT may alleviate breast cancer through p53 overexpression, which is linked to tumor suppression. Conversely, the combination of HIIT and SAE did not result in any modifications to the expression levels of p53 and SIRT1, suggesting that this combination may inhibit tumor progression through alternative mechanisms [92]. A research study was conducted to investigate the effects of four weeks of high-intensity interval training (HIIT) and supplementation with saffron aqueous extract (SAE) on changes in body weight and apoptotic markers in the skeletal muscles of 4T1 breast cancer-bearing mice experiencing cachexia. The findings indicated that the control group exhibited a significant weight loss during the third- and fourth-weeks following tumor injection. In contrast, the interventions of HIIT and SAE, though not their combination (HIIT + SAE), appeared to mitigate this detrimental effect. Compared to the control group, the HIIT and SAE treatments, each of them alone, resulted in lower levels of caspase-3 and Bax. Following these treatments, Bcl-2 levels were found to be elevated relative to the control group. Additionally, both the HIIT and SAE groups showed a significantly higher Bcl-2 to Bax ratio, whereas this ratio was lower in the HIIT + SAE group compared to the sham group. These results suggest that either HIIT or SAE individually may serve as effective strategies for managing muscle wasting and apoptosis in the context of cancer cachexia. Consequently, it can be inferred that while HIIT is linked to a decreased risk of cancer-related muscle loss, and SAE contributes to the improvement of muscle deterioration and apoptotic markers, the combination of HIIT and SAE does not yield additional benefits in addressing cancer-related muscle mass loss or in modulating apoptotic activity [93] (Table 1).

A similar study has investigated the synergistic role of HIIT and SAE on reduction of tumor volume as well as the expression of anti- and pro-apoptotic proteins in mice with 4T1 breast cancer. Compared to the control group, the tumor volume was markedly reduced in the HIIT, SAE, and combined HIIT + SAE groups. Additionally, the caspase-3 protein levels in the HIIT and SAE groups were found to be elevated relative to both the control and HIIT + SAE groups. In contrast, the Bax protein levels in the SAE group surpassed those observed in the control group, while the HIIT + SAE group exhibited lower Bax levels than either the HIIT or SAE groups. Furthermore, the Bcl-2 protein levels were significantly higher in the HIIT + SAE group compared to both the HIIT and SAE groups. Notably, the Bax/Bcl-2 ratio was substantially elevated in the HIIT and SAE groups when compared to the HIIT + SAE and control groups. These results suggest

Table 1 Studies investigating the role of saffron combined with exercise training in breast cancer

Subjects	Exercise duration/interval	Findings	Ref.
Female mice	High-intensity interval training (HIIT)	SIRT1 (P = 0.007) and p53 (P = 0.03) significantly increased in the HIIT + SAE group. No change in the expression of hTERT was found	[93]
Breast cancer-bearing mice experiencing cachexia	High-intensity interval training (HIIT)	Either HIIT or SAE are effective for managing muscle wasting and apoptosis but not the combination	[93]
Mice with 4T1 breast cancer	High-intensity interval training (HIIT)	Reducing tumor volume and Bax levels and the Bax/Bcl-2 ratio	[143]
75 breast cancer patients	–	Reducing fatigue and FSS	[144]

that the integration of HIIT and SAE interventions does not enhance apoptotic induction within tumor tissue. However, both HIIT and SAE treatments may facilitate the apoptotic pathway, as indicated by the increased Bax/Bcl-2 ratio and elevated caspase-3 levels during the progression of tumors in mice with breast cancer [94].

There is a very limited number of clinical trials in this area; for instance, Mirzaei and colleagues [95] used saffron on 75 breast cancer patients and assessed cancer-related fatigue in these patients. They found that using Jollab (containing saffron, honey, and rose water) for 4 weeks reduces fatigue in women with BC. In the Jollab group, there was a significant reduction in Visual Analogue Fatigue Scale (VAFS) (P = 0.000), whereas the placebo group did not exhibit a significant change (P = 0.258). Additionally, the Jollab group experienced a notable decrease in Fatigue Severity Scale (FSS) (P = 0.000), while the placebo group showed only a slight decrease (P = 0.096). The Cancer Fatigue Scale (CFS) physical and cognitive subscales indicated an improvement in fatigue for the Jollab group compared to the placebo group (P < 0.05). However, the affective subscale scores did not demonstrate a significant change following the intervention in either group (P > 0.05) [95].

According to the reviewed articles, it seems that saffron and exercise are able to exert favorable effects on breast cancer cells but the combination of them is not quite effective and might even have paradoxical effects. Therefore, we suggest that more in vitro studies might help clarifying the effects of this combination and help us to take the investigations to the next level.

Curcumin

Curcumin and its applications

The genus Curcuma boasts a rich history of medicinal uses and comprises approximately 120 species [96, 97]. Among these, Curcuma longa L. (commonly known as Turmeric) stands out as the most well-known [98]. Curcuma species are recognized for their extensive range of pharmacological benefits, which encompass properties such as antiproliferative, anti-inflammatory, antitumor, anti-thrombotic, antihepatotoxic, diuretic, hypotensive, antimicrobial, antioxidant, and antityrosinase effects, among others [99–102].

Curcumin in breast cancer

A wide variety of studies have been investigated the role of curcumin in breast cancer. For instance, Mehta and colleagues have demonstrated the anti-proliferative properties of curcumin when tested against a variety of breast tumor cell lines, including both hormone-dependent and hormone-independent, as well as multidrug-resistant (MDR) lines. Their findings suggest that the growth-inhibitory effects of curcumin are influenced by both the duration and dosage of exposure, with a notable preference for inducing cell cycle arrest in the G2/S phase. Additionally, it is revealed that curcumin has the capacity to counteract adriamycin resistance in MCF-7 cells, thereby inhibiting the progression of breast cancer cells [103]. Sripriya and colleagues have also reported that curcumin effectively suppresses the proliferation of the HER-2/neu overexpressing human breast cancer cell line, SK-BR-3. This suppression has been linked to G2/M phase arrest, the activation of p21, and a reduction in cyclin D1. Moreover, the suppression of cell growth has been associated with decreased total HER-2 levels and phosphorylated-HER-2 proteins. Notably, higher concentrations of curcumin results in apoptosis within 24 h, with over 80% of the cells accumulating in the S and G2/M phases of the cell cycle [104]. Curcumin influences various molecular signaling pathways, including Wnt/β-catenin, Nrf2, AMPK, and mitogen-activated protein kinase, among others. In this review, we assess curcumin's potential in regulating the TGF-β signaling pathway to connect it with its therapeutic effects. By modulating TGF-β—both through upregulation and downregulation—curcumin helps improve conditions such as fibrosis, neurological disorders, liver disease, diabetes, and asthma. Additionally, curcumin targets the TGF-β signaling pathway, which can inhibit the proliferation of tumor cells and the invasion of cancer cells [105].

Recent studies indicate that curcumin alters noncoding RNA (ncRNA) types, including long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs), across different cancer types. Both circRNAs and lncRNAs are forms

of ncRNAs that can epigenetically influence the expression of various genes through post-transcriptional regulation [106].

Curcumin combined with exercise in breast cancer

Guo et al. [107] have investigated the synergistic effects of curcumin treatment alongside swimming exercise in a mouse model breast tumor. Findings indicated that the combined approach of curcumin administration and exercise yielded a more pronounced inhibitory effect on breast cancer compared to either treatment alone. The group receiving the combination treatment exhibited 445 differentially expressed genes, with 154 being upregulated and 291 downregulated. Further analyses have revealed that some signaling pathways are involved in anti-tumor effects of curcumin combined with exercise training, including IL-17, calcium signaling pathway, PI3K-Akt, and Wnt signaling pathway. Furthermore, synergistic effects of curcumin and exercise engage two distinct metabolic pathways, including amino sugar and nucleotide sugar metabolism. These pathways include compounds such as chitosan, D-glucosamine 6-phosphate, L-fucose, and N-acetyl beta-mannosamine as well as amino acid biosynthesis, comprising DL-isoleucine, DL-tyrosine, and homocysteine [107]. Delfan and colleagues conducted a study to examine the synergistic effects of endurance exercise and curcumin on the progression of breast cancer, focusing on the TNF-α/NF-κB signaling pathways in female BALB/c mice with breast cancer. The findings revealed a significant reduction in both cancer growth and the gene expression levels of NF-κB and TNF-α in the groups receiving exercise, curcumin, and the combination of both, compared to the control group. Additionally, the expression of these genes has been reduced in the combination group when compared to the endurance exercise group alone. Consequently, it can be concluded that the integration of endurance training with curcumin supplementation is more effective in reducing TNF-α and NF-κB levels, subsequently inhibiting the growth of breast cancer cells, compared to the individual interventions [108]. Kouchaki and colleagues have also assessed the impact of endurance training combined with curcumin supplementation on cancer progression, as well as the intratumoral gene expression of angiomiR-126 and Angiopoietin-1 in female BALB/c mice with breast cancer. The findings revealed a marked reduction in tumor growth, along with a significant increase in the gene expression level of miR-126 and a decrease in the gene expression level of Angiopoietin-1 in the exercise, curcumin, and particularly the exercise training + curcumin groups when compared to the control group. Notably, these effects were significantly more pronounced in the training + curcumin group than in the other treatment groups. Altogether, the results suggest that five weeks of endurance training in combination with curcumin may enhance the suppression of breast cancer tumor growth by targeting the miR-126/angiopoietin-1 axis more effectively than the interventions conducted in isolation [109].

An investigation examined the impact of aerobic exercise and curcumin on oxidative stress markers in the livers of cancerous mice treated with doxorubicin. The findings indicated that the combined effects of curcumin and aerobic exercise on the expression levels of the *GSH*, *SOD*, and *CAT* genes, as well as the concentration of MDA, did not reach statistical significance. Consequently, it can be concluded that the combination of aerobic exercise and curcumin may not provide protective benefits to the liver against oxidative stress induced by the chemotherapeutic drugs in breast cancer [110]. In contrast to the findings of this study, Sadeghian et al. conducted an investigation into the impact of aerobic exercise combined with curcumin on the gene expression of apoptotic markers in the liver tissue of mice with breast cancer during the treatment with doxorubicin. Utilizing the 4T1 cell line to induce breast cancer in female Balb/c mice, the study revealed that both curcumin and aerobic exercise significantly influenced the expression levels of the *Cas3* and *Bcl2* genes. Specifically, in group who received both curcumin and exercise training, there was an increase in *Bcl2* gene expression relative to the other groups. Meanwhile, in mice who received curcumin or curcumin + exercise training, there was a decrease in Cas3 expression when compared to control group. Thus, it is reported that the combination of aerobic exercise and nanocurcumin following doxorubicin therapy may suppress apoptosis in the liver tissue of mice with breast cancer [111]. A study on 40 overweight women with breast cancer after radiotherapy treatment has indicated that serum levels of high-sensitivity C-reactive protein (hs-CRP) are elevated following aerobic exercise training. However, the inclusion of curcumin supplementation alongside aerobic training effectively mitigates the increase in hs-CRP associated with this exercise regimen. Furthermore, the combination of aerobic training and curcumin supplementation result in a significant reduction of serum pentraxin-3 (PTX3). However, both the percentage of body fat and body mass index (BMI) exhibit a decline after the aerobic training, regardless of whether curcumin was included. Additionally, improvements in quality of life were observed with aerobic training, both with and without curcumin supplementation. Therefore, it is suggested that an 8-week program of exercise training combined with curcumin supplementation leads to a synergistic reduction in inflammatory

markers through the decrease in body fat percentage and BMI among overweight women with breast cancer post-chemotherapy and/or radiation therapy [112].

Moghiseh and colleagues conducted a study on beneficial effects of aerobic training alongside the administration of curcumin nano micelles on decreasing doxorubicin's side effects on the expression levels of CAS3, CAS9, BCL2, and BAX genes in the cardiac tissues of Balb/C mice with breast cancer induced by the 4T1 cell line. Aerobic exercise training is shown to be able to significantly reduce the expression of the CAS3, CAS9, and BAX genes. However, it does not change the expression of BCL2 gene significantly. The supplementation of curcumin in nano micelle form also leads to a reduction in the gene levels of CAS3 and CAS9 without affecting the expression of the BAX gene. Conversely, it results in a significant increase in the expression of the BCL2 gene. Therefore, it is implied that aerobic exercise training and the intake of curcumin, either individually or in combination, effectively reduce sensitivity to cardiac apoptosis and provide protection to non-target cardiac tissues against doxorubicin [113]. Another study has reported that mice who received curcumin or exercise intervention or their combination have shown a decrease in tumor growth when compared to the control group. The combination of endurance training with curcumin lead to a reduction in the intratumoral expression levels of Il4 and Stat-6 compared to the control group. Furthermore, mice who only undergo endurance exercise demonstrated a significant decline in Il4 and Stat-6 expression. Curcumin alone also results in a reduction of Stat-6 gene expression when compared to the control group. Thus, it is implied that a five-week regimen of endurance training combined with curcumin appears to be more effective in cancer treatment than utilizing either of these non-pharmacological approaches independently [114] (Fig. 1) (Table 2).

There are a few clinical trials in this field like the work of Hemati and colleagues [115] which tried to confirm the effects of curcumin on a diversity of chemotherapy side effects in BC patients. They detected that curcumin supplementation showed a protective benefit against tamoxifen-induced non-alcoholic fatty liver disease in patients with ER + breast cancer, indicating its possible role as a preventive addition to tamoxifen treatment

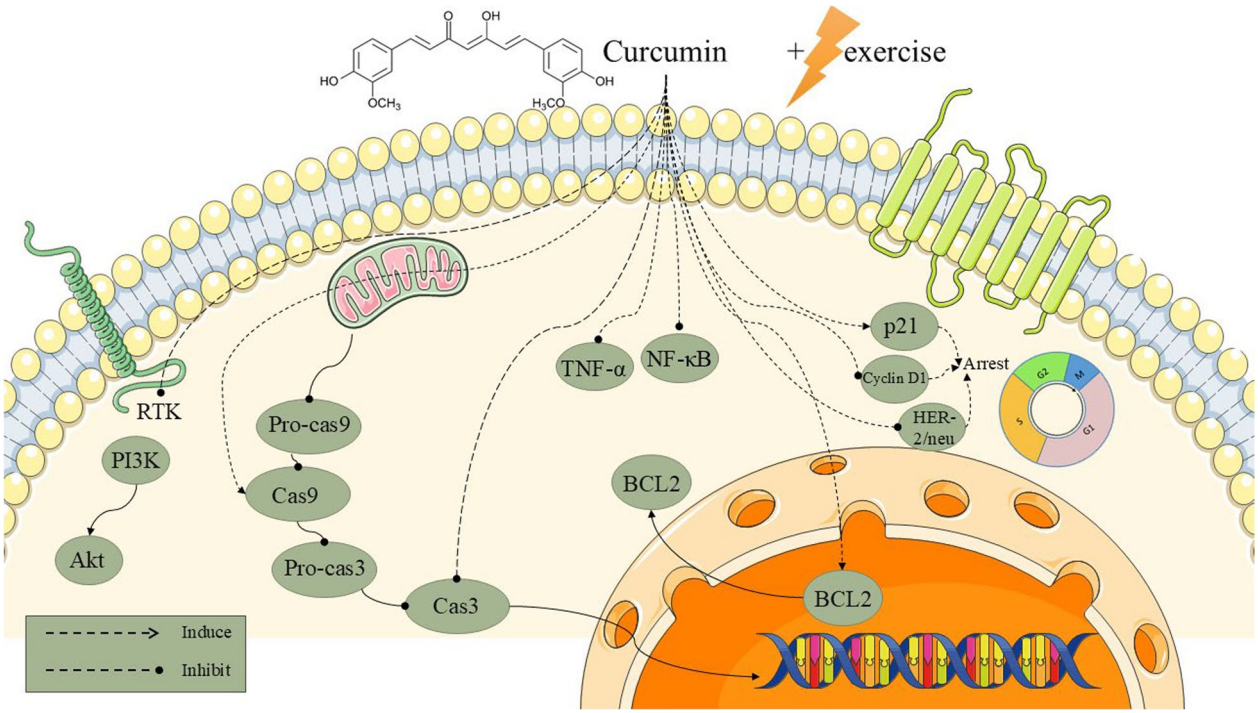

Fig. 1 The combination of Curcumin and exercise affects breast cancer cells in a diversity of mechanisms. Curcumin exerts its anti-proliferating effects through inducing cell cycle arrest in the G2/S phase. curcumin effectively suppresses the proliferation of the HER-2/neu overexpressing human breast cancer cells. This suppression has been linked to G2/M phase arrest, the activation of p21, and a reduction in cyclin D1. Curcumin also affects the inflammation of these cells as findings revealed a significant reduction in both cancer growth and the gene expression levels of NF-κB and TNF-α in the groups receiving exercise, curcumin, and the combination of both, compared to the control group. The combination of curcumin and exercise also sensitizes tumor cells to apoptosis which is mostly through reducing the gene levels of CAS3 and CAS9 without affecting the expression of the BAX gene. Conversely, it results in a significant increase in the expression of the BCL2 gene

Table 2 Studies investigating the role of curcumin combined with exercise training in breast cancer

Subjects	Dose of curcumin	Exercise duration/interval	Findings	Ref.
Female BALB/c mice	200 µL	30-min swimming exercise	Inhibitory effect of curcumin + exercise is greater on breast cancer rather than each intervention alone	[107]
Female BALB/c mice	100 mg/kg	30-min running exercise, five days/week for 5 weeks	Endurance training + curcumin has a more effective role in reducing TNF-α and NF-κβ, and slowing the growth of breast cancer cells	[108]
40 overweight women with breast cancer after radiotherapy treatment	–	–	Exercise training + curcumin for 8 weeks synergistically decrease inflammation markers by body-fat percentage and BMI reduction in overweight women	[112]
Female BALB/c mice	100 mg/kg	30-min running exercise, five days/week for 6 weeks	Exercise + curcumin may not provide protective benefits to the liver against oxidative stress induced by the chemotherapeutic drugs in breast cancer	[110]
Female BALB/c mice	100 mg/kg	30-min running exercise, five days/week for 6 weeks	Training + curcumin, either individually or in combination, effectively reduce sensitivity to cardiac apoptosis following doxorubicin administration	[113]
Female BALB/c mice	100 mg/kg	30-min running exercise, five days/week for 6 weeks	exercise + nanocurcumin following doxorubicin therapy suppress apoptosis in the liver tissue of mice with breast cancer	[111]
Female BALB/c mice	100 mg/kg	30-min running exercise, five days/week for 5 weeks	Training + curcumin appears to be more effective in cancer treatment than utilizing non-pharmacological approaches independently	[114]
Female BALB/c mice	100 mg/kg	40-min running exercise, five days/week for 5 weeks	Training + curcumin enhance the suppression of breast cancer by targeting the miR-126/angiopoietin-1 axis more effectively than the interventions conducted in isolation	[109]

[115]. However, we could not find any clinical trials examining the combination of curcumin and exercise on BC patients and further studies are required in this area.

In summary:

1. Synergistic effects on tumor growth: combining curcumin with exercise (e.g., swimming or endurance training) significantly inhibited breast cancer growth compared to either treatment alone. This effect was associated with changes in gene expression and signaling pathways like IL-17, PI3K-Akt, Wnt, and calcium signaling.
2. Regulation of inflammatory pathways: the combination of curcumin and exercise reduced the gene expression of inflammatory markers, such as NF-κB and TNF-α, and was more effective than exercise or curcumin alone in reducing tumor growth in certain models.
3. Impact on angiogenesis: curcumin combined with exercise influenced angiogenesis-related markers, such as miR-126 and Angiopoietin-1, enhancing the suppression of tumor growth.
4. Oxidative stress and apoptosis: in contrast to some studies, certain investigations found that curcumin and exercise had no significant impact on oxidative stress markers in liver tissue. However, other studies observed that the combination influenced apoptotic markers, such as Cas3 and Bcl2, and suppressed liver apoptosis in mice.
5. Inflammation and body composition in humans: in overweight women post-radiotherapy, a combination of curcumin and exercise reduced inflammation (hs-CRP, PTX3), body fat percentage, and BMI, while also improving quality of life.
6. Cardiac protection: curcumin and exercise were found to reduce cardiac apoptosis induced by doxorubicin, with changes in gene expression of apoptosis markers (CAS3, CAS9, BAX, and BCL2) in cardiac tissues.
7. Gene expression modulation: the combination treatment reduced the expression of genes like Il4 and Stat-6 in tumor tissues, indicating its potential for improving cancer treatment outcomes.

These findings suggest that curcumin combined with exercise provides more significant therapeutic effects on breast cancer than either treatment alone, influencing key molecular and metabolic pathways involved in cancer progression and treatment resistance.

Quercetin

Quercetin and its applications

Quercetin (3,5,7,3′,4′-pentahydroxyflavone) is commonly found in various natural sources including flowers, bark, stems, roots, wine, vegetables, and fruits (i.e. onions, apples, berries, and cilantro) [116]. It is characterized as a crystalline, yellow compound that demonstrates complete insolubility in cold water while it is soluble in both lipids and alcohol. Furthermore, it has limited solubility in hot water and it is considered to have a bitter flavor [117]. Quercetin has been recognized for its potential therapeutic applications in addressing multiple diseases and disorders, including allergies, diabetes, obesity, hyperuricemia, gouty arthritis, and cancer [118–122]. Notably, quercetin's most significant effect is its capacity to inhibit the progression of specific cancers, including cancers of liver, breast, prostate, cervix, lung, and colon [123]. The administration of quercetin is advantageous in alleviating ischemia/reperfusion (I/R) injury by lowering ROS levels, suppressing inflammation, and influencing molecular pathways such as TLR4/NF-κB and MAPK. Quercetin enhances the integrity of cell membranes by reducing lipid peroxidation. It also prevents apoptotic cell death by downregulating Bax and caspases while upregulating Bcl-2. Additionally, quercetin can modulate autophagy, either inhibiting or inducing it, to help reduce I/R injury [124].

Quercetin in combination with exercise in breast cancer

Jalali and colleagues conducted a study examining the effects of quercetin supplementation and six weeks of continuous aerobic training on the expression levels of TIE-2 and VEGF-A in a mice model of breast cancer. The findings revealed that the combination of aerobic exercise and quercetin leads to a significant reduction in the expression level of VEGF-A, with a decrease of 4.09 times compared to the control group. Additionally, quercetin administration in the mice who received aerobic exercise in addition to quercetin resulted in a noteworthy reduction in VEGF-A expression when compared to the mice who only received aerobic exercise. Conversely, aerobic exercise alone did not affect TIE-2 expression, whether administered alone or in combination with quercetin. Hence, it is concluded that the combined effects of aerobic exercise and quercetin supplementation may play a pivotal role in inhibiting tumor angiogenesis [125]. In another investigation by Barrilleaux, the influence of aerobic exercise and quercetin supplementation on tumor advancement in the C3(1)SV40Tag mouse model has been investigated. The C3(1)SV40Tag mice were categorized into groups based on quercetin supplementation and activity levels (exercise or sedentary), as well as placebo conditions. The experimental regimen involved treadmill training for 60 min per day, six days a week, over a span of 20 weeks. The results demonstrated a significant positive effect of physical exercise on reducing the overall number of tumors, with a reduction of approximately 75% in the placebo group and around 40% in the quercetin group. Although plasma levels of IL-6 and MCP-1 increased in this model, only IL-6 showed a correlation with tumor burden. Collectively, these findings indicate that both exercise and quercetin independently contribute to reducing factors associated with breast cancer in the C3(1)SV40Tag mouse model [126].

Unfortunately, there is no evidence approving the effects of quercetin on human participants and therefore, for using this agent in clinical practice more investigations are required. Furthermore, most of the studies on quercetin have used aerobic training. We suggest that using the combination of quercetin with other types including high-intensity training may also be beneficial and/or even have more effects on breast cancer cells.

Berberine

Research has demonstrated that the combination of exercise and berberine co-treatment significantly inhibit the progression of breast cancer in mice bearing 4T1 tumors. Notably, there was a marked increase in the infiltration of natural killer (NK) cells in the group receiving both berberine and exercise compared to the control group, alongside a modulation in the expression of various immune factors and cytokines. Furthermore, the collaborative effect of these treatments substantially elevated the levels of short-chain fatty acids (SCFAs) which are known to enhance apoptosis in 4T1 cells and alter inflammatory responses in vitro. Notably, the expression of anti-apoptotic proteins bcl-2 and XIAP in tumor tissues decreased, whereas pro-apoptotic factors such as Fas, Fadd, Bid, Cyto-C, and Caspase-3/8/9 exhibit increased expression. In conclusion, these findings suggest that the combined therapeutic approach of berberine administration and exercise training may enhance immune function while regulating the production of SCFAs and activate both the the Fas death receptor apoptosis and mitochondrial apoptosis pathways [127]. Mudge has also conducted an investigation on the effects of oral berberine consumption combined with exercise on the activation of T lymphocytes as well as decreasing myeloid-derived suppressor cells (MDSCs) in bone marrow, bloodstream and tumor microenvironment of mice models of mammary

adenocarcinoma. In the lung, spleen, and tumor microenvironment of mice models with tumor, no changes have been observed following the intervention in a transcription factor that is correlated with antigen-specific T cell activation, NUR77. Conversely, the assessment of T regulatory lymphocyte FOXP3 demonstrated a significant increase in the lungs of tumor-bearing subjects. These results imply that the combination of berberine and physical activity may have notable immunological effects on T cell activation and their infiltration into the tumor microenvironment [128].

Currently, there is no conclusive scientific evidence supporting the effectiveness of berberine in human participants. While numerous preclinical studies and in vitro experiments have highlighted its potential therapeutic properties, including antioxidant, anti-inflammatory, and anticancer effects, these findings have not yet been sufficiently validated in human clinical trials. The majority of available data comes from animal models and laboratory-based research, which, although promising, do not necessarily translate to the same outcomes in humans due to differences in metabolism, bioavailability, and physiological responses.

Daidzein

To examine the effects of daidzein and/or regular exercise on breast cancer, Wang et al. used BALB/c mice who underwent a 20-day regimen of regular exercise training followed by a 22-day treatment of daidzein. The findings indicated that both exercise and daidzein exhibited varying degrees of tumor growth inhibition in the mice. Notably, the concurrent application of exercise and daidzein resulted in a significantly enhanced inhibitory effect on tumor growth compared to the control group. Additional analyses revealed that the combination of exercise and daidzein synergistically result in an increase in epinephrine and IL-6 level, leading to the activation and redistribution of natural killer cells. Furthermore, this combination has been shown to induce apoptosis in cancer cells through the Fas/FasL-initiated mitochondrial apoptosis signaling pathway. These findings suggest that the integrated approach of regular exercise and daidzein may represent a viable strategy for the prevention and treatment of breast cancer [129].

However, this study is the only evidence we could found and a definite conclusion cannot be drawn based on just 1 study and therefore, for a better understanding of the roles and side effects of this combination, more research is required.

Gallic acid and kaempferol

A recent study explored the impact of aerobic exercise, Gallic acid, and Kaempferol on neurogenesis affected by the adverse effects of the chemotherapeutic agent paclitaxel in a model of breast cancer using female BALB/c mice. The findings indicated that Jagged1 (JAG1) expression has been diminished in the subjects who received chemotherapy. Supplementation with Gallic acid and Kaempferol, in addition to aerobic exercise, significantly reduced the expression of JAG1 in comparison to the subjects who only received chemotherapy agent. Notably, the combination of Gallic acid and Kaempferol supplements in addition to aerobic exercise led to a marked decrease in the expression level of JAG1 relative to other experimental groups. Conversely, in subjects who received supplementation or those who did aerobic exercise, BDNF and NGF genes expressions are shown to be increased. Furthermore, BDNF and NGF genes are increased in mice who received a combination of supplementation and aerobic exercise when compared to all other groups. Hence, it is suggested that the integration of exercise training and combination of kaempferol and gallic acid effectively mitigated the side effects of paclitaxel while enhancing neurogenesis [130].

Given these uncertainties, Gallic acid and Kaempferol cannot yet be recommended for routine clinical use. Before it can be incorporated into medical practice, more extensive and high-quality clinical trials are necessary to establish its safety, optimal dosage, long-term effects, and therapeutic potential in humans. Future research should focus on addressing these gaps by conducting randomized controlled trials with larger populations and standardized methodologies. Until such evidence is available, the use of gallic acid as a therapeutic agent should be approached with caution, and its potential role in clinical settings remains speculative rather than evidence-based.

Polyphenols affecting ferroptosis of BC cells

There is a limited number of studies which have tried to examine the markers of ferroptosis after the administration of polyphenols on breast cancer cells.

The most recent study in this area is conducted in 2025 which has tried Rosmarinic acid (RA) on TNBC cell lines [131]. In this study, it was shown that RA suppressed the growth of TNBC cells in a dose-dependent manner and lowered intracellular levels of ROS. Additionally, RA caused cell cycle arrest in the G1/G0 phase and enhanced apoptosis by reducing the mitochondrial membrane potential. Furthermore, The RNA-seq differential expression analysis revealed a total of 1,929 differentially expressed genes, which comprised 601 upregulated genes and 1,328 downregulated genes. Analyses from the Kyoto Encyclopedia of Genes and Genomes (KEGG) and gene set enrichment analysis (GSEA) indicated that these differentially expressed genes were notably enriched in pathways linked to ferroptosis, ABC transporters,

and fatty acid metabolism. In addition, RA significantly enhanced the expression of dynamin-related protein 1 (DRP1) in MDA-MB-231 cells, which facilitated mitochondrial fission, disrupted mitochondrial dynamics, and caused dysfunction. Moreover, RA led to increased levels of intracellular ferroportin and heme oxygenase 1 (HMOX-1), contributing to a rise in intracellular iron concentrations. This research suggests that RA hampers the proliferation of TNBC cells through various mechanisms, indicating its potential as a therapeutic option for TNBC treatment [131].

More previous studies also showed the effects of some polyphenols like curcumin, ononin [132], and quercetin [133] on ferroptosis.

Quercetin can cause breast cancer cells to die and increase the levels of iron, MDA, and carbonyl proteins in a concentration-dependent manner in these cells. At the same time, transcription factor EB (TFEB) was found to be highly expressed in the nucleus of BC cells while showing lower levels in the cytoplasm. The elevated expression of TFEB enhanced the expression of the lysosome-related gene LAMP-1, which facilitated the breakdown of ferritin and the release of ferric ions. The pharmacological effects of quercetin can be inhibited by TFEB siRNA. Thus, quercetin boosts TFEB expression and nuclear transcription, triggers iron death, and thereby demonstrates its pharmacological ability to eliminate breast cancer cells [133].

In another research, Gong et al. [132] sought to determine if a natural flavonoid known as ononin could be effective in treating TNBC by inducing ferroptosis in the MDA-MB-231 and 4T1 cell lines, as well as in a nude mouse model with MDA-MB-231 xenografts. Their findings indicated that treatment with ononin resulted in elevated levels of malondialdehyde and reactive oxygen species, along with a reduction in superoxide dismutase activity, all of which are indicators of ferroptosis. Additionally, we observed that ononin downregulated two important markers of ferroptosis, SLC7A11 and Nrf2, at both the transcriptional and translational levels [132].

Curcumin is another well-studied polyphenol which is also regulating ferroptosis in BC cells. Curcumin was found to reduce the viability of both MDA-MB-453 and MCF-7 cells in a dose-dependent manner. Further investigations showed that curcumin promoted ferroptosis mediated by the solute carrier family 1 member 5 (SLC1A5) in these cell lines by increasing levels of lipid reactive oxygen species (ROS), accumulating the lipid peroxidation byproduct malondialdehyde (MDA), and raising intracellular Fe2 + levels. In vivo studies indicated that curcumin significantly inhibited tumor growth. Overall, the findings suggest that curcumin has antitumor effects in breast cancer by enhancing SLC1A5-mediated ferroptosis, indicating its potential as a therapeutic agent for breast cancer treatment [134]. Another study also indicated that Curcumin led to a significant increase in intracellular levels of iron, reactive oxygen species, lipid peroxides, and malondialdehyde, while glutathione levels were notably decreased. These alterations are indicative of ferroptosis. Additionally, curcumin enhances the expression of various ferroptosis-related target genes involved in redox regulation, particularly heme oxygenase-1 (HO-1). To validate these findings, the specific inhibitor zinc protoporphyrin 9 (ZnPP) was used, which demonstrated that, in comparison to the curcumin treatment group, ZnPP not only significantly enhanced cell viability but also decreased the accumulation of intracellular iron ions and other ferroptosis-related effects. Thus, these results indicate that curcumin induces the molecular and cellular features of ferroptosis in breast cancer cells, with HO-1 playing a role in promoting curcumin-induced ferroptosis [135].

Although there are plenty of investigations about the effects of polyphenols on ferroptosis, we could not find any evidence approving the fact that using the combination of exercise and polyphenols on breast cancer cells can lead to the regulation of ferroptosis and therefore, further studies are required in this area.

Conclusions

According to the statistics provided by WHO, in 2022, there were 2.3 million women diagnosed with breast cancer worldwide, resulting in 670,000 deaths. Breast cancer can affect women of any age after puberty in every country, although the incidence rates tend to rise as women get older [136]. Global data highlights significant disparities in the impact of breast cancer based on human development levels. For example, in nations with a very high Human Development Index, 1 in 12 women is expected to be diagnosed with breast cancer during their lifetime, and 1 in 71 will die from the disease. Conversely, in countries with a low HDI, while the lifetime diagnosis rate is lower at 1 in 27 women, the mortality rate is higher, with 1 in 48 women succumbing to breast cancer [136].

Natural products obtained from plants have been explored for their medicinal properties for centuries, particularly for their effectiveness in treating various diseases. In the field of oncology, many anticancer agents that are currently used in clinical settings are derived from these natural products and exhibit significant therapeutic benefits. Importantly, recent research has shown a direct relationship between exercise training and the modulation of tumor biology, which may improve clinical results. Furthermore, recent experiments conducted on murine models have demonstrated that exercise training can influence tumor progression by impacting inherent

tumor characteristics such as growth, metastasis, metabolism, and immunogenicity. As we have thoroughly discussed in this article, the combination of exercise training and supplementation of natural products, such as curcumin, saffron, and kaempferol can exert more useful effects against breast cancer compared to each of these interventions alone. Indeed, studies have shown that exercise training and natural products play a synergistic role in modulating signaling pathways involved in breast cancer pathogenesis (Fig. 2).

In curcumin point of view, a body of research explored the synergistic effects of curcumin combined with exercise on breast cancer using various mouse models. However, contrasting results were observed in studies examining oxidative stress markers in the livers of cancerous mice treated with doxorubicin. About other polyphenols, research investigated the effects of daidzein and regular exercise and found that the combination of exercise and daidzein showing a significantly greater inhibitory effect against BC. This synergistic impact was linked to immune response. Additionally, this combination promoted apoptosis in cancer cells via the Fas/FasL-initiated mitochondrial apoptosis signaling pathway. These results suggest that integrating regular exercise with daidzein supplementation could serve as a promising strategy for breast cancer prevention and treatment. Other polyphenols like gallic acid, and kaempferol are mostly studied on neurogenesis and revealed that chemotherapy reduced JAG1 expression, while supplementation with gallic acid and kaempferol, along with aerobic exercise, significantly decreased JAG1 levels compared to chemotherapy alone and suggested that the combined approach of exercise and these dietary supplements effectively alleviates the side effects of paclitaxel while promoting neurogenesis. Except for these polyphenols, there are other members of this family like green tea catechins [137, 138], resveratrol [139], luteolin [140], genistein [141], and apigenin [142] which are approved to have beneficial effects for inhibiting breast cancer; however, we could not find studies examining the combination of these polyphenols with exercise on breast cancer cells.

Notably, there are some limitations in these studies that makes it challenging to draw a definite conclusion on this subject, including the small number of studies and the small number of samples in each study as well as

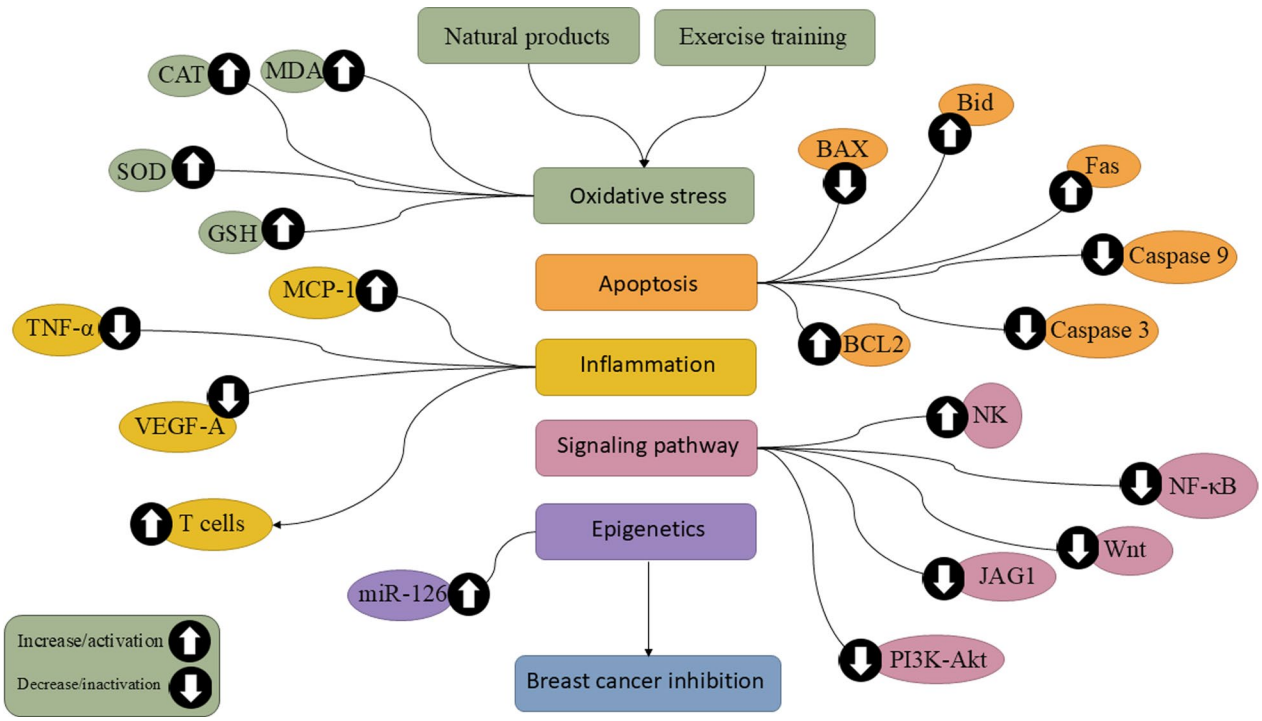

Fig. 2 A summary of how the combination of different polyphenols affects breast cancer cells. Polyphenols are able to affect apoptosis through regulating anti- and pro-apoptotic proteins; for instance, curcumin significantly reduces the expression of the CAS3, CAS9, and BAX genes. Different components of inflammation are also affected by polyphenols; for instance, The combination of curcumin and exercise reduced the gene expression of inflammatory markers, such as NF-κB and TNF-α, and was more effective than exercise or curcumin alone. Polyphenols are also effective on epigenetic regulations; for instance, Curcumin combined with exercise influenced angiogenesis-related markers, such as miR-126 enhancing the suppression of tumor growth

the in vitro, in vivo, and animal studies instead of clinical trials.

In practical applications, healthcare providers may consider recommending structured exercise programs alongside dietary supplementation with saffron for breast cancer patients. This integrated approach could potentially improve overall health outcomes, enhance quality of life, and mitigate some of the debilitating effects associated with cancer treatment. Future clinical trials are warranted to investigate these interventions' efficacy further and to explore optimal combinations or sequences of exercise and supplementation that maximize therapeutic benefits while minimizing adverse effects. Overall, this research contributes to a growing body of evidence supporting lifestyle interventions as a vital component of comprehensive cancer care. The synergistic effects observed in various studies suggest that integrating lifestyle modifications with dietary interventions may enhance therapeutic efficacy and mitigate cancer progression. Further clinical investigations are warranted to validate these results and explore their applicability in human subjects. The evidence supports a holistic strategy for breast cancer management that could improve patient outcomes and quality of life during treatment. From another point of view, Exercise might also be able to influence the bioavailability and metabolism of plant-derived compounds, including polyphenols, through several mechanisms such as enhancing gastrointestinal motility and blood flow, potentially improving the absorption of polyphenols. Additionally, exercise-induced changes in enzymatic activity, in the liver, may alter the metabolism and bioactivation of these compounds. However, there is not enough evidence in this area and more attempts might be helpful for understanding the effects of exercise on polyphenol absorption and metabolism.

Abbreviations

TNBC	Triple-negative breast cancers
IGF1	Insulin-like growth factor 1
DALYs	Disability-adjusted life years
CTCs	Circulating tumor cells
ctDNA	Circulating tumor DNA
MRI	Magnetic resonance imaging
BLBC	Basal-like breast cancers
PR	Progesterone receptors
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HT	Hormone therapy
JAG1	Jagged1
MDSCs	Myeloid-derived suppressor cells
SCFAs	Short-chain fatty acids
NK	Natural killer
hs-CRP	High-sensitivity C-reactive protein
PTX3	Pentraxin-3
circRNAs	Circular RNAs
lncRNAs	Long noncoding RNAs
ncRNA	Noncoding RNA
SOD	Superoxide dismutase
IL-1β	Interleukin-1 beta
TNF-α	Tumor necrosis factor-alpha
PRKCQ	Protein kinase C theta
hTERT	Human telomerase reverse transcriptase
SAE	Saffron aqueous extract
SIRT1	Sirtuin-1
HIIT.	High-intensity interval training

Acknowledgements
None.

Author contributions
HP and BB contributed in data collection and manuscript drafting. HP and BB approved the final version for submission. All authors reviewed the manuscript."

Funding
No funding.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 30 January 2025 Accepted: 28 March 2025
Published online: 15 April 2025

References

1. Bellanger M, Zeinomar N, Tehranifar P, Terry MB. Are global breast cancer incidence and mortality patterns related to country-specific economic development and prevention strategies? J Glob Oncol. 2018. https://doi.org/10.1200/JGO.17.00207.
2. Nardin S, Mora E, Varughese FM, D'Avanzo F, Vachanaram AR, Rossi V, et al. Breast cancer survivorship, quality of life, and late toxicities. Front Oncol. 2020;10:864.
3. Carmocan C, Drăgănescu M. Hormone therapy in breast cancer. Chirurgia. 2017;112(10):21614.
4. Mehanna J, Haddad FG, Eid R, Lambertini M, Kourie HR. Triple-negative breast cancer: current perspective on the evolving therapeutic landscape. Int J Women Health. 2019;11:431–7.
5. Lester SC, Bose S, Chen Y-Y, Connolly JL, de Baca ME, Fitzgibbons PL, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med. 2009;133:1515–38.
6. Bhattacharya T, Dutta S, Akter R, Rahman MH, Karthika C, Nagaswarupa HP, et al. Role of phytonutrients in nutrigenetics and nutrigenomics perspective in curing breast cancer. Biomolecules. 2021. https://doi.org/10.3390/biom11081176.
7. Choudhari AS, Mandave PC, Deshpande M, Ranjekar P, Prakash O. Phytochemicals in cancer treatment: from preclinical studies to clinical practice. Front Pharmacol. 2020;10.
8. Rayan A, Raiyn J, Falah M. Nature is the best source of anticancer drugs: Indexing natural products for their anticancer bioactivity. PLoS ONE. 2017;12: e0187925.
9. Saxena M, Saxena J, Nema R, Singh D, Gupta A. Phytochemistry of medicinal plants. J Pharmacogn Phytochem. 2013;1:168–82.
10. Saklani A, Kutty SK. Plant-derived compounds in clinical trials. Drug Discov Today. 2008;13:161–71.

11. Rahimi A, Alimohammadi M, Faramarzi F, Alizadeh-Navaei R, Rafiei A. The effects of apigenin administration on the inhibition of inflammatory responses and oxidative stress in the lung injury models: a systematic review and meta-analysis of preclinical evidence. Inflammopharmacology. 2022;30:1259–76.
12. Keshavarzmotamed A, Mousavi V, Masihipour N, Rahmati A, Mousavi Dehmordi R, Ghezelbash B, et al. Regulating miRNAs expression by resveratrol: novel insights based on molecular mechanism and strategies for cancer therapy. Curr Mol Pharmacol. 2023. https://doi.org/10.2174/0118761429249717230920113227.
13. Ashrafizadeh M, Najafi M, Orouei S, Zabolian A, Saleki H, Azami N, et al. Resveratrol modulates transforming growth factor-beta (TGF-β) signaling pathway for disease therapy: a new insight into its pharmacological activities. Biomedicines. 2020. https://doi.org/10.3390/biomedicines8080261.
14. Institute NC. Drugs approved for breast cancer. 2025. https://www.cancer.gov/about-cancer/treatment/drugs/breast#2. Accessed 2025.
15. Gabriel BM, Zierath JR. The limits of exercise physiology: from performance to health. Cell Metab. 2017;25:1000–11.
16. Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of exercise. Cell. 2014;159:738–49.
17. Neufer PD, Bamman MM, Muoio DM, Bouchard C, Cooper DM, Goodpaster BH, et al. Understanding the cellular and molecular mechanisms of physical activity-induced health benefits. Cell Metab. 2015;22:4–11.
18. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst. 2012;104:815–40.
19. Sasso JP, Eves ND, Christensen JF, Koelwyn GJ, Scott J, Jones LW. A framework for prescription in exercise-oncology research. Wiley Online Library; 2015. p. 115–24.
20. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer. 2008;8:205–11.
21. Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metab. 2018;27:10–21.
22. World Health Organization S. Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016. Geneva: World Health Organization. 2018:1242–7.
23. Li N, Deng Y, Zhou L, Tian T, Yang S, Wu Y, et al. Global burden of breast cancer and attributable risk factors in 195 countries and territories, from 1990 to 2017: results from the Global Burden of Disease Study 2017. J Hematol Oncol. 2019;12:1–12.
24. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. Lyon: International agency for research on cancer. 2020;20182020.
25. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. CA Cancer J Clin. 2016;66:31–42.
26. Tao Z, Shi A, Lu C, Song T, Zhang Z, Zhao J. Breast cancer: epidemiology and etiology. Cell Biochem Biophys. 2015;72:333–8.
27. Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. The global burden of women's cancers: a grand challenge in global health. Lancet. 2017;389:847–60.
28. Society AC. Breast cancer facts & figures 2019–2020. https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html.
29. Barone I, Giordano C, Bonofiglio D, Ando S, Catalano S. The weight of obesity in breast cancer progression and metastasis: clinical and molecular perspectives. Semin Cancer Biol. 2020. https://doi.org/10.1016/j.semcancer.2019.09.001.
30. Cancer CGoHFiB. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019;394:1159–68.
31. Friis S, Kesminiene A, Espina C, Auvinen A, Straif K, Schüz J. European Code against Cancer 4th Edition: medical exposures, including hormone therapy, and cancer. Cancer Epidemiol. 2015;39:S107–19.
32. Jung S, Wang M, Anderson K, Baglietto L, Bergkvist L, Bernstein L, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol. 2016;45:916–28.
33. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. Lancet Oncol. 2017;18:e457–71.
34. Land SR, Liu Q, Wickerham DL, Costantino JP, Ganz PA. Cigarette smoking, physical activity, and alcohol consumption as predictors of cancer incidence among women at high risk of breast cancer in the NSABP P-1 trial. Cancer Epidemiol Biomark Prev. 2014;23:823–32.
35. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the IARC Working Group. N Engl J Med. 2016;375:794–8.
36. Pizot C, Boniol M, Mullie P, Koechlin A, Boniol M, Boyle P, et al. Physical activity, hormone replacement therapy and breast cancer risk: a meta-analysis of prospective studies. Eur J Cancer. 2016;52:138–54.
37. Zakhari S, Hoek JB. Epidemiology of moderate alcohol consumption and breast cancer: association or causation? Cancers. 2018;10:349.
38. Gaudet MM, Carter BD, Brinton LA, Falk RT, Gram IT, Luo J, et al. Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. Int J Epidemiol. 2017;46:881–93.
39. Barclay J, Ernster V, Kerlikowske K, Grady D, Sickles EA. Comparison of risk factors for ductal carcinoma in situ and invasive breast cancer. J Natl Cancer Inst. 1997;89:76–82.
40. Peila R, Arthur R, Rohan TE. Risk factors for ductal carcinoma in situ of the breast in the UK Biobank cohort study. Cancer Epidemiol. 2020;64:101648.
41. Lilleborge M, Falk RS, Sørlie T, Ursin G, Hofvind S. Can breast cancer be stopped? Modifiable risk factors of breast cancer among women with a prior benign or premalignant lesion. Int J Cancer. 2021;149:1247–56.
42. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017;50:1–23.
43. Manna S, Holz MK. Tamoxifen action in ER-negative breast cancer. Signal Transduct Insights. 2016. https://doi.org/10.4137/STI.S29901.
44. Dembinski R, Prasath V, Bohnak C, Siotos C, Sebai ME, Psoter K, et al. Estrogen receptor positive and progesterone receptor negative breast cancer: the role of hormone therapy. Hormones Cancer. 2020;11:148–54.
45. Pernas S, Tolaney SM. HER2-positive breast cancer: new therapeutic frontiers and overcoming resistance. Ther Adv Med Oncol. 2019;11:1758835919833519.
46. Provenzano E, Ulaner GA, Chin SF. Molecular classification of breast cancer. PET Clin. 2018;13:325–38.
47. Roy M, Fowler AM, Ulaner GA, Mahajan A. Molecular classification of breast cancer. PET Clin. 2023;18:441–58.
48. Tsang JYS, Tse GM. Molecular classification of breast cancer. Adv Anat Pathol. 2020;27:27–35.
49. Vagia E, Mahalingam D, Cristofanilli M. The landscape of targeted therapies in TNBC. Cancers (Basel). 2020. https://doi.org/10.3390/cancers12040916.
50. Liu H, Lyu H, Jiang G, Chen D, Ruan S, Liu S, et al. ALKBH5-mediated m6A demethylation of GLUT4 mRNA promotes glycolysis and resistance to HER2-targeted therapy in breast cancer. Cancer Res. 2022;82:3974–86.
51. Bailey C, Black JRM, Reading JL, Litchfield K, Turajlic S, McGranahan N, et al. Tracking cancer evolution through the disease course. Cancer Discov. 2021;11:916–32.
52. Pedroza DA, Subramani R, Tiula K, Do A, Rashiraj N, Galvez A, et al. Crosstalk between progesterone receptor membrane component 1 and estrogen receptor α promotes breast cancer cell proliferation. Lab Invest. 2021;101:733–44.
53. Schiff R, Massarweh S, Shou J, Osborne CK. Breast cancer endocrine resistance: how growth factor signaling and estrogen receptor coregulators modulate response. Clin Cancer Res. 2003;9:447s-s454.
54. Stoica GE, Franke TF, Moroni M, Mueller S, Morgan E, Iann MC, et al. Effect of estradiol on estrogen receptor-alpha gene expression and activity can be modulated by the ErbB2/PI 3-K/Akt pathway. Oncogene. 2003;22:7998–8011.
55. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021;22:266–82.
56. Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, et al. Ferroptosis: past, present and future. Cell Death Dis. 2020;11:88.
57. Liang D, Minikes AM, Jiang X. Ferroptosis at the intersection of lipid metabolism and cellular signaling. Mol Cell. 2022;82:2215–27.

58. Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. Cell Res. 2021;31:107–25.
59. Zeng F, Nijiati S, Tang L, Ye J, Zhou Z, Chen X. Ferroptosis detection: from approaches to applications. Angew Chem Int Ed Engl. 2023;62: e202300379.
60. Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, et al. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015;520:57–62.
61. Jennis M, Kung CP, Basu S, Budina-Kolomets A, Leu JI, Khaku S, et al. An African-specific polymorphism in the TP53 gene impairs p53 tumor suppressor function in a mouse model. Genes Dev. 2016;30:918–30.
62. Rusolo F, Capone F, Pasquale R, Angiolillo A, Colonna G, Castello G, et al. Comparison of the seleno-transcriptome expression between human non-cancerous mammary epithelial cells and two human breast cancer cell lines. Oncol Lett. 2017;13:2411–7.
63. Dinarvand N, Khanahmad H, Hakimian SM, Sheikhi A, Rashidi B, Pourfarzam M. Evaluation of long-chain acyl-coenzyme A synthetase 4 (ACSL4) expression in human breast cancer. Res Pharm Sci. 2020;15:48–56.
64. Jackson VP. Diagnostic mammography. Radiol Clin N Am. 2004;42(853–70):vi.
65. Mann RM, Kuhl CK, Moy L. Contrast-enhanced MRI for breast cancer screening. J Magnet Reson Imaging JMRI. 2019;50:377–90.
66. Nielsen S, Narayan AK. Breast cancer screening modalities, recommendations, and novel imaging techniques. Surg Clin N Am. 2023;103:63–82.
67. Magny SJ, Shikhman R, Keppke AL. Breast Imaging Reporting and Data System. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Rachel Shikhman declares no relevant financial relationships with ineligible companies. Disclosure: Ana Keppke declares no relevant financial relationships with ineligible companies.: StatPearls Publishing. Copyright © 2024, StatPearls Publishing LLC.; 2024.
68. Verma P, Sharma R, Sharma N, Gulati A, Parashar A, Kaundal A. Fine-needle aspiration cytology versus core-needle biopsy for breast lesions: a dilemma of superiority between the two. Acta Cytol. 2021;65:411–6.
69. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Comprehensive Cancer Network JNCCN. 2022;20:691–722.
70. Anderson DJ, Anderson RG, Moug SJ, Baker MJ. Liquid biopsy for cancer diagnosis using vibrational spectroscopy: systematic review. BJS Open. 2020;4:554–62.
71. Pankotai-Bodó G, Oláh-Németh O, Sükösd F, Pankotai T. Routine molecular applications and recent advances in breast cancer diagnostics. J Biotechnol. 2024;380:20–8.
72. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321:288–300.
73. Hosseinzadeh H, Nassiri-Asl M. Avicenna's (Ibn Sina) the Canon of Medicine and saffron (Crocus sativus): a review. Phytotherapy Res PTR. 2013;27:475–83.
74. Shariati-Moghaddam A, editor. New saffron products and food technology. I International Symposium on Saffron Biology and Biotechnology 650; 2003.
75. Omidkhoda SF, Hosseinzadeh H. Saffron and its active ingredients against human disorders: A literature review on existing clinical evidence. Iran J Basic Med Sci. 2022;25:913–33.
76. Khazdair MR, Boskabady MH, Hosseini M, Rezaee R, Tsatsakis AM. The effects of Crocus sativus (saffron) and its constituents on nervous system: a review. Avicenna J Phytomed. 2015;5:376–91.
77. Ghaffari S, Roshanravan N. Saffron; an updated review on biological properties with special focus on cardiovascular effects. Biomed Pharmacother. 2019;109:21–7.
78. Hatziagapiou K, Lambrou GI. The protective role of Crocus sativus L. (Saffron) against ischemia-reperfusion injury, hyperlipidemia and atherosclerosis: nature opposing cardiovascular diseases. Curr Cardiol Rev. 2018;14:272–89.
79. Namdar H, Emaratkar E, Hadavand MB. Persian traditional medicine and ocular health. Med Hypothesis Discov Innov Ophthalmol. 2015;4:162.
80. Fernández-Albarral JA, De Hoz R, Ramírez AI, López-Cuenca I, Salobrar-García E, Pinazo-Durán MD, et al. Beneficial effects of saffron (Crocus sativus L.) in ocular pathologies, particularly neurodegenerative retinal diseases. Neural Regener Res. 2020;15:1408–16.
81. Iranshahy M, Javadi B. Diet therapy for the treatment of Alzheimer's disease in view of traditional Persian medicine: a review. Iran J Basic Med Sci. 2019;22:1102.
82. Saeedi M, Rashidy-Pour A. Association between chronic stress and Alzheimer's disease: therapeutic effects of Saffron. Biomed Pharmacother. 2021;133: 110995.
83. Yaribeygi H, Zare V, Butler AE, Barreto GE, Sahebkar A. Antidiabetic potential of saffron and its active constituents. J Cell Physiol. 2019;234:8610–7.
84. Leone S, Recinella L, Chiavaroli A, Orlando G, Ferrante C, Leporini L, et al. Phytotherapic use of the Crocus sativus L. (Saffron) and its potential applications: a brief overview. Phytotherapy Res. 2018;32:2364–75.
85. Zeinali M, Zirak MR, Rezaee SA, Karimi G, Hosseinzadeh H. Immunoregulatory and anti-inflammatory properties of Crocus sativus (Saffron) and its main active constituents: a review. Iran J Basic Med Sci. 2019;22:334.
86. Hosseini A, Razavi BM, Hosseinzadeh H. Saffron (Crocus sativus) petal as a new pharmacological target: a review. Iran J Basic Med Sci. 2018;21:1091.
87. Hashemi M, Hosseinzadeh H. A comprehensive review on biological activities and toxicology of crocetin. Food Chem Toxicol. 2019;130:44–60.
88. Hashemi SA, Karami M, Bathaie SZ. Saffron carotenoids change the superoxide dismutase activity in breast cancer: in vitro, in vivo and in silico studies. Int J Biol Macromol. 2020;158:845–53.
89. Xu Q, Yu J, Jia G, Li Z, Xiong H. Crocin attenuates NF-κB-mediated inflammation and proliferation in breast cancer cells by down-regulating PRKCQ. Cytokine. 2022;154: 155888.
90. Arzi L, Riazi G, Sadeghizadeh M, Hoshyar R, Jafarzadeh N. A comparative study on anti-invasion, antimigration, and antiadhesion effects of the bioactive carotenoids of saffron on 4T1 breast cancer cells through their effects on Wnt/β-catenin pathway genes. DNA Cell Biol. 2018;37:697–707.
91. Ghorbanzadeh V, Hassan Aljaf KA, Wasman HM, Dariushnejad H. Crocin inhibit the metastasis of MDA-MB-231 cell line by suppressing epithelial to mesenchymal transition through WNT/β-catenin signalling pathway. Ann Med Surg. 2012;2024(86):1401–7.
92. Nezamdoost Z, Saghebjoo M, Hoshyar R, Hedayati M, Keska A. High-intensity training and saffron: effects on breast cancer-related gene expression. Med Sci Sports Exerc. 2020;52:1470–6.
93. Ahmadabadi F, Saghebjoo M, Huang CJ, Saffari I, Zardast M. The effects of high-intensity interval training and saffron aqueous extract supplementation on alterations of body weight and apoptotic indices in skeletal muscle of 4T1 breast cancer-bearing mice with cachexia. Appl Physiol Nutr Metab. 2020;45:555–63.
94. Ahmadabadi F, Saghebjoo M, Hedayati M, Hoshyar R, Huang CJ. Treatment-induced tumor cell apoptosis following high-intensity interval training and saffron aqueous extract in mice with breast cancer. Physiol Int. 2021. https://doi.org/10.1556/2060.2021.00009.
95. Mirzaei H, Gharehgozlou R, Heydarirad G, Fahimi S, Ghafari S, Mosavat SH, et al. Efficacy and safety of Jollab (a saffron-based beverage) on cancer-related fatigue in breast cancer patients: a double-blind randomized clinical trial. Complement Med Res. 2022;29:437–45.
96. Akarchariya N, Sirilun S, Julsrigival J, Chansakaowa S. Chemical profiling and antimicrobial activity of essential oil from Curcuma aeruginosa Roxb., Curcuma glans K. Larsen & J. Mood and Curcuma cf. xanthorrhiza Roxb. collected in Thailand. Asian Pac J Trop Biomed. 2017;7:881–5.
97. Dosoky NS, Setzer WN. Chemical composition and biological activities of essential oils of Curcuma species. Nutrients. 2018;10:1196.
98. Wu D, Liu N, Ye Y. Zingiberaceae Resource of China. Wuhan, China: Huazhong University of Science and Technology Press; 2015.
99. Angel G, Menon N, Vimala B, Nambisan B. Essential oil composition of eight starchy Curcuma species. Ind Crops Prod. 2014;60:233–8.
100. Lin C-M, Sheu S-R, Hsu S-C, Tsai Y-H. Determination of bactericidal efficacy of essential oil extracted from orange peel on the food contact surfaces. Food Control. 2010;21:1710–5.
101. Reanmongkol W, Subhadhirasakul S, Khaisombat N, Fuengnawakit P, Jantasila S, Khamjun A. Investigation the antinociceptive, antipyretic and anti-inflammatory activities of Curcuma aeruginosa Roxb. extracts in experimental animals. Songklanakarin J Sci Technol. 2006;28:999–1008.

102. Wilson B, Abraham G, Manju V, Mathew M, Vimala B, Sundaresan S, et al. Antimicrobial activity of Curcuma zedoaria and Curcuma malabarica tubers. J Ethnopharmacol. 2005;99:147–51.
103. Mehta K, Pantazis P, McQueen T, Aggarwal BB. Antiproliferative effect of curcumin (diferuloylmethane) against human breast tumor cell lines. Anticancer Drugs. 1997;8:470–81.
104. Venkiteswaran S, Thomas T, Thomas T. Curcumin inhibits the growth of HER-2 overexpressing human breast cancer cells by interference with the glutathione pathway. Cancer Res. 2007;67:3467.
105. Ashrafizadeh M, Zarrabi A, Hushmandi K, Zarrin V, Moghadam ER, Hashemi F, et al. Toward regulatory effects of curcumin on transforming growth factor-beta across different diseases: a review. Front Pharmacol. 2020;11: 585413.
106. Rismanchi H, Malek Mohammadi M, Mafi A, Khalilzadeh P, Farahani N, Mirzaei S, et al. The role of curcumin in modulating circular RNAs and long non-coding RNAs in cancer. Clin Transl Oncol. 2024. https://doi.org/10.1007/s12094-024-03782-0.
107. Guo Y, Su J, Jiang S, Xu Y, Dou B, Li T, et al. Transcriptomics and metabonomics study on the effect of exercise combined with curcumin supplementation on breast cancer in mice. Heliyon. 2024;10: e28807.
108. Delfan M, Ramzi F. Efficient synergistic combination effect of endurance exercise with Curcumin on breast cancer progression through inflammatory pathway inhibition in BALB/C mice. J Shahid Sadoughi Univ Med Sci. 2021. https://doi.org/10.18502/ssu.v29i4.6497.
109. Kouchaki Langroudi F, Peeri M, Delfan M. The effect of endurance training in combination with curcumin on intratumoral gene expression of AngiomiR-126 and Angiopoietin-1 in female mice with breast cancer. J Ardabil Univ Med Sci. 2020;20:410–20.
110. Sadeghian S, Kazemzadeh Y, Mirzayan SS, Sedaghati S. Effect of concomitant use of curcumin during six weeks of aerobic exercise on antioxidant indices of liver tissue in mice with induced breast cancer in the doxorubicin treatment phase. 2023.
111. Sadeghian S, Kazemzadeh Y, Mohammadnejadpanah Kandi Y, Mirzayan Shanjani S, Sedaghati S. The effect of aerobic exercise with curcumin consumption on tissue apoptosis indices in the liver tissue of rats induced by breast cancer in the doxorubicin treatment phase: an experimental study. J Rafsanjan Univ Med Sci. 2022;21:433–48.
112. Daryanoosh F, Zolfaghari M, Hashemi SM, Jahromi MK, Jalili A, Khazaei H, et al. Synergistic effect of exercise training and curcumin supplementation on inflammation indices in overweight breast-cancer patients after adjuvant chemotherapy and/or radiation therapy: a randomized controlled trial study. Sport Sci Health. 2024. https://doi.org/10.1007/s11332-024-01252-2.
113. Moghiseh M, Mirzayan SS, Banaifar AA, Kazemzadeh Y. The effect of aerobic exercise training and micelles on the consumption of curcumin nano expression level of CASP3, CASP9, Bax and BCL2 with genes on cardiac tissues of Balb/C mice induced breast cancer treated with doxorubicin. Iran J Breast Dis. 2023. https://doi.org/10.30699/ijbd.16.2.67.
114. Branch T. Synergistic effect of endurance training combined with curcumin on intratumoral expression of interleukin-4 (Il4) and Stat-6 in female mice with breast cancer. 2020.
115. Hemati S, Mehrabinejad F, Elhaie M, Najafizade N. Curcumin supplementation as a preventive strategy against tamoxifen-induced nonalcoholic fatty liver disease in ER+ breast cancer patients: a triple-blind randomized placebo-controlled trial. J Diet Suppl. 2025;22:274–83.
116. Aghababaei F, Hadidi M. Recent advances in potential health benefits of quercetin. Pharmaceuticals (Basel, Switzerland). 2023;16.
117. Batiha GE-S, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, et al. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. Foods (Basel, Switzerland). 2020;9:374.
118. Ding Y, Li C, Zhang Y, Ma P, Zhao T, Che D, et al. Quercetin as a Lyn kinase inhibitor inhibits IgE-mediated allergic conjunctivitis. Food Chem Toxicol. 2020;135: 110924.
119. Nutmakul T. A review on benefits of quercetin in hyperuricemia and gouty arthritis. Saudi Pharm J. 2022;30:918–26.
120. Perdicaro DJ, Lanzi CR, Tudela JG, Miatello RM, Oteiza PI, Prieto MAV. Quercetin attenuates adipose hypertrophy, in part through activation of adipogenesis in rats fed a high-fat diet. J Nutr Biochem. 2020;79: 108352.
121. Rauf A, Imran M, Khan IA, UrRehman M, Gilani SA, Mehmood Z, et al. Anticancer potential of quercetin: a comprehensive review. Phytotherapy Res. 2018;32:2109–30.
122. Yao Z, Gu Y, Zhang Q, Liu L, Meng G, Wu H, et al. Estimated daily quercetin intake and association with the prevalence of type 2 diabetes mellitus in Chinese adults. Eur J Nutr. 2019;58:819–30.
123. Liu Y, Tang Z-G, Lin Y, Qu X-G, Lv W, Wang G-B, et al. Effects of quercetin on proliferation and migration of human glioblastoma U251 cells. Biomed Pharmacother. 2017;92:33–8.
124. Ashrafizadeh M, Samarghandian S, Hushmandi K, Zabolian A, Shahinozzaman M, Saleki H, et al. Quercetin in attenuation of ischemic/reperfusion injury: a review. Curr Mol Pharmacol. 2021;14:537–58.
125. Jalali Z, Shahidi F. Interactive effect of 6 weeks of aerobic exercise and quercetin supplementation on TIE-2 and VEGF-A expression in tumor tissue of female mice with breast cancer. Iran J Breast Dis. 2021;14:46–56.
126. Barrilleaux TL. Effects of quercetin and exercise on tumor progression in a breast cancer mouse model: University of South Carolina; 2009.
127. Ma W, Zhang Y, Yu M, Wang B, Xu S, Zhang J, et al. In-vitro and in-vivo anti-breast cancer activity of synergistic effect of berberine and exercise through promoting the apoptosis and immunomodulatory effects. Int Immunopharmacol. 2020;87: 106787.
128. Mudge J. Immunological effects of berberine and physical activity in a murine breast cancer model. 2022.
129. Wang B, Xu H, Hu X, Ma W, Zhang J, Li Y, et al. Synergetic inhibition of daidzein and regular exercise on breast cancer in bearing-4T1 mice by regulating NK cells and apoptosis pathway. Life Sci. 2020;245: 117387.
130. Malekpoor Z, Taghian F, Jalali Dehkordi K. The effect of aerobic exercise combined with the combination of gallic acid and kaempferol on neurogenesis caused by the side effects of paclitaxel in mice with breast cancer. J Isfahan Med School. 2023;41:427–37.
131. Xie C, Chan L, Pang Y, Shang Y, Wang W, Zhao L. Rosmarinic acid promotes mitochondrial fission and induces ferroptosis in triple-negative breast cancer cells. Naunyn Schmiedebergs Arch Pharmacol. 2025. https://doi.org/10.1007/s00210-025-03927-0.
132. Gong G, Wan Y, Liu Y, Zhang Z, Zheng Y. Ononin triggers ferroptosis-mediated disruption in the triple negative breast cancer both in vitro and in vivo. Int Immunopharmacol. 2024;132: 111959.
133. An S, Hu M. Quercetin promotes TFEB nuclear translocation and activates lysosomal degradation of ferritin to induce ferroptosis in breast cancer cells. Comput Intell Neurosci. 2022;2022:5299218.
134. Cao X, Li Y, Wang Y, Yu T, Zhu C, Zhang X, et al. Curcumin suppresses tumorigenesis by ferroptosis in breast cancer. PLoS ONE. 2022;17: e0261370.
135. Li R, Zhang J, Zhou Y, Gao Q, Wang R, Fu Y, et al. Transcriptome investigation and in vitro verification of curcumin-induced HO-1 as a feature of ferroptosis in breast cancer cells. Oxid Med Cell Longev. 2020;2020:3469840.
136. Organization WH. Breast cancer. 2024. https://www.who.int/news-room/fact-sheets/detail/breast-cancer. Accessed 2024.
137. Samavat H, Wu AH, Ursin G, Torkelson CJ, Wang R, Yu MC, et al. Green tea catechin extract supplementation does not influence circulating sex hormones and insulin-like growth factor axis proteins in a randomized controlled trial of postmenopausal women at high risk of breast cancer. J Nutr. 2019;149:619–27.
138. Wang L, Du X, Yue D, Chen X. Catechin, rutin and quercetin in Quercus mongolica Fisch leaves exert inhibitory effects on multiple cancer cells. J Food Biochem. 2022;46: e14486.
139. Sun Y, Zhou QM, Lu YY, Zhang H, Chen QL, Zhao M, et al. Resveratrol inhibits the migration and metastasis of MDA-MB-231 human breast cancer by reversing TGF-β1-induced epithelial-mesenchymal transition. Molecules. 2019. https://doi.org/10.3390/molecules24061131.
140. Wu HT, Lin J, Liu YE, Chen HF, Hsu KW, Lin SH, et al. Luteolin suppresses androgen receptor-positive triple-negative breast cancer cell proliferation and metastasis by epigenetic regulation of MMP9 expression via the AKT/mTOR signaling pathway. Phytomedicine. 2021;81: 153437.
141. Hu C, Wang M, Hu M, Ma S, Yang B, Xiao W, et al. Genistein induces endocrine resistance in human breast cancer by suppressing H3K27 trimethylation. Endocr Relat Cancer. 2023. https://doi.org/10.1530/ERC-22-0191.

142. Maashi MS, Al-Mualm M, Al-Awsi GRL, Opulencia MJC, Al-Gazally ME, Abdullaev B, et al. Apigenin alleviates resistance to doxorubicin in breast cancer cells by acting on the JAK/STAT signaling pathway. Mol Biol Rep. 2022;49:8777–84.
143. Ahmadabadi F, Saghebjoo M, Hedayati M, Hoshyar R, Huang C-J. Treatment-induced tumor cell apoptosis following high-intensity interval training and saffron aqueous extract in mice with breast cancer. Physiol Int. 2021;108:19–26.
144. Mirzaei H, Gharehgozlou R, Heydarirad G, Fahimi S, Ghafari S, Mosavat SH, et al. Efficacy and safety of Jollab (a saffron-based beverage) on cancer-related fatigue in breast cancer patients: a double-blind randomized clinical trial. Complementary Med Res. 2022;29:437–45.

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