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REVIEW ARTICLE

Combined Phytochemicals, A Potential Approach to Reduce the Disparity of Breast Cancer in African American Women

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Abstract: Estrogen Receptor-positive (ER+) breast cancer, constituting 75% of cases, presents a significant health disparity in African American women (AAW) compared to Caucasian American women (CAW). Lower vegetable and fruit consumption may contribute to this breast cancer disparity among AAW. Phytochemicals, such as luteolin (LUT) from broccoli, celery, and peppers and indole-3-carbinol (I3C) from cruciferous vegetables, exhibit anti-cancer properties. However, there is a significant phytochemicals dosage gap between in vitro studies and human physiological levels after oral intake of vegetables or pure phytochemicals. In this mini-review, we focused on combining two or more phytochemicals at relatively low levels to synergistically exert ER-positive breast cancer in animals and cells. We concluded that selective eating of phytochemical-rich foods might lower the chance of developing ER+ breast cancer, particularly among AAW who had lower fruit and vegetable consumption and higher levels of ER+ breast cancer death compared to CAW.

Keywords: Breast Cancer; Phytochemicals; Combination; Synergistic; Indole-3-Carbinol; Luteolin

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1. Introduction

Breast cancer is the most common cancer in which women are diagnosed; although rare in men, it does exist. It affects more than 1.5 million women annually and is also responsible for most women's cancer-related deaths [1]. As of 2021, the World Health Organization reports that female breast cancer has surpassed lung cancer as the top cause of cancer incidence globally, accounting for an estimated 2.3 million new cases per year globally [2]. The major methods utilized to treat breast cancer now include surgery, radiation, chemotherapy, and endocrine therapy. However, the high rate of tumor recurrence and progression of the disease following these traditional therapies is highly concerning. Hence, new therapies must be created to treat breast cancer without these side effects [1]. Phytochemicals, natural plant metabolites with healthy benefits, have the potential to enhance cancer patients' response to treatment and reduce side effects [3, 4]. Epidemiological studies have consistently shown an inverse association between phytochemical consumption and breast cancer risk. Phytochemicals exert their preventive effects through multiple mechanisms, including antioxidant activity, modulation of hormone metabolism, anti-inflammatory properties, and regulation of cell proliferation and apoptosis. By targeting these key pathways, phytochemicals may reduce the initiation and progression of breast cancer [5]. Phytochemicals, such as flavonoids and carotenoids, exhibit potent antioxidant properties. They scavenge free radicals and reactive oxygen species, protecting cells from oxidative damage and DNA mutations [6]. Phytochemicals with estrogenic or antiestrogenic properties, such as isoflavones and lignans, can modulate estrogen receptor activity and estrogen metabolism. These compounds may compete with endogenous estrogens, reducing the proliferative effects of estrogen and lowering the risk of hormone receptor-positive breast cancer [7]. Phytochemicals polyphenols and curcumin exhibit anti-inflammatory effects by inhibiting pro-inflammatory signaling pathways and suppressing the production of inflammatory mediators. Moreover, phytochemicals can modulate the immune system, enhancing immune surveillance against cancer cells. These anti-inflammatory and immunomodulatory properties contribute to the prevention of breast cancer development [8]. Phytochemicals can inhibit cell proliferation by regulating key signaling pathways, such as the PI3K/Akt and MAPK

pathways, which are dysregulated in breast cancer. Additionally, phytochemicals can promote apoptosis through various mechanisms, including activation of tumor suppressor genes and inhibition of anti-apoptotic proteins [7]. Understanding the preventive potential of phytochemicals in breast cancer provides valuable insights for developing personalized strategies and interventions for individuals at high risk of breast cancer [9].

2. There is a significant disparity of breast cancer prevalence and death in African Americans

Breast cancer is a significant health concern for all women, but there is a considerable disparity in its prevalence and death rates in African American women (AAW) compared to women of other racial and ethnic groups [10]. According to the American Cancer Society, AAW have a higher incidence of breast cancer before the age of 45 than Caucasian American women (CAW), and they are also more likely to be diagnosed with breast cancer at a later stage. Moreover, AAW are more likely to die from breast cancer than women of other racial and ethnic groups. The mortality rate is 40% higher for AAW than for CAW [11]. In addition, updated estimates of cancer incidence and death were released by GLOBOCAN in 2020, and there were 19.3 million new occurrences of cancer worldwide in 2020, and close to 10 million individuals passed away from the disease [12]. AAW have a disproportionately high cancer mortality rate compared to CAW, with a risk of 33% greater [13]. The reasons for this disparity are complex and not yet fully understood. Lifestyle factors such as obesity, physical inactivity, and alcohol consumption can increase the risk of breast cancer. AAW have higher rates of obesity and physical inactivity than CAW, which may contribute to the higher incidence of breast cancer. Based on molecular profiles, breast cancer is divided into three primary subtypes: hormone receptor-positive (estrogen receptor (ER+), human epidermal growth factor receptor (EGFR) 2 (HER2)-positive, and triple-negative cancers [14]. Around 75% of breast cancer cases are ER, making them the most prevalent subtype [13]. Evaluated regression models showed that the risk of breast cancer death was at least four times higher among ER+ patients who were AAW than among CAW. The observation of a racial disparity in breast cancer survival for those with ER+ tumors suggests that there may be racial differences in the molecular characteristics of hormone receptor-positive tumors, and thus, ER+ tumors in black patients may be less responsive to standard treatments [15]. Also, the disparities in ER+ breast cancer prevalence and mortality among AAW are influenced by a combination of genetic and physiological factors. Genetic variations, such as specific BRCA mutations and distinct tumor biology, contribute to the higher incidence and aggressive subtypes observed in this population [16]. Mutations in the BRCA1 and BRCA2 genes are strongly associated with an increased risk of breast cancer. While these mutations occur across populations, studies have shown that specific BRCA mutations, such as BRCA1 c.5266dupC, are more prevalent among African Americans [17]. Genetic variations, including single nucleotide polymorphisms (SNPs), have been associated with ER-positive breast cancer risk. Studies have identified specific SNPs, such as those in the estrogen receptor alpha (ESR1) gene, that may contribute to the higher prevalence of ER+ breast cancer in AAW. These genetic differences may affect estrogen signaling pathways and contribute to tumor development and progression [18]. AAW tend to have higher estrogen levels compared to women of other ethnicities, which, in combination with other factors, can contribute to a higher incidence of ER+ breast cancer [19]. Understanding the mechanisms of hormonal imbalances specific to AAW is essential for developing targeted preventive and therapeutic approaches [20].

3. Current treatments for breast cancer have disadvantages.

While some unfavorable consequences are transient and have little impact on the quality of life of breast cancer patients, the side effects of the most current treatments may develop over time and contribute to increased morbidity and death among survivors [21]. For instance, the most used endocrine therapies are selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) [22, 23]. SERMs such as tamoxifen can cause hot flashes, vaginal dryness, and fatigue. AIs such as letrozole and anastrozole can cause joint pain, hot flashes, and fatigue. Both SERMs and AIs can increase the risk of osteoporosis and fractures due to reduced estrogen levels [24]. Anti-HER2 therapy is another type of treatment that targets the HER2 protein, which is overexpressed in about 20-25% of breast cancers. The most used anti-HER2 therapies trastuzumab and epratuzumab, induced nausea, vomiting, diarrhea, fatigue, and heart failure [25, 26]. Both trastuzumab and epratuzumab can increase the risk of infection due to their effects on the immune system [27]. Radiotherapy is a standard treatment for breast cancer that uses high-energy X-rays to kill cancer cells. However, radiation therapy can induce fatigue, skin changes, hair loss, and mouth problems [28]. Surgery is a primary treatment option for breast cancer, but it can also lead to various side effects, such as lymphedema, negative impact on body image and quality of life, which may persist long after treatment [29]. Moreover, the escalating reoccurrence and drug resistance also deters the chemotherapies for breast cancer [30]. Therefore, new approaches without these side effects are urgently required to treat breast cancer.

4. Phytochemicals and breast cancer prevention and treatment

Phytochemicals, bioactive compounds derived from plants, have gained attention for their potential anti-cancer properties [31]. Phytochemicals exert their anti-cancer effects through various molecular mechanisms, including apoptosis induction, cell cycle regulation, inhibition of angiogenesis, modulation of hormonal signaling, and antioxidant activity [32]. Numerous preclinical and increasing clinical studies have investigated the efficacy of phytochemicals in breast cancer treatment [33]. Preclinical studies using cell lines and animal models have provided valuable insights into the anti-cancer properties of phytochemicals [34].

Luteolin is a bioactive phytochemical classified as a flavonoid, found abundantly in various plant-based foods. It is known for its potential health benefits because of its antioxidant, anti-inflammatory, and anti-cancer properties [35]. Foods that are excellent sources of luteolin include celery, parsley, thyme, chamomile tea, peppers, carrots, olive oil, and various fruits such as oranges and lemons [36]. Luteolin has been researched for its potential role in preventing ER+ breast cancer [37]. One mechanism of luteolin inhibiting breast cancer involves modulating estrogen signaling pathways. Luteolin has been shown to interact with estrogen receptors and exert both estrogenic and anti-estrogenic effects depending on the cellular context. It can bind to estrogen receptors and inhibit estrogen-induced proliferation of ER+ breast cancer cells, thereby reducing the growth-promoting effects of estrogen [38]. The suppression of aromatase, the enzyme in charge of turning androgens into estrogens, is another mechanism of luteolin preventing ER+ breast cancer. By lowering estrogen levels, luteolin may assist in preventing the stimulation of the growth of ER+ breast cancer cells [39]. Additionally, studies have demonstrated that luteolin has antioxidant and anti-inflammatory properties. The onset and spread of several malignancies, including breast cancer, have been associated with the increased chronic inflammation and oxidative stress. Luteolin can block inflammatory pathways and eliminate reactive oxygen species, potentially lowering the risk of cancer development [40]. Luteolin has been shown to modulate multiple signaling pathways involved in cancer development and progression, including the PI3K/Akt pathway, MAPK pathway, and NF-κB pathway. By interfering with these pathways, luteolin can inhibit cell survival, proliferation, and metastasis, and induce apoptosis in breast cancer cells. One study showed that luteolin exerted very little proliferative effects at a relatively low concentration (10uM) and cytotoxic effects at a high concentration (50uM) in MCF-7 cells after 48 hours of treatment [41]. Another study shows that luteolin at a concentration of 80uM exerts about 45% breast cancer inhibitory effect in ER+ breast cancer cells (MCF-7) through inhibiting cell proliferation after 24 hours and about 70% inhibitory effect after 48 hours. [42]. In addition, rats induced with 7,12-dimethylbenz(a)anthracene mammary tumor and administered with luteolin dosage of 30 mg/kg individually achieved 54% of tumor reduction after 20 days of treatment [43]. These effects collectively highlight the potential of luteolin as a natural compound for the prevention and treatment of breast cancer [39].

Indole-3-carbinol (I3C) is a phytochemical derived from cruciferous vegetables, such as broccoli, cabbage, cauliflower, and Brussels sprouts [44]. It is formed when these vegetables are chewed or cooked. I3C has gained attention for its potential health benefits, particularly in cancer prevention and hormone regulation [45]. It is known to modulate estrogen metabolism, promoting the conversion of potentially harmful estrogens to less potent forms, which may reduce the risk of hormone-related cancers, including breast, ovarian, and prostate cancers [46]. Moreover, I3C exhibits antioxidant and anti-inflammatory properties. I3C has been investigated for its potential mechanisms in targeting ER+ breast cancer [47]. I3C has been shown to enhance the conversion of estrogen into less active metabolites through the induction of cytochrome P450 enzymes, such as CYP1A1 and CYP1B1. These enzymes metabolize estrogen into 2-hydroxyestrone (2-OHE1), a less potent form of estrogen, which has been associated with a reduced risk of breast cancer development [48]. Furthermore, I3C can affect inhibit estrogen receptor activity by competing with estrogen for binding to the receptor, resulting in reduced estrogen-dependent gene expression and cell proliferation [49]. I3C has also been shown to interfere with estrogen receptor-mediated signaling pathways, such as the PI3K/Akt and MAPK pathways, which play a crucial role in breast cancer growth and survival [45]. A study showed that 100 μM I3C inhibited ER+ breast cancer cell proliferation (MCF-7 and T-47D) up to 50% after 24 hours compared with the control [50]. In another study, treatment with I3C increased the apoptotic cell death and significantly decreased the proliferation of ER+ breast cancer cell lines (MCF-7, T-47D, and ZR75.1) compared to the control at a concentration of 200uM after 48 hours of treatment [51]. Studies by Grubbs et al [52] using the 7,12-dimethylbenz[α]anthracene (DMBA) model has demonstrated that mammary tumor multiplicity in Sprague-Dawley rats may be decreased by 91-96% after administration of 50mg I3C/kg of diet per day five times a week. Similarly, feeding Sprague Dawley rats 50mg I3C/kg of diet before and after MNU (a direct acting carcinogen) therapy resulted in a 65% reduction in breast tumor multiplicity. Bradlow et al [53] have demonstrated that fed diets containing 500–2000 ppm I3C for 8 months in C3H/OuJ mice had considerably reduced incidence and multiplicity of spontaneous mammary tumors than mice without I3C. To our knowledge, there have not been clinical trials using individual luteolin or I3C.

Although individual phytochemicals have shown promise in preventing/treating breast cancer by targeting various cellular pathways as aforementioned, there is a big gap between the required dosages of the individual chemicals in cells and the circulating levels of the chemicals in animals/humans after oral intake of phytochemicals or relevant foods. For instance, the effective inhibitory concentrations of luteolin and I3C in

ER+ cells are 50-80uM and 200-490uM, respectively [41]. However, the maximum plasma concentrations of luteolin, I3C, and its metabolites are 15uM (50 mol/kg, gastric intubation in rats) [54] and 0.04uM (250 mg/kg, oral in mice), respectively [55]. To bridge this concentration/dosage gap, combining two or more phytochemicals to inhibit breast cancer synergistically has been proposed and conducted in cells and animals.

5. A combination of phytochemicals may be an efficient approach to prevent and treat breast cancer.

Recent research switched to the combination of phytochemicals at lower dosages to enhance their efficacy and to combat breast cancer [56]. Studies have suggested that combining phytochemicals with similar or complementary mechanisms of action can lead to synergistic effects, where the combined effect is greater than the sum of their individual effects [57]. For instance, it was discovered that a unique combination of luteolin at 30uM (LUT30) and I3C at 40uM (I3C40) synergistically inhibits the growth of ER+ breast cancer cells (MCF-7 and T-47D). LUT30 and I3C40 alone, on the other hand, do not have this anti-proliferative effect on ER+ breast cancer cells. In addition, when compared to the currently available commercial medications, the combination LUT30+I3C40 has no harmful effects on endothelial cells. Similar to this, the individual doses of LUT (10 mg/kg/day) and I3C (20 mg/kg/day) do not have an inhibitory impact, but the combination of LUT and I3C (LUT10 mg + I3C10 mg/kg/day) (IP injection) synergistically reduces tumor growth in MCF-7 cells-derived xenograft mice [58]. Both in cultured cells and xenograft tumors, this combination synergistically downregulates two important therapeutic targets: ER and the CDK4/6/retinoblastoma (Rb) pathway [59]. We also recently reported that the proliferation of human colon cancer CL-188 cells was effectively inhibited by the combination of curcumin (CUR) at 15uM and luteolin (LUT) at 30uM, whereas the individual compounds only had a little inhibitory effect at the chosen doses (CUR 15 and LUT 30). In CL-188 cells, the combination also synergistically inhibited wound healing (wound closure assay) and administering CUR and LUT together (at doses of 20 mg/kg/day and 10 mg/kg/day, respectively, IP injection, 5 days for 2 weeks) effectively slowed the formation of tumors in mice bearing xenografts made from CL-188 cells [60]. Similarly, caco2 cell number were significantly reduced by 74% with a combination of 10uM quercetin and kaempferol, but only a 29% reduction by separately with quercetin and kaempferol at the same treatment concentrations [61]. This synergy may enhance the efficacy of phytochemicals and improve their ability to inhibit cancer cell proliferation, induce apoptosis (cell death), inhibit angiogenesis (blood vessel formation), and suppress metastasis [1]. The synergistic effects observed with the combination of phytochemicals can be attributed to multiple mechanisms of action. For example, phytochemical combinations can enhance the antioxidant defense system, reduce oxidative stress, and inhibit DNA damage, thereby preventing the initiation of cancerous changes in cells [62]. Additionally, combined phytochemicals can modulate multiple signaling pathways involved in cell cycle regulation, inflammation, apoptosis, and angiogenesis, leading to a more comprehensive and effective approach against breast cancer [63]. Another advantage of combining phytochemicals is the potential to enhance their bioavailability. Most phytochemicals exhibit poor absorption or rapid metabolism when consumed alone, limiting their therapeutic benefits. However, combining phytochemicals can lead to improved absorption, distribution, and stability in the body, resulting in higher concentrations at the target site [64]. Furthermore, the use of lower individual doses in combination therapy may help reduce the risk of adverse side effects or toxicity associated with higher individual doses. Therefore, the combination of phytochemicals represents a promising and efficient approach to prevent and treat breast cancer, although more studies are required.

6. African Americans consume much less vegetables than Caucasian Americans.

In comparison to Caucasian Americans, racial and ethnic minorities in the US have greater incidences of nutrition-related health issues. Cardiovascular disease, diabetes, obesity, and several cancers are more common in African Americans [65]. Lifestyle variables are undoubtedly involved in the complicated and multifaceted causes of the discrepancy in various diseases and disorders. In comparison to other minority and majority populations, African Americans score worse on overall food quality and consume less fruit and vegetables, which is a source of phytochemicals, therefore contributing to health disparities [66]. For instance, a recent study examined a sample of 9200 moms, 66.3% of whom were Latinas, 17.3% were white, 12.6% were African Americans, and 3.8% were Asian Americans, Native Hawaiians, or Pacific Islanders (AANHPI). In comparison to Latinas, Whites, and AANHPIs, African American mothers consumed the fewest cups of fruits and vegetables and the most teaspoons of added sugar, reported poor food quality, and had the greatest obesity rate at 54.7% [67]. Noteworthy, vegetable consumption has been significantly lower among blacks than whites in the past three decades [68]. This disparity continues, with only 5.5% of African Americans meeting the federal vegetable intake recommendations while 9.5% of white Americans reached the recommendation in 2015, the most recent available data [69]. These results suggest that low vegetable intake may partly contribute to the breast cancer disparity in African Americans. Therefore, consuming more bioactive chemicals in abundant vegetables may be an efficient approach to reduce the

breast cancer disparity in African Americans, which has been significantly lower among blacks than whites in the past three decades.

7. Conclusions

Increasing reports support that combining two or more phytochemicals at a relatively low level is an effective approach to preventing or treating breast cancer without side effects compared to the current breast cancer treatments, including surgery, radiotherapy, and chemotherapy. This approach may be more promising for African American women, who had lower fruit and vegetable consumption and higher levels of breast cancer death compared to white women. Therefore, selecting two or more foods having high contents of phytochemicals may be a practical way to reduce/prevent breast cancer in African American women after clinical trials.

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