

Case Study and Protocol for Natural Ingredients used to Support Breast Cancer Patients

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Overview

Breast cancer remains a significant global health issue, prompting the need for further exploration of alternatives to conventional treatments. Through the years, this has led to the formulation and investigation of protocols using natural ingredients as potential remedies for holistic control of breast cancer. An integrated protocol with a case study of a 58-year-old woman diagnosed with breast carcinoma will be discussed to ascertain this approach. The case study details the patient's discovery of a lump, followed by a detailed analysis using more precise breast imaging methods. The examination identified a hypoechoic and dense tumor in her right breast. The subsequent core biopsy confirmed the diagnosis of carcinoma lobular mammae, emphasizing the necessity for an effective and personalized therapeutic approach.

Aware of the patient's case and her need for a holistic approach, a breast cancer protocol was developed, and is highlighted in Table 2. This protocol is significant in that it proposes the administration of supplements and herbal extracts through a phased approach as an adjuvant to the patient's existing therapy. This is a four-stage protocol starting with the proprietary blend I, twice per day for three days. Doses are then adjusted every three days, increasing to adequate dose intensity but starting with this combination of proprietary blend I, composed of Silica, Vitamin C, and Trace Minerals. The subsequent stages include proprietary blend II blended with Black Cumin Seed Oil, Resveratrol, Turmeric, Raspberry Ketones, and others with the aim of enhancing the treatment regime of the patient. There are two different blended support protocols that work on important aspects of immune improvement and body strengthening. Employing these formulations, which include vitamins, minerals, and targeted supplements that incrementally intensify, serves as a means to enhance the patient's physiological resilience against the detrimental advancement of the disease.

Brief overview of breast cancer and its treatment methods

Treating breast cancer, which affects 1 in 3 women annually, requires a holistic approach. Ji Young You et al. (2023) conducted a comprehensive literature review on the treatment options for breast cancer. Here, the complexity of breast cancer is demonstrated, stressing the need for local as well as systemic treatment approaches. In their review, they highlight the importance of local treatments such as surgery and radiation therapy in the management of breast cancer. It presents the complexities of surgical management, describing them as breast surgery and axillary lymph node surgery. This helps in comprehending localized treatment modalities. More so, the administration of radiation

therapy is highlighted in explaining its supplementary role in improving the efficacy of surgical treatments.

Additionally, Ji Young You et al. (2023) elaborate on systemic treatment in conjunction with local treatments. They outline the temporal nature of treatment planning, emphasizing the difference between pre-surgery neoadjuvant therapy and post-surgery adjuvant therapy. Within this framework, the review traverses through the range of systemic treatments, namely chemotherapy, hormone therapy, targeted therapy, and immunotherapy (Ji Young You et al., 2023). Through this inclusive perspective, the changing scenery of cancer drugs and their ever-changing use in breast cancer therapy management is illuminated. The main strength of this literature review is that it is able to capture the complex aspects of breast cancer treatment. It provides detailed insight into the local and systemic treatment modalities so that readers are conversant with the multiple approaches used in controlling breast cancer (Ji Young You et al., 2023). Additionally, it acts as a connecting link between the established breast cancer treatment paradigms and the novel therapeutic methods, and thus, provides a complete perception of the developing breast cancer care environment. The article by Ji Young You et al. (2023) provides fundamental information on the different treatments in breast cancer therapy. The research on treatment methodologies is a relevant input in comprehending the intricate tactics that are employed by breast cancer survivors.

Waks and Winer (2019) start by pointing out that in the US, breast cancer is one of the most prominent cancers, with over a tenth of women falling victim to it throughout their lives. This type of cancer is a heterogeneous entity, and its various subtypes demand dedicated treatment plans. Specifically, they give an in-depth discussion of contemporary practices and new systemic therapy models for breast cancer (Waks & Winer, 2019). These subtypes of breast cancers are described based on the presence and absence of markers for estrogen or progesterone receptors, together with human epidermal growth factor 2 (ERBB2). These subtypes are HER2-negative, triple-negative-negative, and hormone receptor-positive. In each of these subtypes, the molecular characteristics determine some treatment options and the prognosis. From the reviews, it is important to note that the survival outcomes differ across subtypes. Triple-negative breast cancer without conventional molecular markers is extremely high risk for recurrence compared with the hormone receptor-positive and ERBB2-positive subtypes (Waks & Winer, 2019). This is illustrated by the large divergence in 5-year breast cancer-specific survival rates that highlight the importance of individualized treatment.

According to Ji Young You et al. (2023), the treatment for non-metastatic breast cancer depends on the tumor subtype. The vast majority of patients with hormone receptor-positive tumors are treated with endocrine therapy; some of these patients may also receive chemotherapy. The management of ERBB2-positive tumors is done by giving targeted ERBB2 therapy combined with chemotherapy, while triple-negative tumors are mostly treated with chemotherapy. Systemic therapy in breast cancer is now guided by the molecular subtypes and the evolving precision medicine approach. Surgical resection is the main pillar of local therapy, while lumpectomy cases are complemented by postoperative radiotherapy. The emerging paradigm highlighted in the review is the growing trend of administering systemic therapy preoperatively, which will enable individual postoperative treatments based on response—a rapidly expanding field of study in breast cancer therapy.

Treatment strategies for metastatic breast cancer are mainly subtype-directed in order to prolong life and relieve symptoms. The reviews by (Ji Young You et al., 2023; Waks & Winer, 2019) highlights the striking difference in median overall survival between subtypes, with metastatic triple-negative breast cancer having a narrower window compared to others. This underscores the need for the evaluation of tumor subtypes during the design of efficient therapeutic interventions (Ji Young You et al., 2023). Hence, this is a guide towards choosing the treatments according to subtypes, tumor stage, and preference of the patient. This focus on tumor biology and subtype-dependent therapies heralds a new paradigm in the management of breast cancers, including personalized medicine.

Overview of Natural Supplements and Plants to Support Breast Cancer Patients

Common approaches involve depending on natural supplements to alleviate diverse side effects in breast cancer patients or turning to phytotherapeutic products for relief. Lopes et al. (2017) point out that women with a history of breast cancer mostly employ phytotherapeutic products and nutritional supplements as alternative or complementary therapies. The second leading cause of cancer-related mortality in women is breast cancer, warranting the need to evaluate complementary therapies like phytotherapy and nutrition

supplementation (Lopes et al., 2017). Fortunately, most of these modality complements are sought with the objective of relieving the usual Cancer symptoms and side effects associated with conventional therapies. However, an important caveat raised by the article is that these supplements are not well-regulated and lack scientific proof.

Natural products exhibit complexity and multifaceted targeting, leading to potential synergies and complexities. These may involve metabolic interactions or simply manifest synergistic effects. They can also reduce or negate the therapeutic benefits of common cancer therapies (Lopes et al., 2017). Furthermore, the lack of good scientific evidence calls for more rigorous clinical trials to determine the safety and usefulness of these complementary therapies. The tabulated summaries of clinical effects from the article emphasize the heterogeneity of phytotherapeutic products and nutritional supplements administered in breast cancer therapy. These supplements demonstrate various effects throughout different phases of breast cancer history: pre-treatment preventive effects, use during standard treatments after diagnosis, and post-treatment survival (Lopes et al., 2017). For example, flaxseeds and green tea are useful preventive measures, while *U. tomentosa*, *Curcuma longa*, and vitamin combinations support treatment phases (Lopes et al., 2017). The clinical data presented outlines specific supplements with their functions in various phases of breast cancer, including treatment augmentation and immunological support during the post-treatment survival period.

Understanding the Mechanisms of Natural Ingredients

Black Cumin Seed Oil

One of the most important natural remedies that can be used in the management of breast cancer is black cumin seed (*Nigella sativa*) oil and its active compound, thymoquinone. In this natural product, Chaudhry et al. (2017) probe the inhibitory role of thymoquinone on breast cancer cell proliferation in MCF-7 and MDA-MB-231. In this context, their objective was to determine the minimum effective dosage of black cumin seed oil and TQ to halt the growth of malignant cells while preserving the integrity of normal cells. It is important to note that TQ exhibited a great ability to hinder the growth of MCF-7 and MDA-MB-231 cells. Nevertheless, Ballout et al. (2018) used high TQ concentrations above the lowest effective dose. Hence, their translational ability becomes limited. In addition, the existence of lipid-carrier molecules is another factor that could have a profound influence on the experimental procedures, hence requiring more examination.

Chaudhry et al. (2017) study highlights the establishment of minimum effective dosages for black cumin seed oil and TQ: For black cumin seed oil, 3 μ L; and TQ, 1.0 μ M. It inhibited the proliferation of MDA-MB-231 cells for about twenty-nine percent, yet in the less aggressive MCF-7 cells, these concentrations only caused a modest growth of 15 to 17 % (Chaudhry et al., 2017). This implies that the efficacy should be balanced against the harm to non-aggressive cells. It is interesting to note that the time dependency of TQ's effectiveness is compared to that of black cumin seed oil. This distinction shows that the performance for TQ might depend more on the duration of exposure rather than that of black seed oil. Such a delicate sense of their temporal effectiveness could shape treatment methods, thereby improving the precision and effectiveness of treatment approaches. Based on the implications of the study, minimum effective doses of black cumin seed oil or TQ should be used for the purpose of breast cancer therapy. However, this approach promises to reduce the aggressiveness characteristic of some cancer cells without harming non-aggressive cells (Chaudhry et al., 2017). This research, in particular, sets the stage for more inquiries and future studies that will seek to establish the optimal treatments for breast cancer using black cumin seed oil and TQ. As pointed out in the study, it is important to note that the findings are preliminary and require further translational studies and human clinical trials to verify the efficacy and safety of these findings in human breast cancer cases. The study provides a new avenue for exploiting nature against cancer and the use of black seed oil and thymoquinone effective versus non-aggressive cell damage in breast cancer.

Akrom & Darmawan (2017) analyzed the tolerability and safety of black cumin seed oil in healthy subjects through a randomized study. The phase 1 clinical trial comprised three groups that were divided according to the dose level administered and a total of 36 normal individuals. Group I received 1 \times 3 mg of BCSO soft capsules daily. Group II was given twice the content of Group one (2 \times 3) and three times for Group III (3 \times 3) soft capsules. This was designed to evaluate the influence of BCSO on hematology, liver enzymes (AST/ALT) levels, urea and creatinine levels, as well as immune response (Akrom & Darmawan, 2017). On the 21st day of adminis-

tration, blood cell counts, AST/ALT levels, urea and creatinine concentrations, and immune cell parameters were measured. BCSO administered at different doses did not affect blood cell counts, liver functions (AST/ALT), urea, creatinine, and immune parameters significantly from initial values in this study. However, in statistical analyses, there were no significant differences ($p > 0.05$) among such parameters that testify to BCSO tolerability and safety at a dose "1.5 ml" as well as '3 ml' or even '4.5 ml/day" for about three weeks applied in healthy volunteers.

Akrom and Darmawan (2017) studied the tolerability safety profile of BCSO oral administration in healthy subjects for 20 days. Normal volunteers to a phase I clinical trial received 36 people, and each group received various doses of BCSO. Group I had 1×3 BCSO soft capsules daily, Group II 2×3 , and Group III 3×9 . The objective was to determine the effects of BCSO on hematology, liver enzymes (AST/ALT), urea/creatinine levels, and immunologic response. On the last day of the 21-day administration, blood cell counts, AST/ALT levels, and immune cell parameters were evaluated. First of all, the administration didn't cause significant alterations in blood cell counts, including liver enzyme levels (AST/ALT), except the normal range for urea and creatinine were shed: pre- and post-immunotherapy cell parameters (Akrom & Darmawan, 2017). The tolerability and safety of 1.5 ml, 3 ml, and 4.5 ml per day BCSO for a duration of three weeks in healthy subjects was evidenced by mean values on these parameters not showing any significant difference statistically ($p > 0.05$). Including these findings in the discussion of the benefits of black cumin seed oil to breast cancer support is important.

This study by Akrom and Darmawan (2017) confirms the safety profile for BCSO intake at various doses, which has been shown to be well-tolerated in healthy subjects. Considering safety parameters for natural supplements for cancer management, especially for possible side effects or adverse reactions. These findings inform on the safety threshold and tolerance in a healthy population in the context of breast cancer treatment where BCSO is considered as an adjunctive therapy. However, the study does not directly deal with cancer patients, but it provides a basis by showing that consumption of BCSO, even in relatively higher doses, has no significant adverse effects on important health markers among healthy people, providing hope for its possible incorporation in the overall treatment regime (Akrom & Darmawan, 2017). However, as the author pointed out, it is important to note that some of these findings cannot be generalized directly to cancer patients. Rigorously conducted investigations in cancer cohorts are needed to determine the safety, efficacy, and possible interactions of black cumin seed oil in cancer management. Integrating these safety considerations into the existing efficacy studies on black cumin seed oil in cancer cells should provide a more comprehensive understanding of the role black cumin seed oil may play in support of breast cancer treatment.

Resveratrol

Resveratrol, a nonflavonoid polyphenol found abundantly in dietary sources such as grapes, berries, soybeans, pomegranates, and peanuts, has demonstrated significant potential as a phytochemical for preventing and addressing breast cancer. Sinha et al. (2016) conducted a study investigating the comprehensive role of Resveratrol in breast cancer, encompassing aspects like tumor proliferation, metastasis, epigenetic alterations, and apoptosis in vitro. The study also highlighted Resveratrol's crucial role in sensitizing cancer cells to chemotherapy, overcoming the common challenge of drug resistance in cancer therapy. Additionally, Resveratrol acts as a phytoestrogen and aromatase inhibitor, implying that it might be useful in managing hormonal pathways implicated in breast cancer advancement. Furthermore, the effect of Resveratrol on stem cell therapy and adjuvant treatment emphasizes the multiple ways through which Resveratrol may contribute to breast cancer management (Sinha et al., 2016). The review demonstrates the great promise of Resveratrol while also highlighting that more studies need to be carried out to deal with the present restrictions to realizing this promise in regard to breast cancer prevention and treatment. Such a study thus gives a genetic basis for future investigations and application of Resveratrol as a treatment therapy against breast cancer.

Alamolhodaie et al. (2017) explain potential tactics that may be used in the provision of Resveratrol as a molecule to reverse multidrug resistance (MDR) in breast cancer. In this context, some of the breast cancer therapy problems include drugs from numerous classes and high levels of heterogeneity among patients, adverse effects of combinations, as well as re-emergence of drug resistance to various treatments (Alamolhodaie et al., 2017). This review underscores Resveratrol's role as a potential phytonutrient with a focus on its phytoestrogenic properties in the management of breast cancer. Phytoestrogens, present in soy, vegetables, and fruits, include

isoflavonoids, flavonoids, stilbenes like Resveratrol, and lignans. Particularly, trans-resveratrol has antioxidative, anticarcinogenic, and anti-tumor properties, as well as estrogenic and anti-estrogenic activity.

This study is in agreement with Sinha et al. (2016), demonstrating multiple advantages of Resveratrol in breast cancer treatment. The ability of the compound to reverse drug resistance in various in vitro cell systems through sensitization of tumor cells to other chemotherapeutic agents is emphasized. Relating this study to the benefits of Resveratrol in breast cancer depicted by Sinha et al. (2016) reveals its full potential. Unlike Alamolhodaei et al.'s (2017) study, which focused on various molecular processes and therapy attributes concerning Resveratrol, this current research delves deeper into its ability to fight against cancer drug resistance, which is a major setback in cancer management. The collective evidence underscores the adaptability of Resveratrol in treating breast cancer. Its therapeutic potential resides in its capacity to enhance the sensitivity of cancer cells to chemotherapy, offering a potential solution for overcoming drug resistance. Resveratrol may be a friend who helps to improve the effectiveness of the drugs used, especially where drug resistance is the barrier.

Turmeric

A study by Wright et al. (2013) sheds invaluable light on the bioactivity of curcuminoids and metabolites in breast cancer. It examines the potential of curcuminoids, the main compounds of turmeric, in preventing the growth of human breast cancer cells and the secretion of parathyroid hormone-related protein (PTHrP), which plays a major role in cancer bone metastasis. The study evaluates the effects of chemically intricate turmeric extracts, resembling traditional medicinal preparations, focusing on the three primary curcuminoids (curcumin, bis-demethoxycurcumin, and demethoxycurcumin). An important finding is that these turmeric extracts, containing various additional natural agents like essential oils and polar compounds, demonstrated comparable effectiveness in both inhibiting the growth of breast cancer cells (MDA-MB-231) and secreting PTHrP (Wright et al., 2013). Significantly, these effects were associated with curcuminoids and not with extracts from botanically related ones such as gingerol.

Wright et al. (2013) further explain that curcumin and bis-demethoxycurcumin have potency comparable to natural curcuminoid mixtures. Demethoxycurcumin, however, was ineffective in this regard. However, all individual curcuminoids, including demethoxycurcumin that did not suppress cell growth considerably, inhibited PTHrP secretion, too. This underscores the complex functions of these compounds in various manifestations of breast cancer. The study also focused on curcuminoid metabolites. Some degradative metabolites, such as vanillin and ferulic acid, were found to have no inhibitory effects on cell growth and parathyroid hormone-related protein (PTHrP) secretion, while other reduced metabolites, such as tetrahydro curcuminoids were found to be inhibitory. The findings also question recent assertions suggesting a specific association between the observed anti-cancer effects of studied curcuminoid metabolites and any particular curcuminoid metabolites. The study, however, emphasizes the structural and biological aspects of curcuminoids themselves in the anti-breast cancer effects of turmeric. In their comprehensive exploration, Wright et al. (2013) show that curcuminoids are the main actors in the tumor suppression effects of turmeric. Differential impacts on cell growth and PTHrP secretion by the three main curcuminoids provide insights into their specific roles in breast cancer management. In addition, the research provides essential information on the weak nature of some metabolites, refuting their purported role in turmeric's anti-cancer effects.

Fabianowska-Majewska et al. (2021) explore curcumin as a DNA methylation-modulating agent in breast cancer inhibition. Curcumin, an agent found in the rhizome of the plant *Curcuma longa* L, has received a lot of attention for its potential ability to target epigenetic mechanisms such as DNA methylation, which is a key player in cancer development and progression. DNA methylation is a dynamic process that occurs in different diseases, such as cancer (Fabianowska-Majewska et al., 2021). Breast cancer, one of the most diagnosed and fatal cancers among women globally, has certain DNA methylation patterns like hypermethylation of tumor suppressor genes, alteration in methylation pattern in oncogenes, and genes associated with metastasis.

Fabianowska-Majewska et al. 2021, suggest that curcumin can change the abnormal DNA methylation patterns observed in breast cancer. Curcumin targets dysregulated epigenetic events that could either prevent cancer development or augment conventional anti-cancer drugs. It is crucial to indicate that curcumin is multi-dimensional in reversing hypermethylated and hypomethylated can-

cer-related genes. Therefore, through a comprehensive review of this study, the promising role of curcumin in cancer chemoprevention and how it might influence epigenetic mechanisms may be revealed. It highlights the importance of unraveling the exact epigenome modifications caused by curcumin as well as the specific genes implicated in breast cancer development (Fabianowska-Majewska et al., 2021). In addition, the study provides clues that other bioactive constituents from the turmeric root could also act as epigenetic modifiers, indicating a more comprehensive approach involving turmeric beyond turmeric for potentially helpful effects in breast cancer therapy.

Raspberry Ketones

Choi et al. (2014) examined the inhibitory potential of commonly consumed berries, including raspberry ketones, on certain UGTs. These enzymes are important in drug metabolism, especially in drug conjugation with glucuronic acid elimination. It was found that raspberry ketones had a weak inhibitory effect upon UGT2B7 only with an $IC_{50} = 248 \pm 28.2 \mu\text{g/mL}$. These results indicate that raspberry ketones have a slight effect of inhibiting the activity of this drug-metabolizing enzyme. Nevertheless, one must also observe that although this inhibitory effect in vitro was reported, the study did not reveal any significant influence of raspberry ketones on irinotecan's pharmacokinetics and SN-38 metabolism in vivo. This implies that raspberry ketone inhibitors were of a very weak nature towards the UGT2B7 in a laboratory. However, the inhibition was not clinically significant in the case of drugs metabolized through UGT1A1, at least in the case of the studied drug.

Hence, according to Choi et al. (2014), raspberry ketones consumed with popularly consumed berries are unlikely to result in considerable herb-drug interactions on drug metabolism mediated by UGT enzymes. The observed weak inhibitory effects in vitro did not significantly change the drug metabolism in vivo, highlighting the significance of considering both in vitro findings and clinical implications. The study may reveal the metabolizing impact of raspberry ketones on other drug-metabolizing enzymes and how it affects other medications to ensure complete safety guidelines for herbal formulations.

Apple Cider Vinegar

Rani et al. (2022) examined the use of apple cider vinegar (ACV) for the production of silver nanoparticles (AgNPs) and evaluated their possible anti-cancer activity against HeLa cells as a model for cervical cancer studies. Recently, the green synthesis of AgNPs has been in the limelight due to its eco-friendly aspect. It uses ACV as a bio-reducing and stabilizing agent. The synthesis of AgNPs was confirmed using characterization techniques such as FTIR, UV-visible spectroscopy, SEM, and HPLC. Different assays were used to evaluate the anti-cancer effects of these AgNPs derived from ACV. The MTT assay led to dose-dependent cell inhibition of HeLa cancer cells: 50.66% cell viability at 100 $\mu\text{g/mL}$ and 90.50% cell viability at 10 $\mu\text{g/mL}$. When the IC_{50} value was calculated (90 $\mu\text{g/mL}$) for dose-dependent cytotoxic effects, it could be revealed that biosynthesized AgNPs have this impact on HeLa cells as well.

Secondly, DAPI and PI staining helped understand the cytotoxic effects at a cellular level. PI staining showed higher PI-positive cells with increasing concentrations of AgNPs, indicating more membrane-damaged and necrotic cells. DAPI staining also showed increased cell permeability as the AgNP concentration increased, showing an increasing apoptotic efficiency of AgNPs in HeLa cells as a dosage-dependent phenomenon. Further, intracellular reactive oxidative stress (ROS) analysis revealed a dose-dependent increase in ROS generation as compared to the control. The increase in oxidative stress is an indication of early apoptosis in HeLa cells brought about by the AgNPs, showing their ability to induce cell death via oxidative stress processes. The results of this study support the anti-cancer capacity of ACV-made AgNPs that lead to apoptosis and cytotoxicity effects in HeLa cells. These encouraging results pave the way for the use of ACV-extracted AgNPs in therapeutic and pharmaceutical applications for the treatment of cancer. Nevertheless, the mechanisms of action require further research; their efficacy in more diverse cancer cell lines, as well as in vivo models, need to be investigated for validation of their clinical relevance and safety as a therapeutic agent.

Aloe Vera

Aloe-emodin (AE) is the compound found in Aloe Vera leaves, is the subject of the study by Fakhari et al. (2014). Recently, Hydroxy-anthraquinone named Aloe-emodin, which has been shown to have antiviral, antimicrobial, and hepatoprotective activity, has been drawing interest. However, this study focuses on its impact on breast cancer using the human breast cancer cell line MCF-7. Studies of compounds like Aloe-emodin for their anti-cancer potential might open up new frontiers in the treatment of cancer. The impact of the Aloe-emodin on the MCF-7 deaths for each time interval was evaluated using various concentrations of this compound. The viability of MCF-7 cells decreased with the increase in dose and time for aloe-emodin. The most important effect was observed after 3 days of treatment at a concentration of 100 μ M. Lastly, apoptosis and the CD95 (Fas) expression were done to determine this decrease in cell viability. Annexin-PI and Fas (CD95) expression measured by flow cytometry analysis 72 hours after treatment showed that the most apoptosis is induced in a concentration of 100 μ M Aloe-emodin. Aloe-emodin is thought to encourage apoptosis, a critical element in the other two in repressing cancer cells, particularly breast cancer cells.

The results on Aloe-emodin-induced apoptosis and Fas expression suggest the compound could be used as an anti-cancer agent on breast cancer cells. Therefore, these perceptible results call for more generalizable exploratory *in vitro* and *in vivo* research. More research is needed to determine mechanisms for Aloe-Emodin's anti-cancer effects and the viability of the compound in breast cancer therapy. Therefore, the research of Fakhari et al. (2014) emphasizes the necessity to explore new cancer drugs from natural product components Aloe vera and Aloe-emodin. Despite the fact that these findings may be encouraging, additional trials with more evidence are necessary to provide the facts of safety and efficacy as well as suitability for clinical use. Additionally, further studies on animal species or clinical trials can offer more elaborative data about the entity and its effectiveness in helping fight the disease. This may indicate novel approaches in cancer therapy.

In addition, Jiang et al. (2020) provide more details of anti-cancer activities expounded for AE extracted from Aloe vera against BT cells. The present work is dedicated to the molecular basis of AE-mediated growth inhibition and apoptosis induction in breast cancer cell lines. The study exposed the AE to MCF-10A, MCF-10AT, MC-F7, and MD-MB 231 cell lines. This study found that there was selective growth suppression and subsequent apoptosis activation in MCF-10AT and MCF-7 cells but had no significant effect on the growth of MDA-MB-231 or puppy kidney epithelial cells, virally transformed with SV40 (COS7) lines.

The research also explored how AE acts on these cells at the molecular level. In MCF-10AT and MCD-7 cells, AE significantly decreased the levels of Bcl-2 and Bcl-xl protein in a dose-dependent manner while showing an increase in the expression of Bax protein. The changes in protein expression were in line with the changes observed at the level of mRNAs for Bcl-XL and BAX, implying that AEs could have some role in the translational activity of these genes. Interestingly, AE had no effect on Bcl-2 mRNA levels, but the study postulated miRNA control of Bcl-2 protein expression (21). They used an AE concentration of 20 - 80 mg/ml, with which they established that it led to downregulation of miR-15a and miR-16-1, two of the various microRNA (miRNAs) binding to the 3' UTR sequence on Bcl-2. This would facilitate AE reversal of the cell growth suppression and its reciprocal fallen redoing of mRNA inhibition and Bcl-2 down-regulation. This suggests that this is the effect of AE on these mRNA. The work of Jiang et al., 2020, adds to that of Fakhari et al., 2014, reinforcing the potentiality of Aloe-emodin to inhibit breast cancers only. Investigating complex molecular mechanisms, especially miRNAs like miR-15a/miR-16-1 that downregulate BCL2 and induce apoptosis in breast cancer cells, helps one understand how AE acts against breast tumor cells. Exploration of its mechanism continues reiterating Aloe-Emodin's candidature as a possible remedy against breast cancer in future approaches.

D-Ribose

Estrada-Pérez et al. (2022) carried out research on the influence of valproic acid, an HDACi, on breast cancer cell lines (MCF7) using LC-MS/MS metabolomics. Curiously, the research established that VPA activated different metabolic pathways, which included PPP and catabolism of 2'-deoxy- α -D-ribose-1-phosphat, on the importance of breakdown of 2'-deoxy- α -D-ribose-1-phosphate in relation to breast cancer treatment. It goes via d-ribose, which is important in nucleotide synthesis and cellular production of energy.

The altered ribose metabolism implicated in the observed changes caused by VPA points towards this association. Disruptions of cellular pathways dependent on D-ribose metabolism may affect various mechanisms important for cancer development. For example, reduced rate of division and growth of cell populations, disturbed energy sources, and increased ROS levels may jointly hamper the survival and proliferative capacity of cancer cells.

Finally, the study proposes a role for mechanisms such as ferroptosis through dysregulation of L-cysteine. There is growing awareness that ferroptosis, the build-up of lipid peroxides, could be an approach to treat cancers. The knowledge about the effect of VPA treatment on cancer cells with altered D-ribose metabolism gives a hint into therapy. These metabolic pathways, particularly D-ribose, should be considered in developing novel approaches for breast cancer treatments. Metabolomic studies show the need to know more about the complicated mechanisms through which HDAC works in a way similar to VPA and open new corridors for medical therapy of breast malignancy management.

Case Study: Patient Profile and Treatment

<i>Aspect</i>	<i>Details</i>
Patient Information	A 58-year-old female with a lump in the right breast leading to further investigations.
History	No family history of breast cancer.
Diagnostic Tests	Mammography, breast and axilla ultrasound, MRI, PET CT, and core biopsy revealed malignancy in the right breast.
Diagnosis	B5 Carcinoma lobular mammae.
Treatment Plan	Integrated natural ingredient protocol alongside conventional treatments.
Natural Ingredient Use	Utilizing a protocol involving various natural supplements targeting immune support, antioxidants, and more.
Proposed Diet	Personalized diet plan for over 10 years, exercises for mental and emotional well-being integrated into therapy.

Table 1: Patient Information.

Imaging test results and core biopsy confirmed diagnosis of cancer of the breast—carcinoma lobular mammae. Afterward, a specialized protocol was devised by combining naturally sourced products. The purpose of this protocol was to supplement traditional therapies with an emphasis on immunity boosting, administration of antioxidants, and holistic health practices. Further, the therapy design incorporated a personalized diet for life and exercises to aid mental and spiritual health. This approach aimed at ensuring that the patient was supported physically through taking medications and supplements, as well as maintaining a healthy diet and exercising while undergoing chemotherapy for breast cancer treatment.

Protocols for Integrating Natural Ingredients in Breast Cancer Care

Presentation and explanation of a specific breast cancer protocol integrating natural supplements

Using natural supplements for the management of breast cancer, one needs to be particularly careful, as illustrated by the specific example of a 58-year-old woman who developed lobular breast carcinoma. There is no published study about the efficacy of using these natural substances (proprietary blends) in this way; however, we expect that using them safely without interfering with effective cancer treatments or causing significant side effects could result in good outcomes for our patients.

- i. Proprietary Blend I: The blend starts with 2X6 drops in the morning and in the evening for 3 days, each progressing by 1- 1 drops every 3 days until it reaches 2X10 quantities. Silica, vitamin C, and trace minerals in this blend are said to contain antioxidants, which could help reduce oxidation stress.

- ii. Proprietary Blend II: This blend consists of Black Cumin Seed Oil, Ribose, Resveratrol, turmeric, raspberry ketone, apple cider vinegar, and aloe vera. It starts with one sachet per day for three days and progresses. Their actions against cancer cells are associated with processes such as apoptosis induction, epigenetic modification, and metabolic changes that have been confirmed by research about breast cancer.
- iii. Proprietary Blend IV: It contains vitamins C, D, and zinc in measured quantities, beginning with 1/2 teaspoon per day for a week before upgrading to one teaspoon daily. These components are very important in immunomodulation as well as for cellular functioning, contributing to the cancer body's immune response.
- iv. Proprietary Blend V: Consisting of B-Nicotinamide Adenine Dinucleotide (NAD+), magnesium, quercetin, vitamin D, vitamin C, as well as vitamin K2, the mix begins with one teaspoon at night. These elements promote immunological boosts, DNA fixation, and general health provision in cancer treatment.
- v. Proprietary Blend VI: This blend starts at one capsule two times daily for seven days, then increases to two per day. It comprises Magnesium, Trace minerals, Quercetin, and Vitamins D, C, and K2 that help the body remain strong and improve cellular functioning.

Natural Ingredient	Source	Potential Benefits
Silica	Horsetail extract	Supports connective tissue health, aids in bone strength, and collagen formation. It may contribute to tissue repair and body structure.
Vitamin C	Various fruits and vegetables	Potent antioxidant, scavenges free radicals, reduces oxidative stress, supports immune function, and may aid in combating cancerous cell growth.
Trace Minerals	Zinc, selenium, copper, etc.	Essential for immune health, enzymatic reactions, and cellular processes. Supports overall metabolic function and immune system activity.
Black Cumin Seed Oil	Extracted from black cumin seeds	Rich in thymoquinone, exhibits antioxidant, anti-inflammatory, and potential anti-cancer properties. May reduce inflammation and support the body's defense against cancer.
Resveratrol	Grapes, red wine	Antioxidant, anti-inflammatory, and anti-cancer properties. Shows potential in inhibiting cancer cell growth and preventing tumor development.
Turmeric	Curcumin from turmeric root	Potent anti-inflammatory and antioxidant. Influences molecular pathways involved in tumor growth and metastasis, potentially aiding in cancer treatment.
Raspberry Ketones	Found in raspberries	Exhibits antioxidant and anti-inflammatory properties. May contribute to overall health and immune function.
Apple Cider Vinegar	Fermented apple juice	Contains acetic acid and antioxidants. May support detoxification processes and overall wellness.
Aloe Vera	Extracted from aloe vera plant	Known for anti-inflammatory and antioxidant effects. May aid in wound healing and support cellular health.
D-Ribose	Naturally occurring sugar molecule	Involved in energy production, potentially aiding in cellular energy restoration, supporting cellular function, and tissue repair.

A nutritional diet, as well as exercises aiming at good mental and emotional health, is essential too. The body's response to the treatment may also be supported by a diet that is rich in nutrients and anti-inflammatory foods. Emotional health is also included in the process of healing, comprising reduction of stress and strengthening of mental health; physical activities catered to patients' abilities add to that, contributing to an overall healthy condition. Such an all-inclusive way together with the patient's sticking to this treatment for three months, proves that a wholesome approach is a crucial issue in cancer treatment. It is crucial to follow up regularly clinically and radiologically to evaluate responses to therapy and patients' safety. However, by combining the protocol with those that will work best for individual patients, effective collaboration alongside medical professionals can help enhance effectiveness and safety throughout the period of treatment.

Challenges and Limitations in Using Natural Ingredients

Interactions and Side Effects

Drug Interactions

The integration of natural supplements, such as black cumin seed oil (BCSO), Resveratrol, and other complementary and alternative medicine (CAM) modalities, into conventional breast cancer treatments introduces a critical concern: potential drug interactions. Although many people consider the supplements to be natural and safe, they cannot be combined with prescribed medications without unexpected consequences for the effectiveness of the treatment and the patient's health. Bioactive components in BCSO are known to affect drugs metabolized by the liver. The liver has enzymes, including the cytochrome P 450, which assist in the breakdown of many medications. These enzymatic pathways, however, may be interrupted by BCSO components that would lead to impaired breakdown and excretion of drugs metabolized via similar pathways. Therefore, this could change the amount of medication in the blood system, making it less effective or increasing its side effects.

In a similar way, Resveratrol, which is known as an antioxidant agent found in red grapes and some berries, has been attributed to healthy attributes. This is because it can also disrupt the CYPDrug-metabolising enzyme pathway, such as the CYP3A4. Interaction of Resveratrol with some chemotherapy agents and hormonal therapy drugs applied mainly in breast cancer may cause them to be more effective than expected but can also increase potential side effects. Healthcare practitioners must exercise caution in order to safeguard their patients against unanticipated complications due to the increased complexities that result when drugs interact with each other. It is important to understand that patients undergoing breast cancer treatment may not necessarily reveal their use of CAM modalities as they are perceived to be harmless and might seem insignificant in relation to the overall treatment plan. The failure to communicate makes it hard to establish any likely risk factors that exist for this type of interaction.

Hence, this case study requires an upfront role where there are free discussions with patients on their CAM activities. Patient encouragement for the disclosure of all supplements such as BCSO, Resveratrol, and others helps for a thorough assessment of possible interactions. Such conversations allow health professionals to develop therapy schemes, adjust dose regimens, or take other precautions to minimize adverse results related to medicine interferences on a comprehensive approach towards breast cancer care.

Choi et al. (2014) investigated naturally occurring raspberry ketones, which inhibit certain enzyme activities linked to drug metabolism. Raspberry ketones have a low inhibition towards some UGTs, including the ones that are responsible for the removal of substances like drugs from the body. This raises important issues about whether raspberry ketones can inhibit drugs and medical treatments that are processed from the UGT enzyme. Though the inhibitory findings obtained in the study were rather modest, one should nonetheless acknowledge that even low interaction may result in dramatic consequences for cancer patient's treatment. Examples of metabolic pathways include the use of numerous oxidative enzymes like UGTs in drugs that are employed during breast cancer therapy, particularly hormonal therapies and some chemotherapeutic drugs. Any impairment in these metabolic pathways, even slight, will alter the pharmacokinetics and potency of these medications.

The study by Choi et al. (2014) is worth mentioning as it pointed out the low activity of UGT2B7 when using raspberry ketones. It involves the breakdown of different substances, which includes some of the breast cancer drugs, UGT2B7. The observed inhibition may not necessarily be clinically significant in itself, but the cumulated effects or interactions with several drugs could alter the clinical response to breast cancer medications. Hence, one should always be aware of the possible drug interactions associated with taking raspberry ketones supplements. The results might imply the limited anti-inhibitory effect. However, it should be observed with care if a patient uses both prescribed breast cancer treatments and the raspberry ketones or supplements containing it. Therefore, frequent evaluation of the patient response and a careful dialogue on additional substance application may be necessary for reducing possible complications and effective therapy.

Efficacy and Dosage Control

Using natural supplements in treating breast cancer proves extremely challenging in terms of effectiveness and regulation. Several different studies have made positive predictions about these supplements, but they may not work equally well for different people because absorption, metabolism, and an individual's general state of health play a role in this. Such studies reveal potential benefits associated with these supplements under specific circumstances. For example, Rani et al. (2022) focused on exploring the anti-tumor efficacy of green synthesis of AgNPs using apple cider vinegar. Though this study showed some encouraging results, such as inducing cancer cell death, the use of dosage in the clinic should be approached with due care.

It is one of the most important factors that need to be emphasized, and in particular, apple cider vinegar dosage management. Rani et al., 2022 studied the use of apple cider vinegar for nanoparticle synthesis and its effect on cancer cells in vitro. However, more research is needed to establish safe and appropriate dosages that could be administered clinically. The study suggests possible applications, but further research is needed to derive safe and manageable amounts that can be consumed by humans. Additionally, people experience variable efficacy, which exacerbates this complexity. It is pertinent to note that the variations in metabolism, personal absorption rates, and general health status, among other factors, greatly contribute to the reactions of these supplements inside the body. Standardized treatment is difficult to have on the grounds that what works magic in the case of one patient might end up being utterly useless to someone else.

As it relates to the case study, where treatments are highly person-focused, one understands the importance of individual variants towards those supplements. The effectiveness and safety of these products may be influenced by patients' varied health problems, simultaneous use of several medicines, and metabolic peculiarities. These require in-depth clinical studies that look beyond merely the possible advantages to the complex issues of dosage control and individual variation. These supplements should be integrated safely into breast cancer treatment protocols, and collaboration among researchers, clinicians, and regulatory bodies is necessary.

Safety Concerns

There is a need to understand natural supplement side effects and how they affect the outcome. Although there are trials on the tolerance of healthy subjects for BCSO like that by Akrom and Darmawan (2017), indicate that this tolerance is possible, some people can nevertheless have allergic and GI problems, justifying why monitoring is needed as well as evaluation individualism. In addition, trials of Resveratrol and curcumin also showcase reservations with large amounts. While lauded to have tremendous potential in cancer therapy, Resveratrol, in excess, could potentially evoke other unfavorable consequences. Likewise, taking large portions of food may stimulate excessive secretion of liver enzymes or induce stomach upset, and for this reason, it is vital to adhere to proper dosing guidelines. It is worth noting that turmeric contains one of its main active substances, curcumin, which demonstrates a great anti-inflammatory effect, but some patients may experience problems associated with overuse. Hence, monitoring dosage and the consideration of individual sensitivities becomes paramount in order to control such detrimental effects and exploit their benefits.

Fakhari et al. (2014) report that it is an excellent prospect for aloe vera in the anti-tumor effect. Although, there is a need for more research to prove its suitability in an anti-cancer therapy. Therefore, safety and tolerance studies of Aloe-emodin should be performed in relation to any side effects and its interaction with conventional drugs prior to clinical application. Metabolite D-ribose with poten-

tial for therapeutic use. Nevertheless, the question of how efficient it is in cancer treatment is still questionable and need to be further described. Its role in energy production and cellular function is an interesting, but also thorough analysis regarding its safety profile has to be conducted focusing specifically on oncological settings. The question is about open observation, personal evaluation, and more medical investigation with links under strict safety considerations. Nonetheless, natural supplements used during breast cancer treatment must be considered well with regard to probable side effects in addition to an individual's health risks. Proper dosages, side effects and the most objective medical testing must be outlined. Multidisciplinary initiatives such as these should involve researchers, clinicians and regulators to ensure the safety and effectiveness of incorporating natural supplements into breast cancer treatment guidelines. Through this strategy, their positive characteristics would be exploited without exposing cancer patients to any potential risks.

Patient Perspectives and Acceptance of Natural Ingredients Exploration of patient attitudes, beliefs, and experiences

It is paramount in developing viable therapeutic approaches for patients to understand the patient's standpoint and accept natural ingredients in breast cancer treatment. Evidence-based patient choice (EBPC) focuses on informed involvement in matters of health care. The work of Ford, Schofield, and Hope (2003) highlights crucial elements comprising an EBPC consultation and considers the views of professionals as well as laypersons. Many patients' views about treatment choices, including nutritional supplements in a breast cancer cure, center upon information availability and medical evidence. This further underlines the need for awareness of research findings among both doctors and patients in line with the core tenet of evidence-based medicine. This has been consistent with our review of several relevant research studies on natural products such as Resveratrol, curcumin, and aloe vera, in which evidence-based information was important for understanding their possible impacts on breast cancer.

The EBPC method also advocates for joint decision-making with patients actively participating in the selection of management strategy. This aligns with the various findings discussed in the literature review. Certain studies emphasize potential natural ingredient advantages, but others describe their limitations and contradictions. Similar views of the patients (as the study participants) could be different about their involvement in decision-making and the level of guidance required by the healthcare givers. For this reason, healthcare professionals using this approach in breast cancer care must openly discuss natural supplements. These include clear evidence-based information on these components and their effects with regard to possible complications.) Diversity in patient perspectives makes it essential to engage in customized consultations that are tolerant of diverse preferences, values, and comprehension of natural products. From this finding, it is evident that there were no clear, practical measures indicating how to integrate EBPC into consultations. The same is happening with respect to using natural supplements as part of breast cancer treatment. There is empirical support, but organized frameworks and guidelines are required to accommodate variability in patients' preferences about the level of decision-making.

The work presented by Kavita et al. (2015) explores CAM awareness, beliefs/opinions, and behavior among patients. A cross-sectional study was carried out in the outpatient department of a tertiary care teaching hospital, enrolling 100 patients. The results indicate that there is a high extent of awareness and practice of CAM among the participants. The overwhelming majority of people were familiar with CAM, as it was estimated that about 79.0%. Surprisingly, 46.0 % of the respondents indicated they were actively involved in CAM. The most popular system among CAM was Ayurveda, taking up 71.73%. This is in line with the contextual setting of India, where the age-old approaches of Ayurveda continue to play a significant role in the overall health system of this nation. Chronic conditions seemed more prone to seek treatment through CAM, as 30.43% of ailments were due to arthritis. A considerable number of patients used quacks (43.47%) and self-medicated (15.21%), implying an underlying trend towards unorthodox therapies. However, there were some respondents who thought that CAM was based on scientific evidence, implying a more complex notion about such treatments.

Nevertheless, various patient responses about CAM safety and efficacy versus modern medicine differed. About 20 percent of the respondents thought that CAM was safer than conventional medicines, and more women leaned towards this opinion. Respondents above forty years of age viewed CAM as more effective compared to conventional medicine. The concept that CAM offers a full cure is easily accessible and has fewer adverse effects; thus, it is considered one of its positives. On the other hand, high costs associated with some CAM therapies, lack of effective results for some diseases, and the provision of simple relief were listed. As such, this study emphasizes the importance of acknowledging the frequent utilization of CAM by patients and health practitioners. For that reason, understanding patient expectations, integrating conversations on CAM use into clinical history taking, and examining possible interactions between CAM and standard treatment are essential requirements for comprehensive patient care. Healthcare providers must watch out for possible drug interaction and the simultaneous use of a therapy like CAM, especially among seniors who are at a higher risk. Patient attitudes and practice toward CAM remains a difficult landscape that demands the healthcare practitioner to take into consideration patients' preference and practices within the conventional healthcare context.

Factors influencing patient acceptance or reluctance toward incorporating these supplements into their treatment plan

The acceptance or refusal to accept nutritional supplements as an important component in breast cancer management is determined by several factors. Angarita et al. (2018) evaluate several patient perceived elements that impact on old women's informed decisions concerning early stages of Breast Cancer. Among the studies included in this systematic review of qualitative data, ten were devoted to highly abstract issues that informed older women's decisions making while choosing breast surgical treatments. There were several specified factors of which quite a number of themes that considerably influenced decision making were noted.

- i. **Treatment Characteristics:** Various treatment-specific attributes proved instrumental in determining patient acceptability or otherwise of treatment. These included invasiveness, possible harmful side effects, and efficacy of perceived treatment. This is consistent with people evaluating the benefits as compared to the possibilities of harm resulting from medical treatments, such as the use of supplements (Angarita et al., 2018).
- ii. **Personal Goals/Beliefs:** Decision-making in this study was influenced by the extent to which a person's treatment goals matched his/her beliefs as well as the corresponding values associated with a particular course of treatment. More often than not, patients are concerned about the compatibility of treatments with the attainment of objectives, lifestyles, and beliefs. This would depend on whether the supplement is part of a patient's total health objectives and the individual philosophies she has regarding healthcare.
- iii. **Patient Characteristics:** The decision-making processes were based on each patient's respective background, health status, and individual circumstances. The acceptance of the use of supplements in their treatment regimen might depend on things like age, already existing health issues, and lifestyle choices.
- iv. **Physician's Recommendation:** Patients' choices were largely guided by the advice of healthcare experts. The trust placed in the caregiver's expertise and degree of shared decision-making between the patient and physician was also vital. Some of these natural supplements may be included depending on recommendations from a provider.
- v. **Personal/Family Experience:** Personal and/or family experience in relation to breast cancer or treatment influences a patient's decision-making. The perception and acceptance of alternative treatments, such as natural supplements, could be influenced by previous experiences or anecdotes from peers and family members (Angarita et al., 2018).

The variation within patient-reported measures across the studies highlights the multi-dimensional and patient-specific approach to making treatment decisions. Patient perceptions, experiences, as well as contextual considerations significantly affect their attitude of accepting or not toward adding supplements to their treatment regimen. In fact, breast cancer treatment that involves the use of natural agents requires a patient-centered approach, with health professionals understanding and addressing the multi-dimensional influences to promote informed and personalized decision-making processes.

The use of CAM in breast cancer patients at the initial stage of diagnosis constitutes an important aspect of patient behavior, which affects treatment choices and medical services. Zulkipli et al. (2017) studied how common CAM use is among newly diagnosed Malaysian breast cancer patients and what patterns can be observed as well as how likely patients are to disclose CAM use, adding valuable information regarding an initial stage on the patient. A total of 400 newly-diagnosed cases of breast cancer were interviewed in the research study conducted at the UMMC. These results demonstrated that 34.8 % of these patients were CAM users, which indicated a significant amount of CAM usage prior to pursuing conventional therapy (Zulkipli et al., 2017). Dietary supplementation was reported as the most common form of CAM employed at 77.0%, followed by Spiritual Healing at 28.8% and traditional Chinese medicine at 23.0%. Malay patients constituted the majority of these patients who used CAM (43.9 %), whereas the second highest was represented by the Chinese (41.0%) and the Indians formed the least (14.4%). Intriguingly, two-thirds of respondents (73.1%) admitted they never informed their medical doctors about using CAM (Zulkipli et al., 2017). However, it was driven by advice from families and friends.

Several key issues of CAM implementation by recently diagnosed breast cancer patients are indicated by the study's conclusions. Such modalities are important in patients' initial mechanisms of coping with the disease and healthcare-seeking behavior at this point in time. Nevertheless, nondisclosure by patients to healthcare providers raises questions about drug toxicity, interaction, and coordination with CAM treatment and orthodox medicine (Zulkipli et al., 2017). This brings light to social capital, ethnicity, cultures, and social networks affecting patients' utilization patterns for alternative medicine. Healthcare providers should be aware that the preferences and recommendations from people within the patient's family, friends, and colleagues significantly influence their preferences when making a decision about choosing an alternative treatment. However, failure to disclose CAM use presents difficulties in providing holistic and integrated treatment regimens (Zulkipli et al., 2017). Healthcare providers should be active in this process by creating an atmosphere whereby the patients feel free to discuss their CAM activities without any form of discrimination. This encourages teamwork that helps identify possible risks, formulate appropriate treatment options, and provide comprehensive care tailored to patients' practices and desires/preferences (Zulkipli et al., 2017). Furthermore, early-stage detection of CAM use by breast cancer patients highlights the importance of health-related practitioners' knowledge of different CAM modalities. With such information, they can take part in meaningful discussions about health issues, advise their patients, and guarantee safe healing through the integrative approach used.

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