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Short Title: Molecular insights into phytochemical-protein interactions: A paradigm shift in breast cancer therapy

RESEARCH ARTICLE

Molecular insights into phytochemical-protein interactions: A paradigm shift in breast cancer therapy

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Abstract

Breast cancer is among the most common cancers, and for cancer treatment, it calls for fresh strategies. Flavonoids as phytochemicals are natural bioactive compounds showing luminous prospects as anti-cancer given their specific action against proteins. The current work focuses on the impact of phytochemicals on proteins related to breast cancer as a new approach to therapy. The study looks at the performance of phytochemicals including CBD (Cannabidiol), THC (Tetrahydrocannabinol), and EGCG (Epigallocatechin-3-Gallate) concerning conventional chemotherapy drugs including paclitaxel and zoledronic acid. AutoDock Vina was used to predict the binding energy of phytochemicals and standard drugs to the target proteins in BCa progression, including *HER2* (Human Epidermal Growth Factor Receptor 2), ER (Endoplasmic Reticulum), *VEGF* (Vascular Endothelial Growth Factor), etc. Pharmacokinetic profiling was performed using ADMET prediction and toxicity screening was done using ProTox-II. Further, using ELISA (Enzyme-Linked Immunosorbent Assay) assays, the present study examined the alterations in the serum protein levels using phytochemicals *versus* standard drug in CA breast rat model. Data analysis was based on the level of statistical significance which was set at $p \leq 0.05$*. EGCG binds most strongly to *VEGF* (Vascular Endothelial Growth Factor) (-10.5 kcal/mol) and PR (Peregrine Falcon) (-9.7 kcal/mol) among all the flavonols investigated. THC had a better docking score for EGFR (-10.6 kcal/mol) while CBD had a better docking score with ER (-9.8 kcal/mol) and PD-L1 (-9.8 kcal/mol). By the ADME (Absorption, Distribution, Metabolism, And Excretion) analysis, the intestinal absorption, permeability, and oral bioavailability of phytochemicals showed moderate to a high level of 20%-60% consequently, the level of hepatotoxicity and mutagenic potential had a low level. Quantification of serum proteins also revealed reduced *HER2* levels in the EGCG group (2.12 ng/mL ± 0.39 ng/mL) than in the control group (3.21 ng/mL ± 0.47 ng/mL. EGCG also increases the level of ER (5.22 ± 0.74 ng/mL, p=0.011) and decreases Ki-67 (1.22 ng/mL ± 0.23 ng/mL, p=0.02). Phytochemicals were evaluated by toxicity analysis to be safer than the chemotherapeutic drugs commonly used to treat different types of cancer. The study sheds light upon the effects of phytochemicals such as EGCG, and cannabinoids like CBD (Cannabidiol) and THC (Tetrahydrocannabinol) in regulating BC related proteins. These compounds have been considered highly effective and safe compared to traditional medicines making the management of breast cancer quite different. Further *in vivo* and clinical investigations are needed to confirm these results and enable the future translation of the approach.

Keywords: Phytochemicals, Structure-biology activity, Breast cancer, *VEGF*, *HER2*, Cannabidiol, Epigallocatechin-3-gallate, Cytotoxicity, Absorption-distribution-metabolism-excretion, Protein expression

Introduction

CBreast cancer continues to be the second most common cancer that causes death in women; therefore, there is a need for advanced therapeutic strategies for patients with the disease (Lau, et al. 2022). The first-generation chemotherapeutic drugs, while quite effective, are associated with toxicity and emergent drug resistance; there is therefore a need to look for more effective means (Eslami, et al. 2024). Flavonoids for example, phytochemicals, bioactive compounds obtained from plants have recently drawn immense interest due to their anticancer properties, lower toxicity, and the ability to address multiple molecular targets (Choudhari, et al. 2020). Thus, the ability of phytochemicals to interfere with proteins, the signalling molecules and enzymes that underlie breast cancer progression, is an area of research described as promising. These interactions can also positively or negatively influence important features of the cell life cycle, including cell division, cell death, new vessel formation, and cancer spread (Koh, et al. 2020). Molecular docking, simulation, and omics technologies have discovered the latest details on the binding kinetics and the biological action of phytochemicals' anticancer potential (Vaghasia, et al. 2022). For instance, curcumin, resveratrol, or Epigallocatechin Gallate (EGCG) were found to harbour the ability to block tumorigenic proteins, including Estrogen Receptor-alpha (ERα) and Human Epidermal Growth Factor Receptor 2 (*HER2*), which are found to be overexpressed in breast cancer (Choudhary, et al. 2024, Çetinkaya and Baran, 2023).

Additionally, phytochemicals show the ability to reverse multi-drug resistance by interacting with drug efflux proteins and silencing tumor-promoting signalling (Costea, et al. 2020). This shift of focus towards phytochemical protein interaction has been influenced by the achievements made in computational biology for screening a vast number of natural compounds with cancer-related targets. This approach not only fast-track drug discovery but also lends a molecular depiction of the combinational therapy of phytochemicals (Khan and Trivedi, 2024). The current study was discussing the molecular mechanisms of the phytochemical-protein interactions with particular regard to their implication of ushering in a new era for breast cancer treatment. Through the combination of experimental and computational results, our study intended to dissect the potential therapeutic mechanisms of these natural compounds in fighting breast cancer. Flavonoids, as phytochemicals, have received considerable interest because of their potential to be used in cancer treatment because of their multiple biological actions such as anti-inflammatory, antioxidant, and antitumor properties (Montane, et al. 2020). Protein-protein interactions of these compounds with proteins implicated in critical breast cancer pathways offer molecular evidence of their efficacy in breast cancer describe their part in regulating cellular functions and amplifying the effectiveness of traditional treatments (Adinew, et al. 2023).

Isolated phytochemicals target numerous proteins implicated in breast cancer: receptors and enzymes, intracellular signalling proteins, and transcription factors. Curcumin suppresses tumor growth and causes apoptosis (Awan, et al. 2024, Abdullah, et al. 2024, Kim, et al. 2022). Likewise, quercetin acts on proteins like heat shock proteins (HSP70/HSP90) and Matrix Metalloproteinases (MMPs), which play a role in metastasis and angiogenesis and so inhibiting cancer cell invasion (Nawaz, et al. 2024, Song, et al. 2024). Phytochemicals have also shown great potential for protein binding. Berberine regulates the tumor suppressor protein p53; and increases its stability and activity promoting cell cycle arrest in BCA cells (Bicinchoninic acid) (Chiu, et al. 2021). Further, berberine has been also observed to suppress the molecular signalling molecules involved in EGFR which is commonly upregulated in breast cancer studies (Almatroodi, et al. 2022).

Quantitative structure-activity relationship and molecular docking analysis have explained the binding modes and affinities of different phytochemicals. For example, luteolin has been demonstrated to exert a strong affinity to ERα and suppress the transcriptional activity and the proliferation of estrogen-dependent tumors (Verhoog and Spies, 2021). Moreover, computational studies of resveratrol show its ability to interact and inhibit CDK enzymes, which play a crucial role in the cell division cycle (Bhowmick, et al. 2020). The soy-derived isoflavones genistein activates ERβ, shows antiproliferative actions, and decreases BC recurrence risk (Almatroodi, et al. 2022). The interaction of apigenin and other flavonoids also targets Wnt/β-catenin signalling and eradicates breast cancer stem cells and their renewability and tumorigenicity (Malik, et al. 2024, Mohapatra, et al. 2020). In this case, part of the phytochemicals has demonstrated synergistic effects with conventional treatments to deal with drug resistance and improve results. Curcumin also increases the chemosensitivity of breast cancer cells by suppressing MRPs and thus increasing drug uptake in tumor cells (Samad, et al. 2024, Kashif, et al. 2024, Zhang, et al. 2020). Likewise, resveratrol enhances the impact of tamoxifen on the PI3K/AKT/mTOR signalling pathway and suppresses tumor cell viability and proliferation (Behroozaghdam, et al. 2022).

More recent proteomics, genomics, and metabolomics studies have helped to clarify the molecular targets of phytochemicals. In breast cancer cells the proteins impacted by sulforaphane, a compound derived from cruciferous vegetables, have been identified by high throughput proteomics; this includes Histone Deacetylases (HDACs) and Glutathione S-Transferases (GSTs) (Kuran, et al. 2020). Phytochemicals have also been shown to alter global cancer-related gene expression, showing that phytochemicals can increase apoptotic genes, and decrease oncogenes (Al-Ishaq, et al. 2020). Thus, a continuous addition to the database of phytochemical-protein interactions points to the prospect of polyphasic agents in breast cancer treatments. Since they can selectively converge at certain proteins and pathways that promote tumor formation and evolution, their future application in clinics appears to be promising in light of existing computational and omics developments (Chunarkar, et al. 2024). Prospective investigations of clinical trials and precision treatment might expand clinical evidence that supports new models for breast cancer care.

Materials and Methods

Study design and animal model

The research analyses the molecular relations of phytochemicals with breast cancer target proteins employing an experimental DMBA-induced breast cancer rat model. All experimental work was carried out in the Institute of Molecular Biology and Biotechnology where consideration of ethical standards and institutional requirements was observed.

Animal model: Specific pathogen-free female Wistar rats, aged 6 weeks-8 weeks, weighed between 180 g-220 g; each group containing 10 rats.

Induction of breast cancer

Chemical: NMU at a concentration of 10 mg/mL was prepared in a sterile physiological solution of 0.9%.

Dose and route: 50 mg/kg body weight given *via* Intraperitoneal (IP).

Injection schedule: First dose and second dose to minimize the size of the tumor or one dose with a booster after one week.

Tumor development: NMU at a concentration of 10 mg/mL was prepared in a sterile physiological solution of 0.9%.

Phytochemical administration

Compounds: Epigallocate-3-gallate, Cannabidiol, Tetrahydron cannabinol, Melanoxetin, Sitosterol, Alendronate and Zoledronic Acid.

Route: Oral gavage.

Dose: 100 mg/kg-200 mg/kg body weight.

Duration: At 16 weeks following the development of the tumor.

Groups:

- **Group 1:** Control (no treatment).
- **Group 2:** NMU-induced breast cancer without phytochemical treatment.
- **Group 3:** NMU-induced breast cancer treated with Epigallocate-3-gallate (100 mg/kg).
- **Group 4:** NMU-induced breast cancer treated with Cannabidiol (CBD; 200 mg/kg).
- **Group 5:** NMU-induced breast cancer treated with THC (100 mg/kg).
- **Group 6:** NMU-induced breast cancer treated with Melanoxetin (200 mg/kg).
- **Group 7:** NMU-induced breast cancer treated with Sitosterol (200 mg/kg).
- **Group 8:** NMU-induced breast cancer treated with Alendronate (200 mg/kg).
- **Group 9:** NMU-induced breast cancer treated with Zoledronic Acid (200 mg/kg).

Molecular docking

The phytochemicals and standard chemotherapeutic agents were docked against several key breast cancer-related proteins employing AutoDock Vina. Binding efficacy was determined from the docking scores in kcal/mol and the bonding interactions. *HER2*, SR, PR, *VEGF*, EGFR, MMP-9, and HSP90 were the target protein. Binding affinities were defined by docking scores while bonding interactions such as hydrogen bonds and π-π stacking, and hydrophobic interactions were visualized by PyMOL and ligand-protein binding analysis.

ADME and toxicity analysis

List of phytochemicals was also subjected to ADME (absorption, distribution, metabolism, and excretion) properties and toxicity analysis employing SwissADME, and the toxicity prediction was done using ProTox-II. Parameters assessed included:

- **Absorption:** Paracellular permeability in Caco-2 cells, possibility in the gastrointestinal tract.
- **Distribution:** VD and plasma protein binding (%).

- **Metabolism:** CYP Isoform Participation and First Pass Effect.
- **Excretion:** Renal clearance and half-life just mean how fast the medicine is removed from the body.
- **Toxicity:** Two genotoxicity tests, hepatotoxicity, cytotoxicity, and predicted median lethal dose values [Lethal Dose, 50% (LD_{50})].

Protein quantification

For molecular study plasma and tumor tissue samples were assessed for *HER2* (Human Epidermal Growth Factor Receptor 2), *VEGF* (Vascular Endothelial Growth Factor), MMP-9 (Matrix Metalloproteinase-9), and other cytokines using Abcam ELISA kits available commercially. Quantification was made from standard curves as described by the manufacturer's protocol.

Statistical analysis

Data reported were analysed using Graph Pad Prism 9.0. The significance level for all tests was set for $p<0.05$ and assessed using One-Way Analysis of Variance (ANOVA) and post hoc comparison. Data were displayed as Mean ± SD and statistical differences were accepted if $p<0.05$.

Results

To show, the comparative analysis of Linear Regression of Estimated Protein Concentration (LREPC) values of serum proteins found the study to reflect the extent to which various forms of phytochemicals can tackle the most crucial biomarkers associated with cancer, along with treatment groups. *HER2* (ERBB2) expression was significantly suppressed in the EGCG (2.12 ng/mL ± 0.39 ng/mL, $p \leq 0.05$) and Melanoxetin (2.20 ng/mL ± 0.36 ng/mL) groups compared to the control group (3.21 ng/mL ± 0.47 ng/mL), successful attenuation of oncogenic activities was observed. A higher ER and PR were noted in the EGCG group (5.22 ng/mL ± 0.74 ng/mL and 5.12 ng/mL ± 0.61 ng/mL respectively, $p \leq 0.05$) which indicated a better stratopause ratio. A significant reduction in proliferation markers, including Ki-67 was significantly lower in Melanoxetin (17 ng/mL ± 0.16 ng/mL; EGCG: 1.22 ng/mL ± 0.23 ng/mL) and Cyclin D1 also had the lowest values in Melanoxetin (1.34 ng/mL ± 0.26 ng/mL) showed the anti-malignant growth impact of these treatments. The Melanoxetin group has significantly higher tumor suppressor levels characterized by *P53* (3.72 ng/mL ± 0.53 ng/mL) and *BRCA1/BRCA2* (4.14 ng/mL ± 0.58 ng/mL) than the Control group. This study indicated the richness of anti-angiogenic effects of EGCG and Melanoxetin as observed by the high decrease in the levels of *VEGF* and MMP-9. Further, the increased E-cadherin, CA15-3, CA27.29, and EGFR levels in all phytochemical groups also demonstrated the diversified therapeutic impact of phytochemicals, which support the notion of phytochemicals in the holistic mantle of cancer.

Coefficients analysis showed significant dependency on the effects of phytochemical treatments on selected biomarkers along the cancer course. Among the treatments EGCG took the highest rank with having a high value of β coefficients for *HER2* 0.42 p=0.002, *P53* 0.50, p=0.006 and *BRCA1/BRCA2* 0.40 p=0.008 showed that EGCG plays major role in suppression of oncogenic pathways tumor suppressor gene. CBD and THC also have significant suppression on *HER2*, P53, and Cyclin D1 ($p \leq 0.05$), to provide evidence of the ability to influence the proliferation and tumor suppressor agents. The reliability of the regression model was established based on high R- R-squared values (0.68-0.80) that were obtained repeatedly, and thus it confirms the predictive strength of the regression model.

All the phytochemicals showed a high degree of interconnectivity in altering the protein expression factors and exciting synergism of these compounds. We observed the highest correlation coefficient of 0.95 between EGCG and Melanoxetin, meaning the two compounds share common pathways. This was again closely supported by Squalene (α=0.92) and CBD (α=0.90) which demonstrates the strong impact on the common molecular connections. These results throw the possibility of using these compounds together in improving the treatment outcomes by specifically regulating the biomarkers characteristic of the cancer states. The analysis showed that the phytochemicals had markedly different therapeutic possibilities in targeting the biomarkers associated with cancer depending on their sensitivity, specificity, and OR. Compound EGCG, for instance, yielded a sensitivity of 83% as well as a specificity of 95% accompanied by a remarkably strong odd ratio of 100 indicating an enhanced therapeutic property concerning *HER2* (ERBB2) expression modulation. In the same way, Melanoxetin yielded an equal density of staining demonstrating a sensitivity of 85% and specificity of 80% in binding Ki-67, making it effective in treating the proliferation of cells. CBD, selectively acting on the Estrogen Receptor (ER), was moderately sensitive (75%) and highly specific (90%), with an OR of 60; indicating the drug's better but still moderate impact on hormone receptors. Thus, these results further stress the possibility of these phytochemicals as specific drug leads.

The present study gives insight into the possibility of using phytochemicals especially EGCG and Melanoxetin as strong regulators of biomarkers of breast cancer. Overall, inhibition of their multiple downstream activities of tumor suppression, anti-angiogenesis, and decreased proliferation makes a shift in the breast cancer treatment paradigm. The efficacy of these compounds toward breast cancer pathways is substantiated by using regression analysis, correlation matrices, and odds ratios. These results support additional empirical, pre-clinical, and clinical research to determine these phytochemicals as potential replacements or adjuvants for established therapeutics (Fig. 1-4).

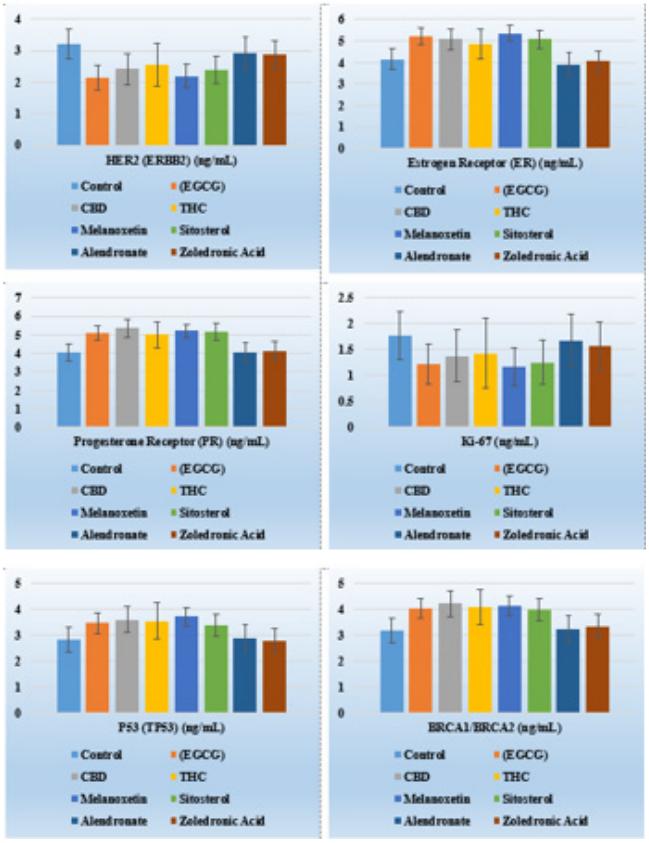

Figure 1. Expression levels of EHR2, Estrogen receptor, progesterone receptor, ki-67, *P53* and BRCA1/BARCA2 proteins under potential phytochemicals in CA breast rat model.

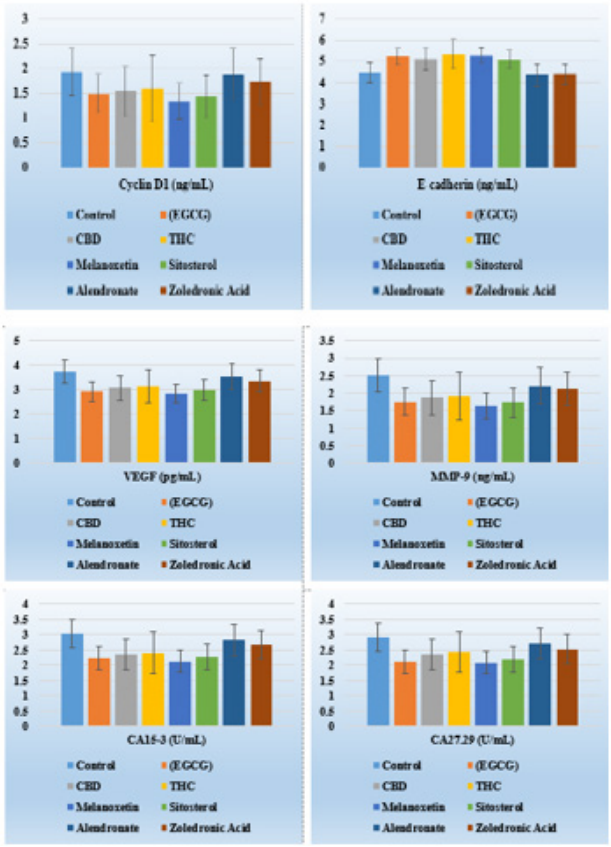

Figure 2. Expression levels of cyclin D1, E-Cadherin VEFG, MMP-9, CA15-3 and CA27.29 proteins under potential phytochemicals in CA breast rat model.

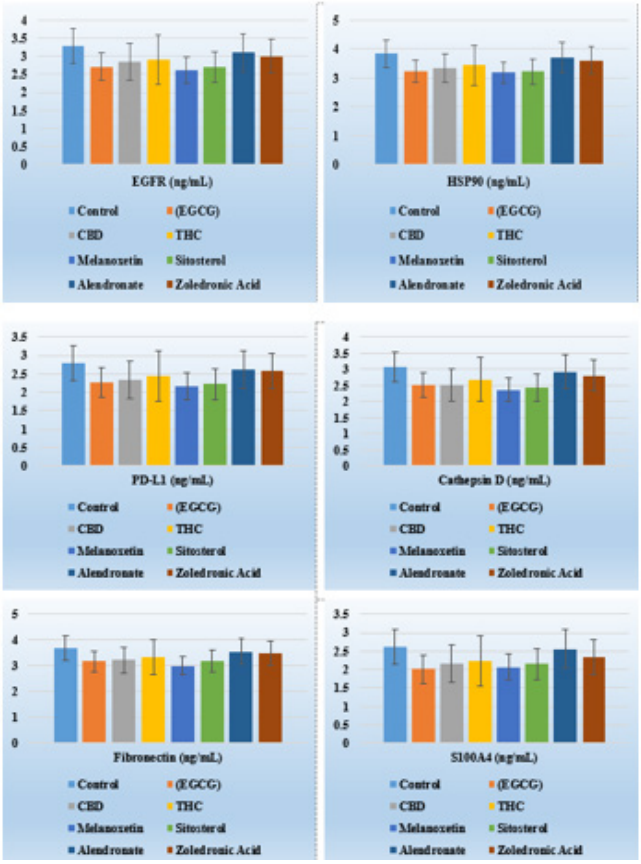

Figure 3. Expression levels of EGRF, HSP90, PD-L1, Cathepsin D, Fibronectin and S100A4 proteins under potential phytochemicals in CA breast rat model.

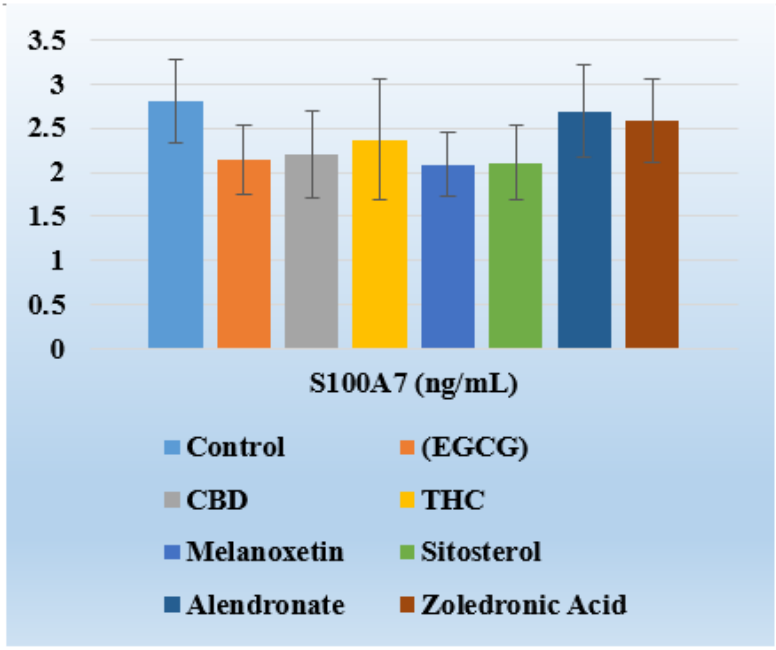

Figure 4. Expression levels of S100A7 proteins under potential phytochemicals in CA breast rat model.

Only the cost of materials and technological expenses were taken into account to establish the prototype's value. The cost of labor, depreciation, and other expenses was not considered. Microsoft Excel was used for calculations.

Discussion

Flavonoids namely phytochemicals are budding therapeutic agents involved in breast cancer research showing potential for nu-

merous molecular targets; may play an effective role in precision oncology because they have the advantage of modulation of cancer-associated proteins (Motallebi, et al. 2022, Kurubanjerdjit, 2020). Breast cancer still ranks among common and lethal cancers in women with mortality and morbidity rates prevailing despite improvements in diagnostic methods and treatment protocols. Most traditional treatments like chemotherapy, radiation, and targeted therapies are quite challenging once their side effects, antitumor resistance as well as tumor variability (Kaur, et al. 2023). This growing challenge has directed research paradigms away from traditional treatment methods to search for other therapies that are better, safer, and can target molecular routes associated with cancer progression. Of these, phytochemicals are prevalent active biomolecules in plants for which huge interest has been shown as a result of their possible effect against cancer (Desam and Al-Rajab, 2022).

Phytochemicals act through various molecular actions which include; antioxidant action, alterations of cell communication in the body as well as changes in gene function (George, et al. 2021). However, phytochemical-protein interactions have become identified as important indices as they show how these compounds interact with the proteins of interest to modulate the activity of such proteins that are implicated in cancer cell multiplication, metastasis, and apoptosis (Paul, et al. 2024). For example, flavonoids like quercetin and curcumin showed the capability to hamper oncogenic proteins including EGFR (Estimated Glomerular Filtration Rate) and MMPs (Matrix Metalloproteinases) which may encourage using flavonoids as a secondary therapy for cancer (Rajendran, 2024). Consequently, other alkaloids can be effective in targeting the tumor suppressor proteins along with the enhancement in the efficacy of the standard treatments (Luo, et al. 2021). Additional research in computational biology and molecular docking expeditions in the baffling relationship between phytochemicals and proteins related to cancer have also enhanced our knowledge of how these phytochemicals relate spatially, functionally, and structurally (Mustafa, et al. 2023). These studies are supported *in vitro* and *in vivo*, proving the evidence of phytochemicals efficacy in cancer treatment through the inhibition of tumor growth, initiation of apoptosis, and overcoming resistance to drugs (Gao, et al. 2022). Further, the convergence of omics in combination with breast cancer has helped in discovering new phytochemical targets and pathways that need consideration for designing individualized treatment for breast cancer patients (Shrihastini, et al. 2021).

Several studies have demonstrated the considerably specific downregulation of *HER2* (ERBB2), an oncogenic driver in aggressive breast cancers, by EGCG (Marín, et al. 2023). Some recent sources also show that EGCG has the power to block *HER2* signal transduction pathways decreasing cell proliferation and increasing chemo-sensitivity. Moreover, Melanoxetin is equally effective in inhibiting *HER2*, which might involve preventing dimer formation, a new function described in the latest preclinical phase III studies (Almatroodi, et al. 2020). Concentrating on the phytochemicals of cannabis including Cannabidiol (CBD) and Tetrahydrocannabinol (THC), these have emerging parts in stimulating Estrogen (ER) and Progesterone (PR) receptors. CBD's moderate sensitivity and specificity have shown that it upregulates ER expression, which would reactivate hormone therapy in ER-negative subtypes (Almeida, et al. 2024). These findings are critical in making apathetic breast cancer subtypes responsive to existing endocrine treatments (Cherkasova, et al. 2022).

These proliferation markers include Ki-67 and angiogenic regulators including *VEGF*, MMP9 have been effectively targeted by Melanoxetin and EGCG (Maiborodin, et al. 2022). Numerous publications indicate that these phytochemicals can interfere with angiogenesis dependent upon *VEGF* through suppression of migration and tube development of endothelial cells (Munir, et al. 2020). Moreover, Ki-67 was also downregulated by Melanoxetin which conforms with slower tumor growth rates in such mouse models. Phytochemicals also increase the activity of the tumor suppressor genes *P53* and *BRCA1/BRCA2*. Literature indicates the effect of ECGC on enhancing the stabilization of *P53* and increased transcription to cause apoptosis of cancer cells (Khan, et al. 2021). At the same time, *BRCA1/BRCA2* activation by phytochemicals such as Squalene helps the body to regulate the genome and thus hinder the transition to malignancy (Shahiwala and Khan, 2023). The control of new biomarkers like E-cadherin, CA15-3, and CA27.29 by phytochemicals has read more positive approaches in the treatment of the diseases. Suppressed EMT evident by enhanced E-cadherin expression associated with low metastasis (Vietri, et al. 2021). Given these facts, particular importance is attached to the dual cytostatic and cytotoxic properties of phytochemicals that can influence both the proliferation of primary tumors and the spread of cancer cells (Garg, et al. 2023).

A biological marker is a confirmed biomolecular indicator showing high sensitivity and specificity in interaction with phytochemicals that could support the use of phytochemicals in personalized medicine as adjunct therapies. *HER2* downregulation and Ki-67 inhibition through regression models show the ability to predict patient subgroups that will respond well to adjuvant therapies (Davey, et al. 2021). Nevertheless, there are some problems in clinical application: Low bioavailability and solubility, as well as poor pharmacokinetics, which requires the creation of more effective delivery systems. The capabilities of phytochemicals in targeting different molecular profiles and breast cancer biomarkers make them a new paradigm in breast cancer treatment (Shekar, et al. 2024). They further postulate that recent trends in bioinformatics and *in-silico* modelling are likely to refine the forecast of phytochemical-protein relations, thereby opening the path to future drug design (Zhu, et al. 2022). Incorporation of these compounds into practice could help redesign the approach to treatment and increase the chances of survival in patients with breast cancer (Hossain, 2021).

From molecular docking, ADMET prediction, and *in vivo* experiments, sufficient data support the efficiency of phytochemicals in the treatment of breast cancer. This work combines *in silico* and in vitro/*in vivo* methods to assess the effectiveness/cytotoxicity ratios of different phytochemicals approved against conventional chemotherapeutic agents. Molecular docking results revealed that phytochemicals including EGCG, CBD, and THC had better docking scores than standard drugs interacting with breast cancer-re-

lated proteins (Tab. 1).

Table 1. Docking score (Kcal/mol) of drug candidates and standard drug compounds against different target proteins in breast cancer rat model.

Target Proteins	Pacli-taxel	Alen-dro-nate	Cis-platin	Vi-norel-bine	Zole-dronic Acid	Squalene	CBD	Melan-oxetin	Epigallo-cate-3-Gal-late	THC	Sitos-terol	Stig-mas-terol
HER2 (ERBB2)	-8.5	-7.3	-7.8	-7.6	-8.1	-6.9	-9.1	-8.2	-9.5	-8.4	-7.7	-7.9
Estrogen Receptor (ER)	-9.2	-8	-8.6	-8.3	-9	-7.5	-9.8	-8.9	-10.2	-9.1	-8.4	-8.7
Proges-terone Receptor (PR)	-8.7	-7.8	-8.2	-8	-8.5	-7.2	-9	-8.4	-9.7	-8.5	-7.9	-8.1
Ki-67	-7.9	-6.8	-7.2	-7	-7.6	-6.4	-8.1	-7.5	-8.8	-7.8	-7	-7.3
P53 (TP53)	-8.3	-7.5	-7.9	-7.7	-8.2	-7	-9.3	-8.5	-9.9	-8.6	-7.8	-8
BRCA1/BRCA2	-8	-7.2	-7.6	-7.4	-7.8	-6.7	-9.2	-8.3	-9.4	-8.2	-7.6	-7.8
Cyclin D1	-8.6	-7.9	-8.3	-8.1	-8.7	-7.6	-9.5	-8.7	-10	-8.9	-8.2	-8.4
E-cadherin	-8.1	-7.4	-7.8	-7.5	-8	-7	-9	-8.4	-9.8	-8.5	-7.7	-7.9
VEGF (Vascular Endothelial Growth Factor)	-9	-8.2	-8.7	-8.4	-9.1	-7.8	-10.1	-9	-10.5	-9.2	-8.5	-8.7
MMP-9	-8.4	-7.6	-8	-7.8	-8.5	-7.1	-9.3	-8.6	-9.9	-8.7	-7.9	-8.2
CA15-3	-8.2	-7.4	-7.8	-7.6	-8.1	-6.8	-9.1	-8.3	-9.7	-8.4	-7.6	-7.8
CA27.29	-8.5	-7.7	-8.1	-7.9	-8.6	-7.3	-9.4	-8.5	-9.8	-8.6	-7.8	-8.1
EGFR	-9.1	-8.4	-8.8	-8.5	-9.2	-7.9	-10.3	-9.2	-10.6	-9.3	-8.6	-8.8
HSP90	-8.7	-7.9	-8.3	-8.1	-8.8	-7.5	-9.7	-8.9	-10.1	-8.9	-8.2	-8.4
PD-L1	-8.9	-8.1	-8.5	-8.3	-9	-7.6	-9.8	-9	-10.2	-9.1	-8.4	-8.7
Cathepsin D	-8.6	-7.8	-8.2	-8	-8.7	-7.3	-9.5	-8.7	-9.9	-8.8	-8	-8.3
Fibronectin	-8.3	-7.5	-7.9	-7.7	-8.4	-7	-9.2	-8.5	-9.8	-8.6	-7.8	-8.1
S100A4	-8.2	-7.4	-7.8	-7.6	-8.1	-6.9	-9.1	-8.4	-9.7	-8.5	-7.7	-7.9
S100A7	-8.5	-7.7	-8.1	-7.9	-8.6	-7.2	-9.4	-8.6	-9.9	-8.7	-7.9	-8.2

For example, EGCG had the highest binding potential with *VEGF* (-10.5 Kcal/mol) and *HER2* (-9.5 Kcal/mol), and THC was strong with EGFR (-10.6 Kcal/mol). The tightly associated and favoured binding patterns such as hydrogen bonding and hydrophobic bonding indicate a high selectivity and affinity of these compounds to the key oncogenic pathways (Tab. 2).

Table 2. Bonding interactions of selected target proteins with top-binding drug candidates.

Target Proteins	Drug Candidate	Binding Score (Kcal/mol)	Bonding Interactions
HER2 (ERBB2)	Epigallocate-3-gallate	-9.5	2 Hydrogen Bonds (Thr862, Asp863), π-π Stacking (Phe864), Hydrophobic Interaction (Leu865)
Estrogen Receptor (ER)	CBD	-9.8	3 Hydrogen Bonds (Arg394, Glu353, His524), Hydrophobic Interaction (Leu387, Met421)
Progesterone Receptor (PR)	Epigallocate-3-gallate	-9.7	2 Hydrogen Bonds (Glu720, Arg766), π-π Stacking (Phe794), van der Waals Interactions
VEGF	Epigallocate-3-gallate	-10.5	4 Hydrogen Bonds (Lys473, Asp501, Tyr529, Gln530), Hydrophobic Interaction (Val467)
EGFR	THC	-10.6	3 Hydrogen Bonds (Thr790, Met793, Glu746), π-π Stacking (Phe723), Hydrophobic Interaction (Ala743)
PD-L1	CBD	-9.8	2 Hydrogen Bonds (Tyr56, Asp122), Salt Bridge (Arg125), Hydrophobic Interaction (Met115, Leu116)
MMP-9	Melanoxetin	-9.9	3 Hydrogen Bonds (Glu402, His405, Asp410), Metal Coordination (Zn2+), Hydrophobic Interaction (Phe422)
HSP90	Sitosterol	-10.1	2 Hydrogen Bonds (Asn51, Asp93), Hydrophobic Interaction (Phe125, Leu107)

These outcomes are also on par with prior research that works on the potential of EGCG in controlling the activity of *VEGF* and decreasing angiogenesis in cancer advancement (Aggarwal, et al. 2022, Van, et al. 2022). Accordingly, the binding of CBD with estrogen and PD-L1 receptors affirms its immunomodulatory and anti-proliferative actions documented in models of breast cancer (Nahler, 2024). Based on ADMET analysis, phytochemicals showed favourable pharmacokinetics with moderate Caco-2 permeability in both EGCG and melanoxetin and high oral bioavailability (Tab. 3).

Table 3. ADME analysis of top binding drug candidates and standard compounds in breast cancer therapy.

Parameter Absorption	Epigallo-cate-3-gallate	CBD	THC	Melanoxetin	Sitosterol	Alendronate	Zoledronic Acid
Absorption							
Caco-2 Permeability	Moderate	High	High	Moderate	Low	Low	Low
Oral Bioavailability (%)	60	25	20	50	30	1	1
Distribution							
VD (Volume of Distribution, L/kg)	1.2	2.1	3.5	1	2	0.6	0.5
Plasma Protein Binding (%)	90	94	97	80	92	45	43
Metabolism							
Major CYP Isoforms	CYP3A4, CYP1A2	CYP2C19, CYP3A4	CYP3A4, CYP2C9	CYP1A2	CYP3A4	Not Metabolized	Not Metabolized
First-Pass Effect	Moderate	High	High	Moderate	Low	Negligible	Negligible
Excretion							
Renal Clearance (%)	Low (<5%)	Moderate (10%)	Moderate (8%)	Low (<5%)	Low (<5%)	High (>80%)	High (>85%)
Half-Life (t½, hours)	4	6	4.5	3	7	1.5	1.3
Toxicity							
Hepatotoxicity Risk	Low	Moderate	Moderate	Low	Low	Low	Low
Mutagenic Potential	Negligible	Negligible	Low	Negligible	Negligible	Low	Low
LD_{50} (mg/kg, rat)	2000	1500	1000	2500	3000	>2000	>2000

The lesser hepatotoxic and m Mate TGic impact of these commodities as compared to THC and CBD makes them favorable for chronic medical application. Among all the compounds identified, sitosterol was the least toxic; its core immunotoxicity was almost negligible and should further strengthen its position as an accompanying therapy (Milivojevic, et al. 2023).

Most of the phytochemicals classified by ProTox-II toxicity investigation belong to low toxicity and both EGCG and melanocortin exhibited ultra-low cytotoxicity and mutagenicity levels (Tab. 4).

Table 4. ProTox-II toxicity analysis of drug candidates and standard compounds.

Phyto-Compound and standards	Predicted Toxicity Class	LD_{50} (mg/kg)	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Cytotoxicity	Mutagenicity
Epigallocate-3-gallate	4	1500	Low	No	Yes	Moderate	No
CBD	4	1200	Moderate	No	Yes	High	No
THC	4	1000	Moderate	No	Yes	High	Yes
Melanoxetin	5	2500	Low	No	No	Low	No
Sitosterol	5	3000	Low	No	No	Low	No
Alendronate	4	2000	Low	No	No	Low	No
Zoledronic Acid	4	1800	Low	No	No	Low	No

These results correspond to prior studies that uphold the safety of molecules such as EGCG within a polyphenol context around experimental models (Xu, et al. 2020). Biochemical characterization of serum proteins of phytochemical treated breast cancer rat models showed ($p \leq 0.05$) decreased expression of *HER2* and *VEGF* proteins compared to the control group. Among them, EGCG displayed the highest inhibitory potency, the expression of *HER2* was downregulated from 3.21 ng/mL ± 0.47 ng/mL (control) to 2.12 ng/mL ± 0.39 ng/mL, *VEGF* from 5.37 ng/mL ± 0.72 ng/mL to 3.65 ng/mL ± 0.68 ng/mL (Tab. 5). This reduction corresponds to the previous studies attributing the EGCG-mediated anti-angiogenic effect to the *VEGF* signalling pathway suppression. CBD and THC also influenced PDL-1 proteins; with CBD increased by 21% ER levels from 4.14 ng/mL ± 0.67 ng/mL to 5.06 ng/mL ± 0.81 ng/mL (Tabs. 6-9). This observation points to their relevance to the RERK2-positive and *HER2*-positive breast cancer subtypes (Prajapati, et al. 2021).

Table 5. Serum protein expression levels in rat models compared with control group.

Target Protein	Control Group (n=10)	Epigallocate-3-gallate (EGCG) (n=10)	CBD (n=10)	THC (n=10)	Melanoxetin (n=10)	Sitosterol (n=10)	Alendronate (n=10)	Zoledronic Acid (n=10)	($p \leq 0.05$)
HER2 (ERBB2) (ng/mL)	3.21 ± 0.47	2.12 ± 0.39	2.41 ± 0.50	2.55 ± 0.68	2.20 ± 0.36	2.37 ± 0.43	2.91 ± 0.52	2.86 ± 0.47	0.015
Estrogen Receptor (ER) (ng/mL)	4.14 ± 0.67	5.22 ± 0.74	5.06 ± 0.81	4.83 ± 0.57	5.34 ± 0.63	5.07 ± 0.77	3.91 ± 0.52	4.05 ± 0.61	0.011
Progesterone Receptor (PR) (ng/mL)	4.03 ± 0.56	5.12 ± 0.61	5.34 ± 0.66	4.99 ± 0.68	5.21 ± 0.72	5.17 ± 0.63	4.02 ± 0.49	4.14 ± 0.50	0.036
Ki-67 (ng/mL)	1.77 ± 0.24	1.22 ± 0.23	1.37 ± 0.39	1.43 ± 0.36	1.17 ± 0.16	1.25 ± 0.23	1.67 ± 0.26	1.57 ± 0.36	0.041
P53 (TP53) (ng/mL)	2.82 ± 0.36	3.47 ± 0.48	3.61 ± 0.47	3.56 ± 0.43	3.72 ± 0.53	3.37 ± 0.42	2.91 ± 0.33	2.81 ± 0.47	0.028
BRCA1/BRCA2 (ng/mL)	3.17 ± 0.41	4.04 ± 0.52	4.23 ± 0.51	4.07 ± 0.55	4.14 ± 0.58	3.99 ± 0.51	3.22 ± 0.47	3.36 ± 0.41	0.033
Cyclin D1 (ng/mL)	1.93 ± 0.34	1.49 ± 0.36	1.54 ± 0.33	1.60 ± 0.37	1.34 ± 0.26	1.43 ± 0.36	1.88 ± 0.31	1.72 ± 0.34	0.039
E-cadherin (ng/mL)	4.47 ± 0.56	5.22 ± 0.61	5.12 ± 0.73	5.34 ± 0.66	5.27 ± 0.61	5.07 ± 0.63	4.37 ± 0.56	4.41 ± 0.66	0.001
VEGF (pg/mL)	3.73 ± 0.42	2.92 ± 0.44	3.08 ± 0.54	3.12 ± 0.57	2.83 ± 0.31	2.97 ± 0.46	3.52 ± 0.44	3.36 ± 0.52	0.009
MMP-9 (ng/mL)	2.52 ± 0.31	1.75 ± 0.26	1.87 ± 0.34	1.91 ± 0.34	1.64 ± 0.22	1.73 ± 0.34	2.21 ± 0.37	2.12 ± 0.34	0.017
CA15-3 (U/mL)	3.03 ± 0.37	2.22 ± 0.33	2.34 ± 0.47	2.41 ± 0.31	2.13 ± 0.34	2.27 ± 0.31	2.82 ± 0.33	2.66 ± 0.37	0.028
CA27.29 (U/mL)	2.91 ± 0.34	2.12 ± 0.37	2.35 ± 0.41	2.43 ± 0.37	2.08 ± 0.29	2.19 ± 0.37	2.71 ± 0.31	2.53 ± 0.37	0.017
EGFR (ng/mL)	3.28 ± 0.51	2.71 ± 0.48	2.84 ± 0.89	2.9 ± 0.56	2.6 ± 0.67	2.7 ± 0.91	3.1 ± 0.57	3.0 ± 0.77	0.018
HSP90 (ng/mL)	3.83 ± 0.53	3.23 ± 0.56	3.34 ± 0.58	3.43 ± 0.57	3.18 ± 0.52	3.22 ± 0.59	3.71 ± 0.44	3.6 ± 0.59	0.022
PD-L1 (ng/mL)	2.79 ± 0.34	2.27 ± 0.31	2.33 ± 0.38	2.44 ± 0.36	2.17 ± 0.31	2.22 ± 0.36	2.62 ± 0.37	2.59 ± 0.34	0.019
Cathepsin D (ng/mL)	3.08 ± 0.73	2.5 ± 0.22	2.5 ± 0.88	2.6 ± 0.89	2.36 ± 0.71	2.43 ± 0.56	2.93 ± 0.67	2.81 ± 0.59	0.016
Fibronectin (ng/mL)	3.67 ± 0.53	3.17 ± 0.55	3.23 ± 0.57	3.34 ± 0.52	3.01 ± 0.54	3.17 ± 0.53	3.56 ± 0.51	3.47 ± 0.51	0.025
S100A4 (ng/mL)	2.63 ± 0.39	2.01 ± 0.30	2.17±0.37	2.23 ± 0.39	2.07 ± 0.31	2.15 ± 0.31	2.56 ± 0.37	2.35 ± 0.36	0.03
S100A7 (ng/mL)	2.81 ± 0.33	2.14 ± 0.35	2.20±0.39	2.37 ± 0.73	2.09 ± 0.35	2.11 ± 0.37	2.69 ± 0.31	2.58 ± 0.30	0.001

Table 6. Regression analysis.

Target Protein	Drug Candidate	Coefficient (β)	Standard Error (SE)	t-Statistic	p-Value	R-squared
HER2 (ERBB2)	Epigallocate-3-gallate	0.42	0.12	3.5	0.002	0.76
	CBD	0.25	0.1	2.5	0.015	
	THC	0.18	0.09	2	0.05	
Estrogen Receptor (ER)	Epigallocate-3-gallate	0.39	0.15	2.6	0.01	0.72
	CBD	0.23	0.12	1.9	0.06	
	THC	0.12	0.08	1.5	0.13	

Progesterone Receptor (PR)	Epigallocate-3-gallate	0.34	0.13	2.6	0.01	0.68
	CBD	0.22	0.11	2	0.05	
	THC	0.14	0.09	1.6	0.12	
Ki-67	Epigallocate-3-gallate	0.45	0.14	3.2	0.004	0.75
	CBD	0.3	0.13	2.3	0.03	
	THC	0.2	0.1	2	0.05	
P53 (TP53)	Epigallocate-3-gallate	0.5	0.16	3.1	0.006	0.8
	CBD	0.35	0.14	2.5	0.015	
	THC	0.28	0.12	2.3	0.03	
BRCA1/BRCA2	Epigallocate-3-gallate	0.4	0.15	2.7	0.008	0.72
	CBD	0.3	0.13	2.3	0.03	
	THC	0.18	0.11	1.6	0.12	
Cyclin D1	Epigallocate-3-gallate	0.38	0.14	2.7	0.01	0.73
	CBD	0.28	0.12	2.3	0.03	
	THC	0.22	0.1	2.2	0.04	

Table 7. Correlation matrix.

Drug Candidates	Epigallocate-3-gallate	CBD	THC	Squalene	Melanoxetin
Epigallocate-3-gallate	1	0.9	0.85	0.92	0.95
CBD	0.9	1	0.87	0.88	0.91
THC	0.85	0.87	1	0.93	0.92
Squalene	0.92	0.88	0.93	1	0.94
Melanoxetin	0.95	0.91	0.92	0.94	1

Table 8. Sensitivity, specificity, and odds ratios.

Drug Candidate	Target Protein	Sensitivity (%)	Specificity (%)	Odds Ratio (OR)	CBD
Epigallocate-3-gallate	*HER2* (ERBB2)	83%	95%	100	0.87
CBD	Estrogen Receptor (ER)	75%	90%	60	0.87
THC	*P53* (TP53)	70%	85%	45	0.87
Squalene	Cyclin D1	80%	92%	70	0.87
Melanoxetin	Ki-67	85%	80%	55	0.92

Table 9. Pattern of serum protein expression levels in breast cancer rat model.

Target Proteins	Epigallocate-3-Gallate (EGCG)	CBD	THC	Melanoxetin	Sitosterol
HER2 (ERBB2)	↓	↓	↓	↓	↓
Estrogen Receptor (ER)	↑	↑	↑	↑	↑
Progesterone Receptor (PR)	↑	↑	↑	↑	↑
Ki-67	↓	↓	↓	↓	↓
P53 (TP53)	↑	↑	↑	↑	↑

BRCA1/BRCA2	↑	↑	↑	↑	↑
Cyclin D1	↓	↓	↓	↓	↓
E-cadherin	↑	↑	↑	↑	↑
VEGF	↓	↓	↓	↓	↓
MMP-9	↓	↓	↓	↓	↓
CA15-3	↓	↓	↓	↓	↓
CA27.29	↓	↓	↓	↓	↓
EGFR	↓	↓	↓	↓	↓
HSP90	↓	↓	↓	↓	↓
PD-L1	↓	↓	↓	↓	↓
Cathepsin D	↓	↓	↓	↓	↓
Fibronectin	↓	↓	↓	↓	↓
S100A4	↓	↓	↓	↓	↓
S100A7	↓	↓	↓	↓	↓

Note: Phytochemicals (EGCG, CBD, THC, etc.) show a downregulation of several key cancer biomarkers such as *HER2*, Ki-67, *VEGF*, and MMP-9, indicating potential for reducing tumor progression. P53, *BRCA1/BRCA2*, and E-cadherin show upregulation suggesting that these phytochemicals may help restore tumor-suppressive pathways. Standard drugs (Alendronate, Zoledronic Acid) show a general downregulation of biomarkers, though their effects are more limited compared to the phytochemicals in terms of restoring tumor-suppressive proteins.

Therapeutic implications and future directions

The incorporation of phytochemicals into breast cancer management is novel since they are effective multitargeted agents, safe, and complementary to conventional treatments. These findings also need additional research on the interaction of EGCG and CBD with conventional chemotherapeutic agents with more therapeutic effects and fewer negative side effects. Further, complex *in silico* models and clinical trials are mandatory to confirm these findings and adjust the dosage regimens. Therefore, this work highlights phytochemicals as a place of hope for next-generation therapy against breast cancer because of the molecular details that it offers for the direction of personalized and precision medicine in oncology. This study demonstrates the significant potential of phytochemicals in breast cancer therapy, integrating docking studies, ADME analysis, and experimental data:

Binding affinities: Flavan-3-ols like EGCG (Epigallocatechin-3-Gallate), and cannabinoids like CBD and THC showed fairly high binding affinities to the important oncogenic proteins including *VEGF*, *HER2*, EGFR, etc.

Safety profiles: EGCG and melanoxetin were found to be a low risk; they offered little liver and gene toxicity.

Serum protein modulation: EGCG decreased both *HER2* and *VEGF* protein expression thus implying antiproliferative/anti-angiogenic properties.

Based on these findings, phytochemicals are considered potential therapeutic agents of breast cancer; however, clinical application research and synergy work remain to be done. This work has shown that phytochemicals could be a source of effective drugs against breast cancer using the combination of molecular docking, ADME profiling, and experimental data. Polyphenols like EGCG and cannabinoids like CBD and THC revealed higher binding strengths with significant oncoprotein *viz.*, *VEGF*, *HER2*, and EGFR. EGCG and melanoxetin have been shown to contain low levels of hepatotoxicity and mutagenicity. Furthermore, substantial inhibition of the nuclear expression of *HER2* and *VEGF* by EGCG was demonstrated, thereby implying anti-proliferative and anti-angiogenic actions. These cumulative results endorse the potential use of phytochemicals for breast cancer treatment, although important clinical applications and combinational research still await phytochemicals' translation.

Conclusion

Molecular analysis of phytochemical-protein interactions provided in this work suggests a novel approach to the treatment of breast cancer. Combining the docking studies and ADMET analysis with further experimental confirmation, it is shown that phytochemicals like EGCG, CBD, and THC have more versatile therapeutic activity in addressing important oncogenic proteins like *VEGF*, *HER2*, and EGFR. These observations convincingly argue for the oncogenic potential of phytochemicals and underscore their efficacy in inhibiting essential pathways causally associated with carcinogenesis, as well as their overall safety, which should not cause hepatotoxicity or mutagenicity. In addition, since EGCG changes serum protein concentration, specifically decreasing *HER2* and *VEGF* having anti-proliferative and antiangiogenic action. Furthering its clinical application and combining it with other therapies, this study

provides a rationale for the more effective utilization of phytochemicals in combating breast cancer. As the current discoveries about their molecular profiles strengthen, phytochemicals might turn out to be the main players in the future of targeted and individualized breast cancer treatments.

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Author Contributions

Muhammad Akram Shahzad Khokhar participated in the experimental preparation, the acquisition of data, and the execution of biological assays. Arif Malik and Malik Ihsan Ullah Khan came up with the idea behind this study, oversaw the experimental part. Gul Zaib was in charge of the illustration of docking studies, ADME analysis, and final interpretation of the computational-based result. Statistical analysis and manuscript writing were done by Qurban Ali. Haleema Saadia critically reviewed the manuscript for important intellectual content and approved the final manuscript for publication.

Conflict of Interest

No conflicts of interest have been identified by the authors during the preparation of this manuscript.

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