A Review of Modeling Checkpoint Blockade Therapy and Therapeutic Strategies in Integrative Pharmacological Approach for Metastatic Breast Cancer

Prachi Gurudiwan [1*], Ragini Patel [1], Urvashi Jain [1]

Abstract

Breast cancer remains the leading cause of mortality among women despite advancements in chemotherapy treatments. Natural chemicals are preferred for breast cancer treatment to minimize side effects and target proteins involved in processes. However the effectiveness of checkpoints has been limited, emphasizing the need for indicators to identify individuals who will respond positively. This study introduces an empirical systems pharmacology model that considers the relationship between the system and breast cancer tissue. The model encompasses peripheral, Cancer Draining Lymph Nodes (CDLN) and tumor sections, accurately representing how immune checkpoints influence system mechanisms in CDLN and the tumor microenvironment. This model can predict responses based on measures by replicating tumor responses to checkpoint blocking treatments. It offers a framework that can be customized for immunotherapies and their integration, with targeted molecular treatments.

Keywords: Breast Cancer, Pharmacology, Clinical Trial, Tumour

Significance | Quantitative Systems Pharmacology models immune processes in breast cancer, aiding personalized treatment by identifying biomarkers, resistance mechanisms, and therapeutic options. Network pharmacology highlights Juglanthraquinone C's potential, suggesting promising therapeutic effects for breast cancer. However, further reliable research is needed for confirmation.

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1. Introduction

Breast Cancer (BC) represents 12.5% of all cancer diagnoses and affects a total of two million individuals of both sexes Van Dooijeweert et al. (2022). BC has surpassed lung cancer as the highly detected disease worldwide. Undoubtedly, in 2023, a significant proportion of female cancer scenarios, over 35%, were identified with this particular type of cancer. It is the most widespread form of cancer among females, and its incidence has been increasing worldwide, particularly in developing countries. In 2023, over 7 million females lost their lives due to BC, which constituted 18% of all tumor-related fatalities among women Giaquinto et al. (2022). The World Health Organization (WHO) introduced the Global Breast Tumor Strategy to address the previously insufficient common healthcare measures to address this issue Arnold et al. (2022). Based on the present trajectory, the death rate is projected to reach a worrisome peak of 7.2 million by 2035. Breast cancer is the most prevalent BC in females, and both its incidence and demise proportion have quickly grown in contemporary years Mao et al. (2017). The prolonged living percentage of people living with BC following surgical or chemotherapeutic interventions remains dismal due to the significant hazards of disease relapse and metastasis. Breast cancer

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metastasis is the primary reason of patient death. Triple-negative BC (TNBC), the most aggressive subtype of BC, poses significant issues in terms of effectiveness and has a higher propensity for metastasis following diagnosis Bianchini et al. (2022). Hence, there is a pressing need for novel therapeutic drugs derived from natural sources that have potent and safe effects against this particular cancer.

Breast cancer cells employ many strategies to evade the immune system, enabling their survival against the assault from Cytotoxic T Lymphocytes (CTLs) Rascio et al. (2021). Checkpoint linkages are recognized as a significant mechanism, with the expression of PDL1 on tumor cells being regarded as a prognostic indicator Qayoom et al. (2023). While the interaction between PD1 and its binding partner, PDL1, hinders the proliferation and effectiveness of CTLs, the overexpression of PDL1 is associated with increased rates of metastasis-free survival, general survival and responsiveness to treatment in Cancer-Draining Lymph Node (CDLN) Wu et al. (2022). Recent clinical investigations have shown that a high level of PDL1 gene expression on immune cells that have infiltrated the tumor is linked with better results in participants with metastatic BC who receive either anti PDL1 monotherapy or combination therapies with nanocomposite albumin-bound (nab)-paclitaxel Wang et al. (2017). The improved living and reaction rate might be attributed to the correlation between high PDL1 expression on tumor cells and the high presence of Tumor-Infiltrating Lymphocytes (TILs), that function as a negative loop system Paijens et al. (2021). Therefore, when chemotherapy is administered alongside PDL1 blocking, it is anticipated that the function of CTLs in the tumor microenvironment will be restored, leading to an even greater responsiveness rate in subtypes that have elevated PDL1.

While the relationship between the parameters mentioned above and the reaction of tumors to immunotherapy is well understood in certain forms of cancer, the collective impact of these factors is still not fully understood Lee et al. (2021). The correlation between PDL1 expression and reaction to immunotherapy has been inconsistent, most likely due to the complex nature of immune-cancer cell conversations, which a single indicator cannot accurately represent. Computation networks pharmacological models have the potential to incorporate several interconnected components and procedures, aiding in the understanding of the intricate nature of cancer and immunity. This work presents an integrated pharmacology framework that includes divisions representing numerous interactions between cancer and immune cells in individuals with breast cancer Zhang et al. (2021). This model represents the initial endeavor to combine different components that influence the relationship between tumor tissues and immune cells, such as the lymph nodes connected to the tumor and the microenvironments within the cancer. This framework aims to investigate the impact of the blockade of checkpoint therapy on these interactions Li et al. (2021). The research seeks to enhance the effectiveness of testing and immunotherapy methods in clinical trials.

The related articles recently published in the area of breast cancer are discussed below:

The objective was to examine the molecular process employed by Juglanthraquinone C (JC) in combating BC Qayoom et al. (2023). It used network pharmacology methods to investigate the mode of activity of JC in BC. To verify the research, the form utilized many computational techniques like UALCAN, cBioportal, TIMER, the docking process, and simulations. An analysis using docking techniques showed that the examined medication had a binding affinity towards the essential target protein TGIF1.

The research created highly effective, specific, and able-to-enter-cells small molecules that inhibit SIRT5 Abril et al. (2021). Reduction of SIRT5 repressed the altered characteristics of breast carcinoma cells grown in culture. It markedly decreased the formation of mammary tumors in living organisms, including both genetically modified and transplanted mice models. The SIRT5 antagonists created in this work will serve as valuable instruments for investigating the activities of SIRT5 and examining the therapeutic possibilities of addressing SIRT5 Rathaur et al. (2021).

A Pharmacology framework was constructed using existing data on triple-negative breast tumors Wang et al. (2021). The model created a simulated group of patients to conduct virtual clinical studies and perform retrospective evaluations of the trials. This trial resulted in the acceptance of risks for individuals with triple-negative breast carcinoma who have constructed death-ligand 1 positivity.

The suggested core network is essential for the current efficiency of Conventional Neural Network (CNN) based sensors Mohanakurup et al. (2022). A Composite Dilatation Backbone Network (CDBN) is a novel approach for consolidating several identical foundations into a single resilient backbone. The process involves sequentially transferring high-level output traits from prior foundations to the next spine. CDBN is a more cost-effective and efficient alternative to constructing a new baseline network and undergoing preparation on ImageNet.

The objective is to provide current information on the intensity and time-dependent patterns of Doxorubicin (DOX) processes at clinically relevant concentrations (Nicoletto and Ofner III, 2022). Moreover, there is a focus on the activity of DOX in breast tumor cells because of its frequent utilization as a treatment for this particular illness. The article explains the molecular pathway(s) by which DOX operates at levels observed in individuals and determines the extent of impact for each method.

A novel drug delivery capable of responding to pH changes has been created. This complex comprises a supramolecular organic structure that carries the medication DOX Zhang et al. (2022). The anti-tumor efficacy was examined in vitro using cell-cell death, uptake test, and apoptosis assessment. The discoveries have sparked scientific curiosity in investigating novel medication delivery approaches and overcoming multi-drug resistance in clinical treatment.

This article concisely summarizes the current understanding of the processes by which ESR1 mutations function and their involvement in developing resistance to estrogen inhibition Brett et al. (2021). The research examines the most recent scholarly works about the impact of mutations in ESR1 on the effectiveness of treatments that target estrogen receptors and combined therapy. Therefore, combinations include endocrine solutions to aromatase restriction or pairings where the non-endocrine element works as a standalone treatment, which continues to be effective versus ESR1 mutation.

The suggested approach seeks to ascertain putative prognostic indicators, postulate the plausible immune evasion system, and ultimately forecast the reaction of treatment groups or even specific individuals to chemotherapy. The following sections are arranged in the following manner: section 2 discusses the proposed Pharmacology-based investigation for metastatic breast cancer using clinical trials, section 3 indicates the experimental results and outcomes of the research, and Section 4 concludes the results with significant conclusions and future scope.

2. Proposed Pharmacology-based investigation for metastatic breast cancer

This section features a discussion on the pharmacology-based study for metastatic breast cancer that is now undergoing clinical trials. Analysis is held about the outcomes, the materials, the many procedures utilized for the experiment, and the results themselves.

2.1 Model and cell dynamics

The Quantitative Systems Pharmacology (QSP) has four sections: middle, peripheral blood tumor, and Cancer-Draining Lymph Nodes (CDLN). The center of the sector refers to the overall quantity of blood, whereas the peripheral industry refers to the amount of blood in the periphery cells. The tumor sector refers to the overall volume of the cancer, which is considered to remain constant for studying the pharmacokinetics of antibodies and the transportation of effector T-cells. The CDLN segment denotes a combined lymph edge, presuming that the antigen would be uniformly dispersed throughout several CDLNs that share the antigen and T-cell movements. It is constructed utilizing the SimBiology package in MATLAB.

Fig. 1 depicts the dynamics of the principal species in the framework. The electronic supplemental material contains the entire set of controlling ODEs, variables, and SBML software to guarantee the repeatability of the framework.

2.2 Immune activations

The immune system is triggered within the tumor site, generating neoantigens. Neoantigens are internalized by Antibody-Presenting Cells (APCs) by phagocytosis inside the tumor or transmitted to the nodes through lymphatic channels, or indigenous APCs can capture them in CDLNs. Mature APCs (mAPCs) within the cancer return to the lymph nodes through lymphatic arteries. Once there, they begin priming and stimulation, producing effector T cells. Effector T tissues enter the bloodstream and are carried to the tumor, exiting the blood vessels and entering the tumor microenvironment (TME). TME eliminates tumor cells by cytotoxic actions. Destroyed tumor cells might discharge additional neoantigens to enhance development and trigger the effector T cells' subscription. This creates positive feedback until the BC tissues are eliminated. However, based on the specific variables and conditions within the system, such as in the case of a rapidly developing tumor, the immune response could stabilize or even go the opposite direction, allowing the cancer to persist, albeit at a slower rate than if the feedback loop was absent.

2.3 Immune suppressions

T regulation cells (Tregs) and Myeloided-Derived Suppressive Cells (MDSCs), both of that play a role in suppressing the immune response within the BC ecosystem, are present inside the tumor compartments. The estimation of the amount of MDSC depends on the quantity of tumor tissues presents in BC. The analysis of the number of Tregs in CDLN and the tumor sector is determined by the overall count of T lymphocytes in the lymph nodes after considering the level of MDSC in the tumor—data from the literature support these estimations. The expression of checkpoints such as PD1, PDL1, and CTLA4 carries out their inhibiting effects. The suppressive effects of Tregs and MDSCs on the function of the effector T cells and the development of APCs are primarily attributed to the generation of checkpoints, determined by receptor occupancy and a constraint that describes the maximal inhibitory impact. Tumor cells can partly impede the growth and cytotoxic function of CTLs, either temporarily or continually, through the production of PDL1 and PDL2 checkpoints.

Although mediators and receptors are typically found on the surfaces of cells and engage at immunological connections, CTLA4 can be released and discharged from Treg cellular surfaces into the TME. TME binds to CD80/86 ligands on mAPCs. The inhibitory messages dampen the feedforward cycle of tumor cell destruction and stimulation of T-cells in the patient's defense mechanisms.

2.4 Gene prediction

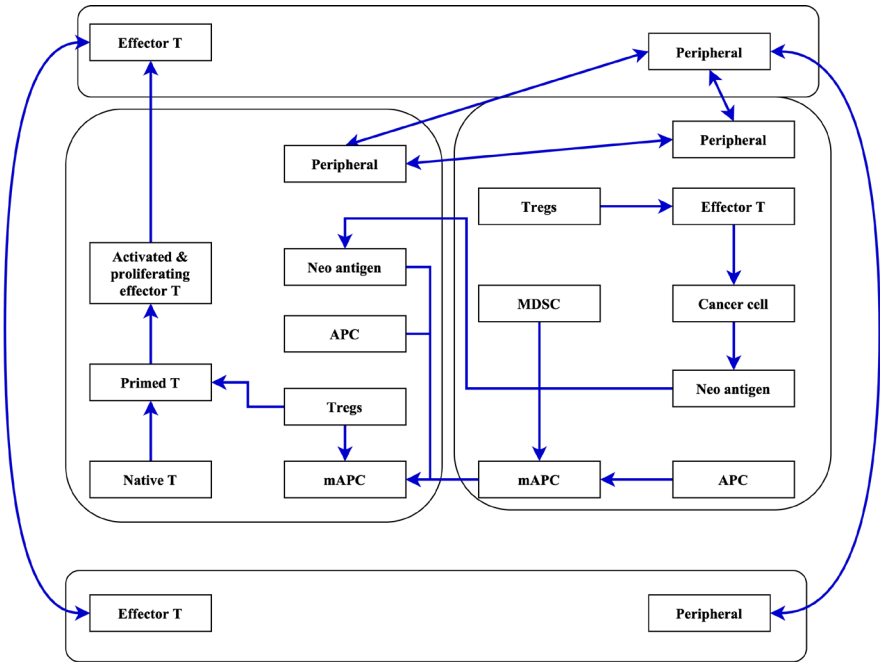

Figure 1. The proposed system dynamics for the breast cancer investigation

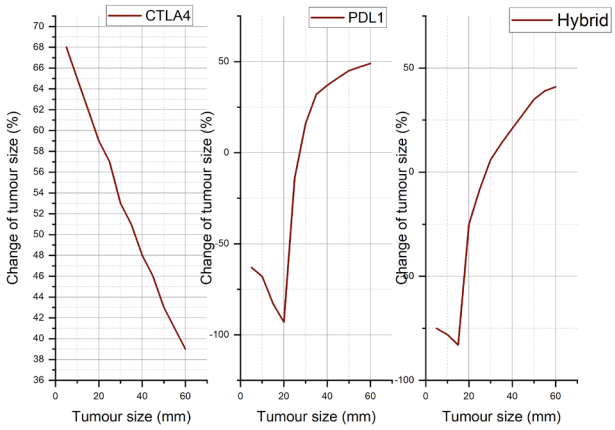

Figure 2(a). Change of tumor size vs. initial tumor size analysis

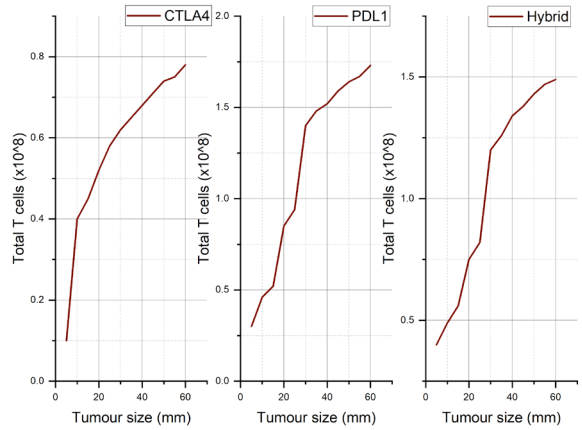

Figure 2(b). Total T cells vs. initial tumor size analysis

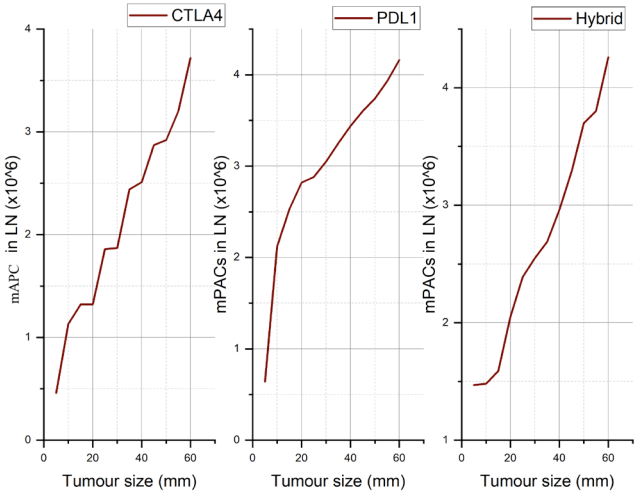

Figure 2(c). mAPC vs. initial tumor size analysis

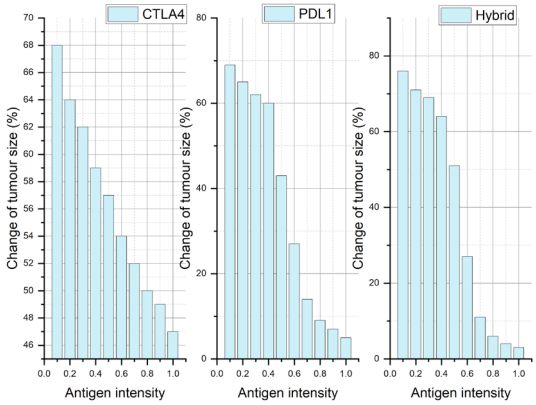

Figure 3(a). Change of tumor size vs. Antigen intensity analysis

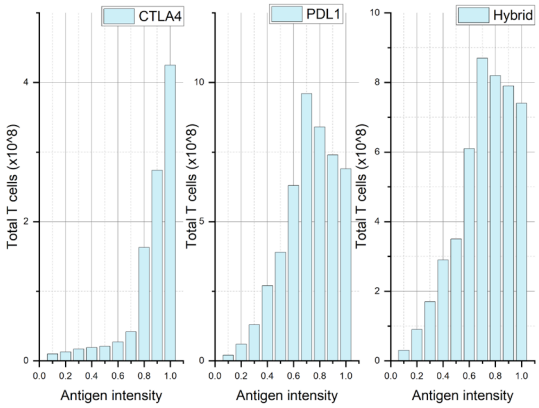

Figure 3(b). Total T cells vs. Antigen intensity analysis

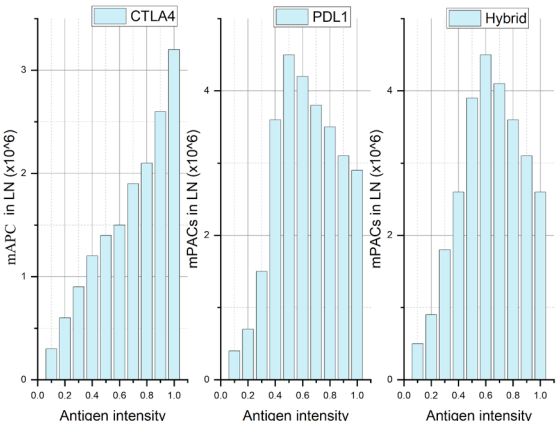

Figure 3(c). mAPCs vs. Antigen intensity analysis

The Integrated Pharmacology-based Breast Tumor Study Platform was utilized to predict the specific genes a chemical compound would influence. The Swiss target forecasting technique offers insights into a tiny molecule's chemical makeup and biological functions while predicting its macromolecular goals. The degree of resemblance to a recognized component was evaluated to forecast the objective. A threshold of below 0.2 was set as the probability score threshold for screening aim from the forecasting dataset to identify desirable targets associated with the chemical of interest. The Gene Cards file, which provides comprehensive and user-friendly information on all projected and discovered genes related to human illnesses, was used to gather the many genes connected with breast tumors. The phrase "breast malignancy" was used as a primary keyword, along with specific keywords like "tripled negative breast cancer," to conduct searches in the dataset. Targets with gene cards imputed functionally, scoring below 30, were selected.

2.5 Construction of a mutual network

The examination of protein-protein connections within the networks achieves the identification of core regulatory genes. The records, which have extensive data on known and predicted protein-protein relationships across several species, are utilized to get Protein-Protein Interactions (PPIs) data. The database was utilized to identify PPIs, using a cutoff criterion of > 0.4 (minimum probability). Only the genus "Homo sapiens" was included in this study. Before sending the verified objectives, only those with confidence ratings more significant than 0.6 were used. The information from PPI was acquired. The 35 enzymes with the highest levels were considered the primary candidates for Juglanthraquinone C in combating breast carcinoma.

2.6 Examining the clinical functions

The mRNA activity of the critical genes was analyzed using the Malignancies Genome Atlas dataset, considering the type of specimen and the degree of cancer. A significance level of 0.05 was employed to assess the impact. The Human Protein Atlas was used to ascertain the hub-targeted protein expression levels in both standard and cancerous breast cells. The TIMER cistrome dataset analyzed the Overall Survival (OS). The logarithmic rank coefficient 0.1 was determined to show a variation. By utilizing the cBioPortal software, it was feasible to discern biological specifics and associations among the mRNA of significant methods. A total of 4135 specimens of breast aggressive carcinoma were studied.

2.7 T-cell priming

The implementation of all ligand-receptor relationships involves two phases. The interaction between two kinds of cells creates a cell–cell (C2C) combination. The C2C mixture might either disintegrate without any consequence or lead to stimulation or inhibition of one of the cells. This choice relies on the checkpoint messages, determined by antigen occupancy or toxin magnitude, pertain to T-cell receptors and binding strength. The process of priming takes place in separate steps within CDLNs. Naïve T cells initially establish brief connections with mAPCs to transition into prepared naïve T cells. They develop persistent contacts that trigger continuous chemokine synthesis, transforming them into proliferative T cells. These cells acquire high motility and fast proliferation, becoming operational T cells. During each encounter, there are two possible outcomes among mAPCs and T cells. The cells might separate without activating the naïve T cell, or they can separate with the inexperienced T cell progressing to the next phase. The outcome relies upon the strength of the epitope and the presence of the PDL1 receptors.

3. Experimental Setup and Outcomes

The model replicates the PK and PD of anti CTLA4, anti PD1, and anti PDL1 antibodies when employed alone and combined with treatment. This study examines explicitly a clinical trial involving 18 breast cancer individuals who were treated with a combination regimen of tremelimumab and durvalumab. The research evaluates multiple variables, such as the number of lymph nodes exhausting the tumor, the rate of tumor development, the levels of checkpoints proteins, and the size of the tumor cells. These variables are related explicitly to metastatic breast malignancy. The electronic supplemental material contains the values, categories, and sources of variables, jointly with the governing formulas, model variables, and SBML program (https://sbml.org/).

The model's objective is to forecast patients' reactions to immunotherapies. The primary outcomes are examining the change in tumor size over time, the generation of effector T-cells, and the development of antibody-present tissues in CDLNs. To demonstrate the forecasts, the research initially examines a baseline scenario. It displays the dosage response for every monotherapy, namely CTLA4 and PDL1, and their combined effect by the treatment plan outlined in the clinical study. Tumor growth is characterized using parameters also employed in clinical research. Figure 2 displays the primary results of 'virtual' individuals, utilizing baseline characteristics, who begin therapy with a tumor size of 30 mm. The figure illustrates the outcomes for different dosages of checkpoint-blocking antibodies. In the case study, tremelimumab is given to individuals with a mean weight of 75 kg. It is administered once a month for a total of four sessions. The dosages given are 0, 1, 2, 5, 10, 15, and 20 of total body weight in CTLA4 monotherapy (Fig. 2(a)). Monotherapy shows a notable rise in effecting T cells and matured APCs. However, according to the standards, patients with various dosages (0, 1, 4) experience progressive illness according to tumor size. For greater dosages (5, 10, 15, 20), individuals initially have stable disease for

approximately five months, then develop progressive illness. Durvalumab is administered as a monthly treatment for PDL1 treatment. The dosages are given four times, with 0, 1, 4, 10, 15, and 20 mg per kilogram of body weight. After the first dosages of 2, 5, 10, 15, and 20, subsequent doses of 1, 2, 5, and 10 are given every two weeks for up to 18 months. While PDL1 monotherapy did not stimulate T-cell generation and APC maturity to the extent of CTLA4 monotherapy, participants had favorable reactions at 1 and above (Fig. 2(b)). When durvalumab is paired with an established dosage T-cell generation is boosted to the start of the treatment, that is greater than PDL1 treatment (Fig. 2(c)). The findings indicate that the PD1/PDL1 path is crucial in the tumor microenvironment as a mechanism of opposition, shielding cancer tissues from the attack of cancer-infiltrating lymphocytes and combining therapies results in an enhance in the generation by blocking CTLA4 in CDLNs, that leads to a moderate improvement in reducing tumor growth compared to using alone PDL1 treatment.

Fig. 3(a) shows the change in tumor size vs. Antigen intensity analysis, Fig. 3(b) shows the total T cells vs. Antigen intensity analysis, and Fig. 3(c) shows the mAPCs vs. Antigen intensity analysis. To examine the impact of initial tumor size, PDL1 levels, and antigen magnitude on tumor response, the research creates graphs that show the variation in tumor size over time, the proportion shifts in tumor size relative to the initial dimensions, and the mean amount of impacting BC tissues in the CDLN over 1 and half year. Each graph focuses on one variable at a time. Based on experimental research, it has been observed that earlier breast tumors with PDL1 levels tend to display a higher presence of T-cells. Therefore, the analysis can infer that PDL1-negative tumor cells can suppress others through the material of the BC microenvironment or PD1/PDL1 inhibition pathways. Although tremelimumab treatment does not yield a reaction, durvalumab treatment leads to a complete response when the PDL1 level is at its greatest. As PDL1 activity diminishes, the tumor response grows less effective. The research examines the impact of antigen concentration. Although CTLA4 alone at the chosen dose and schedule has resulted in modest tumor reaction, PDL1 alone and combined therapy indicate that the tumor responses improve as the neoantigen becomes more potent.

4. Conclusion

The suggested quantitative systems pharmacology incorporates pertinent immunological and tumor-based components and procedures for particular BC individuals. The method has of several parts: central, peripheral, CDLN, and tumor divisions. The framework represents the immune system's suppressing and evasing processes in the CDLN and the tumor ecosystem induced by the checkpoints. Furthermore, the modeling can accurately reproduce the tumor's reaction to checkpoint-blocking medication. It also delineates many mechanisms of immune suppression and evading in the CDLN and the tumor microenvironment. The objective is to discover possible biomarkers, uncover more resistance processes, and provide a foundation for predicting tumor response to immunotherapy in groups of individuals and, ultimately, for customized treatment.

By conducting network pharmacology investigations, investigators found 20 pathways associated with cancer. The enzyme-associated receptor proteins route and controlling cells' dying course were particularly significant among them. The results indicate that Juglanthraquinone C, with its many targets and pathways, is a promising therapeutic option for breast cancer. Furthermore, the study establishes a theoretical basis for forthcoming advancements in the therapy of breast tumors. Due to the limited research on the preventive effects of Juglanthraquinone C on breast tumors and the fact that the study relied on information mining and evaluation, it is necessary to conduct more trustworthy research to support the result.

Author contribution

P.G., R.P., U.J. wrote, reviewed and edited the article. All authors read and approved for publication.

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Competing financial interests

The authors have no conflict of interest.

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