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REVIEW ARTICLE

Recent Developments in Treatment strategies for Triple Negative Breast Cancer

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ABSTRACT

Triple-negative breast cancer (TNBC) is a highly aggressive and heterogeneous subtype of breast cancer, characterized by the lack of estrogen, progesterone, and HER2 receptors, accounting for 15% of all breast cancer cases, with a higher prevalence in premenopausal African and African American women. Despite advances in treatment options, TNBC remains a significant clinical challenge due to its poor prognosis, high recurrence rate, and limited targeted therapies. This review highlights the current understanding of TNBC's molecular landscape, clinical features, and treatment strategies, including chemotherapy, immunotherapy, and emerging targeted agents. However, further research is needed to unravel the complexities of TNBC and develop effective personalized treatment approaches to improve patient outcomes. The lack of effective targeted therapies and high recurrence rates emphasize the need for continued research into the molecular mechanisms driving TNBC, as well as the development of novel therapeutic strategies. By advancing our understanding of TNBC's biology and identifying new targets for therapy, we can hope to improve treatment options and outcomes for patients with this devastating disease. Ultimately, a multidisciplinary approach, combining basic science, clinical research, and patient care, is necessary to make meaningful progress against TNBC and improve the lives of those affected by this disease.

Keywords: Triple negative breast cancer, Apoptosis, Necrosis, Phytochemicals.

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INTRODUCTION

Cancer is the uncontrolled growth of abnormal cells in body. Cancer develops when body's normal control mechanism stops working.[1] Old cells do not die and instead grow out of control, forming new abnormal cells. These extra cells may form a mass of tissue, called a tumor. Cancer is a wide term that encompasses about 277 different forms of cancer disease. Different stages of cancer have been identified, demonstrating that multiple gene mutations are involved in cancer pathogenesis.[2] The aberrant cell growth is caused by these gene alterations. Disorders of the genome induced by hereditary or inheritance factors play an important part in cell proliferation.[3]

On a global scale, cancer is the second most common cause of death.[4] Overall, cancer has become more common; in 2014, roughly 1,665,540 persons in the United States were diagnosed with cancer, with 585,720 of them dying as a result of the disease.[5] In 2021/ 78,22, 644 peoples has died because of cancer so far. As a result, cancer is a major public health concern that affects all human communities.[6] Unfortunately, it is a heterogeneous disease at the tissue level, and this heterogeneity is a key problem for accurate diagnosis and therapeutic efficacy.[7] Prostate cancer, lung and bronchus cancer, colon and rectum cancer, and urinary bladder cancer all have significant percentages of cancer types in men.[8] Breast, lung, and bronchus cancer, colon and rectum cancer, uterine corpus cancer, and thyroid cancer are the most common cancers in women. Prostate and breast cancer account for a significant part of cancer in both men and women, according to this data.

Classification of Cancer

Cancer can be classified in two ways: by the types of tissue in which the cancer originates (histological type) and by primary site or the location in the body where the cancer first developed.[9,10] FROM a histological standpoint there are hundreds of different cancers, which are grouped into six major categories:

1. Carcinoma (Epithelial origin)
2. Sarcoma (Connective tissue origin)
3. Myeloma (originates into plasma cells of bone marrow)
4. Leukemia (blood cancers)
5. Lymphma (origin in lymphatic system)

Hence, Breast Cancer is a type of carcinoma or that arise from epithelial tissue.[11] Breast Cancer happens when

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cells in your breast grow and divide in an uncontrolled way , Creating a mass of tissues called a tumor.[12] The risk of developing breast cancer increases with your age and with your weight gain. Signs of breast cancer can include feeling a lump breast, experiencing a change in the size of your breast and seeing changes to the skin on your breasts. Early detection is aided by mammograms (a breast examination using X-rays to check for cancer).[13]

* About 1 in 8 women will develop breast cancer.[14]

Breast Cancer can also be classified into different subgroups

1. On the basis of molecular pattern
2. On the basis of Histological pattern[15]

According to molecular classification Breast cancer divided into 5- subgroups[16]

- Luminal A type breast cancer (Her-2–ve), Estrogen and progesterone receptor positive , good prognosis , Associated with BRCA-2 gene mutation.
- Luminal B type breast cancer (her-2+ve), Estrogen and Progesterone positive, poor prognosis , Associated with BRCA-2 gene mutation.
- Her-2 rich type breast cancer, Her-2+ve , but Estrogen and progesterone receptors negative , poor prognosis.
- Basal type of breast cancer (They are Her-2 negative, Estrogen and progesterone receptor negative means absent), so these breast cancers called triple negative breast cancer and these types of breast cancer will be having worse type of prognosis. Usually associated with BRCA-1 type of gene mutations.
- Claudin type of breast cancer (associated with tight junction molecules)[17]

According to histological classification ,

1. Non – invasive (this type of cancer does not invade to other organs)
2. Invasive (that can invade to other organs also)[18]

Triple-negative Breast Cancer

Triple-negative breast cancer is one of the subgroup of breast cancer, that can be defined as the lack of expression of oestrogen, progestron ,and ERRB2 receptors.[19] This subgroup accounts for 15% of all types of breast cancer and for a higher percentage of breast cancer arising in African and African American women who are premenopausal.[20] It's called as triple negative because it does not have three markers associated with other types of breast cancer, which is important for prognosis and treatment. Its one of the more challenging breast cancers to treat.

Breast cancer cells' receptors are open to estrogen and progesterone.[21] Understanding if your breast cancer cells have receptors and if they are housing hormones helps providers determine how your breast cancer might spread and what treatment might be most effective.

The other type of breast cancer that has another receptor is called her-2 neu.[22] This receptors makes the cells more active ,but allows healthcare providers to treat the cancer with specific medicines that target her-2 proteins. If your breast cancer doesn't have her-2 and hormone receptors, it's called triple negative breast cancer.[23]

- Its an aggressive form of breast cancer
- Highly metastatic/migratory, invasive
- Poorer prognosis,advanced disease stage,and a higher histological grade
- High risk of early recurrence
- Survival rate – 40%[24]

TNBC is more often associated with hereditary conditions as compared to other breast cancer subtypes. For instance, among newly diagnosed breast cancer patients, <10% have BRCA1 or BRCA2 mutated genes but this percentage is higher among patients with TNBC with around 35% of BRCA1 and 8% of BRCA2 mutations in this population.[25] Triple negative breast cancer appears more frequently in women age 40 and younger then in older women. Black and Latina women are more likely to develop TNBC then white women.[26] Women who have the gene change BRCA1 are more likely to develop TNBC than other women.[27] When the BRCA1 mutates, it stopes preventing cancer and appears to make your body's cells more vulnerable to cancer.[28]

Symptoms

- A new lumps or mass.
- Swelling in all parts of a breast.
- Dimpled skin.
- Breast or nipple pain.
- Nipple retraction, when your nipple turns inwards.
- Nipple or breast skin that's dry, flaking, thickened or red.
- Nipple discharge that is not breast milk
- Swollen lymph nodes. This symptom happens when breast cancer spreads to the lymph nodes under your arm or near your collarbone.[29]

Etiology

Researchers don't know what causes TNBC, but they think BRCA1 genetic mutation might play a part. The BRCA1 gene is meant to prevent cancer. When it mutates, however, the gene reverses course and makes your cells more vulnerable to cancer.[30]

Diagnosis

- Mammogram to evaluate a suspicious mass or lump in your breast.

- Biopsy to remove breast tissue for examination purpose.
- Magnetic resonance imaging.
- Ultrasound
- Computed tomography scan.[31]

Treatment Stratigies

Surgery

This could be a lumpectomy to remove an individual lump, or a mastectomy to remove an entire breast.[32]

Radiation therapy

Post-surgery radiation therapy helps reduce the chances your cancer will return or recur.[33]

Immunotherapy

This treatment stimulates your immune system to produce more cancer fighting cells or help healthy cells identify and attack cancer cells.[34]

Chemotherapy

Chemotherapy is often recommended for treating triple negative breast cancer.[35] Unlike most other types of breast cancer, triple negative breast cancer does not respond to the presence of certain hormones , such as estrogen, progesterone, nor does it have an abnormally high level of Her2 receptors. Therefore, hormone therapy is largely ineffective for treatment purposes. Nevertheless, triple negative breast cancer often responds very well to chemotherapy.

Depending on when chemo is administered, its goals vary. For instance, chemotherapy may be recommended prior to surgery to attempt to destroy rapidly dividing cancer cells. In this way, it may be possible to shrink tumors and make them easier to remove, which can increase the likelihood of a successful surgical outcome.

Additionally, because it is not always possible for a surgeon to completely remove a patient's cancer, chemotherapy may be recommended after surgery to target any remaining cancer cells and help prevent spread and recurrence.[36]

Alternatively, chemo can be used as a primary form of treatment to control the growth and ease the symptoms of large tumors that cannot be surgically removed.

As a systemic form of treatment, chemotherapy is effective because it can potentially reach and destroy cancer cells located throughout a patient's blood stream.[37]

Commonly Used Chemotherapy Regimens for Patients with Metastatic TNBC

Paclitaxel	> Capecitabine
ERIBULIN	> Vinorelbine
Carboplatin	> Nab-Paclitaxel
Cisplatin	> Liposomal Dxorubicin
Gemcitabine	> Doxetaxel[38]

Chemo is often used first when the cancer has spread to other parts of the body (stage 4th). Common chemo drugs used include anthracyclines, capecitabine, gemcitabine, eribulin, and others.[39] Different therapies have also been summarized in Table 1. For women with TNBC who have BRCA mutation and whose cancer no longer respond to common breast cancer chemo drugs, other chemo drugs called platinum drugs (Like Cisplatin or carboplatin) or targeted drugs called PARP inhibitors, such as olaparib (lynparza) or talazoparib (Talzenna), may considered.[40]

In patients with advanced TNBC treated with an anthracycline with or without a taxane in the neoadjuvant or adjuvant setting, carboplatin demonstrated comparable efficacy and a more favourable toxicity profile than docetaxel.[41]

Poly ADP-ribose polymerase (PARP) inhibitors

Olaparib FDA- and EMA-approved targeted therapy[42]

In metastitics patients harboring a germline BRCA mutation, olaparib has shown important activity in both TNBC and Luminal-like disease. The olympiAD study was designed to compare the use of olaparib versus standard single-agent chemotherapy (Capecitabine, eribulin, or vinorelbine in 21-day cycles) in BRCA-mutated breast cancer patients.[43] Among the 302 patients that underwent randomization, 205 received olaparib and 97 received standard chemotherapy.[44] Response rate was 59.9% in patients receiving olaparib and 28.8% in patients receiving standard chemotherapy.[45]

Talazoparib FDA- approved targeted therapy

With a similar design as the OlympiAD study, the EMBRACA trial showed important activity for Talazoparib in the treatment of metaststic breast cancer patients harboring a germline BRCA mutation including women with TNBC.[46] This was a randomized open label phase 3rd study that included 431 patients divided into two groups: 287 patients received talazoparib and 144 received standard chemotherapy (capecitabine, eribulin, gemcitabine and vinorelbine) (Figure 1).[47] THE objective response rate was also higher in the talazoparib group than in the chemotherapy group.[48]

Immunotherapy Atezolizumab

- Atezolizumab has shown safety and good clinical activity in TNBC. Chemotherapy taxanes in particular ,may enhance tumors antigens release by activating tll-like receptors and promoting dendritic cell activity.[49] Based on this rationale , a phase 3rd trial randomized patients with metastatic TNBC to first

Table 1: Different Therapies used for treatment of TNBC

S. No.	Therapy	Targeted part/cells	Research Outcomes	References
1	Immune-therapy	To stimulate or modulate the immune system to fight disease	More effective , As some drugs have FDA approval of immunotherapy such as atezolizumab with nab-paclitaxel	52
2	Targeted therapies	PARP inhibitors, EGFR inhibitors, Angiogenesis inhibitors, Src inhibitors, mTOR inhibitors	Higher response rate was found in this case	53
3	Surgery and Radiation therapy	Masectomy, Breast conserving surgery (Lupectomy), Lumpectomy with radiation therapy	There remain a number of grey zones with respect to optimization of the extent and timing of surgery and radiation therapy.	54
4	Chemotherapy	Target DNA repairing	Biologically aggressive , such as anthracycline drug, taxanes, antimetabolites, platinum agents	55

line atezolizumab plus nab-paclitaxel and placebo plus nab-paclitaxel (Figure 2).[50]

- Recently the combinations of atezolizumab plus nab-paclitaxel has been approved by FDA as first-line therapy in patients with PD-L1 positive TNBC.[51]

Ongoing PARP Trials

- 17- 428 (TBCRC 048): 'OLAPARIB extended'
- Will allow for a variety of other hereditary breast cancer gene mutations
- And , for BRCA ½ mutations that are in the tumor (but not inherited)
- Phase lb/2nd Olaparib + Sapacitabine in BRCA mutated breast cancer.[56]

PARP inhibitor (olaparib) leads to tumor shrinkage in clinical trials of patients with BRCA1/2 – associated breast cancer.[57,58]

Summary of Phase Trials

- Fewer side effects overall in the olaparib group
- Benefits seen in ER+ and TNBC patients
- Benefits seen in BRCA1 And BRCA2 patients
- Waiting to follow patients longer to understand effects on survival.[60]

FDA approval granted on Jan 2018-2024.

Talazoparib v/s Chemotherapy in gBRCA-Associated Breast Cancer[61]

- Better quality of life in the Talazoparib group
- Benefits seen in ER+ and TNBC patients
- Benefits seen in BRCA1 and BRCA2 patients
- Waiting to follow patients longer to understand effects on survival[62]

FDA approval on October 16, 2018

- Improvement in average length of survival for patients who received chemotherapy + immunotherapy
- But only seen in patients with PDL1 tumors
- Immune side effects were seen

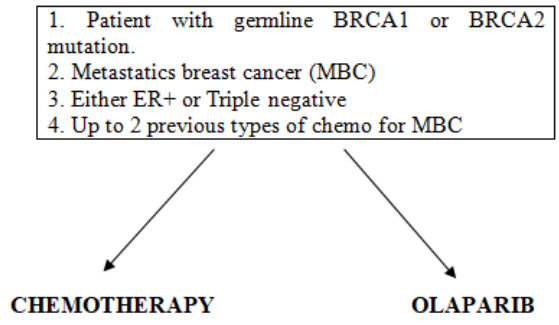

Figure 1: Phase 3 OlympiAD trials: olaparib v/s chemotherapy in gBRCA-associated breast cancer [58]

- A good start, but still more progress to be made.[64,65,

FDA approval on March 8, 2019

Antibody Drug Conjugates

Moa: Antibody, Linker, Drug

- Antibody that recognizes a marker on tumor cells that is not/less present on normal cells. Linker that is stable in circulation but releases the drug in target cells. Potent drug designed to attack the cell when internalized and released.[66,67] Different derivatives which have been approved in phase 3 and 4 trials are discussed shown in Table 2.

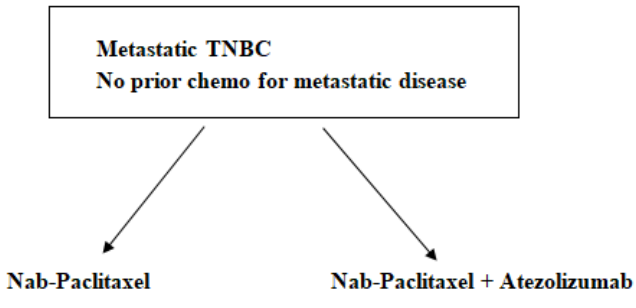

Figure 2: Impassion 130: Randomized phase 3 trial for first-line metastatic TNBC[63]

Table 2: Recently approved drugs under phase 3/4 drugs or recent derivatives acting against TNBC

S. No.	Newer drugs	Chemical structure	Targeted part/cells	Research outcomes	References
1	Anthracycline (Doxorubicin)	C27H29NO11	Inhibits the DNA and RNA synthesis, block cell division	Anthracyclie and taxane regimens yield unsatifactorily low rates of pathologic complete response	68
2	Tivozanib	C22H19ClN405	Actions by inhibiting the phosphorylation of VEGFR-1 and 2 , angiogenesis	Tivozanib alon with weekly paclitaxel improves clinical outcomes in patients	69
3	dasatinib	C22H26ClN702S	Work by blocking the action of abnormal protein that signals cancer cells to multiply	Dasatinib is a promising anti-BCSC drug that could be used in combination with paclitaxel to overcome chemoresistance in TNBC	70
4	Trodelvy (sacituzumab govitecan-hziy)	C76H104N12O24S	Targeted therapy, trop-2 antibody and topoisomerase inhibitor drug conjugate	FDA approved this drug for TNBC, who have already tried two prior therapies.	71
5	Pembrolizumab (keytruda)	C6534H10004N1 716O2036S46	Shrinkage of tumor , works by targeting the cellular payhway of proteins of immune system.	FDA approved this drug, after surgery it can be taken by patients.	72
6	Capecitabine (xeloda)	C15H22FN3O6	Both normal and tumor cells metabolize 5-fu or 5-fluorouracil to 5-fluoro-2- deoxyuridine monophosphate (FdUMP) and 5- fluorouridine triphosphate (FUTP).	Approval after surgery, for 18-24 weeks ,reduce chances of reccurence. Or at stage 4th	73
7	Olaparib	C24H23FN4O3	PARP inhibitor, exploits tumor DNA repair pathway deficiencies and kill cancer cells	Approval for the patients who have BRCA Mutation and after surgery also, for one year , so as to prevent recurring	74
8	Carboplatin	C6H12N2O4Pt	An alkylating agent, covalently binds to DNA and interferes with DNA function by producing interstrand DNA crosslink	Potentially Life saving treatment option for advanced clinical stage TNBC .	75
9	Nab-Paclitaxel	C47H51NO14	Enhance the action of tubuline dimmers, stabilizing existing microtubules and inhibiting their disassembly, interferring with the late G2 mitotic phase, and cell replication	Effective in patients with more aggressive tumors, TNBC	76
10	Adriamycin	C27H29NO11	Inhibits DNA and RNA synthesis	Tpically used after surgery to reduce the risk of early-stage breast cancer coming back	77
11	Cyclophosphamide	C7H15Cl2N2O2P.H2O	Prevents cell division by cross-linking DNAstrands and reducing DNA synthesis	More effective in TNBC	78
12	Glembatumumab		PARP enzyme fixes DNA damage incells, including damage caused by chemotherapy agents	Effective with some Chemotherap-eutic drugs	79
13	Metformin	C4H11N5	Work on reduction of cell proliferation ,oncogenicity and motility,inhibtion of pro-oncogenic signaling pathways, apoptosis	Potent against triple negative breast cancer	80
14	MUCl vaccine	C6H10O8	Enhance the patients immune response against MUC1 protien and suppress the tumors ability to grow	Build effective immune response to kill tumor cells	81
15	Eribulin	C40H59NO11	Eribulin is an inhibitor of microtubule dynamics with a unique tubulin based that results in inhibition of the growth phase of the microtubule.	Approved in 2010 for metastatic breast cancer	82
16	Trestuzumab (HERCEPTIN)	C6470H10012N1 726O2013S42	Monoclonal antibody	Patients do not benefits from hormonal or trastuzumab-based targeted thrapy because of the loss of target receptors	83
17	Alpesilib	C19H22F3N5O2S	PI3K/AKT PATHWAY Inhibitors, regulate cell proliferation, growth and survival	Very effective by blocking cell proliferation pathway	84

Table 3: Intervention of cancer using different phytochemicals

S. No.	Plant name	Botanical name and family	Name of chemical constituents	MOA	Research outcomes	Reff
1	Turmeric	*Curcuma longa*, zingiberaceae	Curcumin	Inducing apoptosis, proliferation and invasion of tumors	Able to inhibits TNBC cells proliferation, inhibition of EGFR signalling	101
2	Chinese goldthread	*Coptis chinensis*, Ranunculales	Berberine	Inhibits cell proliferation by regulating cell cycle and cell autophagy	Reduce viability of MDA-MB-231cells and reduction of proinflammat-ory cytokines	102
3	olive	*Ola europaea*, oleaceae	Ursolic	Could affect the resistance of TNBC cells to other drugs such as doxorubicin	UA promotes the TNBC cell sensitivity to DOX through inactivating ZEB1-AS1/miR-186-5p/ABCC1 signalling	103
4	wormwood	*Artemisia absinthium*, Asteraceae	Artemisinin	The Artemisia annua flavonols chrysosplenol Induce autophagy	Potential anticancer therapeutics	104
5	soyabean	*Glycine max*, fabceae	Genistein (isoflavon)	Inhibits MDA-MB-231triple negative breast cancer cell growth by NF-kB activity	Study revealed that Gen elicited a dramatic effect on cell growth inhibition	105
6	Stephenia	*Stephania cephalantha hayata*, menispermeaceae	Cepharanthine	Sensitizes TNBC cells to chemotherapeutic agent such as epirubicin via inducingcofilin oxidation mediated mitochondrial apoptosis	Combination of cepharanthine with chemotherpeutic agents represent novel treatment	106
7	Green tea plant	*Camellia sinensis*, theaceae	Epigallocatechin gallate	Antiproliferation, antimetastasis, apoptosis induction	Action of EGCG may exert a suppressive effect on gynecological cancers	107
8	Chinese rhubarb	*Rheum palmatum*, polygonaceae	Emodin	Interferes with AKT1-mediated DNA damage and decrease resistance of breast cancer cells to doxorubicin	Beneficial Affects cell proliferation , confers sensitization of BC to doxorubicin	108
9	Gamboge	*Garcinia hanburyi,* clusiaceae	Gambogic acid	Increases the sensitivity to paclitaxel in drug-resistant TNBC via the SHH signaling pathway	Combination of GA with paclitaxel may increase effects on paclitaxel-resistant TNBC	109
10	Milk thistle	*Silybum marianum*, asteraceae	Silibinin	Inhibitory effect of silibinin on TGF-beta2 action in TNBC cells	Suppresses metastatic potential of TNBC cells by inhibiting TGF-beta2 expression in TNBCC cells	110
11	Alkanna tinctoria	*Dyers alkanet*, boraginaceae	Shikonin	Inhibits migration and invasion of TNBC cells by suppressing epithelial-mesenchymal transition via miR-17-5p/ PTEN/Akt pathway	Shikonin as a promising therapeutic agent to counteract metastasis in the TNBC patients	111
12	mugwort	*Artemisia vulgaris*, Asteraceae	Artesunate	It is antimalerial drug causes cell cycle arrest and apoptosis of triple negative MDA-MB468 and HER2-Enriched SK-BR-3 breast cancer cells	May have clinical utility in the treatment of TNBC HER2-cancer	112
13	Raloxifene	--	Raloxifene	Reduce tumor cells growth and decreases EGFR expression	Acts independendtly of the estrogen receptor and may be relevant for the treatment as well as control the progression of TNBC	113
14	Rabdosia	*Rabdosia rubescens*, lamiaceae	Oridonin	Oridine-56 , derivative of oridine acts as a antiproliferative	Compound 56 exhibited more potent anticancer activity than paclitaxel, may warrant further investigation	114

Other Targets

- AKT1, PTEN, PIK3CA – Ipatasertib, capivasertib, etc
- Androgen receptor
- DNA repair – ATR inhibitors, etc.
- MYC – Bromodomain inhibitors, CDK7 or CDK9 inhibitors , Aurora kinase Inhibitors, CHK1 inhibitors[85]

CHRYSIN, a naturally occurring flavonoid, inhibits migration and invasion in triple negative breast cancer cell via PI3K/AKT PATHWAY.[86]

Favonoids are polyphenolic compounds that are ubiquitously in plants. *The role of dietary flavonoids in cancer prevention.*[87]

Mechanism of action : Carcinogen inactivation, Antiprolifiration, Cell cycle arrest, induction of apoptosis and differentiation.[88]

Lycopene (carotenoid) has been shown to block breast cancer cell metastasis.[89]

Mechanism of action

Lycopene treatments inhibits cancer cell growth, induces apoptosis by suppressing ERK signaling pathway. Bcl-2 family and Caspases are considered to be the most effective apoptotic regulators. Lycopene decreases Bcl-2 and increases Bax expression, which induce cytochrome C from Mitochondria, leading to apoptosis.[90]

Herbal agents in cancer management

Plant extracts as a chemotherapeutic drugs

- Red Guava extracts purified from leaf and bark have many bio-active molecules with anti- cancer activities.[91] In addition, lycopene-rich extracts obtained from red guava fruit can induce apoptosis in estrogen receptors-positive breast cancers. Triple-negative breast cancer (TNBC) lacks estrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 (HER2) and, therefore, hormone therapy and targeted therapy are not used in clinic.[92] The purpose of this study was to determine whether red guava fruits extracts can affect the proliferation of TNBC cells.[93] In this study, cell viability was determined by using the MTT assay. Apoptosis and necrosis were analyzed using flow cytometry. Cleaved caspase-3 activation and PARP were analyzed by western blotting.[94] We found that red guava extracts can, through caspase-3 activation and PARP cleavage signaling, induce apoptotic and necrotic death in TNBC cells.[95] Our results thus show the therapeutic benefits of red guava extracts as a potential cancer treatment for TNBC in combination with doxorubicin or targeted therapy.[96]
- Rosehip extracts decrease cell proliferation in all cell lines without inducing apoptosis.[97] Rosehip extracts prevent cell migration in breast cancer cell.[98] Rosehip extracts synergize with doxorubicin to inhibit cell proliferation and cell apoptosis.[99]
- Doxorubicin and the combination with rosehip extracts prevent cell metastasis in breast cancer cell lines.[100] Different other herbal agents active against TNBC also have been listed in Table 3.

CONCLUSION

Recent advancements in treatment strategies for triple-negative breast cancer (TNBC) underscore the urgent need for continued research to address its aggressive nature and high recurrence rates. A multidisciplinary approach that integrates molecular understanding, clinical research, and innovative therapeutic options is essential to enhance patient outcomes and combat this challenging subtype of breast cancer.

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CONFLICTS OF INTEREST

Authors declare none conflicts of interest.

REFERENCES

1. Prasad, R. Bhanu, et al. "Cancer prevalence in south Indian hospitals: A prospective observational study." *Cancer* 6.2 (2020): 48-51
2. Shigematsu, Hisayuki, and Adi F. Gazdar. "Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers." *International journal of cancer* 118.2 (2006): 257-262.
3. Kanwal, R., & Gupta, S. (2012). Epigenetic modifications in cancer. *Clinical genetics*, *81*(4), 303-311.]
4. Tam, Alda. "Cancer remains the second most common cause of death in the United States, accounting for nearly 1 of every 4 deaths, introduction." *Techniques in vascular and interventional radiology* 14.3 (2011): 109.]
5. Shockney, Lillie D. "Oncology Across the Trajectory." *Textbook of Palliative Care Communication* 1 (2015): 183.]
6. Ezzati, Majid, and Alan D. Lopez. "Estimates of global mortality attributable to smoking in 2000." *The lancet* 362.9387 (2003): 847-852.]
7. Simon, R., and S. J. Wang. "Use of genomic signatures in therapeutics development in oncology and other diseases." *The pharmacogenomics journal* 6.3 (2006): 166-173.]
8. Greenlee, Robert T., et al. "Cancer statistics, 2000." *CA: a cancer journal for clinicians* 50.1 (2000): 7-33.]
9. Muir, C. S., and Constance Percy. "Classification and coding for neoplasms." *Cancer registration: principles and methods. Lyon: IARC* 81 (1991).]
10. Pervin, Farjana. *Identification of Common Cancers and Risk Factors in Poverty Level People in Bangladesh*. Diss. East West University, 2012.]
11. Fillmore, Christine M., and Charlotte Kuperwasser. "Human

breast cancer cell lines contain stem-like cells that self-renew, give rise to phenotypically diverse progeny and survive chemotherapy." *Breast cancer research* 10.2 (2008): 1-13.]
12. Stage, I. and Stage, I.I., Breast cancer happens when cells in your breast grow and divide in an uncontrolled way, creating a mass of tissue called a tumor. The risk of developing breast cancer increases you age and with weight gain. Signs of breast cancer can include feeling a lump in a breast, experiencing a change in the size of your breast and seeing changes to the skin on your breasts. Early detection is aided by mammograms.]
13. Padmanabhan, Sharanya, and Raji Sundararajan. "Enhanced accuracy of breast cancer detection in digital mammograms using wavelet analysis." In *2012 International Conference on Machine Vision and Image Processing (MVIP)*, pp. 153-156. IEEE, 2012.]
14. George, Sharon A. "Barriers to breast cancer screening: an integrative review." *Health care for women international* 21.1 (2000): 53-65.]
15. Weigelt, Britta, and Jorge S. Reis-Filho. "Histological and molecular types of breast cancer: is there a unifying taxonomy?." *Nature reviews Clinical oncology* 6.12 (2009): 718-730.]
16. Prado-Vázquez, Guillermo, et al. "A novel approach to triple-negative breast cancer molecular classification reveals a luminal immune-positive subgroup with good prognoses." *Scientific reports* 9.1 (2019): 1-12.]
17. Khosravi-Shahi, Parham, Luis Cabezón-Gutiérrez, and Sara Custodio-Cabello. "Metastatic triple negative breast cancer: optimizing treatment options, new and emerging targeted therapies." *Asia-Pacific Journal of Clinical Oncology* 14.1 (2018): 32-39].
18. Koga, Kenji, et al. "A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma." *Pathology international* 44.5 (1994): 359-367.]
19. Cleator, Susan, Wolfgang Heller, and R. Charles Coombes. "Triple-negative breast cancer: therapeutic options." *The lancet oncology* 8.3 (2007): 235-244.]
20. Cleator, Susan, Wolfgang Heller, and R. Charles Coombes. "Triple-negative breast cancer: therapeutic options." *The lancet oncology* 8.3 (2007): 235-244.]
21. Colditz, Graham A., et al. "Risk factors for breast cancer according to estrogen and progesterone receptor status." *Journal of the national cancer institute* 96.3 (2004): 218-228.
22. Artemov, Dmitri, et al. "MR molecular imaging of the Her-2/neu receptor in breast cancer cells using targeted iron oxide nanoparticles." *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine* 49.3 (2003): 403-408.
23. Dowaidar, Moataz. "Triple-negative breast cancer, which lacks the expression of hormone receptors and HER2, has a worse prognosis. Massive parallel sequencing is capable of reliably breaking down the intra-tumor and inter-tumor heterogeneity." (2021).
24. O'Brien, C. S., Farnie, G., Howell, S. J., & Clarke, R. B. (2011). Breast cancer stem cells and their role in resistance to endocrine therapy. *Hormones and Cancer*, *2*(2), 91-103.
25. Carey, Lisa, et al. "Triple-negative breast cancer: disease entity or title of convenience?." *Nature reviews Clinical oncology* 7.12 (2010): 683-692.
26. Amirikia, Kathryn C., et al. "Higher population-based incidence rates of triple-negative breast cancer among young African-American women: implications for breast cancer screening recommendations." *Cancer* 117.12 (2011): 2747-2753.
27. Dietze, Eric C., et al. "Triple-negative breast cancer in African-American women: disparities versus biology." *Nature Reviews Cancer* 15.4 (2015): 248-254.
28. Singletary, S. Eva. "Rating the risk factors for breast cancer." *Annals of surgery* 237.4 (2003): 474.
29. Pandey, P., et al. "Gold nanoparticles as a potential treatment for breast cancer: a review. AJPTI. 2021; 9 (2): 21-28." *Ductal carcinoma in situ*.
30. Burrell, Rebecca A., et al. "The causes and consequences of genetic heterogeneity in cancer evolution." *Nature* 501.7467 (2013): 338-345.
31. Chala, Luciano Fernandes, et al. "Fat necrosis of the breast: mammographic, sonographic, computed tomography, and magnetic resonance imaging findings." *Current problems in diagnostic radiology* 33.3 (2004): 106-126.
32. Anderson, Benjamin O., Riccardo Masetti, and Melvin J. Silverstein. "Oncoplastic approaches to partial mastectomy: an overview of volume-displacement techniques." *The lancet oncology* 6.3 (2005): 145-157.
33. Widder, J., et al. "Preoperative short-term radiation therapy (25 Gy, 2.5 Gy twice daily) for primary resectable rectal cancer (phase II)." *British journal of cancer* 92.7 (2005): 1209-1214.
34. Blattman, Joseph N., and Philip D. Greenberg. "Cancer immunotherapy: a treatment for the masses." *Science* 305.5681 (2004): 200-205.
35. da Silva, Jesse Lopes, et al. "Triple negative breast cancer: A thorough review of biomarkers." *Critical reviews in oncology/hematology* 145 (2020): 102855.
36. Demaria, Marco, et al. "Cellular senescence promotes adverse effects of chemotherapy and cancer relapse." *Cancer discovery* 7.2 (2017): 165-176.
37. Gavrilovic, Igor T., and Jerome B. Posner. "Brain metastases: epidemiology and pathophysiology." *Journal of neuro-oncology* 75.1 (2005): 5-14.
38. Caparica, Rafael, Matteo Lambertini, and Evandro de Azambuja. "How I treat metastatic triple-negative breast cancer." *ESMO open* 4 (2019): e000504.
39. Andreopoulou, Eleni, and Joseph A. Sparano. "Chemotherapy in patients with anthracycline and taxane-pretreated metastatic breast cancer: an overview." *Current breast cancer reports* 5.1 (2013): 42-50.
40. Silver, Daniel P., et al. "Efficacy of neoadjuvant Cisplatin in triple-negative breast cancer." *Journal of clinical oncology* 28.7 (2010): 1145.
41. Silver, Daniel P., et al. "Efficacy of neoadjuvant Cisplatin in triple-negative breast cancer." *Journal of clinical oncology* 28.7 (2010): 1145.
42. Boussios, Stergios, et al. "Development of new poly (ADP-ribose) polymerase (PARP) inhibitors in ovarian cancer: Quo Vadis?." *Annals of translational medicine* 8.24 (2020).
43. Robson, Mark, et al. "Olaparib for metastatic breast cancer in patients with a germline BRCA mutation." *New England Journal of Medicine* 377.6 (2017): 523-533
44. Robson, M., Im, S. A., Senkus, E., Xu, B., Domchek, S. M., Masuda, N., ... & Conte, P. (2017). Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *New England Journal of Medicine*, *377*(6), 523-533.
45. Robson, Mark, et al. "Olaparib for metastatic breast cancer in patients with a germline BRCA mutation." *New England Journal of Medicine* 377.6 (2017): 523-533.
46. Mehanna, Joe, et al. "Triple-negative breast cancer: current

perspective on the evolving therapeutic landscape." *International journal of women's health* 11 (2019): 431.
47. Mehanna, Joe, et al. "Triple-negative breast cancer: current perspective on the evolving therapeutic landscape." *International journal of women's health* 11 (2019): 431.
48. Litton, Jennifer K., et al. "Talazoparib in patients with advanced breast cancer and a germline BRCA mutation." *New England Journal of Medicine* 379.8 (2018): 753-763.
49. Emens, Leisha A., et al. "Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study." *JAMA oncology* 5.1 (2019): 74-82.
50. Mittendorf, E. A., Zhang, H., Barrios, C. H., Saji, S., Jung, K. H., Hegg, R., ... & Harbeck, N. (2020). Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *The Lancet*, *396*(10257), 1090-1100.
51. Narayan, Preeti, et al. "FDA approval summary: atezolizumab plus paclitaxel protein-bound for the treatment of patients with advanced or metastatic TNBC whose tumors express PD-L1." *Clinical cancer research* 26.10 (2020): 2284-2289.
52. Force, J., Leal, J. H. S., & McArthur, H. L. (2019). Checkpoint blockade strategies in the treatment of breast cancer: where we are and where we are heading. *Current treatment options in oncology*, *20*(4), 1-14.
53. Di Cosimo, S., & Baselga, J. (2008). Targeted therapies in breast cancer: where are we now?. *European Journal of Cancer*, *44*(18), 2781-2790.
54. Bernier, Jacques, and Philip MP Poortmans. "Surgery and radiation therapy of triple-negative breast cancers: From biology to clinics." *The Breast* 28 (2016): 148-155.
55. Wahba, H. A., & El-Hadaad, H. A. (2015). Current approaches in treatment of triple-negative breast cancer. *Cancer biology & medicine*, *12*(2), 106.
56. McCann, Kelly E. "Advances in the use of PARP inhibitors for BRCA1/2-associated breast cancer: talazoparib." *Future Oncology* 15.15 (2019): 1707-1715.
57. McCann, Kelly E. "Advances in the use of PARP inhibitors for BRCA1/2-associated breast cancer: talazoparib." *Future Oncology* 15.15 (2019): 1707-1715.
58. Robson, Mark, et al. "Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial." *European Journal of Cancer* 120 (2019): 20-30.
59. Robson, M. E., et al. "OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer." *Annals of Oncology* 30.4 (2019): 558-566.
60. Ribnikar, D., et al. "Breast cancer under age 40: a different approach." *Current treatment options in oncology* 16.4 (2015): 16.
61. Michel, Laura L., et al. "Immune checkpoint blockade in patients with triple-negative breast cancer." *Targeted Oncology* 15 (2020): 415-428.
62. Garrido-Castro, Ana C., Nancy U. Lin, and Kornelia Polyak. "Insights into molecular classifications of triple-negative breast cancer: improving patient selection for treatment." *Cancer discovery* 9.2 (2019): 176-198.
63. Schmid, P., Rugo, H. S., Adams, S., Schneeweiss, A., Barrios, C. H., Iwata, H., ... & IMpassion130 Investigators. (2020). Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*, *21*(1), 44-59.
64. Adams, Sylvia, et al. "Atezolizumab plus nab-paclitaxel in the treatment of metastatic triple-negative breast cancer with 2-year survival follow-up: a phase 1b clinical trial." *JAMA oncology* 5.3 (2019): 334-342.
65. Zhao, Qian, Jinming Yu, and Xue Meng. "A good start of immunotherapy in esophageal cancer." *Cancer medicine* 8.10 (2019): 4519-4526.
66. Jeswani, Gunjan, et al. "Recent approaches for reducing hemolytic activity of chemotherapeutic agents." *Journal of Controlled Release* 211 (2015): 10-21.
67. Thakur, Vikram, and Rajaletchumy Veloo Kutty. "Recent advances in nanotheranostics for triple negative breast cancer treatment." *Journal of Experimental & Clinical Cancer Research* 38.1 (2019): 1-22
68. Ling, Yi-He, Waldemar Priebe, and Roman Perez-Soler. "Apoptosis induced by anthracycline antibiotics in P388 parent and multidrug-resistant cells." *Cancer research* 53.8 (1993): 1845-1852.
69. Lacal, Pedro Miguel, and Grazia Graziani. "Therapeutic implication of vascular endothelial growth factor receptor-1 (VEGFR-1) targeting in cancer cells and tumor microenvironment by competitive and non-competitive inhibitors." *Pharmacological research* 136 (2018): 97-107
70. Vickers, Elaine, Maggie Uzzell, and Karen Burnet. "Understanding how targeted therapies work." *Cancer Nursing Practice* 11.7 (2012).
71. Seligson, John M., et al. "Sacituzumab Govitecan-hziy: An antibody-drug conjugate for the treatment of refractory, metastatic, triple-negative breast cancer." *Annals of Pharmacotherapy* 55.7 (2021): 921-931.
72. Mahoney, Kathleen M., Paul D. Rennert, and Gordon J. Freeman. "Combination cancer immunotherapy and new immunomodulatory targets." *Nature reviews Drug discovery* 14.8 (2015): 561-
73. Miura, Koh, et al. "5-fu metabolism in cancer and orally-administrable 5-fu drugs." *Cancers* 2.3 (2010): 1717-1730
74. Min, A., Im, S. A., Kim, D. K., Song, S. H., Kim, H. J., Lee, K. H., ... & Bang, Y. J. (2015). Histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA), enhances anti-tumor effects of the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib in triple-negative breast cancer cells. *Breast Cancer Research*, *17*(1), 1-13.
75. Siddik, Zahid H. "Mechanisms of action of cancer chemotherapeutic agents: DNA-interactive alkylating agents and antitumour platinum-based drugs." *The cancer handbook* 1 (2002).
76. Albahde, M. A. H., Abdrakhimov, B., Li, G. Q., Zhou, X., Zhou, D., Xu, H., ... & Wang, W. (2021). The Role of Microtubules in Pancreatic Cancer: Therapeutic Progress. *Frontiers in Oncology*, *11*.
77. Maughan, K. L., Lutterbie, M. A., & Ham, P. (2010). Treatment of breast cancer. *American family physician*, *81*(11), 1339-1346.
78. Falvo, P., Orecchioni, S., Hillje, R., Raveane, A., Mancuso, P., Camisaschi, C., ... & Bertolini, F. (2021). Cyclophosphamide and vinorelbine activate stem-like CD8+ T cells and improve anti-PD-1 efficacy in triple-negative breast cancer. *Cancer Research*, *81*(3), 685-697.

79. Azim, H. A., Ghosn, M., Oualla, K., & Kassem, L. (2020). Personalized treatment in metastatic triple-negative breast cancer: The outlook in 2020. *The breast journal*, *26*(1), 69-80.
80. Wahdan-Alaswad, R. S., Edgerton, S. M., Salem, H. S., & Thor, A. D. (2018). Metformin targets glucose metabolism in triple negative breast cancer. *Journal of oncology translational research*, *4*(1).
81. Finn, Olivera J. "Assessing the important effector mechanisms in the immune response against cancer." (2001).
82. Huyck, Timothy K., et al. "Eribulin mesylate." *Nature reviews drug discovery* 10.3 (2011): 173.
83. Nahta, R., Yu, D., Hung, M. C., Hortobagyi, G. N., & Esteva, F. J. (2006). Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. *Nature clinical practice Oncology*, *3*(5), 269-280
84. du Rusquec, P., Blonz, C., Frenel, J. S., & Campone, M. (2020). Targeting the PI3K/Akt/mTOR pathway in estrogen-receptor positive HER2 negative advanced breast cancer. *Therapeutic Advances in Medical Oncology*, *12*, 1758835920940939.
85. Conteduca, Vincenza, et al. "New prognostic biomarkers in metastatic castration-resistant prostate cancer." *Cells* 10.1 (2021): 193.
86. Yang, Bing, et al. "Chrysin inhibits metastatic potential of human triple-negative breast cancer cells by modulating matrix metalloproteinase-10, epithelial to mesenchymal transition, and PI3K/Akt signaling pathway." *Journal of Applied Toxicology* 34.1 (2014): 105-112.
87. Hendrich, Andrzej B. "Flavonoid-membrane interactions: possible consequences for biological effects of some polyphenolic compounds 1." *Acta Pharmacologica Sinica* 27.1 (2006): 27-40.
88. Ren, Wenying, et al. "Flavonoids: promising anticancer agents." *Medicinal research reviews* 23.4 (2003): 519-534.
89. Trejo-Solís, Cristina, et al. "Multiple molecular and cellular mechanisms of action of lycopene in cancer inhibition." *Evidence-based complementary and alternative medicine* 2013 (2013).
90. Han, Hwana, Joo Weon Lim, and Hyeyoung Kim. "Lycopene inhibits activation of epidermal growth factor receptor and expression of cyclooxygenase-2 in gastric cancer cells." *Nutrients* 11.9 (2019): 2113.
91. Liu, Hsiao-Chun, et al. "Anti-cancer therapeutic benefit of red guava extracts as a potential therapy in combination with doxorubicin or targeted therapy for triple-negative breast cancer cells." *International journal of medical sciences* 17.8 (2020): 1015.
92. Liu, Hsiao-Chun, et al. "Anti-cancer therapeutic benefit of red guava extracts as a potential therapy in combination with doxorubicin or targeted therapy for triple-negative breast cancer cells." *International journal of medical sciences* 17.8 (2020): 1015.
93. Liu, H. C., Chiang, C. C., Lin, C. H., Chen, C. S., Wei, C. W., Lin, S. Y., ... & Yu, Y. L. (2020). Anti-cancer therapeutic benefit of red guava extracts as a potential therapy in combination with doxorubicin or targeted therapy for triple-negative breast cancer cells. *International journal of medical sciences*, *17*(8), 1015.
94. Chen, Y. C., Shen, S. C., Lee, W. R., Lin, H. Y., Ko, C. H., Shih, C. M., & Yang, L. L. (2002). Wogonin and fisetin induction of apoptosis through activation of caspase 3 cascade and alternative expression of p21 protein in hepatocellular carcinoma cells SK-HEP-1. *Archives of toxicology*, *76*(5), 351-359.
95. Liu, Hsiao-Chun, Chien-Chuan Chiang, Ching-Hsiang Lin, Chien-Sheng Chen, Chyou-Wei Wei, Shu-Yu Lin, Giou-Teng Yiang, and Yung-Luen Yu. "Anti-cancer therapeutic benefit of red guava extracts as a potential therapy in combination with doxorubicin or targeted therapy for triple-negative breast cancer cells." *International journal of medical sciences* 17, no. 8 (2020): 1015.
96. Liu, Hsiao-Chun, Chien-Chuan Chiang, Ching-Hsiang Lin, Chien-Sheng Chen, Chyou-Wei Wei, Shu-Yu Lin, Giou-Teng Yiang, and Yung-Luen Yu. "Anti-cancer therapeutic benefit of red guava extracts as a potential therapy in combination with doxorubicin or targeted therapy for triple-negative breast cancer cells." *International journal of medical sciences* 17, no. 8 (2020): 1015.
97. Cagle, Patrice, et al. "Effect of Rosehip (Rosa canina) extracts on human brain tumor cell proliferation and apoptosis." (2012).
98. Cagle, Patrice, et al. "Rosehip (Rosa canina) Extracts Prevent Cell Proliferation and Migration in Triple Negative Breast Cancer Cells." *The FASEB Journal* 29 (2015): 629-14.
99. Grabowska, K., Galanty, A., Koczurkiewicz-Adamczyk, P., Wróbel-Biedrawa, D., Żmudzki, P., Załuski, D., ... & Podolak, I. (2021). Multidirectional anti-melanoma effect of galactolipids (MGDG-1 and DGDG-1) from Impatiens parviflora DC. and their synergy with doxorubicin. *Toxicology in Vitro*, *76*, 105231.
100. Coburn, Tonisha LeStar. *The Role of Crude Rosehip Extracts in the Regulation of African-American Breast Cancer Cell Proliferation*. Diss. North Carolina Agricultural and Technical State University, 2013.
101. Zhao, G., Han, X., Zheng, S., Li, Z., Sha, Y., Ni, J., ... & Song, Z. (2016). Curcumin induces autophagy, inhibits proliferation and invasion by downregulating AKT/mTOR signaling pathway in human melanoma cells. *Oncology reports*, *35*(2), 1065-1074.
102. Pezzani, R., Vitalini, S., & Iriti, M. (2017). Bioactivities of Origanum vulgare L.: an update. *Phytochemistry reviews*, *16*(6), 1253-1268.
103. Eliaa, Shenouda G., et al. "Empagliflozin and doxorubicin synergistically inhibit the survival of triple-negative breast cancer cells via interfering with the mtor pathway and inhibition of calmodulin: In vitro and molecular docking studies." *ACS Pharmacology & Translational Science* 3.6 (2020): 1330-1338.
104. Khan, Tabassum, et al. "Polysaccharides as potential anticancer agents—A review of their progress." *Carbohydrate polymers* 210 (2019): 412-428.
105. Pabona, John Mark P., et al. "The soybean peptide lunasin promotes apoptosis of mammary epithelial cells via induction of tumor suppressor PTEN: similarities and distinct actions from soy isoflavone genistein." *Genes & nutrition* 8.1 (2013): 79-90.
106. Zhou, Pengjun, et al. "Cepharanthine hydrochloride reverses the mdr1 (P-glycoprotein)-mediated esophageal squamous cell carcinoma cell cisplatin resistance through JNK and p53 signals." *Oncotarget* 8.67 (2017): 111144.
107. Hayakawa, S., Ohishi, T., Miyoshi, N., Oishi, Y., Nakamura, Y., & Isemura, M. (2020). Anti-cancer effects of green tea epigallocatchin-3-gallate and coffee chlorogenic acid. *Molecules*, *25*(19), 4553.
108. Wang, Zhixue, et al. "An update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics." *Bioscience Trends* 12.3 (2018): 220-239.
109. Wang, Y., Sui, Y., & Tao, Y. (2019). Gambogic acid increases the sensitivity to paclitaxel in drug-resistant triple-negative breast cancer via the SHH signaling pathway. *Molecular medicine reports*, *20*(5), 4515-4522

110. Khoshakhlagh, Mahdieh, et al. "Therapeutic potential of pharmacological TGF-β signaling pathway inhibitors in the pathogenesis of breast cancer." *Biochemical pharmacology* 164 (2019): 17-22.
111. Cui, Qingbin, Shijun Wen, and Peng Huang. "Targeting cancer cell mitochondria as a therapeutic approach: recent updates." *Future medicinal chemistry* 9.9 (2017): 929-949.
112. Georgieva, Ani, et al. "Antiproliferative and antitumour activity of saponins from Astragalus glycyphyllos on myeloid Graffi tumour." *Journal of Ethnopharmacology* 267 (2021): 113519.
113. Taurin, S., Allen, K. M., Scandlyn, M. J., & Rosengren, R. J. (2013). Raloxifene reduces triple-negative breast cancer tumor growth and decreases EGFR expression. *International journal of oncology*, *43*(3), 785-792.
114. Yao, H., Xie, S., Ma, X., Liu, J., Wu, H., Lin, A., ... & Xu, J. (2020). Identification of a potent oridonin analogue for treatment of triple-negative breast cancer. *Journal of Medicinal Chemistry*, *63*(15), 8157-8178.