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(REVIEW ARTICLE)

Triple Negative Breast Cancer (TNBC): Signalling pathways-Role of plant-based inhibitors

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Abstract

This review paper highlights and updates the role of plant based inhibitors in controlling the triple-negative breast cancer (TNBC) via blocking the TNBC signalling pathways. Breast cancer is the most common cancer in women. There are several identified types, among which the triple-negative breast cancer (TNBC) is the most fatal for patients. Conventionally, the triple-negative breast cancer (TNBC) is defined by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal receptor 2 (HER2) in breast cancer cells. It is well-known for its metastatic, aggressive characteristics and poor outcome in the clinic. Till today, the treatment of TNBC patients is still a challenging task due to the absence of appropriate targets for drugs. Despite the successes of emerging targeted therapies, relapse, recurrence, and therapy failure rates in TNBC significantly outpace other subtypes of breast cancer. Mounting evidence suggests an accumulation of therapy resistant, Cancer Stem Cell (CSC) populations within TNBCs contributes to poor clinical outcomes. These Cancer Stem Cells (CSC) are enriched in TNBC compared to non-TNBC breast cancers. Approximately 60% of drugs currently used for cancer treatment have been isolated from natural products. Natural plant based products are a well-known treasure house for the development of novel anticancer drugs. Many plant-derived natural compounds have anti-cancer properties, including berberine quercetin, formononetin, calycosin, polyphenols, bioflavonoids, carotene, vitamins, and andminerals. Many plant-derived natural compounds, including vinka alkaloids, vinblastine and vincristine**,** luteolin, α-mangostin, piperine, silibinin, apigenin, quercetin, fisetin, resveratrol, genistein, 10-gingerol, chalcones, curcumin, epigallocatechin gallate, cyanidin-3-O-glucoside, and glycyrrhizin, have shown anti-cancer properties, especially in the treatment of TNBCs. Therefore, more human clinical trial data is warranted for further evaluation of plant extracts for the treatment of TNBCs.

Keywords: Antitumor; Breast cancer; Cancer stem cells; Inhibitors; Triple-negative breast cancer; Tumor-initiating cells; Signalling pathways

1. Introduction

Breast cancer represents a heterogeneous collection of cancer subtypes that arise as a consequence of altered gene expression and mutations acquired during carcinogenesis [1- 44-108]. Generally, breast cancer is well-established as a

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heterogeneous disease in the clinic. Globally, breast cancer is the primary cause of cancer-related death in women and affects two million women annually, with more than 600,000 cases of mortality related to recurrence and metastases [1- 50]. The biology of TNBC is still poorly understood. Triple-negative breast cancer (TNBC) cells are identified by the lack of receptor targeted therapies including human epidermal receptor 2 (HER2), estrogen receptor (ER) and progesterone receptor (PR) [1-83-108-131, 276]. TNBC is the major cause of lack of better therapies, consisting about 15–20% of recently diagnosed breast cancer. TNBC tumors are mostly difficult to currently existing therapies due to distinct molecular profile [1-83-108-131]. TNBC is characterized by the high mitotic rate and enhanced lymphocytic infiltration [1- 82-108]. Based on biomarker-driven therapeutic approaches, TNBCs are categorized into luminal androgen receptor, immune-enriched, PI3K/Akt/ mTOR activated and DNA repair deficiency. Based on tumors' characteristics including size, morbidity, and the number of involved lymph nodes, chemotherapeutic agents have been the primary systemic options for TNBC patients [1- 82-108]. However, resistance to chemotherapeutic agents, such as anthracyclines, taxanes, capecitabine, gemcitabine, eribulin as well as biomarker-based treatments and immune checkpoint inhibitor-based immunotherapy mostly occurs and causes limited results or no response to the treatments [1- 82-108]. Across all patients and in the TNBC and HR+/ HER2− subtypes, median overall survival (OS) was highest in patients who received eribulin [1-83-108-131]. One of the study by Kazmi et al., (2020) demonstrated consistency of eribulin effectiveness in metastatic breast cancer (MBC) patients with visceral metastases across the TNBC and HR+/HER2− subtypes [1-83-108, 276].

Triple-negative breast cancer (TNBC), an aggressive subtype of breast cancer with a poor prognosis, is characterized by tumors that do not express estrogen receptors (ERs) or progesterone receptors (PRs), nor display an over-expression of human epidermal growth factor receptor 2 (HER2) [1- 82-108, 276]. Therapies targeted against HER2-positive breast cancers, such as trastuzumab (Herceptin), and those targeted against ER-positive breast cancers, such as tamoxifen, have no therapeutic benefit to individuals with the TNBC subtype [1- 82-108]. Surgical intervention and chemotherapy have been the major treatment avenues for TNBC [1- 82-108]. However, recently developed small molecules and immunotherapeutics are showing promise [1- 42, 276].

Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype with a high rate of proliferation and metastasis, as well as poor prognosis for advanced-stage disease [1- 82-108-131, 276]. Originally, the molecular profile of TNBC has been linked to the basal group of breast cancers, the phenotype of which is characterized by a gene expression profile similar to the basal myo-epithelial layer of normal breast cells [1- 82-108-131]. However, gene expression profiling suggests that TNBC and basal-like breast tumors are heterogeneous, and overlap is incomplete. Additional subtypes of breast cancer have been identified in TNBC, including claudin-low, HER2-enriched but without HER2 gene amplification, luminal A, luminal B, molecular apocrine, and immunomodulatory, mesenchymal stemlike subtypes. TNBC has also been associated with BRCA1/2-related breast cancers [1- 82-108-131, 276]. However, although germline *BRCA1* mutations can be predictive for TNBC, only 10% of TNBCs are associated with *BRCA1* mutations, and other molecular signatures have not been well elucidated [1- 82-108-131, 276]. TNBC is associated with high rates of proliferation and has a poorer prognosis than other breast cancer subtypes, as demonstrated by diminished progression-free survival and overall survival rates [1- 82-108-131, 276]. There is also a sharp decrease in survival relative to other breast cancers within the first 3 to 5 years after diagnosis [1- 82-108-131]. However, distant relapse after 5 to 10 years becomes less common than in other breast cancers, and TNBC can be a potentially curable disease despite its overall aggressive nature. Although early TNBC can be sensitive to standard chemotherapy, traditional hormone therapies and targeted agents such as trastuzumab are not effective in this phenotype of cancer [1- 82-108-131, 276]. A greater understanding of the molecular mechanisms of TNBC may facilitate the identification of therapeutic targets, as well as predictive or prognostic biomarkers, and enable an understanding of the mechanisms of response or failure to current cancer treatments. Gene expression profiling using microarrays is a straightforward, robust method for the study of the molecular features of cancer at a systems [1- 82-108, 276]. Triple-negative breast cancer (TNBC) is not as prevalent as hormone receptor or HER2-positive breast cancers and all receptor tests come back negative [1- 82-108]. More importantly, the heterogeneity, complexity of the TNBC on the molecular and clinical levels have limited the successful development of novel therapeutic strategies. This has led to intrinsic or developed resistance to chemotherapies and new therapeutic agents [1-83-108-131, 276].

In India, breast cancer is diagnosed in approximately 100,000 women, with a case fatality ratio of 40% [1-82-108-131]. This shows that India has become a country of high breast cancer-related deaths worldwide [1-82-108-131]. Currently, TNBC is highly prevalent among Indian women and develops an approximately 20% to 43% of all patients with breast cancer. Breast cancer has been found to be the most common among urban Indian women and the second most common among the rural Indian women [1-82-131, 276].

In India, breast cancer (BC) has emerged as the second most common type of malignancy within the past 25 years [1-82-131]. In terms of disability-adjusted life years (DALYs), where BC used to be less prevalent than the more prevalent

stomach, cervical, and leukemia diagnoses, according to data accumulated until 2016, BC is surpassed only by cervical cancer [1-108]. Moreover, India has one of the highest rates of the most aggressive subtype of BC referred to as triple-negative breast cancer (TNBC) [1-82-131]. The rates of TNBC in India are almost double that of the United States (US) with estimates as high as 28% to one-third of all BC in India compared to 12–15% in the US [1-82-131]. There was general agreement that BC in India is more often seen in a younger population when compared to Western cohorts [1-82-131]. Data from Banaras Hindu University (BHU) revealed a mean age of 51, and data from the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS) in Lucknow, India reports a mean age of 49.7 years [1-82-131]. Data from the Indian Council of Medical Research between 1982 and 2005 observed an annual percent change (APC) as high as 4.2% in Nagpur among women age 15–34 [1-82-131]. Triple-negative breast cancer (TNBC) is an aggressive malignancy that requires effective targeted drug therapy. Patients with TNBC develop metastasis, recurrence over time and have reduced survival compared to patients with other subtypes of breast cancer [1-82-131, 276].

2. Triple Negative Breast Cancer (TNBC): Breast cancer stem cells

Metabolism reprogramming is a hallmark of cancers. Breast cancer remains the most commonly diagnosed cancer in women and the second leading cause of cancer-related deaths in women worldwide [83-108-131]. Breast cancer represents a highly heterogeneous group of neoplasmsa encompassing varied cell phenotypes with significant clinical implications [83-108-131]. To explain the tumor heterogeneity, people propose two widely accepted models, 1) **Cancer stem cell (CSC) model,** and 2) **Clonal evolution model** [83-108-131]. In clonal evolution model, cancer is supposed to originate from any cell, and these cells accumulate various mutations over time and different cells may acquire different mutations leading to the heterogeneity of cancer cells [83-108-131]. Clonal evolution model is a prevailing explanation for the tumorigenesis and heterogeneous of tumor [83-108]. The **Cancer stem cell (CSC) model** is a relative new model, which states that there are a small proportion of cancer cells in tumors, named **cancer stem cell (CSC)**, which can self-renew, differentiate to different cell lineages leading to the tumor heterogeneity. They are responsible for tumorigenesis, metastasis, recurrence and drug resistance as well as the major source for heterogeneity of cancer cells [83-108-131, 276].

In breast cancer, breast cancer stem cells (BCSCs) are well defined [83-108-131]. More and more research showed targeting breast cancer stem cells (BCSCs) is a promising way to cure breast cancer and lots of efforts are devoted to understand the molecular mechanisms of breast cancer stem cells (BCSCs) maintenance and differentiation. Studies showed that breast cancer stem cells (BCSCs) are also heterogeneous [83-108-131]. Breast cancer stem cells (BCSCs) have been reported as a promising targeted population for breast cancer therapy. Several kinds of treatments have been developed to target breast cancer stem cells (BCSCs), including targeting intrinsic signalling pathways, interfering immune microenvironment, and metabolic reprogramming [83-108-131]. Breast cancer stem cells (BCSCs) have shed a light on breast cancer therapy which play a vital role in the regulation of self-renewal and metastasis of heterogeneous breast cancer stem cells (BCSCs). This in part owing to their heterogeneity to identify through various markers and their plasticity to make transitions among different states including EMT and MET[83-108-131]. Breast cancer stem cells (CSCs) or tumor-initiating cells are thought to play an important role in tumor development, therapy resistance, and progression of triple-negative breast cancer (TNBC) [83-108-131]. To overcome the poor prognosis of TNBC, novel therapies targeting BCSCs need to be developed [83-108-131]. Research has moved from single surface proteins as biomarkers and targets for BCSCs toward signalling pathways essential for the tumor-initiating ability and therapy resistance of BCSCs [83-108-131].

Malignant tumors, including breast cancer, are thought to contain a small population of cancer cells, so-called tumor-initiating cells or CSCs, which exhibit self-renewal, differentiation capabilities and are responsible for driving tumor growth [83-108-131]. Human breast CSCs were first identified as tumor-initiating cells following transplantation into immunocompromised mice, were further described to have proliferative capability, to be associated with metastasis formation and resistance to chemotherapy and radiation therapy [83-108-131]. Chemotherapy effectively suppresses the bulk of primary tumors by eradicating proliferating cells, but commonly fails to target CSCs, leading to relapse [83-108-131]. It is a generally believed that there are two types of resistant CSCs: quiescent non-proliferative CSCs and proliferative CSCs. The latter CSCs will be killed by anti-mitotic agents, whereas the resident quiescent CSCs can survive chemotherapeutic treatments [1-83-108-131]. Moreover, proliferative CSCs can be drug-resistant either through acquired resistance in response to treatment or intrinsic resistance that persists at the initiation of treatment [83-108-131]. CSCs are located in a specialized microenvironment or niche composed of, for example, fibroblasts, endothelial and mesenchymal cells, which play different roles in orchestrating therapy resistance[1-83-108-131]. For example, endothelial cells secrete tumor necrosis factor (TNF)α, which activates the NF-κB signaling pathway in CSCs and induces secretion of several factors, including chemokine (C-X-C) ligand 1 and 2 (CXCL1/2) from tumor-associated macrophages, in breast cancer [83-108-131]. This attracts immune cells and induces the production of chemokines or other mediators, including S100A8/A9, which consequently induces chemoresistance to doxorubicin and

cyclophosphamide [1-83-108-131]. Thus, identifying molecular drivers and signalling pathways that govern the chemoresistance and expansion of CSCs has the potential to inspire new treatment options [83-108-131, 276].

Cancer stem cells (CSCs) are a small population of self-renewing tumor cells that persist after therapy and differentiate into all the cell types within the original tumor, reprising its heterogeneity [83-108-131]. Originally identified as self-renewing cells in leukemia with a CD34+CD38- phenotype, they have since been identified in several solid and hematologic malignancies, including breast cancer, as both hype-rproliferative and slow-cycling cells with a consensus CD44+CD24-/ALDH1+ phenotype [83-108-131]. During embryonic development and throughout life, highly plastic stem cells differentiate into various cell and tissue types in processes spatiotemporally regulated by developmental pathways such as the signalling pathways, (Wnt)/β-catenin, Notch (neurogenic locus notch homolog protein, and Sonic Hedgehog pathways**.** During carcinogenesis, aberrant regulation of these pathways allows cancer cells to acquire a "stem-cell"-like phenotype with increased ability to proliferate, tolerate hostile environments, and differentiate into different cell types [83-108-131]. This stem-cell oncogenic conversion is also mediated by factors within the tumor microenvironment (TME) and deregulated epigenetic and transcriptional programs [1-83-108-131, 276]. These tumor-initiating CSCs are especially adopt at repopulating tumors in animal disease models compared to non-CSC tumor cells. Breast cancer stem cells (BCSCs) are tumor-initiating cells with invasive capacity that mediate metastasis, contribute to treatment resistance and cancer relapse, and are prevalent in TNBCs [1-83-108]. TNBCs with BCSC characteristics are associated with adverse clinical outcome, treatment resistance, tumor relapse, and aggressive tumor features. Nevertheless, it is still unclear whether BCSC distribution differs between the TNBC subtypes [83-108-131, 276].

Mounting evidence suggests the accumulation of therapy resistant Cancer Stem Cell (CSC) populations within TNBCs contributes to poor clinical outcomes [1- 83-108-131]. These Cancer Stem Cells (CSC) are enriched in TNBC compared to non-TNBC breast cancers [83-108-131]. TNBC is the most aggressive subtype of breast cancer and is characterized by hyperproliferative cells lacking expression of hormone receptors (estrogen and progesterone) and HER2. Therapeutic avenues for TNBC are often limited due to the absence of these receptors and mortality rates far exceed other subtypes [83-108-131]. Additionally, TNBCs respond less to conventional chemotherapy and patients are at increased risk of recurrence and relapse [83-108]. Overall survival also lags far behind than other non-TNBC subtypes predominantly due to therapy failure and/or relapse [83-108-131]. Accumulating evidence now suggests that TNBCs are enriched in therapy resistant Cancer Stem Cells (CSC), compared to non-TNBC subtypes, which significantly contribute to heightened mortality, therapy failure, and recurrence [83-108-131]. The TNBC subtypes [basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal androgen receptor (LAR)] are biologically and clinically distinct entities that respond differently to local and systemic therapies [1-83-108-131, 276].

Triple-negative breast cancer (TNBC) is an aggressive subtype with the most unfavorable clinical outcomes, in part due to tumor heterogeneity, treatment resistance, and tumor relapse [1-83-108-131, 276]. Triple Negative Breast Cancer (TNBC) is the most lethal subtype of breast cancer. Despite the successes of emerging targeted therapies, relapse, recurrence, and therapy failure rates in TNBC significantly outpace other subtypes of breast cancer [83-108-131]. Breast cancer stem cells (BCSCs) represent a small proportion of breast cancer cells, possessing properties of self-renewal and generating differentiated cancer cells. Breast cancer stem cells (BCSCs) exhibit highly capacity to form tumors. As few as 50–100 breast cancer stem cells (BCSCs) could form tumors in mice [1-83-108-131, 276]. More and more researchers defined and verified breast cancer stem cells (BCSCs) markers, especially cell surface markers, and further reported that these markers could be used to identify different populations of breast cancer stem cells (BCSCs) [1-83-108-131]. Tumors consist of heterogeneous cell populations, and tumor heterogeneity plays key roles in regulating tumorigenesis, metastasis, recurrence and resistance to anti-tumor therapies. More and more studies suggest that cancer stem cells (CSCs) promote tumorigenesis, metastasis, recurrence and drug resistance as well as are the major source for heterogeneity of cancer cells. CD24- CD44+ and ALDH+ are the most common markers for breast cancer stem cells (BCSCs) [1-83-108-131]. Previous studies showed that different BCSC markers label different BCSC populations, indicating the heterogeneity of BCSCs [1-83-108-131]. Currently, the most common used markers for breast cancer stem cells (BCSCs) are CD24- CD44+ and ALDH. One set of the most commonly used markers for breast cancer stem cells (BCSCs) is CD24- CD44+. CD44 is glycol-protein located on cell surface and play vital role in cell-cell interactions, cell adhesion and migration, while CD24 is also a cell surface protein responsible for signal transduction [1-83-108-131]. The percentage of CD24-CD44+ breast cancer stem cells (BCSCs) vary greatly, from 0 % to 97 %. among breast cancers and breast cancer cell lines. CD24-CD44+ breast cancer stem cells (BCSCs) exhibit enhanced invasive properties, are located at the invasive edge of breast tumor and characterized as mesenchymal-like breast cancer stem cells (BCSCs). Aldehyde dehydrogenase (ALDH) is another common marker for breast cancer stem cells (BCSCs) [1-83-108]. Although there are 19 ALDH isoforms in human genome [1-83-108]. Almost all previous studies acknowledge ALDH1 as the main isoform to label ALDH+ breast cancer stem cells (BCSCs) [1-83-108-131]. Functional studies showed that ALDH+ cells are more prone to form colonies and tumors than CD24- CD44+ cells, and to be more chemoresistant [1-83-108]. ALDH+ breast cancer stem cells (BCSCs) are required and responded for self-renewal. ALDH+ breast cancer

stem cells (BCSCs) are located at the tumor interior of breast tumor, and characterized as epithelial-like breast cancer stem cells (BCSCs) [1-83-108-131, 276].

Cell heterogeneity usually originate from the feature of cell plasticity [1-83-108-131]. The most well studied plasticity feature of breast cancer stem cells (BCSCs) is the transition between mesenchymal-like and epithelial-like states in response to the stimulates[1-83-108-131]. Breast cancer stem cells (BCSCs) are a minor population of breast cancer cells that exhibit multiple characteristics and functions, such as migration, invasion, self-renewal, recurrence and resistance to chemotherapy and radiation therapy, resulting in refractory natures of breast cancers [1-83-108-131]. The heterogeneity and plasticity of breast cancer stem cells play an important role in their self-renewal ability. A number of pathways are related to the stemness and self-renewal ability of breast cancer stem cells (BCSCs) such as Wnt, Notch , JNK, TGF-β pathway and a series of transcription factors. [1-83-108-131]. In addition, the heterogeneity and plasticity of breast cancer stem cells (BCSCs) are inextricably linked to tumor metastasis and recurrence. Many dysregulated pathways in breast cancer stem cells (BCSCs) are involved in epithelial-mesenchymal transition (EMT), which is a forwarding process from epithelial cells to mesenchymal cells that enter systemic circulation and diffuse to distant sites [1-83-108-131]. Studies have reported that the enrichment of breast cancer stem cells (BCSCs) played a critical role in the chemotherapy resistance of breast cancer [1-83-108-131]. Therefore, taking together, the heterogeneity and plasticity of breast cancer stem cells (BCSCs) are regulated by a variety of complex molecular networks, leading to tumor recurrence, metastasis and drug resistance, which has become one of the fundamental problems that breast cancer is difficult to overcome [1-83-108-131].

Identification and recognition of the signalling pathways and molecular mechanisms related to stemness phenotypes of breast cancer stem cells (BCSCs) can effectively discover new targeting strategies for breast cancer stem cells (BCSCs). A growing number of studies have shown that breast cancer stem cells (BCSCs) is capable of driving tumor initiation, maintenance, recurrence, and resistant to chemotherapy and radiotherapy [1-83-108-131]. Transcription factors (TFs) such as SOX2 (sex determining region YHMG box 2), OCT4 (octamer-binding transcription factor 4), BMI1 (B-lymphoma moloney murine leukemia virus insertion region-1) and NANOG (Nanog Homeobox) and signaling pathways such as Wnt, Notch, Hippo and Hedgehog pathways are known to play essential roles in regulating the plasticity and heterogeneity of breast cancer stem cells (BCSCs) [1-83-108-131, 276].

Several inhibitors have been found to decrease CD24- CD44+ and/or ALDH+ breast cancer stem cells (BCSCs) in Wnt/β-catenin signaling pathway, hippo signaling pathway, Notch signaling pathway and Hh signaling pathway[1-83-108]. Recently, more and more non-coding RNAs are documented to involve in the regulation of breast cancer stem cells (BCSCs), which play the key roles in promoting or inhibiting the property of breast cancer stem cells (BCSCs) [1-83-108-131]. Interestingly, the rich and complex tumor microenvironment, composed of diverse cell types, regulates breast cancer stem cells (BCSCs) state equilibrium and phenotypic plasticity via cytokine networks [1-83-108-131]. The transition of breast cancer stem cells (BCSCs) states may be regulated across a spectrum of tumors with diverse regulation factors, which may have broad therapeutic applicability [1-83-108]. Targeting the breast cancer stem cells (BCSCs) plasticity and heterogeneity may be the most promising exploration for breast cancer treatment in the future[1-83-108-131]. Until now, few studies directly focus on the heterogeneity and plasticity of breast cancer stem cells (BCSCs), partially due to the limitation of technical method [1-83-108-131]. Taking the advance of single cell methods, people can explore the expression and mutation profile on single cell level and dissect the heterogeneity and plasticity of breast cancer stem cells (BCSCs) in a cancer cell population without sorting by FACS[1-83-108]. Upon a stimulation possible to regulate the heterogeneity and plasticity of breast cancer stem cells (BCSCs), people can witness the dynamic changes of expression profile of BCSCs and compare the difference between breast cancer stem cells (BCSCs) and non-BCSCs as well as among different types of BCSCs. Besides, it also provides an opportunity to explore the mechanism behind the transition between different types of breast cancer stem cells (BCSCs) which reflect the plasticity of BCSCs[1-83-108-131, 276].

People can also apply scDNA-seq to explore the mutation profiles of BCSCs and the correlation between the different types of mutation profiles and different types of breast cancer stem cells (BCSCs) [1-83-108-131]. It will greatly expand the knowledge related to the heterogeneity and plasticity of breast cancer stem cells (BCSCs). Almost 100 years ago, Otto Warburg reported that cancer cells preferentially utilize glycolysis instead of oxidative phosphorylation (OXPHOS) [1-83-108-131]. Moreover, several genes functioned in glycolysis are over-expressed in BCSCs and maintain the self-renew of BCSCs and BCSC-targeting therapies [1-83-108-131]. Several drug containing nanoparticles were preciously delivered to the BCSCs to improve the local concentration and maximize the anti-cancer effects [1-83-108-131]. For example, lyso-thermosensitive liposomal doxorubicin was tested in clinical trial to achieve higher local drug concentrations in breast cancer patients. Toll-like Receptor (TLR) 2 was found to be over-expressed in BCSCs and up-regulation of TLR2 led to activate the STAT3 and Smad3 signalling pathways by inducing IL-6, TGF-β and VEGF [1-83-108-131, 276].

Breast cancer stem cells have previously been shown to be enriched in estrogen receptor-negative and triple-negative breast cancer [1-83-108-131, 276]. BCSCs are often associated with metastatic spread and treatment resistance. The flow cytometry analysis of breast cancer cell lines revealed distinct patterns of BCSC biomarker expression based on ER status and subtyping (BC and TNBC) [1-83-108-131]. BCSC subpopulations were more prevalent in cell lines derived from ER-negative breast cancer, as well as the M and BL2 TNBC subtypes [1-83-108-131]. In one the study reported by **Olsson et al., (2023**), breast cancer stem cell (BCSC) distribution was investigated using an integrated flow cytometry approach with the ALDEFLUOR™ assay (ALDH) and CD24/CD44 antibodies [1-83-108-131]. In total, 27 commercially available cell lines derived from normal and malignant mammary tissue were characterized into differentiated tumor cells and/or BCSC subpopulations (ALDH−CD44+CD24-/low enriched mesenchymal-like BCSCs, ALDH+non-CD44+CD24−/low enriched epithelial-like BCSCs, and highly purified ALDH+CD44+CD24−/low BCSCs) [1-83-108-131]. Three main BCSC subpopulations have been identified using the CD44+CD24−/low phenotype and high aldehyde dehydrogenase (ALDH+) activity, i.e., ALDH−CD44+CD24−/low enriched mesenchymal-like BCSCs (located along the tumor-invasive edge), ALDH+non-CD44+CD24−/low enriched epithelial-like BCSCs (located centrally within a tumor), and highly purified ALDH+CD44+CD24−/lowBCSCs with both mesenchymal and epithelial characteristics are considered to be the most tumorigenic [1-83-108-131]. The research findings of Olsson et al., (2023), demonstrated that the enrichment of potentially treatment-resistant BCSC subpopulations in the M and BL2 triple-negative- breast cancer subtypes [1-83-108-131]. Triple-negative breast cancer (TNBC) is a heterogeneous disease comprised of four distinct molecular subtypes (basal-like 1 [BL1], basal-like 2 [BL2], mesenchymal [M], and luminal androgen receptor [LAR]) with differing biology, therapeutic vulnerability, and response rates and recurrence rates [1-83-108-131, 276].

In TNBC, deregulation of stemness pathways is even more pronounced than in non-TNBC breast cancers, conferring TNBC CSCs (TNBCSCs) an especially problematic clinical phenotype [1-83-108-131, 276]. Indeed, several analyses of human breast carcinomas have revealed TNBCs harbor the highest percentage of CD44+CD24-ALDH1+CSCs, a feature that usually correlates negatively with chemotherapy response, disease-free survival, metastasis-free survival, and overall survival [1-83-108-131]. In TNBC patients, chemotherapy and radiotherapy eradicate most hyperproliferative cells within the TME but failed to kill quiescent, slow-cycling TNBCSCs, allowing them to reinitiate the tumor (source) [1-83-108-131]. TNBCSCs are resistant to a host of therapeutic agents-a phenomenon referred to as Multi-Drug Resistance (MDR) [1-83-108-131]. The mechanisms of MDR, as well as new therapeutic approaches being pursued in both CSCs and TNBCSCs, have been reviewed extensively in previous publications [1-83-108-131, 276].

3. Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are a class of multipotent stromal cells that possess the capacity to differentiate into various cell types, including bone, cartilage, muscle, and adipose cells [1-83-108-131]. These cells are obtained from diverse tissues, such as bone marrow, umbilical cord blood, adipose tissue, and dental pulp [1-83-108-131]. Mesenchymal stem cells (MSCs) possess several advantageous characteristics that render them attractive for biomedical applications, including their immunomodulatory properties, homing ability, capacity to secrete trophic factors, and low immunogenicity [1-83-108-131]. MSCs exhibit significant potential in numerous fields, such as tissue engineering, regenerative medicine, cell therapy, and gene therapy [1-83-108-131]. These cells have been utilized to treat various ailments, such as osteoarthritis, spinal cord injury, graft-versus-host disease, myocardial infarction, and diabetes mellitus [1-83-108-131]. Nevertheless, MSCs possess a few challenges and constraints, such as variabilities in quality and quantity, a lack of standardized protocols for isolation and expansion, a risk of contamination, and tumorigenicity [1-83-108]. Mesenchymal stem cells (MSCs) present a hopeful avenue for clinical applications in the future [1-83-108-131]. However, more extensive research is necessary to comprehend their biology comprehensively and optimize their safety and efficacy. It is critical to establish clear criteria for identifying MSCs based on their molecular markers and functional properties [1-83-108-131]. Additionally, it is imperative to develop reliable in vivo tracking methods for MSCs after transplantation [1-83-108-131]. Furthermore, evaluating the long-term outcomes of MSC-based therapies in large-scale randomized controlled trials is crucial [1-83-108-131]. Mesenchymal stem cells (MSCs) have demonstrated significant potential as a novel therapeutic approach for rating TNBC [1-83-108-131]. To summarize, Mesenchymal stem cells (MSCs) represent a promising avenue for developing personalized and multifaceted therapies for TNBC that could potentially address the limitations of existing treatments 1-83-108-131]. Nonetheless, additional research is essential to unravel the intricate roles of MSCs in TNBC biology and therapy [1-83-108-131].

4. Triple Negative Breast Cancer (TNBC): Signalling Pathways

Triple-negative breast cancer (TNBC) is a specific subtype of breast cancer defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expressions[1-83-108-131].

Triple-negative breast cancer (TNBC) lacks estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expressions, making targeted therapies ineffective [1-83-108-131, 276]. Mesenchymal stem cells (MSCs) have emerged as a promising approach for TNBC treatment by modulating the tumor microenvironment (TME) and interacting with cancer cells. TNBC has been further subdivided into six distinct molecular subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem–like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR) [1-83-108-131]. Triple negative breast cancer (TNBC) accounts for 15% to 20% of breast cancers [1-83-108-131, 276]. The diagnosis of the triple-negative subtype is made by excluding the expression or amplification of three biomarkers (the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) protein), which are the oncogenic drivers and targets for breast cancer treatment [1-83-108-131]. The disease typically presents as histologically high-grade-infiltrating ductal carcinoma, which mostly affects in younger women (age <40 years) [1-83-108-131, 276]. However, current researches have produced mixed results with varying conclusions [1-83-108-131]. To date, patients with TNBC have the poorest prognosis, with the median progression-free survival (PFS) ranging from 3 to 4 months after the failure of first-line therapy. Disease recurrence in one-half of early-stage patients and up to 37% of 5 year mortality rate after initial surgery [1-83-108-131, 276].

Triple Negative Breast Cancer (TNBC) is the most lethal subtype of breast cancer. Despite the successes of emerging targeted therapies, relapse, recurrence, and therapy failure rates in TNBC significantly outpace other subtypes of breast cancer [1-83-108-131, 276]. Mounting evidence suggests accumulation of therapy resistant Cancer Stem Cell (CSC) populations within TNBCs contributes to poor clinical outcomes. These CSCs are enriched in TNBC compared to non-TNBC breast cancers [1-83-108]. Moreover, TNBC is highly associated with the existence of cancer stem cells (CSCs), which contribute to circulating cancer cell survival before BBB extravasation, evasion from immune surveillance, and plasticity in adaptation to the brain-specific microenvironment [1-83-108-131]. A higher propensity of developing brain metastasis exists in triple-negative breast cancer (TNBC) [1-83-108-131, 276]. TNBC is characterized by high-grade tumors with a high proliferation rate and genomic instability [1-83-108-131]. The clinical and epidemiological behavior of TNBC is heterogeneous due to its biological diversity [1-83-108-131]. Moreover, TNBC is generally unresponsive to hormone therapy or HER2 inhibitors, which are effective for other subtypes [1-83-108-131]. Consequently, chemotherapy remains the primary treatment option, although recent advances showed promise with PARP inhibitors for BRCA-mutated patients and immunotherapy for PD-L1- positive patients [1-83-108-131]. The challenges in treating TNBC include identifying biomarkers for predicting responses to therapy, overcoming drug resistance mechanisms, enhancing immune activation, and addressing social-economic disparities that affect access to care [1-83-108-131]. Future research should focus on developing innovative agents targeting specific molecular pathways or vulnerabilities in TNBC subtype, improving risk assessment, screening, prevention strategies based on genomic and epidemiologic factors [1-83-108-131, 276].

Recent studies have revealed various molecular mechanisms and signalling pathways concerning proliferation, metabolism, survival, and movement in TNBC, which consequently lead to the resistance to novel targeted therapies[1-83-108-131, 276]. Therefore, it is of importance to elucidate the molecular factors behind intrinsic and acquired resistance to restore chemo- and targeted therapies [1-83-108-131]. TNBC is extensively studied over the last few decades on account of its unique clinical pathologies, such as larger tumor size, nodal involvement, high distant recurrence rates, and molecular features [1-83-108-131]. Currently, targeted therapy in combination with chemotherapy is approved to treat locally advanced or metastatic TNBCs [1-83-108-131]. Therefore, screening more reliable biomarkers is imperative, and understanding the signalling pathways that regulate biological behaviors may facilitate the establishment of effective therapeutic strategies. Following are the TNBC signalling pathways leading to the special type of breast caner [1-83-108-131, 276].

4.1. Notch Signalling Pathway

The term Notch was first described by Thomas Hunt Morgan in 1917 and refers to transmembrane receptors and ligands [1-83-108-131]. The Notch signalling pathway plays a central role in the developmental process and uses communication among cells via transmembrane interactions with ligands [1-83-108-131]. Notch signalling pathway plays a crucial role in cell survival, proliferation, differentiation, apoptosis, tissue patterning, cell-fate decision, and morphogenesis. Aberrant activation of the Notch signaling has been associated to the development of many cancers, including breast cancer. Cleavage of Notch receptors in the cytoplasm by γ-secretase is a critical step in their activation. The Notch pathway is a short-range cell-to-cell communication pathway that is critical for metazoan development [1-83-108-131]. The Notch pathway has been identified in *Drosophila melanogaster* [1-83-108-131]. From a structural perspective, Notch receptors share three domains: an intracellular domain, a transmembrane region, and an extracellular domain [1-83-108-131]. This signalling pathway is key in cell proliferation and differentiation, most importantly governs embryonic development and maintains tumor stemness to TNBC tumor metastasis[1-83-108-131].

Notch is aberrantly expressed in breast cancer CSCs where it promotes self-renewal and metastasis [53,54]**.** Notch is more significantly deregulated in TNBC compared to non-TNBC breast cancer. In fact, Notch ligands have been suggested as clinical markers for TNBC [1-83-108-131]. There are four Notch receptors and five ligands in this pathway [1-83-108-131]. The receptors can be named as Notch 1 to 4, while ligands are Delta-like 1, Delta-like 3, Delta-like 4, Jagged-1, and Jagged-2. Notch signaling is a highly conserved developmental pathway that is triggered when Notch ligands (Delta-like-1/3/4, Jagged1, and Jagged2) bind to one of several Notch receptors (NOTCH1-4) on neighboring cells, triggering the latter's proteolytic cleavage and nuclear translocation[1-83-108-131]. Several reports have indicated the over-expression of Jagged 1 and Delta 1 in breast cancer [1-83-108-131]. The Notch 1 is involved in pancreatic cancer and hematological malignancies, while Notch-3/4 has been found to assist in tumor proliferation and survival. Notch-2 over-expression in TNBC appears to play a protective role [1-83-108-131]. Notch expression has been linked to TNBCs, and scientists believed that targeting receptors by monoclonal antibodies can reduce HES and HEY-L families [1-83-108-131]. Inhibitors that target the Notch signalling pathway act at proteolytic cleavage and blocked the formation of multimeric γ-secretase complexes. Thus, these drugs are termed γ- secretase inhibitors [1-83-108-131]. Increased Notch signalling in TNBCSCs might be mediated by transcription factor KLF4 and growth factor BMP4. A significant role for tumor-stroma interactions in promoting Notch activity in TNBC. Altogether, these studies highlight how Notch signalling is intricately regulated in TNBC to promote stemness and invasiveness [1-83-108-131, 276].

4.2. Wnt/β-Catenin Signalling Pathway

Breast cancer represents one of the most significant disease burdens of any cancer worldwide [1-83-108-131]. Today, women have a one in eight chance of developing breast cancer over their lifetime, a risk that is significantly increased if they have inherited harmful mutations in BRCA1 or BRCA2 [1-83-108-131, 276]. However, breast cancer is a complex, heterogeneous disease characterized by a great multitude of aberrations at the genomic and molecular level, which can manifest in dysregulated signaling pathways [1-83-108-131]. A hallmark of many cancers is aberrant regulation of the Wnt signaling pathway, and breast cancer is no exception[1-83-108-131, 276].

Wnt signaling regulates a variety of cellular processes, including cell fate, differentiation, proliferation and stem cell pluripotency. Aberrant Wnt signaling is a hallmark of many cancers [1-83-108-131]. An aggressive subtype of breast cancer, known as triple-negative breast cancer (TNBC), demonstrates dysregulation in canonical and non-canonical Wnt signaling [1-83-108-131]. Wnt/β- catenin signalling pathway is activated in epithelial ovarian cancer and targets gene regulate cell proliferation and apoptosis. Thereby mediating cancer initiation and progression [1-83-108-131]. Furthermore, Wnt inhibitors can destroy drug-resistant cells and cancer stem cells [1-83-108-131]. WNT proteins are a family of secreted proteins with multiple roles in normal cell biology and developmental processes, including generation of cell polarity and cell fate specification [1-83-108-131, 276]. WNT signaling is initiated by the binding of secreted WNT proteins to co-receptors Frizzled (FZD) and low-density lipoprotein receptor-related protein 5 and 6 (LRP5/6). Thereby initiating different intracellular signalling cascades either through β-catenin or by a non-canonical β-cateninin dependent pathway [1-83-108-131]. Aberrant WNT/β-catenin signalling is frequently found in cancers, and clinical evidence suggests that elevated WNT/β-catenin signalling is associated with higher tumor grade and poorer prognosis [1-83-108-131]. Moreover, increased expression levels of β-catenin has been observed across multiple human breast cancer subtypes, especially in TNBC [1-83-108-131, 276]. The complex WNT signaling network affects breast cancer initiation and progression remain uncertain [1-83-108-131, 276]. WNT/β-catenin signaling affects different biological cell functions in breast cancer, including cell proliferation, cell motility and invasion [1-83-108-131, 276]. WNT/β-catenin signaling has been found to be associated with stem cell renewal and differentiation of healthy epithelial cells. In breast CSCs, WNT/β-catenin is associated with self-renewal, mammosphere formation, cell migration, invasion, is involved in resistance to both apoptosis and radiation therapy. Knockdown of β-catenin reduces the stem-cell-like cell populations, tumor size and resistance to doxorubicin of TNBC cells [1-83-108-131]. The canonical-β-catenin-independent signaling pathway signals through WNT-dependent stabilization of proteins (WNT/STOP), which stabilizes cellular proteins and slow down protein degradation to maintain mitotic cell division. In breast cancer cells, which initiates an autocrine WNT signaling loop leading to CSC colony formation in the bone marrow [1-83-108-131, 276]. The blocking WNT/β- catenin signaling reduces CSC expansion as evaluated by a marked reduction in mammosphere formation by cell line-derived tumor initiating cells and patient-derived TNBC cells [1-83-108-131, 276]. Several inhibitors of WNT signaling, both for the canonical β-catenin-driven signaling and the non-canonical signaling, are in pre-clinical, clinical development and promising results for breast cancer have been obtained with the broad-spectrum anti-FZD antibody (OMP-18R5/vantictumab), which blocks FZD1, 2, 5, 7, and 8 [1-83-108-131]. Studies have demonstrated deregulation of Wnt/β-catenin signaling in tumorigenesis which plays decisive roles at the low survival rate of patients and facilitates resistance to currently existing therapies [1-83-108-131, 276]. Wnt/β-catenin signaling's crosstalk with TNBC-associated tumorigenic mechanisms results in amplification of their underlying signaling cascades and development of resistance to different therapeutic agents [1-83-108-131, 276].

The dysregulation of Wnt signaling is synonymous with cancer [1-83-108-131]. TNBC is an aggressive, highly proliferative phenotype, which is characteristic of overactive signalling pathways. Like TNBC, Wnt signaling is highly complex and not yet fully characterized. The discovery of novel regulators in TNBC, such as DDXs, adds to the complexity, but also presents exciting new opportunities for the development of potential therapeutic targets [1-83-108-131, 276].

4.3. TGF-β Signaling Pathway

TGF-beta 1 is expressed exponentially in TGF-β1 and TGF-β1 and has been implicated in its important role in breast cancer stem cells. In vivo analysis, inhibition of TGF-β leads results in multiplication and growth of tumor cells [108-131]. The frequent over-expression of TGF-β in the TNBC tumor microenvironment, particularly in stromal, tumor-associated immune cells, and tumor cells[1-83-108-131, 276]. In these cells, SMAD4 and SMAD2/3 cause metastasis and angiogenesis[1-83-108-131]. Thus, inhibition of TGF-β plays a significant therapeutic role in patients with metastasis. The transforming growth factor beta (TGFB) signalling pathway is involved in many cellular processes in both the adult organism and the developing embryo including cell growth, cell differentiation, cell migration, apoptosis, cellular homeostasis and other cellular functions. The TGFB signaling pathways are conserved [1-83-108-131, 276].

Transforming growth factor-β (TGF-β) represents an evolutionarily conserved family of secreted polypeptide factors that regulate many aspects of physiological embryogenesis and adult tissue homeostasis [1-83-108-131]. The TGF-β family members are also involved in pathophysiological mechanisms that underlie many diseases[1-83-108-131]. The signalling mechanisms of the TGF-β family are controlled at the extracellular level, where ligand secretion, deposition to the extracellular matrix and activation prior to signaling play important roles [1-83-108-131].

4.4. Signalling Pathway of CSPG4 Protein

The CSPG4 protein (non-glial antigen) is expressed as a cell surface proteoglycan by basal breast carcinoma cells [1-83-108-131]. Therapeutically, CSPG4 inhibition allows for efficient management of breast cancer [1-83-108-131]. Monoclonal antibodies can block the CSPG4 protein, which hinders survival signaling pathways in tumor cells. In addition, controlling the over-expression of CSPG4 by targeting therapeutically is seen in different TNBC cells [1-83-108-131].

4.5. Hedgehog (Hh) Signalling Pathway

The Hedgehog signalling pathway is involved in cancer cell invasion, metastasis, drug resistance, and tumor recurrence[1-83-108-131]. Over expression of this pathway results in poor prediction of breast cancer mortality, especially in TNBC patients [1-83-108-131]. The Hedgehog signalling pathway is considered to initiate breast cancer malignancy. Thiostrepton is a novel experimental drug that suppresses TNBC CD44+/CD24− cancer stem cells [1-83-108-131]. Similar to Wnt and Notch, Hh signaling is an important developmental pathway co-opted by tumors to promote stemness and tumor persistence [1-83-108-131]. Hedgehog signalling (Hh) consists of Hh ligands binding to transmembrane receptor Protein patched homolog 1 (PTCH), regulating transmembrane protein smoothened (SMO), which induces downstream activation or repression of transcription via glioma-associated oncogene (GLI) proteins[1-83-108-131]. Normally, Hh signaling regulates morphogenesis in early life and proliferation in adult stem cells [1-83-108-131]. In TNBC, Hh signalling has been associated with highly proliferative high-grade disease, increased metastases, and worse disease-free survival [1-83-108-131]. Several transcriptional targets of Hh signalling in TNBC, including ABCB1, ABCG2, Forkhead box protein M1 (FOXM1), and BMI-1, confer TNBCSCs resistance to chemotherapy [1-83-108-131]. As with Notch signaling, tumor-stroma interactions have been shown to sustain Hh signaling in TNBC promoting stemness. Similarly, pluripotency factor NANOG, which is equally over-expressed in TNBC, was found to inhibit Hh-induced transcription [1-83-108-131]. These findings perhaps emphasize the temporal, intentional and context-dependent nature of Hh regulation in TNBC [1-83-108-131].

4.6. PI3K/AKT/mTOR Signalling Pathway

PI3K/protein kinase B/mechanistic target of rapamycin kinase (mTOR): Rapamycin and paclitaxel drugs are used to inhibit the PI3K/ AKT/mTOR pathway and hence play a significant role in TNBC treatment [1-83-108-131]. Furthermore, mTOR antibodies are considered more effective than mTOR inhibitors alone[1-83-108-131]. In TNBC patients, ipatasertip (an AKT inhibitor) can promote progression-free survival by inactivating the PI3K/AKT pathway [1-83-108-131]. Despite these efforts on PI3K/AKT/mTOR pathway inhibitors, synthesis of novel inhibitors is needed to block the PI3K/Akt/mTOR pathway and act as therapeutic agents against TNBC [1-83-108-131]. The PI3K/Protein Kinase B (AKT) pathway is a ubiquitous growth pathway that regulates cell proliferation, survival, motility, and differentiation in most tissue types 1-83-108-131]. PI3K/AKT hyperactivity has been associated with the progression of several cancers [1-83-108-131]. Recent studies have also linked aberrant PI3K/AKT activation to breast cancer

stemness. PI3K/AKT signalling results in phosphorylation and activation of AKT by mTOR and PDK [1-83-108-131]. TNBCSCs also express higher levels of mTORC1 compared to the bulk of the tumor contributing to self-renewal and growth. HIF-2α drives TNBCSCs activation via induction of CD44 and PI3K/AKT/mTOR signalling [1-83-108-131]. The inhibition of PI3K/AKT/mTOR in TNBC could inadvertently induce IL8 secretion and activate a JAK2/STAT5 axis which promotes stemness and metastases. This suggests compensatory signalling mechanisms might play a bigger role than previously thought in driving CSCs [1-83-108-131].

4.7. The JAK/STAT Signalling pathway

The JAK/STAT pathway is an evolutionarily conserved axis that plays a central role in several cellular processes including proliferation, motility, and stemness [1-83-108-131]. JAK/STAT signalling is initiated when a growth-factor or cytokine binds to a cell surface receptor containing a JAK binding site. In breast cancer, JAK/STAT has been identified as a key regulator of CSC self-renewal and non-CSC cells' dedifferentiation into CSCs [1-83-108-131]. Certain growth factors and cytokines that activate JAK/STAT have been identified as essential drivers of TNBC proliferation and stemness 1-83-108-131]. These include IL6, Prostaglandin-I synthase (PTGIS), Hyaluronan synthase 1 (HAS1), C-X-C Motif Chemokine Ligand 3 (CXCL3), and 6-phosphofructo-2-kinase/fructose-2, 6-biphosphatase 3 (PFKFB3) [1-83-108-131]. Additionally, the IL-6/JAK2/STAT3 pathway is preferentially activated in TNBCSCs compared to non-TNBC BC and is associated with increased risk of metastasis [1-83-108-131]. In TNBC, IFN-β does not activate STAT3 [1-83-108-131]. This suggests IFN-β regulation of stemness, and by extension general CSC regulation, is subtype-specific and context-dependent [1-83-108-131]. It also plays a key role as a pluripotency mediator for somatic cell reprogramming [1-83-108-131]. Constitutive activation of JAK/STAT signalling has been well-characterized as a driving factor in several malignancies [1-83-108-131].

4.8. Growth factor and cytokine-driven pathways

4.8.1. Guanine nucleotide exchange factor (GEF)-H1/PKD

The protein kinase D (PKD) family of actin remodeling proteins are well-characterized cell migration regulators in TNBC and other breast cancers. PKD1 is the predominant isoform in non-malignant tissue where it maintains an epithelial phenotype[1-83-108-131]. Upon oncogenic conversion, PKD1 is silenced via methylation inducing EMT [1-83-108-131]. Because they lack the expression of ER, a transcriptional repressor of PKD expression. TNBCs express high levels of PKD2 and PKD3. PKD3, especially, is associated with increased TNBC metastasis, proliferation, and stemness. Recently one of the study also demonstrated that upstream activation by Rho guanine nucleotide exchange factor 2 (GEF-H1) mediates PKD3 maintenance of TNBCSCs [1-83-108-131].

4.9. Transforming growth factor beta and tumor necrosis factor

Transforming growth factor beta (TGF-β) and tumor necrosis factor (TNF) are two important, antagonistic cytokines, which regulate a plethora of cellular activities including differentiation, survival, proliferation, and homeostasis[1-83-108-131]. They have been implicated in the progression of several cancers[1-83-108-131]. TGF-β is important for early mammary development, regulating morphogenesis via specific regulation of ECM remodeling, and epithelial cell growth and differentiation[1-83-108-131]. Its role in breast cancer, however, is a lot more complex [1-83-108-131]. Early in breast cancer development, TGF-β inhibits cell growth and promotes apoptosis. In later stages, it promotes proliferation, invasiveness, and stemness [1-83-108-131]. TGF-β also promotes EMT in breast and other cancers via activation of downstream transcriptional effectors small mothers against decapentaplegic (SMAD), SNAIL, Zinc-finger E homeobox-binding family (ZEB), and TWIS[1-83-108-131]. In TNBC, treatment with chemotherapeutic agent paclitaxel causes hyperactivation of autocrine TGF-β signalling, promoting therapy resistance and relapse [1-83-108-131]. TGF-β is often enriched in the TNBC microenvironment and can be produced by infiltrating stromal and immune cell populations [1-83-108-131]. These studies suggest TGF-β-induced CSC accumulation as a drug resistance mechanism in TNBC [1-83-108-131]. TNFα is an inflammatory cytokine secreted predominantly by activated macrophages, natural killer cells, MDSCs, and T-cells in the TME[1-83-108-131]. Altogether, these studies suggest a vital role for inflammatory cytokines secreted by tumor and infiltrating immune cells in regulating stemness and self-renewal in TNBC[1-83-108-131].

4.10. SNAIL

Wnt/β-catenin signalling induces SNAIL accumulation. SNAIL mediates E-cadherin repression, inducing EMT[1-83-108-131]. In TNBC, SNAIL is associated with relapse, chemoresistance, and metastases**.** SNAIL also regulates IL-8 expression, which promotes stemness in TNBC [125]. A SNAIL-G9A-DNMT1 complex also epigenetically silences Fructose-Bisphosphatase 1 (FBP1) in TNBCSCs, inducing metabolic reprogramming increasing glucose uptake and ATP production even under hypoxia [1-83-108-131]. The SNAIL-induced glycolytic switch to a more "Warburg"-like state

reduces oxygen consumption and reactive oxygen species (ROS) accumulation, promoting tumorigenesis, survival, and self-renewal [1-83-108-131]. Recent one of the study suggests uncoupling Protein 1 (UCP1), which is down regulated in TNBC, represses SNAIL-mediated FBP1 silencing, suppressing TNBCSC accumulation. BRD4 also promotes SNAIL expression in TNBC, conferring TNBC cells with stem-cell-like traits [1-83-108-131].

4.11. ZEB

ZEB is another key transcriptional regulator of EMT and stemness[1-83-108-131]. Similar to SNAIL and other EMT regulators, it represses E-cadherin and is induced by several stemness-associated signaling pathways including Wnt/β-catenin and cytokine signalling [1-83-108-131]. TNBC cells maintain the ZEB1 promoter in a bivalent chromatin configuration allowing them to quickly respond to microenvironmental cues, modulating ZEB1 expression to switch CSCs give rise to non-CSC cells in a unidirectional manner [1-83-108-131]. Instead, TNBCSCs and non-CSC TNBC cells reserved the ability to switch between stem cell and non-stem cell phenotypes depending on environmental stimuli. This interconversion was not found in other non-TNBC breast cancer subtypes, suggesting ZEB1 modulation as a key mechanism for the problematic tumorigenicity of TNBCs [1-83-108-131].

4.12. Hypoxia

Hypoxia is a vital contributing factor to CSC generation and maintenance [1-83-108-131]. Hypoxia is a hallmark of the TME in several cancers, and it drives CSC accumulation via the activity of Hypoxia-Inducible Factor (HIF) transcription factors. Hypoxia-Inducible Factor (HIF) normally function to maintain oxygen homeostasis, preventing excessive production of toxic ROS [1-83-108-131]. The TNBC TME is highly hypoxic[1-83-108-131]. Treatment with chemotherapeutic agents such as paclitaxel and gemcitabine exacerbates hypoxia in the TNBC TME, inducing HIF activity[1-83-108-131]. These HIFs promote TNBCSC accumulation via induction of IL-6 and IL-8 signaling and increased MDR [1-83-108-131]. Additionally, HIFs regulate the production of Colony Stimulating Factor 1 (CSF1) in TNBCs, which recruits tumor-associated macrophages and myeloid-derived suppressor cells to the TME [1-83-108-131]. Carbonic anhydrase CAIX is another hypoxia-induced factor directly regulated by HIF allowing cancer cells to regulate intracellular pH during hypoxia [1-83-108-131]. It is highly expressed in TNBC where it correlates with poor survival and metastases as well as promotes TNBCSC survival and stemness [1-83-108-131]. HIF-1 also promotes the expression of Glutamate-Cysteine Ligase Modifier Subunit which inhibits mitogen-activated protein kinase kinase (MEK)/extracellular-signal-regulated kinase (ERK) signalling in TNBC cells [1-83-108-131].

4.13. TWIST

TWIST is the third major transcriptional regulator of EMT. TWIST regulates stemness in TNBC by downregulating CD24, inducing the accumulation of CD44+CD24-ALDH+TNBCSCs [1-83-108-131]. Additionally, a TWIST/BRD4 complex induces IL31RA expression in TNBC cells, promoting stemness via IL[1-83-108-131]. A similar TWIST/BRD4 complex transcribes WNT5A in TNBC, promoting stem-cell-like properties and tumorigenicity [1-83-108-131]. In TNBC, deubiquitinating enzyme ubiquitin-specific protease 2 (USP2) promotes TWIST stabilization, allowing it to induce stemness, EMT, and chemoresistance [131]. TWIST also increases the expression of drug efflux pumps in TNBCSCs, promoting chemoresistanc[1-83-108-131].

4.14. Runt-related transcription factor

The Runt-related transcription factor (RUNX) family of transcription factors regulate a plethora of developmental processes including cell growth, differentiation, and lineage specification [1-83-108-131]. One of the work suggests RUNX factors drive EMT and stemness in breast cancer CSCs [1-83-108-131]. In TNBC, RUNX1 is an independent prognostic indicator of poor patient outcomes [1-83-108-131]. In TNBCSCs, RUNX transcription factors and their coregulator CBFβ promote phenotypic plasticity and are essential for maintaining of the mesenchymal, invasive phenotype [1-83-108-131]. RUNX1 was also recently shown to regulate R-Spondin 3 (RSPO3) in TNBCSCs, promoting EMT, motility and stemness [1-83-108-131]. Accumulating evidence also suggests significant interaction between RUNX factors and the hippo pathway, an established self-renewal signalling axis in TNBC [1-83-108-131].

4.15. Hippo YAP/TAZ

The Hippo pathway is a key regulatory axis for cell fate, organ development, tissue regeneration, and self-renewal during development [1-83-108-131]. Aberrations in Hippo signaling have been shown to induce dedifferentiation of mature cells into progenitor cells [1-83-108-131]. It has also been associated with induction of CSC accumulation in various cancers. In breast cancers, TAZ confers CSCs self-renewal and tumor-initiation capacities. In TNBC cells, YAP has been shown to regulate the transcription of stem cell signature genes, promoting tumor sphere formation [1-83-108-131].

4.16. NF-κB

The NF-κB transcriptional complex is a highly conserved transcriptional complex that regulates cell survival, growth, differentiation, and cytokine production [1-83-108-131]. It regulates gene expression in response to a plethora of extracellular stimuli including cytokines, free radicals, and pathologic antigen [1-83-108-131]. The NF-κB family consists of five transcription factors: RelA, RelB, c-Rel, NF-κB1, and NF-κB2 [1-83-108-131]. Deregulated NF-κB activity has been associated with tumorigenesis in several cancers. In breast cancer, TNBCs exhibit the highest levels of constitutively activated NF-κB [1-83-108-131]. Activated NF-κB drives accumulation of TNBCSCs via induction of JAG1/NOTCH signaling [1-83-108-131]. This mechanism of CSC accumulation was found to be exclusive to TNBCs and not other breast cancers [1-83-108-131]. Therefore, a dynamic, cyclical, NF-κB-JAG1/NOTCH-NF-κB signaling axis maintains TNBCSCs accumulation and survival in TNBCs [1-83-108-131].

4.17. Pluripotency Regulators

Pluripotency is a common feature of both CSCs and normal stem cells [1-83-108-131]. During development, pluripotency is maintained and induced by a group of transcription factors regulated by environmental clues to create varied cell and tissue lineages [1-83-108-131]. Perhaps unsurprisingly, TNBC and other tumors similarly overexpress these factors to promote pluripotency and self-renewal. Ectopic over-expression of these transcription factors, including OCT4, SOX2, NANOG, KLF4, and MYC, on non-malignant somatic cells can reprogram them into pluripotent stem cells. OCT4 is overexpressed in TNBC where it correlates with worse clinical outcomes [1-83-108-131]. OCT4 was first identified as an essential regulator of pluripotency and self-renewal in the embryo during development [1-83-108-131]. It has since been identified as a significant oncogene promoting stemness, self-renewal, and tumor recurrence [1-83-108-131]. SOX2 is another regulator of stem cell pluripotency during embryonic development [1-83-108-131]. SOX2 is overexpressed in TNBC where it correlates with increased proliferation, metastasis, and worse clinical outcomes. SOX2 was increased in TNBCSCs induced by chemotherapy, promoting resistance and survival [1-83-108-131]. NANOG is a master regulator of self-renewal and pluripotency highly expressed in early life but silenced in adult somatic cells [1-83-108-131]. In several cancers, aberrant reactivation of NANOG contributes to tumorigenicity and stemness [1-83-108-131]. NANOG has been linked with increased stemness and poorer clinical outcomes in TNBC [1-83-108-131]. NANOG was found to be a favorable prognostic marker for TNBC [1-83-108-131]. This suggests that NANOG might not be a reliable biomarker for TNBC [1-83-108-131]. The formation of this complex was specific to TNBC and not present in non-TNBC cells [1-83-108-131]. KLF4 is another important transcription factor during development [1-83-108-131]. In tumors, it has been shown to have both oncogenic and anti-cancer roles [1-83-108-131]. In TNBC, its role appears to be equally confounding [1-83-108-131]. KLF4 is predominantly expressed in TNBCSCs where it promotes survival, self-renewal, and chemoresistance [1-83-108-131]. They also showed receptor tyrosine kinase (RTK) is a transcriptional target of KLF4 in TNBC, partially contributing to the chemoresistance phenotype[1-83-108-131]. The MYC family of pro-oncogenic transcription factors are ubiquitous gene regulators that regulate several cellular processes including motility, survival, stemness, therapy resistance, and differentiation. In TNBC, MYC is highly expressed in CSCs where it drives self-renewal and chemoresistance [1-83-108-131]. In TNBC, high MYC levels are driven by a vascular endothelial growth factor receptor(VEGFR) -2/STAT3 axis, which transcribes MYC and SOX2 to promote stemness [1-83-108-131].

In TNBC, aberrations in epigenetic mechanisms are key contributing factors to the highly heterogeneous and stem cell-like phenotype often seen in patients [1-83-108-131]. DNA methylation is significantly deregulated in most breast cancers including TNBC [1-83-108-131]. Deregulated chromatin architecture is a feature of several cancers. Deregulation in mechanisms of RNA interference, predominantly microRNAs (miRNA), can similarly contribute to CSC accumulation in TNBC [1-83-108-131]. Altogether, these findings suggest that miRNAs that target known CSC regulators are likely to be negative regulators of TNBCSCs and could be investigated as biomarkers and therapeutics for TNBCSCs [1-83-108-131]. These TNBC-specific mechanisms, however, are appealing therapeutic targets to combat relapse, recurrence, and therapy failure in this especially hard-to-treat cancer [1-83-108-131].

4.18. microRNAs

MicroRNAs (also known as miRNAs) are key epigenomic regulators of biological processes in breast cancer. microRNAs have succeeded in grabbing the key stage in the field of regulation of BCSC development and progression via regulatory networks [1-83-108-131-274]. Recently, miRNAs have been showed to target Wnt, Notch, Hh pathways and transcription factors such as SOX-2, SOX-9, BMI in order to regulate the plasticity and heterogeneity of BCSCs [1-83-108-131-274]. Previous studies strongly suggested that miRNAs had different functional specialization for BCSCs. For example, in TNBC, the tumor-suppressive role of miR-199a has been shown to strongly attribute to affect EMT programs and ALDH+ BCSCs [1-83-108-131-274]. Aberrant expression of miR-199a also repressed the expression of FOXP2 to maintain ALDH+ and CD24- CD44+ BCSC population in TNBC [1-83-108-131-274]. It has also been demonstrated that miR-199a promoted cancer stem cells in human glioblastomas (GBM) and hepatocellular carcinoma (HCC) [1-83-108-

131-274]. However, miR-34a was reported to inhibit colorectal cancer stem cells by degrading WNT/β-catenin. On the other hand, some miRNAs played key roles in inhibiting the self-renewal and maintenance of BCSCs. The WNT/β-catenin pathway is a well-documented target for miRNAs in BCSCs [1-83-108-131-274].

Accumulating evidence indicates that long non coding RNAs (lncRNAs) contributed to the progression of several human cancers [1-83-108-131-274]. Specially, in breast cancer, lncRNAs have been showed to be key regulators of 1) Cell proliferation, invasion, metastasis 2) Apoptosis and autophagy 3) Metabolism 4) Maintenance of BCSCs and EMT 5) Drug resistance [1-83-108-131-274]. Thus, long non coding RNAs (LncRNAs) have been monitoring tools and therapeutic targets in breast cancer[1-83-108-131-274]. Recently, the most well studied regulatory mechanism of lncRNAs is to regulate BCSCs via depleting miRNAs which are supposed to target key components in signaling pathways [1-83-108-131-274]. Recently, long non coding RNAs (lncRNAs) associated with CD24- CD44+ BCSCs have been documented[1-83-108-131-274].

4.19. Glycoprotein Non-Metastatic B (GPNMB)

GPNMB is a type I transmembrane glycoprotein that is overexpressed in 40–60% of breast cancer cases, including triple-negative breast cancer cases [1-83-108-131-274]. In phase I/II trials, glembatumumabvedotin (CDX-101), an antibody targeting GPNMB, exhibited a favorable safety profile on 42 patients with metastatic breast cancer. However, the results of a further phase II clinical trial in TNBC patients with metastatic CDX-011 impact have yet to be reported [1-83-108-131-274].

4.20. Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)

The vascular endothelial growth factor receptor (VEGFR2) is a receptor tyrosine kinase that regulates angiogenesis and pathogenesis in breast cancer [1-83-108-131-274]. VEGF, the ligand to VEGFR2, impacts ligand expression involving tumor invasion and metastasis in TNBC [1-83-108-131]. Patients who have had TNBC surgery have significantly higher levels of VEGF and shorter survival [1-83-108-131]. VEGFR inhibitors, such as bevacizumab, ramucirumab, VEGFR receptor blockers, receptor mimetics (such as aflibercept), and sorafenib, are small-molecule tyrosine kinase inhibitors [1-83-108-131-274]. Patients with TNBC who were treated with the medication of sunitinib for metastasis alone had a worse prognosis than those in a phase II trial [1-83-108-131-274].

4.21. Epidermal Growth Factor Receptor (EGFR)

The epidermal growth factor receptor (EGFR) is an HER family tyrosine kinase receptor that is found in a variety of epithelial tumors [1-83-108-131-274]. EGFR activation has an essential function in the survival of many solid tumors, including metastasis, cell proliferation, invasion, cell cycle progression, differentiation, angiogenesis, and apoptosis. Overexpression EGFR in breast cancer cells is approximately 15–45%, and about 50% in TNBC, which is negatively correlated with patient survival rates [1-83-108-131-274]. Anti-EGFR monoclonal antibodies such as cetuximab (SCT200), and EGFR small-molecule tyrosine kinase inhibitors such as gefitinib and erlotinib, are used to block the EGFR signaling pathway in TNBC [1-83-108-131-274]. Afatinib has been included in clinical studies, however, its status is still unclear. In a phase II trial, erlotinib, in combination with paclitaxel nanoparticle formulation and bevacizumab, showed excellent tolerability [1-83-108-131-274].

4.22. Fibroblast Growth Factor Receptor (FGFR)

FGFR2 is overexpressed in TNBC cells by around 4%, while FGFR1 and FGFR2 mutations were found in roughly 16% and 13% of TNBC patients, respectively [1-83-108-131-274]. The expression of FGFR2 in TNBC patients is an independent prognostic factor [1-83-108-131-274]. Approximately 4% of TNBC have amplification of the FGFR2 gene on chromosome 10q26. Nevertheless, it appears to be a rare occurrence in other tumor subtypes, with just 1–2% of all breast cancers expression [1-83-108-131-274]. IM-412 is a small molecule tyrosine kinase inhibitor or monoclonal antibody in the TNBC subtype [1-83-108-131-274].

4.23. Trophoblast Antigen 2 (Trop-2)

Inhibitor Trop-2 is a cell surface receptor and an epithelial glycoprotein-1. Overexpression of Trop-2 can promote cancer cell proliferation, EMT, migration, invasion, and metastasis in a variety of epithelial malignancies [1-83-108-131-274]. For example, Trop-2 was discovered in TNBC cells, with more than 85% of its expression in tumors [1-83-108-131-274]. Sacituzumab-bound tumor cells are killed by intracellular uptake and extracellular release of SN-38 [1-83-108-131-274]. Sacituzumabgovitecan-hziy (or IMMU-132, Immunomedics, or hRS7- SN-38) is a monoclonal antibody-drug combination in which SN-38, an active metabolite of irinotecan. This is linked to the humanized antitrophoblast

cell-surface antigen 2 (Trop-2) monoclonal antibody hRS7 IgG1 through the cleavable CL2 linker of TNBC patients in phase I/II clinical trial [1-83-108-131-274].

5. Triple Negative Breast Cancer (TNBC): Plant based Inhibitors

The use of medicinal herbs as medicine is the oldest form of medical treatment known to humanity and has been used in all cultures throughout history [133-274]. Since time immemorial, humans have recognized their dependence on nature for healthy living, and have relied on a variety of plant resources for medicine to cure numerous diseases [133-274]. This indigenous knowledge, passed down from generation to generation in different parts of the world, has contributed significantly to the development of traditional medical systems, as well as provided a scientific basis for their traditional uses by exploring various biologically active natural products [133-274]. For instance, between 1981 and 2014, about 26% of new chemical entities were natural products or derived from natural products [5]. They are widely used in the prevention and treatment of clinical diseases as they have the unique advantages of low toxicity and side effects compared with chemical drugs. Most chemotherapeutic drugs for cancer treatment are molecules identified and isolated from plants or their synthetic derivatives [133-274, 276]. In parallel, there is an increasing evidence for the potential of plant-derived compounds as inhibitors of various stages of tumorgenesis and associated inflammatory processes, underlining the importance of these products in cancer prevention and therapy [133-274]. Approximately 60% of drugs currently used for cancer treatment have been isolated from natural products, and the plant kingdom has been the most significant source [133-274, 276]. Plant-derived compounds have a promising synergistic relationship with a variety of chemotherapy regimens, enhancing their effectiveness [133-274]. Genistein and doxorubicin have a synergistic effect and boost the tamoxifen effect, and pomegranate, which promotes the tamoxifen-induced cell viability inhibition, are two examples of these combinations. Natural materials are also preferred over conventional therapies since they are easily accessible in the natural environment and typically have fewer side effects on healthy human cells [133-274]. Vinca alkaloids (CAs or VAs) are frequently utilized as anticancer medications, either alone or in combination with other medicines, to treat a number of cancers, such as breast cancer, osteosarcoma, and acute lymphocytic leukemia[133-274, 276].

Many plant-derived natural compounds have anti-cancer properties, including quercetin, formononetin, calycosin, polyphenols, bioflavonoids, carotene, vitamins, and andminerals [133-274]. Many plant-derived natural compounds, including vinka alkaloids, **vinblastine** and **vincristine,** luteolin, α-mangostin, piperine, silibinin, apigenin, quercetin, fisetin, resveratrol, genistein, 10-gingerol, chalcones, berberine, curcumin, epigallocatechin gallate, cyanidin-3-o-glucoside, and glycyrrhizin, have shown anti-cancer properties, especially in the treatment of TNBCs [133-274, 276]. These compounds exhibit the capability to suppress cell growth, migration, and metastasis by targeting irregular/ regular signaling pathways present in TNBC [133-274]. They can suppress cell growth, migration, and metastasis by targeting irregular/regular signaling pathways present in TNBC, such asWnt/β-Catenin, NF-kB, PI3K/Akt/m-TOR, PD-1/PD-L1, LAG-3, CTLA-4, STAT-3, EGFR, Trop-2, RAF/MEK/ERK, JAK, Glycoprotein NMB (GpNMB), and hedgehog pathways [133-274]. Despite the fact that the natural molecule shows potential against TNBC cell lines, compounds derived from natural resources are currently limited in their usage as TNBC therapeutic agents [133-274]. Further research, on the composition of substances derived from natural resources is needed to determine potential therapeutic candidates and histological characteristics. Data from these studies could provide insight into potential sources of natural compounds that could be used against the aggressive TNBC cells, particularly the metastatic pathway, in a targeted and effective manner [133-274, 276].

Rapamycin and paclitaxel drugs are used to inhibit the PI3K/AKT/mTOR pathway and hence play a significant role in TNBC treatment. Mechanistically, AD inhibited the activation of Akt/mTOR and STAT3 TNBC signaling pathways. LGK974 (a WNT-specific O-acyltransferase porcupine inhibitor) inhibited WNT signaling in a mouse model of breast cancer [133-274]. Demethylzeylasteral (T-96) inhibits triple-negative breast cancer invasion by blocking the canonical and non-canonical TGF-β signaling pathways. Another study reported that the IKK/NF-κB pathway as a potential target for enhancing the efficacy of EGFR inhibition *in* TNBC cells. Another study reported that the DIF-1 suppresses both TNBC growth and metastasis through a common signaling pathway, the AMPK-mTORC1 system [133-274].

Many small-molecule inhibitors of protein kinases have been tested in clinical trials in patients with TNBC, including drugs that target the PI3K/Akt/mTOR and MAPK signaling pathways, receptor tyrosine kinases, cyclin-dependent kinases, and DNA damage response signaling pathways [133-274, 276]. Although some of these agents had limited efficacy in an unselected population of TNBC patients. Recent studies suggested that kinase inhibitors may provide significant clinical benefits in the framework of subtype-based and biomarker-guided therapeutic approaches [133-274]. Inobufacini injection inhibits the proliferation of triple-negative breast cancer through the Pin1–TAZ signaling pathway. Bioactive plant-derived phyto-compounds can be anticipated to play a more and more substantial function in the development of new drugs. The most well-known plant-derived anticancer compounds of medical importance

include those especially good at attacking the cytoskeleton system of cell microtubules which include the vincristine, vinblastine, and taxanes, e.g., docetaxel (Taxotere), paclitaxel (Taxol). Following are the plant based inhibitors for controlling cancer.

1. Luteolin is a flavonoid compound found in many plants such as carrots, celery, broccoli, perilla leaf, and seed [133-135-239]. A study that used two methods to determine the mechanisms of luteolin on TNBC metastasis (in vitro with a xenograft model and in vivo with MDA-MB- 231 and BT5-49 cell lines), found that Luteolin dose-dependently inhibited cell migration and invasion, reversed epithelial–mesenchymal transition (EMT), and suppressed the expression of β-catenin mRNA. This has suppressed metastases to the lung of breast cancer cells at a concentration of 100 μM [133-135]. The results indicated that luteolin had a potent therapeutic effect on invasion and metastasis of TNBC, which may be involved in the reversal of EMT by down-regulation of β -catenin [133- 135-239]. The other research showed in vivo studies of luteolin suppressed lung metastasis of TNBC in MDA-MB-231 (4175) and MDA-MB-435 cell lines LM2 with concentrations of 40 mg/kg and 20 mg/kg, respectively [133- 135]. Luteolin significantly inhibited tumor cell migration to reduce VEGF levels and block VEGF receptors, with IC_{50} of 10 μM in vitro and in vivo [133- 135]. In addition, luteolin from *Taraxacum officinale* extract can inhibit Nrf2 in breast cancer stemness (Cripto1, CD44, ALDH1, ABCG2, NANOG, OCT4, and Sirt3) and chemoresistance, with IC_{50} value 1 μM in an MDA-MB-231 cell line in vitro study [133- 135-239].

2. *μ*-Mangostin: The μ-mangostin is isolated from *Garcinia mangostana* Linn with the mechanism of action as anti-proliferation, apoptosis, suppressed angiogenesis, and metastases [133, 136-138-239]. According to a study in 2018, μ-mangostin could significantly reduce the development of the spheroids in an MDA-MB-231 cell line, with an IC_{50} value of 1.25 μ g/mL [133, 136-138]. This finding points to a novel anti-cancer property of μ-mangostin that could be used to improve the conventional drug penetration into tumor bulk [133, 136-138]. Another research reported that μ-mangostin suppressed the cell proliferation, migration, and invasion of the PI3K/Akt signaling pathway by targeting RXRα and cyclin D1 in vitro and in silico studies [133, 136-138]. This compound was inhibited in the MDA-MB-231 cell line, with an IC_{50} value of 11.37 μ M [133, 136-138-239].

3. Piperine: Piperine is an alkaloid found in the fruits of black pepper (*Piper ningrum* Linn.) and long pepper (*Piper longum* Linn.) [133, 139-140-239]. The research on dose-dependent reduction in the number of TNBC cells (MDA-MB-468, MDA-MB-231) and estrogen receptor-expressing breast cancer cells (MCF-7, T-47D) discovered that piperine decreased the percentage of TNBC cells in the G2 phase of the cell cycle and inhibited the in vitro growth of p53-deficient [133, 136-138]. Piperine also inhibited TNBC cell migration and expression of matrix metalloproteinase- 2 and -9 mRNA in vitro and in immune-deficient mice in vivo with the IC_{50} value of 50 μM [133, 136-138-239].

4. Silibinin: Silibinin is a major bioactive flavanone. It has biological activity in a variety of cancer models such as breast and lung cancers by inhibiting cell proliferation, invasion, and angiogenesis [133, 141]. In the research using Hs578T, MDA-MB-231, BT474, T47D, HCC1806, and HCC1143 cell lines, silibinin significantly decreased TGF-β2-induced FN, MMP-2, and MMP-9 expression levels and suppressed the lung metastasis of TNBC cells [133, 141]. It also decreased TGF- β2 mRNA expression levels but not that of TGF- β1 in TNBC cells, cell migration, as well as basal fibronectin, MMP-2 expression levels, decreased as well in response to silibinin in vitro and in vivo studies with the IC_{50} value of 50 μM [133, 141]. Another study reported that silibinin inhibited the gene-specific transcriptional activation of MMP-2 expression and suppressed the phosphorylation of the Jak2/STAT3 signalling pathway by blocking the STAT3 nuclear translocation, DNA-binding activity, resulting in reduced cell migration and invasion with the IC_{50} value of 200 β M in MDA-MB-231 cell line[133, 141-239].

5. Apigenin: Apigenin is a natural flavonoid compound and has an effect on diabetes, amnesia and Alzheimer's disease, depression, insomnia, and cancer [133, 142-239]. Apigenin is found to be able to decrease the expression of target genes, such as CTGF and CYR61 and YAP/TAZ activity in TNBC cells and disrupt the YAP/TAZ-TEADs protein–protein interaction in MDA-MB-436 cells [133, 142]. Meanwhile, in MDA-MB-231 cells, apigenin disrupts the TAZ–TEADs interaction but has no evidence of the interaction between YAP and TEADs, with the IC_{50} value of 20 μM[133, 142]. In addition, apigenin can inhibit pro-inflammatory proteins such as CCL2, TNFα, and IL-6 at extremely high concentrations in MDA-MB-468 compared to MDA-MB-231 cell lines, with an IC_{50} value of 40 μM [133, 142-239].

6. Quercetin: Quercetin is a plant-derived flavonoid found in fruits, vegetables, and tea, which is known to have multiple biological actions such as antioxidant, anti-inflammatory, and anti-cancer activity [133, 143-145-239]. Quercetin induces apoptosis and cell cycle arrests by modulation of Foxo3a activity and inhibition of JNK activity that reduced the signalling activities of p53, p21, and GADD45 in the MDA-MB-231 cell line, with the IC_{50} value of 20 μM [133, 143-145-239]. Other research showed that quercetin significantly inhibits nuclear accumulation of β-catenin with reduced target genes such as cyclin D1 and c-Myc by inducing the E-chaderin expression and the ability to modulate a mesenchymal-to-epithelial transition (MET) in MDA-MB-231 and MDA-MB-468 cell lines [133, 143-145-239]. The in vitro study had

an IC_{50} value of 50 μM. Additionally, the in vivo study showed that quercetin inhibited tumor growth and FASN expression in tumor xenograft with a concentration of 50 mg/kg. This has induced apoptosis through down-regulation of caspase-3 activity, FASN, β-catenin, and Bcl-2 protein expression in the in vitro study [133, 143-145]. The IC_{50} values were 3 μM and 4 μM in MDA-MB-231 and MDA-MB-157 of TNBC cell lines, respectively [133, 143-145-239].

7. Fisetin: Fisetin is one of the major flavonoids from many fruits and vegetables such as strawberries, apples, persimmons, grapes, onions, and cucumbers [133, 146-147]. Fisetin dose-dependently inhibits cell proliferation, migration, and invasion in MDA-MB-231 and BT549 cells. In vitro assay demonstrated that fisetin suppressed phosphoinositol 3-kinase (PI3K)/Akt/GSK- 3β signalling pathway but up-regulated the expression of PTEN mRNA and protein in a concentration-dependent manner [133, 146-147]. On the other hand, in vivo tests, with a concentration of 100 mg/kg, indicated that fisetin could inhibit the growth of primary breast tumors and reduce lung metastasis while increasing the expression of EMT molecules and PTEN/Akt/GSK-3β with an IC_{50} value of 100 μM [133, 146-147-239].

8. Resveratrol: Resveratrol is a non-flavonoid polyphenolic compound from wine and grape juice, also synthesized in grape leaves and grape skins [133, 148-149-239]. It is reported that resveratrol promoted the apoptosis of TNBC cells by reducing POLD1 expression. Thereby, activating the respective apoptosis pathways in the MDA-MB-231 cell line by in vitro and in vivo assays having an IC_{50} value of 50 μM [133, 148-149]. Another research reported that resveratrol at an IC_{50} value of 185 μM combined with 14 μM cisplatin inhibited fibronectin, vimentin, PI3K/Akt, Smad2, Smad3 JNK, ERK, Nf-KB expressions by TGF-β1, and increasing E-cadherin expression [133, 148-149]. This compound can also inhibit migration, invasion, and tumor growth within in vitro and in vivo studies in MDA-MB-231[133, 148-149-239].

9. Genistein: Genistein (Gen) is a natural isoflavone with biological activities such as anti-breast cancer activity [133, 150-152-239]. In a dose-dependent manner, genistein induced apoptosis and cell cycle arrest in the G2/M phase [133, 150-152]. Gen inhibited NF-kB activity by the Nocth-1 signalling pathway, as well as downregulated cyclin B1, Bcl-2, and Bcl-xL expression in the MDA-MB-231 cell line at an IC_{50} value of 20 μM. Further preclinical and clinical studies are warranted to investigate the application of Gen for the treatment of TNBC [133, 150-152-239]. Other research showed that Gen inhibited CDK1 kinase activity by phosphorylation on the Thr14 and Tyr15 sites by inducing G2/M cell cycle arrest, apoptosis, and DNA damage response pathways such as ATR and BRCA1 activation. An IC_{50} value of 40 μM was present in the MDA-MB-231 cell line [133, 150-152].

10. Gingerol: (10)-gingerol is found in ginger (*Zingiber officinale* Roscoe) oleoresin from a fresh rhizome [133, 153-239]. The results reported that (10)-gingerol induced metastatic dissemination, including lung, bone, brain, and apoptosis death in mouse and human TNBC (MDA-MB-231) cell lines in vitro and in vivo. It also inhibited 4T1Br4 orthotopic tumor growth, with a concentration of 10 mg/kg in the in vivo study. Furthermore, the in vitro study obtained the IC_{50} value of 100 μM in the MDA-MB-231 cell line [133, 150-152]. The other research showed inhibited mitogen-induced activation of Akt and p38MAPK and the suppressing of epidermal growth factor receptor expression [133, 150-152-239]. The result reported cell migration and invasion through the suppression of MMP-2 activity, with an IC_{50} value of 10 μM in the MDA-MB-231 cell line by in vitro study [133, 150-152-239].

11. Chalcones: Chalcones is a natural flavonoid from many flowers and plants, including fruits and vegetables [133, 154-156]. It has pharmacological activities such as hypertension, infectious diseases, neurological disorders, and cancer [133, 154-156]. Chalcone, extracted from Cardamonin, induces invasive, migration, and reverses epithelial–mesenchymal transition (EMT) by downregulation of Wnt/_*β*-catenin signaling in BT-549 and MDA-MB-231 cell lines [133, 154-156]. This result significantly inhibits the phosphorylation of GSK3-β by inhibiting Akt activity [133, 154-156]. The *in vitro* study and concentration of 5 mg/kg in vivo study had an IC_{50} value of 20 μM in BT-549 and MDA-MB-231 cell lines [133, 154-156-239].

12. Berberine: Berberine (BBR) is a natural active principle with potential antitumor activity [133, 157-161-239]. Berberine is a natural isoquinoline alkaloid compound isolated from the stems and roots of plants such as *Berberis vulgaris, Berberis asiatica, Berberis aristata, Coptidis japonica, Coptidis japonica, Coptidis rhizome, Coptidis chinensis, Mahoniaaqui folium,* and *Mahonia beale* [133, 157-161-239]. Berberine significantly induced apoptosis and had the most sensitive reaction to HCC70, BT-20, and MDA-MB-468 cell lines, with IC_{50} values of 0.19 μM, 0.23 μM, and 0.48 μM, respectively. Berberin also induced cell cycle arrest at G1 and/or G2/M phases in MDA-MB-468 and HCC70 cell lines and S phase in BT-20 cell line [133, 157-161]. Berberine induced apoptosis with an IC_{50} value of 1 μM in all of the cell lines by in vitro study. The research suggests berberine as a potential candidate for TNBC therapy [133, 157-161-239]. **Berberine (BBR)** is a natural active principle with potential antitumor activity. The compound targets multiple cell signaling pathways, including proliferation, differentiation, and epithelial–mesenchymal transition [133, 157-161-239]. The expression levels of a panel of 44 selected genes in human colon adenocarcinoma (HCA-7) cell line were quantified by real-time polymerase chain reaction (PCR). **Berberine (BBR)** treatment resulted in a time- and dose-dependent

down regulation of 33 genes differently involved in cell cycle, differentiation, and epithelial–mesenchymal transition [133, 157-161]. The trend was confirmed across the two types of treatment, the two time points, and the different absolute dosage of **Berberine (BBR)** [133, 157-161]. These findings suggest that the presence of BBR in *T. cordifolia* extract significantly contributes to its antiproliferative activity [133, 157-161-239]. One of the study demonstrated that extract of *T. cordifolia* is able to inhibit the expression of several genes involved in colon cancer development and progression [133, 157-161]. The effects of *T. cordifolia* treatment were well resembled by pure **Berberine (BBR)**. This evidence suggested that the main effects of *T. cordifolia* were mediated by **Berberine (BBR)** [133, 157-161]. The ability to strongly reduce expression of genes involved in proliferation, differentiation, cell motility. EMT suggests further research efforts to explore the use of these substances as chemotherapeutic agent in colorectal cancer [133, 157-161-239].

13. Curcumin: Curcumin induces apoptosis and decreased expression levels of extracellular regulated protein kinase (ERK1/2), pERK1/2, EGFR, and pEGFR in MDA-MB-231 cells [133, 162-164, 189-239]. The research suggested curcumin as a potential anti-TNBC due to its ability to promote apoptosis, and to block the cell cycle of TNBC cells (MDA-MB-231) by inhibiting restoring DLC1 and EZH2 expression [133, 162-164]. It also inhibited the migration, invasion, and proliferation in vitro and in vivo studies with an IC_{50} value at 40 μM for both MDA-MB-231 and MDA-MB-468 cell lines [133, 162-164]. Other research showed that curcumin inhibited the SIK3-mediated cyclin D upregulation in the G1/S cell cycle and inhibited cell growth during epithelial-mesenchymal transition (EMT), with an IC_{50} value of 25 μM in the MDA-MB-231 cell line by in vitro and in vivo studies [133, 162-164, 189-239]. Curcumin from rhizomes of *Curcuma longa* (C1386, purity >65%) was purified by column chromatography on silica gel using CHCl3/hexane 90:10 as eluent using TLC for monitoring the reaction [133, 162-164-239]. The result showed that analog curcumin (1–3) compounds can decrease the activity of the NF-kB transcriptional factor [133, 162-164]. The compounds inhibited TNBC cell lines with IC_{50} values of 1.30, 1.59, and 0.88 μM in the SUM149 cell and 0.41, 0.00, and 0.85 in MDA-MB-231, respectively, compared to curcumin monitoring the reaction [133, 162-164, 189-239].

14. Epigallocatechin Gallate: Epigallocatechin gallate (EGCG) is a major natural component of green tea. EGCG has been evaluated in some clinical trials [133, 165-169, -239]. It has been reported that Epigallocatechin gallate suppressed the growth, migration, and invasion of TNBC cells by inhibiting VEGF gene expression in the Hs578T cell line. Wnt/β-catenin activation was downregulated by EGCG [133, 165-169, 239]. However, upregulation of Wnt/ β -catenin extinguished the inhibitory effects of EGCG on lung cancer [133, 165-169-239]. Wnt/ β -catenin signaling was suppressed by EGCG by promoting GSK-3β and PP2A-independent phosphorylation/degradation of β-catenin with the IC_{50} value of 80 μM [133, 165-169, 443]. One of the study reported that EGCG can also inhibit the β -catenin pathway, phosphorylation of Akt, and cyclin D1 expression, with an IC_{50} value of 200 μM in the MDA-MB-231 cell line [133, 165-169, 443]. Other research showed that the synthesis of EGCG analogues are diesters (G28, G37, and G56) and monoesters (M1 and M2) inhibiting the lipogenic enzyme fatty acid synthase (FASN) with an IC_{50} value of 1.5 μM in the MDA-MB-231 cell line [133, 165-169-239].

15. Cyanidin-3-O-Glucoside: Cyanidin-3-O-glucoside is an anthocyanin from the flavonoids group. Cyanidin-3- o-glucoside was reported to effectively promote apoptotic cell death in MDA-MB-231, MDA-MB-436, and BT20 cell lines by inhibiting the estrogen receptor alpha 36 (ERα36) and EGFR/Akt signaling with an IC_{50} value of 500 μM [133, 170-171-239]. Cyanidin-3-o-glucoside also downregulates β-catenin and methylguanine-DNA methyltransferase (MGMT) [133, 170-171-239]. In addition, miR-214-5p mimics β-catenin and downregulates MGMT in LN-18/TR cells, whereas miR-214-5p inhibitors have the opposite effect. Further, miR-214-5p inhibitors significantly block Cyanidin-3-o-glucoside-induced downregulation of β -catenin and MGMT [133, 170-171-239].

16. Glycyrrhizin: Glycyrrhizin is a natural compound from licorice root and its metabolite, glycyrrhetinic acid, is potent against TNBC by inhibiting cell proliferation [133, 172-174-239]. Glycyrrhetinic acid exhibits a synergistic effect of etoposide and upregulation of TOPO 2A with an IC_{50} value of 20 μM in MDA-MB [133, 172-174-239]. The other research showed that glycyrrhizic acid from licorice root extracts inhibited intracellular and reactive oxygen species—mitochondrial, cell death, autophagy by the nuclear translocation of apoptosis-inducing factors (AIF) and LC-3 in the MDA-MB-231 cell line, with an IC_{50} value of 20 μM in vitro study [133, 172-174-239].

17. Ilamycin E: Ilamycin E from marine actinomycete isolated from deep sea-derived Streptomyces atratus, has anti-TNBC activities [133, 175-239] with inhibited G1/S cell cycle progression, induced apoptosis by activation of endoplasmic reticulum (ER) stress, increasing the expression of CHOP, suppressing Bcl-2 transcriptionin cell lines HCC1937 and MDA-MB-468 of TNBC, with IC_{50} values of 14.24 μM in HCC1927 and 24.56 μM in MDA-MB-468, with IC_{50} values of 14.24 μM in HCC1927 and 24.56 μM in MDA-MB-468 cell lines [133, 175-239].

18. Schisandrin A: Schisandrin A, a bioactive phytochemical, is one of the representative lignans species from the fruit of Schisandra chinensis Turcz. (Baill.) [133, 176, 177-239]. It has biological activity such as anti-inflammation and anti-oxidative stress. A study found that Schisandrin A suppressed the development of TNBC cells in vitro and in xenograft mouse models on MDA-MB-231 and BT-549 cells by inducing cell cycle arrest and cell death, as well as an overactivation of Wnt/β signaling in TNBC cells [133, 176, 177]. The IC_{50} values against MDA-MB-231 and BT-549 cells are 1.45 μM and 6.85 μM, respectively [133, 176, 177-239].

19. Ampelopsin E: Ampelopsin E, an oligostilbene derived from the Dryobalanops species, has anticancer and anti-inflammatory activities [133, 178]. It reduces invadopodia formation, migration, transmigration, and invasion of MDA-MB-231 cells by decreasing the expression of PDGF, MMP2, MMP9, and MMP14 significantly ($p < 0.05$) [133, 178-239]. The percentage of cell viability of Ampelopsin E is higher than 80% at a concentration of 15 μM [133, 178-239].

20. *Wedelia chinensis*: This plant is indigenous to India, South-East Asia, and China, is one of the important anticancer plants belonging to family *Asteraceae* which is rich in many important secondary metabolites like phenol, flavonoids, and tannin [133, 190, 226, 230, 233-239]. The essential oils of *W. chinensis* give a positive effect on lung cancer during the *in vitro* study [133, 226, 230, 233, 190]. The GC-MS analysis recorded the presence of two important compounds carvacrol and trans-caryophyllene. High anti-scavenging activities were found at different levels of dose [133, 190, 226, 230, 233-239].

21. *Tussilago farfara* (commonly called coltsfoot) belongs to the family *Asteraceae* is one of the important medicinal plants, grown in Europe and various regions of western and central Asia, commonly used against cancer. It possesses a high quantity of flavonoids and other phenolic compounds and some trace elements (Zn, Mg, and Se) [133, 180- 182, 190-239].The presence of these substances plays a key role in the anticancer activities of this plant particularly antitumor activity [133, 182, 190]. Coltsfoot is often used as a natural remedy for inflammatory conditions like asthma and gout, a type of arthritis that causes swelling and joint pain. Although coltsfoot may provide several health benefits, there are several serious concerns about its safety[133, 180-182, 190]. This is because coltsfoot contains pyrrolizidine alkaloids (PAs), compounds that cause acute and chronic liver damage when taken orally [133, 180-182, 190-239].

22. **Sequesterpenoid** (*Tussilago farfara*): Sequesterpenoid was isolated from Farfarae Flos (*Tussilago farfara*) [133, 180-182, 190-239]. The sequesterpenoid fraction used counter current chromatography (CCC) and isolation by using preparative- HPLC [133, 182, 190]. This compound showed inhibited JAK–STAT3 signalling pathway and suppressed the expression of STAT3 target genes, inducing apoptosis of TNBC MDA-MB-231 cells by extrinsic and intrinsic pathways in the in vitro and in vivo studies [133, 182. 190]. The result of the IC_{50} values is 0.18 μM compared to the positive control of Staurosporine [133, 180-182, 190-239].

23. *Scutellaria barbata*: The barbed skullcap is a key medicinal plant species of family *Lamiaceae*, used to treat inflammatory and cancer diseases [133, 179, 183, 185, 190-239]. It is rich in important secondary metabolites like alkaloids, flavones, steroids, and polysaccharides. Scutellarin (or scutellarein-7-*O*-glucuronide) is a natural drug found among the total flavonoids of barbed skullcap (*Scutellaria barbata*) and blue skullcap (*Scutellaria lateriflora*) [133, 179, 183, 185, 190-239]. *In vitro* studies showed positive activities against a vast range of cancers i.e., breast, colon , lung, hepatoma, and skin cancer [133, 179, 183, 185, 190-249]. The apigenin and luteolin isolated from *S. barbata* gave cytotoxic activity against both human breast cancer cell line MDA-MB-231 and non-transformed breast cell line (MCF10A). *Scutellaria barbata* has a long history of medical use in Traditional Chinese Medicine for removing heat and toxic material, promoting blood circulation, removing blood stasis, and inducing diuresis to reduce edema [133, 179, 183, 185, 190-239]. Recent pharmacology investigations have provided evidence for its anti-cancer, bacteriostasis, anti-virus, anti-inflammation, anti-oxidation and immunity enhancement properties [133, 179, 183, 185, 190]. The efficacy of activating blood circulation and removing blood stasis has unique advantages in the treatment of cardiovascular and cerebrovascular diseases [133, 179, 183, 185, 190-239].

24. *Prunus armeniaca* (Armenian plum) (Apricot Kernel Oil) belongs to an important plant family *Rosacea* [133, 190-239]. Various parts of the plant are used as the major source of some important antioxidant substances and are commonly used against cancer and some other cardiovascular diseases. The fruit part of *P. armeniaca* contains various important secondary metabolites like *β*-carotene, flavonoids, organic acids, thiamine, minerals, and oils [133, 190]. The seeds of *P. armeniaca* contains plenty of cyanogenic glycosides, used against different types of cancers [133, 190-239].

25. Aurantoside C: Aurantoside C (C828), isolated from Sponge (Manihinealyn beazleyae), inhibited the phosphorylation of Akt/m-TOR and NF-kB pathways [133]. Further increased the phosphorylation of p38 MAPK and SAPK/JNK pathways, leading to apoptosis in TNBC cells [133-239]. C828 was effective in reducing cell viability in SUM159PT, MDA-MB-231, and SUM149 with the IC_{50} values of 0.01 μM, 0.01 μM, and 0.02 μM, respectively, compared

to non-TNBC cells and chemotherapeutic drugs (doxorubicin and cisplatin) on SUM159PT cells after 24 h of treatment [133-239].

26. *Amyris texana:* The discovery of isoxazole compound (CIDD-0067106) from *Amyris texana* inhibited the phosphorylation of Akt/mTOR and NF-kB signaling pathways, a model of the Luminal Androgen Receptor (LAR) [133, 190]. The result showed IC_{50} of 0.8 μM in MDA-MB-453 cells [133, 190-239].

27. Diterpen Jatrophone*: Diterpen Jatrophone* is derived from the plant *Jatropha isabelli* [133, 184, 185, 190]. Jatrophone isolated was purified by normal-phase silica gel column chromatography [133, 184, 185, 190-239]. This study compared various TNBC subtypes of MSL-TNBC cell lines in MDA-MB-231 versus MDA-MB-157 with BL-1 subtype TNBC cell lines in HCC-38 versus MDA-MB-468 [133, 184, 185, 190]. This compound showed the capability to inhibit the proliferation of the oncogenic WNT10B/β-Catenin/HMGA-2 signalling axis [133, 184, 185, 190]. However, the IC_{50} values were 2 μM in MDA-MB-231 and 3.5 μM in MDAMB- 157 cell lines, whereas in HCC38 and MDA-MB-468 cell lines were 2 μM and 1 μM, respectively [133, 184, 185, 190-239].

28. Naringin/Flavonoid: Naringin is a flavonoid compound specifically of the flavanone subgroup. This compound of purity ≥95% uses HPLC [133, 186, 190]. Naringin can induce G1 cell cycle arrest, inhibit cell proliferation, and promote cell apoptosis by regulating p21, survivin, and suppressed β-catenin signalling pathway with IC_{50} values of 200 μM in MDA-MB-231, MDA-MB-468, and BT-549 cell lines [133, 186, 190-239].

29. *Myrothamnus flabelli folius*: Galloylquinic acids from *Myrothamnus flabella* folius extracts have the potential of anticancer activity [133, 186, 190]. They inhibit the growth of TNBC cells with a concentration of 31.125 μg/mL in BT-549 and MDA-MB-231 cell lines [133, 186, 190-239].

30. Cryptotanshinone: Cryptotanshinone is a bioactive component from the dried roots of *Salvia miltiorrhiza* that is purified by normal-phase silica gel column chromatography followed by preparative TLC [133, 190-239]. KYZ3 inhibited TNBC cell metastasis by decreasing the levels of MMP-9 which were directly regulated by activated STAT3 [133, 190-239]. A STAT3 plasmid transfecting assay suggested that KYZ3-induced tumor cell apoptosis target STAT3 MDAMB-231 and MDA-MB-468 cells by suppressing the growth of tumors. This resulted from subcutaneous implantation of MDA-MB-231 cells in vivo with IC_{50} values of 0.68 μM and 0.86 μM in MDA-MB-468 [133, 190-239].

31. *Ganoderma lucidum*; *Ganoderma lucidum* is a medicinal mushroom with anti-cancer activity [133, 190]. It was found to reduce cell adhesion, proliferation, survival, invasion, and downregulation of the STAT3 pathway [133, 190-239]. *Ganoderma lucidum* decreases the STAT3 pathway and the expression of OCT4, NANOG, and SOX2 in vitro, as well as in vivo on injected limiting dilutions (CD44+/CD24−) tumormodels with IC_{50} values of 0.50mg/mL in SUM-149 and 0.96 mg/mL inMDA-MB-231 cells[133, 190-239].

32. *Astragalus membranaceus*: *Astragalus membranaceus* major components are comprised of polysaccharides, flavonoids, and saponins with a purity of 98% [133, 190]. It has pharmacology activities, such as immunomodulating, anti-oxidant, and anti-inflammatory [133, 190-239]. The in vitro study reported that *Astragalus* polysaccharides inhibited the proliferation, invasion, and apoptosis of cell lines by the PIK3CG/AKT/BCL2 pathway, with an IC_{50} value of 2 mg/mL inMDA-MB-231[133, 190-239].

33. Vanicoside B: Vanicoside B, isolated from *Persicaria dissitiflora*, has been reported as an antiproliferative agent in cancer cells [133, 190, 194-239]. Vanicoside B suppressed CDK8-mediated signaling pathways and the expression of epithelial-mesenchymal transition proteins. Further induced cell cycle arrest and apoptosis in MDA-MB-231 and HCC38 TNBC cells in vitro and in vivo study, with the IC_{50} values of 9.0 μM [133, 190, 194-239].

34. Eupalinolide J: Eupalinolide J is a new sesquiterpene lactone isolated from *Eupatorium lindleyanum* DC. It has various biological activities, including anti-inflammatory, anti-cancer], and anti-oxidant activities [133, 190, 195-239]. The purity of Eupalinolide J was above 95%. Eupalinolide J suppressed tumor growth by STAT3 signaling pathways in vitro and in vivo in the mouse xenograft model which induces apoptosis, mitochondrial membrane potential (MMP) disruption, proliferation, and cell cycle arrest at the G2/M phase [133, 190, 195]. The IC_{50} values were 0.58 in MDA-MB-231 and 0.39 μM in MDA-MB-468 cells [133, 190, 195-239].

Eupalinolide J (EJ) is one of the main compounds in *Eupatorium lindleyanum* DC., demonstrated to exert inhibitory effects on STAT3 activation. EJ suppressed the growth of TNBC cells mainly through apoptosis induction, cell cycle arrest, and MMP disruption. Persistent activation of STAT3 plays an important role in the development of triple-negative breast cancer (TNBC), and suppression of STAT3 is considered as a novel approach for cancer therapy [275].

One of the study reported by Lou et al (2019) [275] demonstrated that the growth of human TNBC cells (MDA-MB-231 and MDA-MB-468 cells) was obviously inhibited by eupalinolide J (EJ) in TNBC cells [275]. The IC_{50} values were 3.74 ± 0.58 and 4.30 ± 0.39 μM, respectively [275]. Further this study demonstrated that eupalinolide J (EJ) suppressed the proliferation of TNBC cells mainly through cell apoptosis induction, mitochondrial membrane potential (MMP) disruption, and cell cycle arrest [275]. Meanwhile, the STAT3 and p-STAT3 in EJ-treated TNBC cells were remarkably suppressed [275]. The silencing of STAT3 by STAT3-shRNA significantly blunted the anticancer activities of eupalinolide J (EJ) in TNBC cells. This suggesting that eupalinolide J (EJ) suppressed cancer cell proliferation *via* targeting the STAT3 pathway [275]. Notably, further study demonstrated that EJ significantly promoted the degradation of STAT3 in TNBC cells. Finally, eupalinolide J (EJ) exhibited an effective antitumor activity against MDA-MB-231 cells *in vivo*. This study identified that eupalinolide J (EJ) suppressed the growth of TNBC cells *via* targeting the STAT3 signaling pathway [275]. These results strongly support that eupalinolide J (EJ) is a promising therapeutic agent for TNBC [275].

35. Cantaridin: Cantaridin is a terpenoid compound from the blister beetle Mylabris phalerata (Pallas) [133, 190, 196, 197]. Cantaridin inhibited cell proliferation by inducing apoptosis and inhibiting autophagy. Additionally leading to the conversion of LC3-I to LC3-II with suppressed Beclin-1 expression in vitro using flow cytometry and in vivo using nude mice of tumor xenograft with a dose of 10 mg/kg [133, 190, 196, 197]. The IC_{50} value is 5 μg/mL in MDA-MB-231 and MDA-MB-468 TNBC cell lines [133, 190, 196, 197, 200-239].

36. Cucurbitacin E: Cucurbitacin E was isolated from Hemsleya delavayi var. yalungensis (Cucurbitaceae) [133, 190, 200, 201-239]. This compound was extracted with methanol followed by purification using silica gel column chromatography by monitoring TLC and spectroscopic [133, 190, 200, 201]. Cucurbitacin E has been reported to significantly decrease cell viability by inducing cell cycle G2/M phase arrest, decreased expression of cyclin D1, survivin, XIAP, Bcl-2, and Mcl-1 and increased activation of JNK, as well as inhibited AKT and ERK activation [133, 190, 201]. The reported IC_{50} value is 0.2 μM in MDA-MB-468 and SW527 TNBC cell lines. Kong et al. (2014) also reported that IC_{50} of Cucurbitacin E is 10–70 nM in five TNBC cell lines. Among the TNBC cell lines, MDA-MB-468 and SW527, Cucurbitacin E significantly decreased cell viability, induced cell cycle G2/M phase arrest, and trigged apoptosis [133, 190, 201-239]. CuE at a concentration of 0.2 μM decreased the protein levels of CyclinD1, XIAP, Survivin, and Mcl-1[133, 190, 200, 201-239].

37. *Paris polyphylla* (called "Love Apple") belongs to family *Liliaceae* and contains 24 species throughout the world [133, 190, 200-239]. This is also called as Himalayan Paris. *P. polyphylla* is mostly used by Indian and Chinese traditional medicine system for having potential anticancer properties [133, 190, 200-239]. *P. polyphylla* consists of important secondary metabolites such as polyphyllin D, formosanin C, β-ecdysterone, dioscin, daucosterol heptasaccharide, oligosaccharides, octasaccharide, protogracillin, trigofoenoside A, yunnanosides G-J, padelaoside B, pinnatasterone, and other saponins [133, 190, 200]. Steroidal saponins are the main active components because of its structural diversity and bio-activities such as antitumor, immune-stimulator, analgesic, and hemostatic properties [133, 190, 200-217-239]. Aqueous and ethanol extracts of *P. polyphylla* showed potential antitumor activity against human liver carcinoma (HepG2 and SMMC-7721) cell line, human gastric (BGC-823) cell line, human colon adenocarcinoma (LoVo and SW-116) cell line, and human esophagus adenocarcinoma (CaEs-17) cell lines [133, 190, 200-217-239].

38. *Morus alba* commonly called as white mulberry, is native to China, Japan, India and is cultivated throughout the world where silkworm is raised [133, 190, 200-239]. The leaves are the main source of food for silkworms [133, 190, 200]. Extracts from *M. alba* are traditionally used to cure cancer, cough, edema, insomnia, bronchitis, asthma, nose bleeding, wound healing, eye infections, and diabetes [133, 190, 200-249]. *M. alba* contains many pharmaceutically important compounds like kuwanol, hydroxymoricin, moranoline, morusin, calystegin, albafuran, and albanol [133, 190, 200]. The leaves of *M. alba* contain some active compounds such as quercetin, rutin, apigenin, and 1-deoxynojirimycin and these compounds are known for antitumor activity [133, 190, 200-217-239].

39. *Hedyotis diffusa* (*Rubiaceae*): Because of the recent advances in pharmacological practices, this herb has received importance for having antitumor properties and showed effective results in treating cancers of the liver, colon, lungs, brain, and pancreas [133, 190, 200]. *H. diffusa* contains important bioactive derivatives of polysaccharides, triterpenes, and anthraquinones [133, 190, 200-217-239]. Methyl anthraquinonesare, one of the bioactive compounds in *H. diffusa*, is responsible for apoptosis of many cancers. *Hedyotis diffusa* Willd (H. diffusa) is a well-known Chinese medicine with a variety of activities, especially its anti-cancer effect in the clinic [133, 190, 200-239]. Up to now, 171 compounds have been reported from *H. diffusa*, including 32 iridoids, 26 flavonoids, 24 anthraquinones, 26 phenolics and their derivatives, 50 volatile oils and 13 miscellaneous compounds. In vitro and in vivo studies showed these phytochemicals and plant extracts to exhibit a range of pharmacological activities of anti-cancer [133, 190, 200]. It has been proved as the most commonly prescribed single Chinese herb used for colon cancer and breast cancer patients, according to the statistics from the National Health Insurance Research Database of Taiwan. H. diffusa is an annual herb, widely

distributed in the tropical Asia, such as India, China, Japan and Indonesia [133, 190, 200-239]. Modern research on *H. diffusa* has provided much evidence for its anti-cancer effect using in vitro and in vivo experiments and has tried to clarify the mechanism of its action [133, 190, 200-217-239].

40. *Garcinia indica*: *Garcinia indica* commonly known as kokum, is also an important medicinal plant that belongs to the Garcinia genus [133, 190, 202-206-239]. The garcinol of *G. indica* showed positive activities in the experimental HT-29 and HCT-116 colon cancer cells along with normal immortalized intestinal cells (IEC-6 and INT-407). *Garcinia indica* (commonly known as kokum), belonging to the *Clusiaceae* family (mangosteen family), is a tropical evergreen tree distributed in certain regions of India [133, 190, 202-206-239]. It has been used in culinary and industrial applications. This has been used for a variety of purposes, including acidulant in curries, pickles, health drinks, wine, and butter. In particular, *G. indica* has been used in traditional medicine to treat inflammation, dermatitis, and diarrhea, and to promote digestion [133, 190, 202-206-217-239]. According to several studies, various phytochemicals such as garcinol, hydroxycitric acid (HCA), cyanidin-3-sambubioside, and cyanidin-3-glucoside were isolated from *G. indica*. *G. indica* has various pharmacological activities including anticancer, antitumor, antioxidant, anti-obesity, anti-arthritis, anti-inflammatory, antibacterial, hepatoprotective, cardioprotective, antidepressant and anti-anxiety effects. These characteristics are consistent with the previously reported activity of abundant phytochemical components such as garcinol, HCA, cyanidin-3-sambubioside and cyanidin-3-glucoside isolated from *G. indica* [133, 190, 202-206]. These studies suggest the potential of *G. indica* as a promising therapeutic agent for controlling and preventing various diseases [133, 190, 202-206-217-239].

Garcinia indica is a plant native to certain regions of India. It is an underexploited slender evergreen tree and is known as wild mangosteen, kokum, and goa butter tree [133, 190, 202-206-217]. All parts of *G. indica*, i.e., fruits, leaf, seeds, etc., have been used in various culinary, industrial and pharmaceutical applications, as well as fruit drinks and food. Its pharmacological properties including antioxidant, anti-inflammatory activity, antimicrobial, anticancer , and anti-obesity effects have been reported [133, 190, 202-206-217-239].

41. *Garcinia oblongifolia* (Garcinia) belongs to the family of *Clusiaceae.* This plant has a wide range of pharmaceutical activities [133, 190, 202-206-217]. They noted very high cytotoxic activities of these metabolites in the tested MCF-7 breast cancer cell line. However, they found the higher anti-cytotoxic activity of branch as compared to other plant parts [133, 190, 202-206-217-239].

42. *Fagonia indica*, locally known as “dhamasa” is a flowering plant and belongs to the family of caltrop, *Zygophyllaceae*[133, 190, 202-206-217-239]. The aqueous extracts of *F. indica* have been found very effective against different types of cancer specifically breast cancers [133, 190, 202-206-217-239]. One of the study demonstrated significant activity against breast cancer cells line MCF-7 through an aqueous extract of *F. indica*. The family *Zygophyllaceae* has almost 22 genera and more than 250 species. *Fagonia* is an important genus of the family *Zygophyllaceae*[133, 190, 202-206-217-249]. This genus comprises abundant species, which grows in different phyto geographical regions of the world. These species grow in different environmental conditions. It is commonly known as Dhamasa, Dhamana, Sachi booti and Shoka'a and is found in deserts of Asia and Africa. The species of this family are of very high importance [133, 190, 202-206-217-239]. The presence of flavonoids, saponins, tannins, glycosides, pectin and alkaloids was confirmed by different researchers. *F. indica* is a very important medicinal plant because it has different therapeutic and traditional uses such as antidiabetic, anticancer, anti leishmanial, antipyretic, anti-inflammatory, laxative, gastroprotective, hepatoprotective and antioxidant effects [133, 190, 202-206-217-239].

43. *Artemisia annua* (*Asteraceae*) also synthesize scopoletin and 1,8-cineole compounds. Similarly, semisynthetic derivatives of artemisinin are also generated such as arteether, artemether, and artesunate. Artesunate has been studied to be a very effective anticancer compound [133, 190, 202-206-217-239]. Artesunate on 55 different cancer cell lines including leukemia, melanoma, lung cancer, colon cancer, renal cancer, ovarian cancer, and tumors of the central nervous system [133, 190, 202-206-217-239]. They suggested that artesunate was the most effective against leukemia and colon cancers. Furthermore, it was observed through these studies that the artesunate was more active than the drugs used for such cancers. The ethanolic extracts of leaves lead to growth inhibitions (57.24% and 67.07%) in HeLa and AGS cells, respectively at a concentration of 500 mg/mL [133, 190, 202-206-217-239]. Of growing interest, the plant *Artemisia annua*, known for its malarial properties, has been studied for its numerous biological activities including metabolic, anti-tumor, anti-microbial and immunomodulatory properties [133, 90, 202-206-217-239]. *Artemisia annua* is very rich in secondary metabolites such as monoterpenes, sesquiterpenes and phenolic compounds, of which the biological properties have been extensively studied [133, 190, 202-206-217-239]. *Artemisia annua* has been extensively investigated and shows promising activities: antiplasmodial, antiviral, antimicrobial, antitumor, antiinflammatory, antioxidant. Studies reported that artemisinin is the active compound of this plant especially for the antimalarial, anticancer and antitumor activity [133, 190, 202-206-217-239].

44. Gallic acid as the active component was purified from the fruit extract of *P. macrocarpa* and has demonstrated a role in the induction of apoptosis in lung cancer, leukemia, and colon adenocarcinoma cell lines [133-239]. It is a polyhydroxy phenolic compound and a natural antioxidant that can be obtained from a variety of natural products i.e., grapes, strawberries, bananas, green tea, and vegetables [133-239]. It also plays a critical role in preventing malignancy transformation and the development of cancer. Similarly, other compounds such as vinca alkaloids, podophyllotoxin, and camptothecin obtained from various plants are used for the treatment of cancer [133-239].

45. *Bacopa monnieri*: The plant *Bacopa monnieri* constitutes bacosides A and B, alkaloids, namely herpestine and brahmana, tetracyclic triterpenoid saponins, flavonoids, hersaponin, triterpenes such as bacosine, and sterols like bacostero [133-239]. A natural product, phytosterols extracted from the aerial part of the plant species *Bacopa monnieri* have anticancer activity [133-239]. The activity of stigmasterol tested on the growth of murine models of cancer, which becomes transplantable by decreasing the viable cell count, a packed cell volume, tumor volume, inhibiting EAC (Ehrlich ascites carcinoma), was investigated in vivo and increases the life expectancy of the victim, protecting the liver of the EAC tumor-bearing mice [133-239]. The antitumor mechanism functioned by the initiation of PP2A by ceramide causing apoptosis, is indicated by a structure analogous to phytosteroids [133-239].

46. Compounds having anticancer activity include terpenoids, lignans, alkaloids, and flavonoids [133-239]. Terpenoids (steroids) are the major group and widely applicable in chemotherapy cancer treatment, e.g., Taxol can be mentioned. Steroidal saponin with few steroids and their glucosides, triterpenoids, alkaloids, and flavonoids exist in *Asaparagus racemosus* species[133-239]. Shatavarin I to X (shatavarins) are the major steroidal glucosides or saponins extracted from the root. The non-polar and polar extracts from the total extracts and their formulation are capable of immune–pharmacological activity in cancer chemotherapy [133-249]. The 7,12-dimethylbenzanthracene (DMBA)-induced mammary carcinogenesis can be inhibited by the *Asparagus racemosus* plant species extract, as investigated in rats [133-249]. The compound shatavarin IV (84.69 %) with its fraction, codedAR-2B containing 5.05% shatavarin IV, is capable of cytotoxicity. Shatavarin IV from shatavarin's rich fraction has a tremendous anticancer effect in vivo and in vitro [133-249].

47. *Asclepias curassavica*: *Asclepias curassavica* constitutes a wide variety of biologically active compounds such as flavonol glycosides, carbohydrates, triterpenes flavonols, cardenolides, and amino acids [133-239]. The chemical called cardenolides has the constituents calotropin, coroglaucigenin, calactinasclepin, asclepain CI, asclepiadin CII, curassavogenin, asclepogenin, calotropagenin, uzarin, uzarigenin, uscharidin, corotoxigenin, uscharidin, calotroposide, kidjolanin, clepogenin, and desglucouzarin, which are applicable for pharmacological purposes such as anticancer, antipyretic, analgesic, antimicrobial, cardiovascular, and many other pharmacological activities [133-239]. Calotropin (a cardiac glycoside), an alcoholic extract of *Asclepias curassavica* species, has a cytotoxic effect against nasopharynx carcinoma cells[133-249]. A pronounced cytotoxicity activity against four different types of cancer cells was shown by cardenoliedes phytocompounds extracted from the aerial and root part of *Asclepias curassavica* [133-239].

48. *Tinospora cordifolia* (Amruthballi) herbal supplements have recently gained prominence due to their promising immunomodulatory, and anticancer properties [133, 190, 202-206-217-239]. Berberine (BBR) is a natural active principle with potential antitumor activity [133-249]. Significant anti-carcinogenic properties were exhibited by *Tinospora cordifolia*-derived phytocompounds including palmative, berberine, new clerodane furanoditerene glycoside, arabinogalactan, phenolic compounds and epoxy cleodane diterpene [133-239]. Cancer is an extreme metabolic disorder that has seen significant advancement in treatment plans and preventative remedies. It is also called neoplastic disease, characterized by the uncontrolled proliferation followed by the constant multiplication of human cells [133-239]. This leads to the development of tumors of harmful malignant cells with the capacity to be metastatic [133-239]. These plant derived natural resources have proved to be non-toxic and are potential modes of cancer management and therapy [133-239]. *Tinospora cordifolia* extracts demonstrated the potent analogs possess multiple effects on numerous molecular targets of malignant cells [133-239]. These analogs can be developed as non-toxic and therapeutically effective drug products to combat various malignancies [133-239]. *T. cordifolia* extract is used in brain, intestine, breast, head, vaginal, prostate and neck cancer [133-239]. The methanolic, aqueous, and ethanolic extracts of stems caused programmed cell death inhibiting apoptosis. The in vitro cytotoxic effect of DMSO and ethanolic extract from *T. cordifolia* stems against murine monocyte/-macrophages (J-774-A-1), human melanoma (A-375) and human breast cancer (MCF-7) cell lines was determined by the colorimetric MTT assay and TBE method [133-239].

49. *Annona squamosa* or custard apple, a small green tree, 6–8 m tall, is found in deciduous forests [133-239]. The medical applications are constipation, dysentery, antibacterial infection, epilepsy, dysuria, cardiac problems, hemorrhage, abortifacient properties, ulcers, fever, antifertility, antitumor, and worm infection treatments [133-239]. Squamostatin and squamocin extracted from *A. squamosa* seeds compounds of acetogenins showed a cytotoxic effect. By the activation of caspase 3, squamocin prevents human leukemia cell line proliferation and leads to apoptosis [133-

239]. Another part of acetogenin called ascimicin can inhibit and is cytotoxic to 9KB, A549, HT-29, and 9ASK tumor cells [133-239]. To treat chronic diseases such as; skin complaints, insect bites, and cancerous tumors, all parts of *A. squamosa* were used in traditional medicine [133-239]. The phytochemicals existing in the leaves are anti-ulcer, anti-diabetic, anti-fungal, anti-inflammatory, anti-depressant, and antimicrobia [133-249]. The chemical compounds constituted in *Annona squamosa* are phenolic compounds, terpenoids, alkaloids, flavonoids, glycoside, saponin, and steroids which are all-natural products [133-239]. The alkaloids obtained from the aerial part showed anticancer. activity in 0.01 to 100 /g/mL concentration ranges on liver, breast, and colon cancer cell lines. Isoquinoline alkaloid extract possesses a high anticancer activity against colon cancer cells (HCT116) and human breast cancer cells (MCF-7) [133-239].

50. *Arnebia euchroma*: *Arnebia euchroma* is an endangered medicinal plant that grows naturally in extreme cold and arid environments in the Himalayas. Phytochemicals constituted in the *Arnebia euchroma* which have great importance in anti-immune deficiency, anti-microbial and anticancer activity are arnebin-7, acetyl-shikonin, isovaleryl-shikonin, shikonincoumarins, B-hydroxyisovaleryl- shikonin, deoxy-shikonin, β-β-di-methylacryl-shikonin, iso-butyryi-shikonin, stigma sterol, arnebinone, and isobutyl-shikonin [133-239]. A secondary metabolite of *Arnebia euchroma* called shikonin, found mainly in the root, prevents a compound that malfunctions and deletes the process of action in the cell, and causing carcinomas [133-239]. The phytochemicals existing in the *Arnebia euchroma* plant are utilized for treating carcinogenic diseases. The phytochemicals utilized for the treatment are acetyl-shikonin, teracryl-shikonin, and β-β, -dimethylacryl-shikonin[133-239]. The roots of *Arnebia euchroma* also constitute a dimeric naphthoquinone compound called Shikometabolin H, epoxyarnebinol, and 2,3-secodiplopterol dioic acid helps to reduce the STAT3 transcriptions, the activators of human carcinogenic cells, and increase the antitumor immunity [133-239].

Arnebia euchroma (Royle) Johnston, commonly known as Pink Arnebia (family: *Boraginaceae*), is an endangered herb of medicinal value which grows naturally on the slopes in cold desert Himalaya at an altitude ranging from 3,200 to 4,500 m above mean sea level (amsl). The roots of this plant have anti-inflammatory, antimicrobial, and antipyretic properties and are traditionally used in curing eye diseases, cancer, cuts and wounds, and tooth- and earache. Roots of A. euchroma also produce various secondary metabolites including napthoquinone pigments, meroterpenoids, and arnebinols.

51. *Asaparagus racemosus*: *Asparagus racemosus* (A. racemosus) belongs to family Liliaceae and commonly known as Satawar, Satamuli, Satavari found at low altitudes throughout India. The dried roots of the plant are used as drug. The roots are said to be tonic and diuretic and galactgogue, the drug has antitumor, ulcer healing effect probably via strenthening the mucosal resistance or cytoprotection. Compounds having anticancer activity include terpenoids, lignans, alkaloids, and flavonoids world [133-239]. Terpenoids (steroids) are the major group and widely applicable in chemotherapy cancer treatment [133-239]. Steroidal saponin with few steroids and their glucosides, triterpenoids, alkaloids, and flavonoids exist in *Asaparagus racemosus* species [133-239]. Shatavarin I to X (shatavarins) are the major steroidal glucosides or saponins extracted from the root [133-239]. The non-polar and polar extracts from the total extracts and their formulation are capable of immune–pharmacological activity in cancer chemotherapy[133-239]. The 7,12-dimethylbenzanthracene (DMBA)-induced mammary carcinogenesis can be inhibited by the *Asparagus racemosus* plant species extract, as investigated in rats [133-239]. The compound shatavarin IV (84.69 %) with its fraction, codedAR-2B containing 5.05% shatavarin IV, is capable of cytotoxicity [133-239]. Shatavarin IV from shatavarin's rich fraction has a tremendous anticancer effect in vivo and in vitro [133-239].

52. *Camptotheca acuminata* Decne (Nyssaceae): Camptothecin derivatives: In the early 1960's a phytochemical called camptothecin was extracted from a Chinese ornamental tree called *Camptotheca acuminata* Decne (Nyssaceae) species and used as an anticancer agent [133-239]. This shows the advancements in anticancer drug development[133-249]. An extract camptothecin from *Camptotheca acuminata* species showed high anti-tumor and anticancer activity out of 1000 different plant extracts tested for the same activities [133-239]. This is considered as the unique character of the *Camptotheca acuminata* plant species. The active chemicals isolated from plant were identified as camptothecin, declared in the 1970s by the NCI (National Cancer Institute) as a candidate for clinical trials. However, it displayed a flaw in bladder toxicity and was no longer in use [133-239]. SmithKline Beecham (now Glaxo SmithKline) develops Topotecan (Hycamtin) and effective camptothecin derivatives, and Japanese company Yakult Honsha, developed Irinotecan, which are more effective than camptothecin. Irinotecan is utilized to treat colorectal cancers, whereas lung and ovarian cancer are treated by topotecan [133-239]. A natural quinoline, camptothecin (CPT) has anticancer activity and inhibits Topoisomerases 1 [133-239]. It is also used as a chemotherapeutic drug to treat tumors and metastatic colorectal cancer and is known as a bio-available derivative of irinotecan [133-239]. Topotecan is also a CPT derivative that treats ovarian cancer and small cell lung cancer and breast cancer [133-239].

53. The first isolated compound from *Taxus brevifolia* Nutt. (*Taxaceae*) bark was taxol or Paclitaxel. Various parts of Taxus species, such as *T. canadensis Marshall, T. baccata L.,* and *T. brevifolia*, have been used for anticancer activity, for instance for the treatment of ovarian and breast cancers [133-239]. In the ancient Indian holistic and natural medicine called *Ayurveda*, the leaves of *T. baccata* were used in the treatment of cancer [133-249]. Taxanes from *T. wallichiana* plant species have anti-inflammatory, analgesic, antipyretic, antiallergic, immunomodulatory, anticonvulsant, anti-conceptive, anti-osteoporotic, antiplatelet, antifungal, antibacterial activities, as well as antispasmodic effects [133-239]. A Taxus species constituent, paclitaxel, is found in the leaves. Baccatins exist in high amounts and are converted to paclitaxel and active paclitaxel analogs such as docetaxel or Taxotere, which are a significant source and major category of the drugs. These drugs are utilized to treat Kaposi sarcoma, lung cancer, ovarian and breast cancer [133-239]. Paclitaxel also has the potential to treat non-cancerous diseases, such as rheumatoid arthritis, psoriasis, and multiple sclerosis [133-239]. Breast cancer is mainly treated using a semi-synthetic derivative of docetaxel [133-239].

54. ***Podophyllum peltatum*** : The derivatives of podophyllotoxin (PTOX) such as Etoposide, teniposide, and etoposide phosphate, are used for anticancer chemotherapy that is extracted from *Podophyllum peltatum* L. (Family-*Berberidaceae*) and *Podophyllum emodi* (syn. P. hexandrum) [133-239]. PTOX is an aryltetralin-lignan with strong cytotoxic activity. The podophyllotoxin derivatives have antiproliferative activity against germ cell tumors, small cell and non-small cell lung cancers. The 4-aminoalkyl-40-O-demethyl-4-desoxypodophyllotoxin, TOP-53, is a podophyllotoxin derivative with antitumor activity, and anticancer activity against lung cancer and lung metastatic cancer [133-249]. The cytotoxicity activity of TOP-53 was determined using IC_{50} and showed 0.016–0.37 /g/mL against murine tumors and 0.26–8.9 /g/mL against human non-small cell lung cancer (NSCLC) cell lines. TOP-53 podophyllotoxin derivative is also potent in antitumor activity for lung localized tumors and metastatic tumors in the lungs [133-239]. These derivatives prevent the polymerization of tubulin and thereby, could induce cell cycle arrest at mitosis and inhibit the formation of the mitotic-spindles microtubules [133-239].

55. ***Annona muricata***: This is a scientific name of Graviola, which contains acetogenins having huge medicinal importance that hinder the production of ATP (Adenosine Triphosphate) in human cells, and will have a significant impact in the eradication of cancer world [133-239]. *Annona muricata* is extracted from the seeds, bark, fruit, and leaves [133-249]. In addition, acetogenin has a chemotherapeutic ability against multiple drug-resistant cancers world [133-249]. Some acetogenins are toxic for specific cancer cell lines, such as carcinoma tumors, prostatic adenocarcinoma, lung solid human breast cancer, human lymphoma, pancreatic carcinoma, multiple-drug resistant human breast adenocarcinoma, liver cancer, human lymphoma, and colonic adenocarcinoma. The ethanolic extract of *A. muricata* was tested for anticancer activity against MDA and SKBR3 breast cancer cell lines using the MTT assay method [133-239]. The anticancer property of water and ethanolic extracts of *A. muricata* against EACC (Esophageal Adenoid Cystic Carcinoma) was tested using Trypan blue-exclusion assay. An ethanolic leaves extract of *A. muricata* showed 32.9% inhibition of cell death at a concentration of 250 /g/mL and 100% maximum inhibition of cell death at a concentration of 750 /g/mL, even though the water– leaves extract of different concentrations had no inhibition effect on the cancer cell line. IC_{50} of ethanolic extracts was determined to be 335.85 /g/mL [133-239].

56. ***Gloriosa superba*** L. (Family: *Colchicaceae*) is herbaceous perennial semi-woody climber native of tropical Asia and Africa [133, 190, 200, 202-207-217-239]. In Karnataka, it is generally found growing all along the Western Ghats. It is also found growing in Madagascar, Sri Lanka, Indo-China and in the adjacent islands. It is also known by its trade name 'Glory lily'; in English it is known as 'Malabar glory lily' and, in Hindi and Sanskrit as 'Kalihari' and 'Agnisikha [133, 190, 200, 202-207-217-239]. The tubers of the plant are traditionally used to treat chronic ulcers, colic, bruises and sprains, haemorrhoids, leprosy, cancer, and also as a labor pain inducer. The leaves are employed to treat piles, ulcers and to expel the placenta. The seeds are used to cure medical conditions in relation to cancer [133, 190, 200, 202-207-217-239]. The medicinal value of the Glory lily is particularly due to the alkaloids especially colchicine, thiocolchicine and gloriosine as well as to the presence of 10 non-alkaloidal compounds viz. β-sitosterol, stigmasterol, chelidonic acid, luteolin, etc. Colchicine is used as a mitosis-arresting agent which is used in cancer treatment and diabetics in addition to promoting polyploidy in agricultural crops [133, 190, 200, 202-207-217-239]. It is also used to treat cancer, rheumatism and cardiovascular diseases. Colchicine is found in significant quantities only in two plants viz, *Colchicum autumnale* and *Gloriosa* sp [133, 190, 200, 202-207-217]. In *G. superba*, colchicine yield ranges from 0.15% - 0.3% in the rhizomes, and 0.7% - 0.9% in the seeds [133, 190, 200, 202-207-217]. The discovery of high colchicine content in this plant increased its demand in domestic and worldwide markets [133, 190, 200, 202-207-217-239].

57. ***Curcuma mutabilis*** was collected from the Nilambur forest, Malappuram district of Kerala state, India [133, 190, 200, 208-217-239]. The anticancer potential of petroleum ether extract from *C. mutabilis* rhizome (CMRP) and a novel labdane diterpenoid, (*E*)-14, 15-epoxylabda-8(17), 12-dien-16-al (Cm epoxide) isolated. CMRP was found to be a mixture of potent bioactive compounds including Cmepoxide [133, 190, 200, 208-217-239]. Both the extract and the compound displayed superior anti-proliferative activity against several human cancer cell lines, without any display of

cytotoxicity towards normal human cells such as peripheral blood derived lymphocytes and erythrocytes [133, 190, 200, 208-217-239].

58. Polyphenolic compounds include flavonoids, tannins, curcumin, resveratrol and gallacatechins are all considered to be anticancer compounds. Resveratrol can be found in foods including peanuts, grapes and red wine [133, 190, 200, 208-217-239]. Gallacatechins are present in green tea. It is thought including polyphenols in a person's diet can improve health and reduce risk of cancers by being natural antioxidants [133, 190, 200, 208-217-239]. The cytotoxicity of polyphenols on a range of cancer cells has been demonstrated and their antioxidant properties determined [133, 190, 200, 208-217]. Polyphenols are thought to have apoptosis inducing properties showing anticancer properties which can be utilized [133, 190, 200, 208-217-249]. The mechanism in which polyphenols are thought to carry out apoptosis initiation is through regulating the mobilization of copper ions which are bound to chromatin inducing DNA fragmentation [133, 190, 200, 208-217-239]. In the presence of Cu(II), resveratrol was seen to be capable of DNA degradation. Other properties plant polyphenols showed their ability to interfere with proteins which are present in cancer cells and promoting their growth world [133-249]. Cancer agents may be altered through the polyphenol regulating acetylation, methylation or phosphorylation by direct bonding [133, 190, 200, 208-217-239]. For example, curcumin treated cancer cells in various cells lines have shown suppression of the Tumor Necrosis Factor (TNF) expression through interaction with various stimuli [133, 190, 200, 208-217-239].

59. Flavonoids are from the polyphenolic compounds and constitute a large family of plant secondary metabolites with 10,000 known structures [133, 190, 200, 208-217-239]. There is a high content of flavonoid compounds such as anthocyanins, flavones, flavonols, chalcones and many more which can be found in the seeds of plant [3-9-200]. Purified flavonoids have also shown anticancer activities against other human cancers including; hepatoma (Hep-G2), cervical carcinoma (Hela) and breast cancer (MCF-7) [133, 190, 200, 208-217-239]. The flavonoids extracted from *Erythrina suberosa* stem bark (4'-Methoxy licoflavanone (MLF) and *Alpinumi soflavone* (AIF)) were shown to have cytotoxic effects in HL-60 cells (human leukaemia) 12 [133, 190, 200, 208-217]. MLF and AIF induced apoptosis through intrinsic and extrinsic signaling pathways. Other studies have looked at flavonoid extracts from fern species and found that even in low concentrations, they still demonstrated high percentage of anticancer activity [133, 190, 200, 208-217-239]. Also, these flavonoids inhibit the expression of NF-κB which is needed for cancer cell survival and angiogenesis and proliferation [133, 190, 200, 208-217-239].

60. Brassinosteroids (BRs) are naturally occurring compounds found in plants which play roles in hormone signaling to regulate growth and differentiation of cells, elongation of stem, root cells and other roles such as resistance and tolerance against disease and stress [133, 190, 200, 209-217-239]. Also, BRs are used for regulation of plant senescence. Two natural BRs have been used in investigations with cancerous cells to demonstrate the anticancer properties that these compounds possess [133, 190, 200, 209-217-239]. 28-homocastasterone (28-homoCS) and 24-epibrassinolide (24-epiBL) have demonstrated anticancer effects on various cancer cell lines 25-27 and proven to be effective at micromolar concentrations [133, 190, 200, 209-217]. A characteristic of cancer cells is that they do not naturally undergo apoptosis and proliferate indefinitely [133-239]. BRs can induce responses necessary for growth inhibition and induce apoptosis by interacting with the cell cycle [133, 190, 200, 209-217-239]. Along with their anticancer properties, BRs generate different responses in normal and cancer cells [133, 190, 200, 209-217-239].

61. Plant-derived drugs are desired for anticancer treatment as they are natural and readily available [133-239]. Plant-derived drugs can fall under four classes of drugs with the following activities; methytransferase inhibitors, DNA damage preventive drugs or antioxidants, histone deacetylases (HDAC) inhibitors and mitotic disruptors [133-239]. Compounds including sulforaphane, isothiocyanates, isoflavones and pomiferin are considered to be HDAC inhibitors. They inhibit the activity of carcinogenic proteins. Plant-derived compounds which showed inhibition of HDAC can enhance chemotherapeutic sensitivity in human cancers [133-239]. Derivatives of vinca alkaloids, vincristine, vinblastine, vinorelbine, vindesine and vinflunine are drugs which will inhibit the dynamics of microtubules by binding to β-tubulin [133-239]. Taxanes such as paclitaxel and its analogue docetaxel are also microtubule disruptors. These compounds inhibit cell cycle phase transitions from metaphase to anaphase causing cell cycle arrest and apoptosis [133-239]. Replication of cancer cells is reduced by paclitaxel as it stabilizes or polymerizes microtubules in the cells [133-249]. Paclitaxel was one of the first drugs to have a huge impact on cancer treatment and vincristine and vinblastine were two of the initial drugs to be isolated [133-239]. Combinations of drugs derived from vinca alkaloids, Taxus diterpenes, Podiphyllum lignans and Camptotheca alkaloids in plant extracts may enhance their anticancer effects and improve their efficacy as therapeutic agents [133-249]. The investigation showed that the plant extracts with a combination of anticancer compounds were able to have killing activity which was specific to cancer cells and showed no effect on normal human lymphocytes and fibroblasts [133-239]. This makes plant extracts more desirable as therapeutic agents than those that are chemically derived which cause toxic complications in cancer treatment world [133-239]. The plant extracts induced apoptosis which was demonstrated by an increased sub-G1 phase population of

cells with lower DNA content and condensation of chromatin. Also an increase in caspase 3 activation was seen after extract treatment which is a key stage in apoptotic cell death [133-239].

62. The field of nanotechnology is the use of nanoparticles (NPs), as a delivery system for drugs to reach target sites [133-260]. Some compounds that have demonstrated anticancer activities may be limited in their clinical development due to the need for high dosages. Success has also been seen with the drug quercetin using super-paramagnetic magnetite NPs against breast cancer (MCF-7) cell lines world [133-249]. This research demonstrated enhanced activities of the NPs in cytotoxicity of MCF-7 cells compared to free or pure quercetin world [133-270]. Nanoparticles (NPs), in their use for anticancer treatment are of growing interest and showed promise as a natural alternative to current treatments [133-239]. Jyoti *et al*., 2015 world [133-249] investigated the noscapine analogue 9-bromo-noscapine in formulation with nanostructure lipid particles [133-249]. This study showed enhanced cytotoxicity and apoptosis in lung cancer cell lines with increased uptake of drug into cancerous cells of the formulated noscapine analogue compared to the free drug world [133-239].

63. Grape stem extracts :With successful clinical trials drugs being developed from plant origins are popular for clinical development [133-239]. Their non-toxic effects on normal cells and their cytotoxic effects on cancer cells put them in high demand [133-239]. There is a huge demand for medicinal plants in developing countries putting high pressure on the plant populations. Many medicinal plants are cultivated from wild populations for informal trade but this cultivation is not regulated [133-239]. Grape stem extracts have demonstrated to have antioxidant properties, prevent DNA damage from reactive oxygen species and shown anti-carcinogenic potential against an array of cancer cell lines from cervical cancer, breast cancer and thyroid cancer [133-239].

64. *Curcuma longa* (turmeric, Haldi): In folk medicine, turmeric has been used in therapeutic preparations over the centuries in different parts of the world [133-239]. In Ayurvedic and Chinese traditional medicine practices, turmeric is thought to have many medicinal properties including strengthening the overall energy of the body, relieving gas, dispelling worms, improving digestion, regulating menstruation, dissolving gallstones, and relieving arthritis [133-239]. *Curcuma longa*, also called as turmeric and contain curcumin as an ingredient, which is reported as potent anticancer agent and composed of the phenolic content [133-239]. The major active compound responsible for the pharmacodynamic action is the polyphenol curcumin [133-239]. Additionally, this natural polyphenol has been described as an anticancer agent, both in vitro and in vivo on a wide range of cancer types, such as colon, pancreatic, liver, cervical, pulmonary, thymic, brain, breast and bone cancer [133-239]. Curcumin, the main component of C. longa, plays an important role in the therapeutic activities of *C. longa*. Curcumin showed anticancer and anti-inflammatory activities as reported by many different studies. Cyclooxygenase (COX)-2 plays a vital role in the formation of colon cancer. Curcumin may thus play an important role in the prevention of colon cancer. Furthermore, the anticancer effects of curcumin on human breast cancer cell lines (MCF-7) were assessed through lactate dehydrogenase and 3-(4,5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H-tetrazolium bromide assays to assess cytotoxicity and cell viability, respectively [133-239]. The results showed that curcumin induced cytotoxicity and inhibited cells in a time- and concentration-dependent manner[133-239].

Curcuma longa (turmeric, Haldi) belonging to ginger family *Zingiberaceae*. Curcumin being the main constituent of *C. longa* is responsible for its beneficial activities [133-239]. Curcumin displays anticancer, antidiabetic, and anti-inflammatory activities. Cyclooxygenase (C0X-2) has a vital role in initiation of colon cancer. The HT-29 colon cancer. Cells treated with different concentrations of curcumin decreased expression of COX-2 [133-239]. Curcumin aiding in prevention of colon cancer and breast cancer cell lines (MCF-7) was assessed through SRB and MTT assays for cytotoxicity and cell viability, which exhibited augmented caspase 3/9 activity and initiation of apoptosis indicating down- regulation of miR-21 the expression of miR-21 in MCF-7 cells by up-regulation of PTEN/Akt signalling pathway [133-239]. Curcumin's anticancer potential seen through decrease growth in numerous tumor cell types. Curcumin down-regulate the expression lysyl oxidase (LOX), epidermal growth receptor 1 (EGR-1), activator protein 1 (AP-1), NF-kappa B, cycloxygenase 2 (COX2), matrix metallopeptidase 9 (MMP- (HER2), nitric oxide synthase (NOS) genes [133-239]. Turmeric suppresses c-Jun N-terminal kinase, protein tyrosine kinases, and protein serine/threonine kinases activities along with its gene expression impact. Turmeric limited tumor cell raid and metastasis by suppressing MMP-2 activity and HEp2 (epidermoid carcinoma cell line) cell raid in vitro [133-239].

65. Soursop (*Annona muricata)* is a fruit found mainly in the rainforest of Southeast Asia, South America, and Africa [133-239]. It is green with a prickly outer texture, a soft and creamy internal texture [1-17, 18-200]. The taste is commonly compared to a strawberry or pineapple. Research also showed that soursop has natural cytotoxicity effects [133-249]. For cancer patients, chemotherapy and radiation therapy are cytotoxic therapies (meaning they kill cancer cells) [133-239].The fruit also has an ability to reduce the cell growth on a number of cancer cell lines, including breast, lung, pancreatic, prostate, ovarian, and colorectal [133-239]. Ramphal (*Annona reticulata* L.) is one of the traditionally

important plants used for the treatment of various ailments, including cancer [133-239]. Ramphal may with other types of fruits in the *Annona* family, such as custard apple (*Annona sqamosa*) and sweetsop [133-239]. Annonaceous acetogenins are a group of constituents obtained from plants belonging to *Annonaceae*, having potentials of anti-neoplastic agents [133-239].

66. *Acorus calamus* (Bauj) belongs to the *Acoraceae* family. A phytochemical study of *A. calamus* rhizomes resulted in the separation of newer compounds like zingiberene and safrol [133-239]. The cytotoxic action of these bioactive compounds was shown by 3-(4, 5-dimethylthiazol-2-yl)− 2, 5-diphenyltetrazolium bromide [MTT] assay in different human cancer cell lines [133-239].

67. *Ajuga parviflora* (Neelkanthi) is a flowering plant belonging to *Lamiaceae* family. Conventionally being used as a medicine for curing malaria, oedema, fungal, and other microbes [133-239].The cytotoxicity action of aqueous and methanol extracts from *A. parviflora* leaves was explored against leukaemia murine [L-1210] and human chronic myelogenous leukaemia [K-562] cell lines [133-239].

68. *Aloe vera* belonging to *Asphodelaceae* family possesses wide range of pharmaceutical activities [133-239]. The leaves of *A. vera* showed the presence of secondary metabolites like doxorubicin, butyl-p-tolyl sulphide, lupeol isobarbaloin, 6- methyl-4-chromanone, barbaloin, lectin, emodin, aloe-emodin, aloesin, acemannan, anthrone-C-glycosides, sitasterol alexin-B, campesterol and butylated hydroxyanisole [133-239]. Other isolated compounds from *A. vera* leaves were examined against ovarian cancer [OVCAR-3], human colon cancer [HCT-116 and IGROV-1], and breast cancer [MCF-7] cell lines through MTT assay to assess in vitro cytotoxic activity [133-239].

69. ***Asparagus racemosus*** (Satavari) belongs to Asparagus genus [133-239]. The kaempferol of *A. racemosus* displays encouraging actions in the experimental HT-29 and HCT-116 colon cancer cells along with regular immortalized intestinal cells [IEC-6 and INT-407] [133-239]. The root extract of *A. racemosus* helped in tyrosin, histone arginine and shatawarine isolation [133-239]. The chloroform, methanol, ethyl acetate, DMSO, and water extracts of *A. racemosus* tuber, root and leaves showed antitumor growth hang up of human colon cancer cells through MTT test [133-239].

70. *Artemisia* herba-alba (white wormwood) belongs to family *Asteraceae,* genus Artemisia [133-239]. The whole plant and specially leaf extract of *A. herba-alba* showed high anti-cancerous activity against 3 human tumor cell lines like human bladder carcinoma, human laryngeal carcinoma, human myelogenous leukaemia (K-562) cells. The phenol complexes perceived in Indian *A. herba-alba* are herbolide, torrentin, chlorogenic acid, dihydroreynosin, isophorone, rutin, schaftoside, isoschaftoside, vicenin-2, 11-epitaurin, vachanic acid, α,13-dihydrocostunolide, 3-Epi-erivanin, 1-b - hydroxy colartin, pinocarveol, artemisia ketone, deacetyl- torrentin, piperitone and herbalbin[133-239]. The quercetin and apigenin administration in syngeneic mice repressed the development and metastatic budding of melanoma (B-16-BL-6) cells in vitro [133-239]. The chemopreventive activities of chlorogenic acid indicated possible role of microsomal glucose-6- phosphate translocase in the brain tumours growth [133-239].

71. *Boswellia serrata* (Guggul) is a member of the family *Burseraceae* [133-239]. *B. serrata* is frequently used to cure inflammatory diseases i.e., viral, fungal, and asthma [133-239]. The oleo gum resin extract of *B. serrata* had more anticancer activity against 3 human cancer cell lines like human laryngeal carcinoma, bladder carcinoma, human myelogenous leukaemia cells [133-239].

72. *Centella asiatica* (Brahmi) belonging to *Apiaceae* family is a traditional medicinal plant of India and China [133-239].The ethyl acetate, aqueous, acetone and methanol extracts of *C. asiatica* leaves possesses alkaloids that were assessed for their cytotoxicity effect in human lung epithelial carcinoma (A-549) cell line with the help of colorimetric MTT assay [133-239]. *C. asiatica* leaf was physiologically active and had a significant cytotoxic impact. After 48 h of incubation, the leaf ethyl acetate extract of *C. asiatica* displayed the maximum cytotoxic activity, with an IC_{50} of 82 g/mL [133-239]. Some fractions of *C. asiatica* suppressed altered cell lines proliferation like *Ehrlich ascites*, Dalton's lymphoma and ascites tumor cells dose-dependently. In long-term culture, partially purified fractions of *C. asiatica* greatly inhibited the propagation of mouse lung fibroblast cells [133-239]. The direct inhibition of DNA synthesis after oral intake of *C. asiatica* extracts decelerated solid and ascites tumors development to improve life time of tumor mice [133-239].

73. *Catharanthus roseus* (Sadabahar) belongs to family *Apocynaceae* is native to India, and China. Extracts from *C. roseus* are traditionally used to cure asthma, leukaemia, insomnia, cancer, and diabetes [133-239]. The methanolic extracts of *C. roseus* exhibited note- worthy anticancer action on the (Hep-2) cell line. These extracts inhibited cells significantly, lowering viable cell count. The MTT assay was used to test the cytotoxicity effect of ethanolic extract of *C. roseus* flower in human epithelial cervical carcinoma cell line (HeLa). The Catharanthus alkaloids, also known as Vinca

alkaloids (CAs or VAs) have covered approximately 130 terpenoid indole alkaloids [133-239]. Vinblastine (VBL) was the very first alkaloid separated from the periwinkle plant of Madagascar in the 1950s. Vincristine (VCR) and its derivatives are hetero-dimeric (indoloid) alkaloids formed amid the biosynthesis of catharanthine and vindoline, present in pink *Catharanthus roseus* [133-239]. This group is comprised of vinblastine, vincristine, anhydro-vinblastine, the semisynthetic sub-ordinates vindesine (VDS), vinorelbine (VRL), and vinflunine (VFN) (the fluorinated analogue of vinorelbine). Since 2008, a novel synthetic vinca alkaloid known as vinflunine has been licensed for therapeutic use in Europe. Vinblastine and vincristine are now utilized for the treatment of different cancers in the US and other nations, whereas the semisynthetic vindesine is currently in phase II clinical trials for the treatment of hepatocellular cancers, leukemia and non-small cell lung cancer in South Africa [133-239]. The mechanism of the cytotoxic activity of the Catharanthus alkaloids is related to their impact on the microtubules. Vinca alkaloids (CAs or VAs) are frequently utilized as anticancer medications, either alone or in combination with other medicines, to treat a number of cancers, such as breast cancer, osteosarcoma, and acute lymphocytic leukemia [133-239].

74. *Dioscorea bulbifera* (Air Potato) belonging to family *Dioscoreaceae* has 13 species globally [133-239]. It is mostly employed in India and China as traditional medicine for its anticancer and antidiabetic effects. *D. bulbifera* possesses significant secondary metabolites such as diosgenin, kaempferol-3, 5- dimethyl ether, lutein, zeaxanthin, neoxanthins, mono-arachidin, behenic acid, demethyl batatasin-IV, diosbulbin-B- d -F, docosyl ferulate, tristin, protocatechuic acid, adenosine, stigmasterol, azelaic acid and caryatin[133-239]. Aqueous, methanolic and ethanolic extracts of *D. bulbifera* exhibited likely anticancer effect against human gastric (BGC-823), human liver carcinoma (HepG-2 and SMMC-7721), human oesophagus adenocarcinoma (CaEs- 17) cell lines) and human colon adenocarcinoma (LoVo and SW-116) [133-239].

75. *Saussurea costus* (kuth/ Indian costus) belonging to the family *Asteraceae* [133-249]. The leaves and root of *S. costus* are potentially used traditionally in North Korea, Japan, China and India for cancer, diabetes, fungal, microbial, sore throat, inflammation, and cough [133-239]. *S. costus* possesses many biologically active isolated compounds like naringenin, vanillin, chlorogenic acid, kaempferol, ferulic acid, syringic acid, ellagic acid, taxifolin, methyl gallate, cinnamic acid, pyro-catechol, doconexent, and butanedioic acid [133-239]. The anticancer activity of *S. costus* reduced PKC improvement of matrix metal- lopeptidases (MmP-9 and MmP-2) causing death of HT-80 cells dose- dependently [133-239].

76. *Taxus bacata* belonging to family *Taxaceae* have anticancer, antimalarial, antiparasitic, antifungal, analgesic, antibacterial, anti-inflammatory, antimicrobial, anti-nocieptive, aphro-disiac, antipyretic, antirheumatic, anti-spasmodic, antioxidant, and anticon- vulsance effects [133-239]. In vitro and in vivo researches exposed that oridonin persuades apoptosis in a wide range of cancer, including hepatocellular, cutaneous, colorectal, gallbladder, breast, gastric, and pancreatic malignancies [133-239]. The MTT test was used to assess the cytotoxicity of *T. bacata* aqueous and aqueous methanol extracts against human colon cancer (HCT-116) cell lines [133-239].

77. *Withanaia somnifera* (Ashwagandha) belonging to family *Solanaceae* is grown in India, China, Japan, Europe and Asia and frequently used in cancer and diabetes [133-239]. The presence of these substances (withanolides, anahygrine, withananine, anaferine, withanine, *β*-sisterol, tropanol, chlorogenic acid, somniferiene, cysteine, scopoletin and somniferimine) contributes to anticancer and antidiabetic actions [133-239]. The hydroalcoholic extract has the highest scavenging activity when compared to the ethanolic extract [133-239]. The cytotoxicity of ethanolic, aqueous and hydro-alcoholic extracts of *W. somnifera* root, stem, and leaves on Hep-2 cells was examined with the MTT assay and the TBE method Hydro alcoholic (IC50 = 55 g/mL) and ethanolic (IC_{50} = 69 g/mL) extracts were determined to be the most active[133-239].

78. *Andrographis paniculata* is a robust chemoprotective drug showing effect against many viral and neoplastic agents as it can trigger both types of immune response [133-239]. Andrographolide being cytotoxic to cancer cells like KB human epidermoid cancer cells, MCF-7 breast cancer cells, P388 lympho cytic leukaemia cells, and HCT-116 colon cancer cells [133-239]. Andrographolide inhibits colon cancer cell line HT 29 growth, promotes human peripheral blood lymphocytes proliferation as well as division along with pro-differentiative actions in M1 murine myeloid leukaemia cell line [133-239]. *Andrographis paniculata* Wall (family *Acanthaceae*) is one of the most popular medicinal plants used traditionally for the treatment of array of diseases such as cancer, diabetes, high blood pressure, ulcer, leprosy, bronchitis, skin diseases, flatulence, colic, influenza, dysentery, dyspepsia and malaria for centuries in Asia, America and Africa continents [133-239]. It possesses several photochemical constituents with unique and interesting biological properties [133-239]. Ethanol extract of *A. paniculata* leaf has inhibition concentration (IC_{50}) for IMR-32 (M2 subtype mRNA) and human colorectal adenoma–carcinoma (HT-29 cell lines) at 200 /g/mL, whereas other extracts have 50% inhibition effect at 250/g/mL concentration for HT-29 cell lines. Anticancer activity of water, ethanol, and acetone

extracts of *A. paniculata* leaves against HT-29 cancer cell lines had a 50% inhibition at 200 /g/mL concentration [133-239].

79. *Phyllanthus amarus:*** The oral intake of *Phyllanthus amarus* extract greatly improved life duration and decreased tumor size in Dalton's lymphoma ascites and Erlich ascites carcinoma affected mice [133-239]. This plant's chemoprotective qualities may be connected to its capacity to suppress carcinogenic chemical metabolic activation, and interfere with DNA repair [133-239]. *Phyllanthus amarus* is an important plant of Indian *Ayurvedic* system of medicine which is used in the problems of cancer, stomach, genitourinary system, liver, kidney and spleen [133-239]. It is bitter, astringent, stomachic, diuretic, febrifuge and antiseptic [133-239]. The whole plant is used in gonorrhea, menorrhagia and other genital affections. It is useful in gastropathy, diarrhoea, dysentery, intermittent fevers, ophthalmopathy, scabies, ulcers and wounds [133-239].

80. Viscotoxins (VT) and lectins collected from the mistletoe plant (Viscum collection), constitute another group of phytocompounds with cytotoxic activity [133-239]. Viscotoxins are obtained from the extracts isolated from the common mistletoe plant. Viscotoxins are members of the thionin family type III and are characterized by three disulfide bridges [133-239]. They are cationic proteins, rich in cysteine, and comprising of 46 amino acid residues with six isomers, three of which are viscotoxin A2, A3 and B. Viscotoxins can be found inside the leaves and stems of the mistletoe plant. As viscotoxins are hydrophilic, they are present in the aqueous *Viscum album* L. extracts [133-239].

81. *Punica granatum* L. (Pomegranate) *(Lythraceae*, subfamily *Punicaceae*) is one of the important medicinal plant [133, 190, 200, 235-238-249]. Pomegranate components have antioxidant, anti-carcinogenic and anti-inflammatory components, which is effective on prevention, treatment of cancer, other chronic and infection diseases [133, 190, 200, 235-239]. The use of the pomegranate juice, peel and oil has been indicated that pomegranate have anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion and angiogenesis [133-239-239]. These may be related to anti-inflammatory effects of pomegranate. The phytochemistry and pharmacological actions of pomegranate properties indicated a wide variety of clinical usage for the cancer prevention, treatment, and also other diseases where chronic inflammation is reliable to play a main etiologic role [133, 190, 200, 235-238-239]. The most components of the pomegranates are tannin and polyphenolics [133, 190, 200, 235-238]. Phytochemical analyses indicated that pomegranate peels possess active inhibitors, including phenolics and flavonoids [133-239]. Pomegranate peel has ellagitannins, ellagic acid, gallic acid, hydroxybenzoic acids such as ellagic acid, gallagic acid, and ellagic acid glycosides [133-249]. Punicalagin is the major bioactive component of pomegranate peel [133-239]. Anthocyanidins are mainly contained cyanidin, pelargonidin and delphinidin and flavonoids such as kaempferol, luteolin, and quercetin [133, 190, 200, 235-238-239].

82. Whole cell extracts (ethanol extraction) from *Urtica membranacea* (Urticaceae), *Artemesia monosperma* (*Asteraceae*), and *Origanum dayi post* (Labiatae), plants indigenous to the coastal plain and desert areas of Israel [133-239]. These plants exhibited dose and time-dependent killing capabilities on various human derived hematological and solid tumor cell lines and primary cultures established from patients' biopsies [133-239]. The killing activity was specific toward tumor cells, as the plant extracts had no effect on primary cultures of healthy human cells [133-149]. Cell death caused by the whole plant extracts via apoptosis [133-239]. Plant extract from *Urtica membranacea* showed strong anticancer capabilities since it inhibited actual tumor progression in a breast adeno-carcinoma mouse model [133-239]. The results of this study confirmed that whole plant extracts are promising anticancer reagents [133-239]. The killing activity was specific toward tumor cells, as the plant extracts had no effect on primary cultures of healthy human cells [133-239]. Plant extract (*Urtica membranacea*) showed particularly strong anticancer capabilities since it has inhibited actual tumor progression in a breast adenocarcinoma mouse model. Therefore, results of this study confirmed that whole plant extracts are promising anticancer reagents [133-239].

83. One of the study was carried out to evaluate the anticancer, antioxidant, and possible anti-inflammatory properties of diverse medicinal plants frequently used in Indian traditional medication [133-249]. The selected botanicals such as *Soymida fembrifuga* (Roxb.) A. Juss. (Miliaceae), *Tinospora cordifolia* (Willd.) Miers. (Menispermaceae), *Lavandula bipinnata* (L.) O. Ktze. (Lamiaceae), and *Helicteres isora* L. (Sterculiaceae) extracted in different solvents were evaluated for their *in vitro* anticancer and antioxidant activities [133-249]. The results obtained indicated that *H. isora* has a potent cytotoxic activity toward the selected cancer cells such as HeLa-B75 (34.21 ± 0.24%), HL-60 (30.25 ± 1.36%), HEP-3B (25.36 ± 1.78%), and PN-15 (29.21 ± 0.52%) [133-139]. Interestingly, the selected botanicals selectively inhibited cyclooxygenase-2 (COX-2) more than (COX-1), which are the key enzymes implicated in inflammation. COX-2 inhibition was observed to be in the range of 19.66-49.52% as compared to COX-1 inhibition (3.93-19.61%) [133-239]. The results of the antioxidant study revealed that the selected plants were found to be effective 1,1-diphenyl-2-picrylhydrazyl (DPPH), hydroxyl (OH), and superoxide radical (SOR) scavenging agents [133-239]. High-performance thin layer chromatography (HPTLC) fingerprint of flavonoids was used as a measure of quality control of the selected plant

samples [133-239]. The results of the present study findings strengthen the potentiality of the selected plants as a resource for the discovery of novel anticancer, anti-inflammatory, and antioxidant agents [133-239].

84. Cannabis sativa: In the one of the study reported by Lukhele and Motadi, (2016) [249] cervical cancer cell lines (SiHa, HeLa, and ME-180) were exposed to different concentrations of *Cannabis sativa* extracts and that of its compound, cannabidiol, for the investigation of their anti-proliferative activity [240-274, 276]. This study confirmed that *Cannabis sativa* extracts and Cannabidiol (CBD) possess anti-proliferative effects using MTT assay [240-274]. MTT assay determines IC_{50}, which represents the half maximal concentration that induces 50 % cell death [240-274]. *Cannabis sativa* extracts were able to reduce cell viability and increase cell death in SiHa, HeLa, and ME-180 cells [240-274, 276]. These results correlated with the earlier findings, whereby they reported reduced cell proliferation in colorectal cancer cell lines following treatment with *Cannabis sativa* [240-274]. Another study reported that *Cannabis sativa* extracts rich in Cannabidiol (CBD) were able to induce cell death in prostate cancer cell lines LNCaP, DU145, and PC3 at low doses (20–70 μg/ml) [240-274, 276]. It was suggested that Cannabidiol (CBD) might be responsible for the reported activities. Therefore, Cannabidiol (CBD) was included as a reference standard in order to determine whether the reported pharmacological activities displayed by *Cannabis sativa* extracts might have been due to the presence of this compound [240-274,276]. The use of cannabinoids as anti-cancer agents is still under debate due to both cancer promoting and inhibiting effects shown in the last centuries [240-274, 276]. The fact that cannabinoids play a role in cell fate decision, proliferation, and apoptosis might imply different effects under different conditions. Ligresti et al. (2003) demonstrated that the endocannabinoid system may play a role in cancer differentiation (by decreasing the levels of endogenous agonists in differentiated cells vs. undifferentiated ones), cell growth and cell migration leading to metastases [240-274]. On the other hand, their results imply that in the gastrointestinal system, cannabinoid receptors are involved in inhibition of cell proliferation of colorectal carcinoma. In studies using cell lines, the anti-neoplastic effect of both natural and synthetic cannabinoids, cannabinoids agonist, and endocannabinoids have been shown for several cancer types including carcinomas (skin, lung, prostate, and uterine), neuroblastoma, gliomas, lymphomas, thyroid epithelioma, and breast cancer. Although the mode of action leading to these effect is not completely clear, cannabinoids receptors appear to mediate it [240-274, 276].

6. Conclusion

Triple Negative Breast Cancer (TNBC) is a heterogeneous disease that based on immunohistochemistry (IHC) is estrogen receptor (ER) negative, pro-gesterone receptor (PR) negative and human epidermal growth factor receptor 2 (HER2) negative. TNBC is characterized by its unique molecular profile, aggressive nature, distinct metastatic patterns and lack of targeted therapies. Triple-negative breast cancer (TNBC) is an aggressive malignancy that requires effective targeted drug therapy and traditional therapies have lots of problems with severe side effects. TNBC patients only respond to conventional chemotherapies, and even then, with limited success. Shortages of chemotherapeutic medication can lead to resistance, pressured index therapy, non-selectivity, and severe adverse effects. Finding targeted treatments for TNBC is difficult owing to the various features of cancer. Hence, identifying the most effective molecular targets in TNBC pathogenesis is essential for predicting response to targeted therapies and preventing TNBC cell metastases. Nowadays, natural compounds have gained attention as TNBC treatments, and have offered new strategies for solving drug resistance.

The majority of plant extracts have been researched for cancer prevention rather than treatment, resulting in low efficacy and uptake in practice. The problem is that there is insufficient information on the safety, quality, and efficacy of herbal drugs. The debate remains, however, because there have only been a few research on the plants anticancer effects. Every proven medicine or its active ingredients (anticancer chemicals or isolated compounds) requires phase III clinical trials before it can be marketed. The rules of the "Food and Drug Administration" (FDA) and the "European Medicines Agency" (EMA) need at least one controlled trial in phase III with statistically significant outcomes before they can be marketed. Numerous challenging factors have created limitations in the development of natural anticancer bio-molecules as drug products. Along with toxic side effects, lower water solubility, decreased absorption, lack of selectivity to targeted cancer cells, and sub-therapeutic activity are the major obstacles for anticancer drug development from natural sources. The development of these bioactive compounds is a complex and time-consuming process. Moreover, it is evident that plants of the same species grown in different areas vary in their profile of medicinal compounds. This calls for the need to focus on the production of uniform and high-quality plants with a uniform metabolite profile that once tested is declared safe or unsafe. This might be achieved through the help of in vitro growth, biotechnological and genetic studies on these anticancer plants.

Although plant-based compounds have shown be less toxic compared to conventional synthetic compounds. There is a growing evidence on the side effects of the unregulated use of these plants against different diseases. However, it has been observed that pharmaceutical companies deviate from the standard protocol and start testing new compounds on

human subjects earlier than the defined timeline. The reason for such practices is to accelerate the approval of these compounds under the pressure of investors. This means that the drug is presented for approval with insufficient data on its quality, safety, and efficacy. The problem is that there is insufficient data available regarding the quality, safety, and efficacy of herbal drugs. *Fagonia indica*, for instance, has shown potent activity against breast cancer when tested in the MDA-MB-231 cell line. *Fagonia indica* is used traditionally to treat many disorders and people have even started the use of its herbal tea against breast cancer. However, the question remains that there are only a few reports available on the anticancer activity of the plant. There are several regulatory framework models available for prescribing such drugs but there is a need for harmony among regulating agencies and improvement in the regulation process. The traditional belief that a single drug, "silver bullet" is sufficient to treat a single disease has been questioned.

The main disadvantage related to herbal medicines is the lack of international standardization in terms of methods for evaluating their composition, efficacy, safety, and quality, consistent manufacturing practices, regulation and approval processes. Ironically, vast knowledge and experience in drug development is available in the pharmaceutical industry. Therefore, combining the benefits provided by both traditional and modern medicine has been previously suggested as a promising approach in order to reveal and bring to market new plant-derived substances. However, in the last centuries only several herbal medicines or botanical drugs have been approved by health authorities for human use. Further, most of the plant based inhibitors work on artificial tumors induced in animals during in vitro and in vivo experiments but not on human clinical trials. Most of the plant extracts showed promising results in animal clinical trials experiments but failed to show results on human clinical trials. The human clinical trials are warranted to verify the clinical utility of these medicinal plants in such treatment, since there could be positive as well as negative outcomes via pharmacodynamic and pharmacokinetic herbal-drug interactions. Medicinal plants are the only natural resource for developing effective, safe, and quality anticancer drugs. Although some herbal remedies may cause serious health problems and may have side effects if used without the consultation of a professional or medical practitioner. Sometimes, the use of these medicinal plants may interact with regular or other drugs and lead to side effects, for instance, allergies.

Compliance with ethical standards

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No conflict of interest to be disclosed.

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