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World Cancer 2019: Identification and validation of natural anti-drug resistant and anticancer stem cell agents in TNBC stem cells- Prem Prakash Kushwaha - Central University of Punjab

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Introduction: Multidrug resistance (MDR) resulting from different defensive mechanisms in cancer is one of the major obstacles of clinical treatment. To circumvent MDR many reversal agents have been developed, but most of them fail in clinical trials due to severely adverse effects. Recently, certain natural products have been reported to overcome MDR, including flavonoids which are abundant in plants, foods, and herbs. The structure of flavonoids can be abbreviated as C6-C3-C6 (C for carbon), and further categorized into flavonoids, iso-flavonoids and neo-flavonoids, according to their structural backbones. Flavonoids possess multiple bioactivities, and a growing body of research has indicated that both flavonoids and iso-flavonoids can either kill or re-sensitize conventional chemotherapeutics to resistant cancer cells. Here, we summarize the research and discuss the underlying mechanisms, concluding that these flavonoids do not function as specific regulators of target proteins, but rather as multi-functional agents that negatively regulate the key factors contributing to MDR.

Multidrug resistance (MDR) is one of the major challenges in cancer treatment which occurs in a short period of time during/after treatment, and may result in cross resistance to many other structurally and mechanically different chemotherapeutics. MDR may be due to different mechanisms, including ATP-binding cassette (ABC) transporters that pump out chemotherapeutics the mutation of oncogenes that become resistant to former treatments (an evolving adaptation of cancer cells to the microenvironment survived cancer stem cells (CSCs) that escape from conventional therapies and activated cell growth factors as well as cell defense systems, etc.

As membrane-bound proteins, ABCA to ABCG, that locates in the cell membrane and has diverse functions. ABC transporters have two nucleotide-binding domains (NBDs) which bind and hydrolyze ATP, and two trans-membrane binding domains (TMDs) which carry their substrates out of the cell. By using ATP, ABC transporters work to transport their substrates across the cell membrane and the substrates include building blocks/nutrition such as amino acids, sugars, lipids, vitamins, peptides, and certain proteins etc. Importantly, they can protect cells against xenobiotics including some anti-cancer drugs. Higher expressions of these transporters, such as ABCB1 (also known as P-glycoprotein, P-gp), ABCG2 (also known as breast cancer resistant protein, BCRP), and ABCC1, have closely participated in MDR as confirmed by studies from both the laboratory and the clinic. The overexpression of ABC transporters may lead to the resistance of conventional chemotherapeutics, such as doxorubicin (Dox), paclitaxel, colchicine, etc., radiotherapy, and targeted therapies such as imatinib.

Cancer cells may also adapt to the changed microenvironment, e.g., the increased oxidative stress, leading to MDR. Oxidative stress is defined as the phenomenon of imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, which plays a key role in the initialization of many diseases for their impacts on tissue damage. Oxidative stress also contributes to tumor development and responses to anticancer therapies. Generally, certain level of ROS may benefit cancer cell proliferation and DNA mutations, while high level ROS may be a lethal factor that finally induces cell death. Research has shown that ROS levels are higher in cancer cells and in resistant cancer cells due to chemotherapy or radiotherapy. Accordingly, the corresponding antioxidant pathways that eliminate ROS are up-regulated during tumor initiation and progression, rendering them more vulnerable to further oxidative stress assaults. Therefore, targeting oxidative stress is a promising strategy to overcome MDR in cancer. Cancer cells that grow rapidly need more oxygen supply for their energy supply and signal transmission. Tissue hypoxia occurs due to an inadequate amount of oxygen delivery or due to cancer cell metabolism re-programming, rendering cancer cells to adapt to less oxygen by up-regulating several key proteins, including hypoxia-inducible factor-1α (HIF-1α), HIF-2α. More importantly, hypoxia can trigger MDR by impacting the efficacy of anticancer drugs. Furthermore, hypoxia may also induce the expression of ABCB1 and ABCG2 that pump out intracellular chemotherapeutic agents, a common MDR mechanism. Cancer stem cells (CSCs), a subset of cells within the tumor that possess the potential of self-renewal, differentiation and tumorigenicity are thought to be the major cause of cancer therapy failure due to their chemo- and radio-resistance. CSCs are situated in the niche, which are mainly composed of fibroblasts and endothelial, mesenchymal and immune cells, playing pivotal roles in drug resistance. Therefore, the elimination of CSCs represents one promising strategy to overcome MDR.

The cell cycle, the mechanism of cell division, is composed by four phases: the G1 phase, during which a cell begins to grow in size to be ready to DNA synthesis; the S phase during which cell synthesizes DNA the G2 phase, during which a cell continues to grow to be ready for mitosis; the M phase (mitosis), during which the cell stops growing and divides into two cells. The cell cycle is driven by cyclin-dependent kinases (CDKs) which are regulated by cyclins (cyclin A-Y). Studies have shown that certain phases of the cell cycle exhibit resistance to chemotherapeutics, and cancer cells that over-express CDKs and cyclins demonstrate resistance to conventional chemotherapeutics. Autophagy, a self-degradative system in which cells undergo degradation of intracellular components, is important for the energy balance in response to nutrient stress. During chemotherapy, autophagy works as a pro-survival and resistance mechanism; therefore, the inhibition of autophagy can re-sensitize MDR cells and enhance the cytotoxicity of chemotherapeutic agents.

Epithelial mesenchymal transition (EMT), a biologic process that polarized epithelial cells undergoes multiple biochemical changes to achieve mesenchymal cell phenotype including

enhanced metastasis, invasiveness, drug resistance which plays an important role in the morphogenesis of multicellular organisms

Cancer drug resistance reduces the effect of the drug(s) in cancer cells. Triple-negative breast cancer (TNBC) is an aggressive disease with a poor therapy outcome. Drug resistance and self-renewal properties of stem cells make it an attractive target for anticancer drug discovery. ABC transporter and stemness markers are positively involved in stem cell drug resistance. Nowadays natural remedies are of interest due to lesser side effects and cost-effective. Taken together, there is an urgent need to identify novel natural anti-drug resistant and anticancer agents against TNBC stem cells. Different scientific literature database were used to prepare the list of phytochemicals. Molecular docking and simulation approach was used to identify the ABC transporter inhibitor from the enlisted phytochemicals. Literature shows that the enlisted phytochemicals are soluble in the polar solvent. Thus, we prepared the methanolic (polar) extract of Bulbine spp. Anti-drug resistance and anticancer activity of the extract was examined by using MTT, drug efflux, and colony formation assay. Further, the therapeutic potential of the extract was studied in terms of apoptosis induction and reduction in stemness markers (Oct4, Sox2, Nanog, and Myc) at the transcriptional level. In the study revealed potent phytochemical showing better binding affinity with ABC transporter in comparison to standard inhibitors. Extract inhibited the mammosphere formation and reduced colony formation in TNBC cells. Treatment showed reduced drug efflux activity, down-regulated stem cell markers and induced apoptosis in the cells. Present in silico and *in vitro* study suggest that Bulbine spp. phytochemicals have anti-drug resistance and anti-cancer stem cell potential. The phytochemicals may act as the lead candidate for drug development against triple negative breast cancer stem cells

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