2 Plant-Based Compounds as Alternative Adjuvant Therapy for Multidrug-Resistant Cancer

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2.1 INTRODUCTION

Cancer is a term used to describe a collection of diseases widely acknowledged as the leading cause of death worldwide (Kapinova et al. 2018). Breast cancer is one of the most common cancers diagnosed in women. This cancer is associated with many risk factors, like: family history, age, genetic factors, exposure to radiation, menstrual and menopausal history, and other lifestyle changes, among others (Bak et al. 2016). Advances made in cancer research to date have identified chemotherapy as a promising treatment option. Other treatment options include: hormonal therapy, radiation therapy, or a combination of both. Although these therapies have improved the living standards of patients, cancer recurrence still persists because some cells evade the treatment effect and survive, or metastasis to other tissue, thus becoming resistant and regrow (Mansoori et al. 2017). Multidrug cancer resistance is the ability of cancerous cells to tolerate a given drug treatment and, thus, become insensitive to them. Approximately 50% of the tumors treated with chemotherapy become resistant to the same or to any structurally related chemotherapeutic agent, which is a serious problem in cancer treatment (Wang et al. 2018). Evidence have shown that cancer drug resistance is a complex process that involves many factors, such as variation in individual genetic composition especially in somatic cells, apoptotic cell inhibition, enhanced DNA repair, and altering of drug metabolism and targets (Mansoori et al. 2017). The prevalence of these drug-resistant cancers necessitates further research to develop better treatment modalities. Abundant evidences have shown that plant-derived bioactive compounds like: flavonoids, carotenoids, phenolic acids, and organosulfur compounds possess beneficial disease-preventive properties. They possess anticarcinogenic and antimutagenic effects, which can lower various types of neoplasia (Gonzalez-Vallinas et al. 2013; Dandawate et al. 2016). This review summarizes the current knowledge on mechanisms that promote multidrug resistance and outlines some of the bioactive compounds used toward multidrug resistance in cancer treatment.

2.2 MULTIDRUG RESISTANCE MECHANISMS

The mechanism of drug resistance is a critical issue that continues to evolve and disseminate among many cancer types, like: breast, gastrointestinal, lung, and ovarian. These cancer types become tolerant to chemotherapeutic drugs with the same structural and mechanism of action similarities, leading to the phenomenon called multidrug resistance (Eid et al. 2015). One explanation to this may be due to the heterogeneity, stemness, and other changes within the tumor microenvironment (Carli et al. 2013). Several hypotheses with experimental evidence have tried to explain this phenomenon and the mechanisms, such as: altered drug transport across cell membrane, genetic and drug target alterations, and increased DNA repair mechanisms have been proposed to account for cancer drug resistance (Chorawala et al. 2012).

One of the most widely known resistance mechanisms is through altered membrane transport by adenosine triphosphate (ATP)-binding cassette (ABC) transporters. The ABC transporters belong to the ubiquitous superfamily of transmembrane proteins that modulate drug and other biomolecules absorption, distribution, and excretion across cell

membrane. Today, there are 48 identified human ABC genes grouped into seven subclasses (A–G) based on their sequence of homology and genomic organization (Chorawala et al. 2012; Eid et al. 2015). In clinical transport-associated multidrug resistance, the MDR1 gene, which encodes for P-glycoprotein (P-gp; MDR1, ABCB1), is the widely studied. The P-gp has two highly hydrophobic integral membrane and nucleotide-binding domains that make up its structure. This structure enables them to efficiently efflux cytotoxic drugs through a "pump" and "flippase" model of transport from the inner leaflet to the outer leaflet of the lipid bilayer into the extracellular space (Sharom 2014). Other ABC transporters: the multidrug resistance-associated protein 1 (MRP-1, ABCC1) and the breast cancer-resistant protein (BCRP, ABCG2) have been implicated as major efflux transporters responsible for cancer resistance in chemotherapy (Mao and Unadkat 2015). The MRP1 is similar in structure with the P-gp/MDR1 and contains an added amino terminal in the domains attached to the core that can recognize both neutral and anionic hydrophobic natural products and transports glutathione (Eid et al. 2015). The ABCG2 gene located at 4q22 encodes human BCRP. Structurally, the BCRP contains an ATP-binding domain and six transmembrane segments in a homodimer of two-half transporters. The BCRP is highly expressed and widely distributed in the gastrointestinal tract, excretory tissue, and blood-tissue barriers (Fletcher et al. 2016).

Genetic responses that lead to changes in cellular processes have been identified as another drug resistance mechanism. Alterations in cell cycle, increased DNA damage repair, reduced apoptosis, and altered drug metabolism are among the cellular changes that affect the ability of cytotoxic drugs to kill cancerous cells (Cree and Charlton 2017). Rapid downregulation of a target gene expression and mutations are common in cancer cells, which enables them to escape upon DNA damage, and become susceptible to increased DNA repair mechanisms for the replication process to continue. Thus, producing abnormal cells with increased survival proteins to protect themselves and inhibit cell death. These, in addition to reduced apoptosis and other forms of cell death, have underpinned drug resistance. Other factors like tumor microenvironments, where cancer cells reside, and intratumoral genetic heterogeneity with proximity to stromal cells can function in paracrine manner to support the survival of cancer cells. For example, various tumor landscapes create numerous microenvironmental niches, and each niche with genetically identical cancer cells will respond differentially to the same treatment due to different biophysical properties, such as: vascularity, Potential of Hydrogen (PH), hypoxia, and extracellular matrix organization of the niche (Rybinski and Yun 2016). Tumor-initiating cells otherwise known as cancer stem cells may also play a role in tumor resistance. These cells utilize the expression of ABC transporters, altered DNA damage response, and expression of pro-survival proteins to evade and better tolerate drug exposure. The cancer stem cells are thus refractory to drug treatment and often contribute to cancer relapse, recurrence, and resistance (Abdullah and Chow 2013).

2.3 CLASSIFICATIONS OF PLANT-DERIVED COMPOUNDS

Phytochemicals are bioactive compounds found in plants. Many of these compounds are in synergy with several nutrients, vitamins, and minerals found in foods to possess disease preventive effects (Kapinova et al. 2018). These effects are expected to be integrated into the human diet, thus, a growing emphasis has been placed on dietary plant products as an alternative approach toward the prevention and treatment of cancer, especially breast cancer (Bak et al. 2016). Based on the chemical structure and biological properties, phytochemicals can be classified as phenolics, carotenoids, alkaloids, nitrogen-containing, and organosulfur compounds, as discussed in Figure 2.1 (Kapinova et al. 2018).

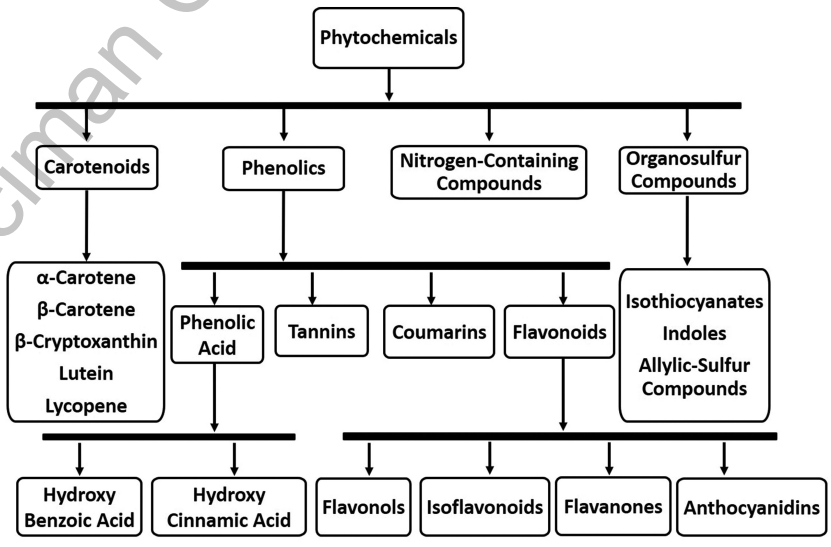

FIGURE 2.1 Basic classification of phytochemicals.

2.3.1 Carotenoids

They are lipid-soluble compounds that play an important role together with chlorophylls in photosynthesis and photoprotection (Kapinova et al. 2018). This molecule has a long conjugated double bond series in its center, which gives them their sharp, chemical reactivity and light-absorbing properties. Carotenoids inhibit the oxidative effects of reactive and singlet oxygen species that are produced from a plant's exposure to light and air. They react with radical molecules and delocalize the unpaired electron, thus inhibiting the oxidative effects of the radicals. This antioxidant activity makes them an excellent free radical scavenger (Ramel et al. 2012). Carotenoids are widely found in nature and can be used to prevent lipid oxidation and other related oxidative stress. Fruits including carrots, watermelons, apricots, pink guavas, tomatoes, pumpkin, mango, and sweet potatoes are rich sources of carotenoids (Jaswir et al. 2011). Generally, carotenoids are classified into α-carotene, β-carotene, β-cryptoxanthin, lutin, and lycopene (Liu 2004). Many epidemiological studies have found beneficial effects of carotenoid-rich foods in the reduction of cancer progression. As a chemoprevention strategy against certain human cancers, carotenoids and other antioxidants could be used, although there appears to be a detrimental interaction between β-carotene, smoke, and alcohol (Tanaka et al. 2012).

2.3.2 Phenolics

These are aromatic compounds with one or more hydroxyl groups that are produced from secondary plant metabolism that provide essential functions in plants growth and reproduction. They are richly found in fruits and vegetables, like cranberry, apple, red grape, pineapple, lemon, spinach, red pepper, carrot, lettuce, cucumber, etc., and are categorized as phenolics acids, flavonoids, stilbenes, coumarins, and tannins. Phenolic compounds act as a defense mechanism for plants to pathogens, predators, parasites, etc. (Kapinova et al. 2018). Researches have shown that regular consumption of fruits rich in phenolics compounds can help improve some chronic disease conditions (Liu 2004). The protective attributes of some phenolics compounds against cancer have been linked to their alterations in various signaling pathways like angiogenesis, cell cycle, and apoptosis (Garvin et al. 2006; Ma et al. 2008; Zhang et al. 2013).

2.3.3 Nitrogen-Containing Compounds

These are groups of molecules unique to fruits from the genus *Capsicum* (chilli peppers). They are purported to have antimicrobial and analgesic effects. Although there are reports linking their consumption with cancer chemoprevention, the exact mechanism of action is not fully understood. Hence, more research is expected to support its therapeutic efficacy against cancer, especially the drug-resistant type.

2.3.4 Organosulfur Compounds

Foods such as cruciferous and *Allium* genus vegetables like onions, garlic, etc. are high in sulfur compounds. These compounds have shown to exert diverse biological effects, like: free radical scavenging and detoxification activity, inhibition of DNA and tumor cell proliferation, cell cycle arrest, and the ultimate cell death (Moriarty et al. 2007). Evidence supports the protective effects of garlic in stomach, colorectal, and breast cancer in humans that appear to be associated with the presence of organosulfur compounds. The predominantly allyl derivatives in these compounds have also shown inhibitory effects against esophagus, colon, mammary gland, and lung carcinogenesis in experimental animals (Omar and Al-Wabel 2010).

2.4 BIOACTIVE PLANT-DERIVED COMPOUNDS WITH ANTITUMOR ACTIVITY AGAINST MULTIDRUG-RESISTANT CELLS

One of the oldest human practices is the use of medicinal plants as a herbal remedy in the treatment of various minor ailments through regular consumption of fruits and vegetables. These earliest practices, though still much practiced, recently have gained popularity in their association with a reduced risk of developing chronic diseases like cancer and cardiovascular diseases (Liu 2004). Although chemically derived drugs have been developed and used for cancer treatment, the search for antitumor drugs from plants continues to dominate due to the major limitations of high toxicity, affordability, and often the resistance of these synthesized drugs (Greenwell and Rahman 2015). These limitations and awareness of the perception that many allopathic drugs currently in use are based on natural products necessitate a further search of a safe and more efficient product without adverse effects to improve treatment efficacy (Song et al. 2014). The availability and abundance of plant compounds make them the desired product to study to find new drugs against tumors. In addition, these natural products, aside from their anti-inflammatory, antifungal, and antiviral properties, also possess antitumor activities. The widely exhibited antitumor properties of phytochemicals thus reported have been classified according to the mechanism of action, namely: DNA damage or antioxidant drugs, mitotic disruptors, histone deacetylase, and methyltransferase inhibitors (Greenwell and Rahman 2015). Based on this, phytochemicals have been proposed to be useful in the treatment and complete elimination of cancer. Furthermore, it has been suggested and showed that naturally occurring phytochemicals have the potential to modulate and reverse the development of MDR in cancer due to their multitargeting properties (Dandawate et al. 2016; Muthusamy et al. 2016; Budisan et al. 2017).

TABLE 2.1
Summary of the Modulatory and Multidrug Resistance Reversal Activities of Selected Bioactive Compounds

Bioactive Compounds	Classification	Mechanisms Against MDR	MDR Cells Used	References
Curcumin	Polyphenol flavonoid	Inhibition of P-gp ATPase activity function. Decrease proliferation and increase cytotoxicity.	Human cervical carcinoma KB-V-1 Human breast cancer MCF-7/MDR	Limtrakul et al. (2007)
		Interaction with the substrate-binding sites. Stimulation of basal ATPase activity and ATP hydrolysis of MRP1.	HEK 293	Chearwae et al. (2006)
		Regulation of NF-kB activity and expression of ABC transporter function.	L1210/Adr cells	Xue et al. (2013); Choi et al. (2008)
Ferulic acid	Phenolic acid	Induction of cell cycle arrest at G2/M phase and apoptotic signaling effect. Inhibition of P-gp transport function. Downregulation of P-gp expression.	MDR KB Ch^R 8-5 cells HEK 293/ABCB1 cells	Muthusamy et al. (2016)
Quercetin	Flavonoid	Reversal of gene-encoding P-gp and inhibition of its expression.	KB/VCR oral cancer-resistant cells	Yuan et al. (2015)
		Modulation and inhibition of FZD7/β-catenin pathway. Downregulation of ABCB1, ABCC1, and ABCG2 protein expression. Increased intracellular accumulation of rhodamine 123 and Adriamycin.	MDR human hepatocellular carcinoma BEL/5-Fu cells	Chen et al. (2018)
Retinoid	Carotenoids	Competitive inhibitor of P-gp. Modulation of pregnan-X-receptors, which regulates P-gp expression.	MDR colon and leukemia cells	Eid et al. (2012)
Xanthophylls	Carotenoids	Inhibition of P-gp activity and enhancement of antiproliferative function of anticancer drugs.	MDR lymphoma and breast cancer cells	Gyemant et al. (2006); Molnar et al. (2006)
Phenethyl Isothiocyanate	Organosulfur compounds	Suppress expression and activation of ABCG2 and pluripotency-associated transcription factors such as Octamer-binding transcription factor (Oct_4), sex-determining region Y-box (Sox-2), and Nanog. Inhibition of self-renewal, clonogenicity, and tumor growth of cancer stem cells.	EpCAM-positive NCCIT human embryonic carcinoma cells	Yun et al. (2017)

The compounds being discussed are represented in Table 2.1 with their origin, resistant cell line used and anticancer activity.

Curcumin polyphenol has been extensively studied in cancer for its ability to reverse MDR. This compound was able to restore drug sensitivity in MDR cancer cells through direct inhibition of P-gp and MRP1 transport pumps (Chearwae et al. 2006; Limtrakul et al. 2007). Similarly, Choi and colleagues (2008) reported that curcumin not only inhibited *mdr1b* gene promoter activity, but also prohibits the constitutive transcription factor nuclear factor $_kB$ (NF-$_kB$) transactivation, thereby regulating the antiapoptotic proteins including: bcl-2, bcl-xL. Thus, curcumin can reverse cancer-resistant phenotypes through the suppression of MDR protein expression and inhibition of P13K/Akt/NF-kB signaling pathways (Xue et al. 2013). Ferulic acid, another phenolic acid richly found in wheat and barley leaves has demonstrated the potential of reversing P-gp-mediated paclitaxel-resistant cells. Muthusamy et al. (2016) reported that ferulic acid inhibits P-gp transport function and significantly downregulates its expression in resistant KB Ch^R 8–5 cell lines. Their report further stated that the compound could also be used to arrest the cell cycle and induce apoptosis in the resistant cell line. These effects were attributed to the chemosensitizing potential of the compound. Quercetin is a flavonoid found in leafy greens, tomatoes, berries, and broccoli. It is considered as one of the most abundant antioxidants in the human diet. Apart from its antioxidant properties, it has also exhibited anti-inflammatory, immunomodulatory, and vasodilating activities (Chen et al. 2018). Hashemzaei and colleagues (2017) studied the putative anticancer potential of quercetin in eight different cancer cell lines, namely, colon, prostrate, pheochromocytoma, breast, ovarian, leukemia, myeloma, and lymphoid cancer and found that quercetin at optimal concentrations was able to induce apoptosis in all the tested cell lines. Importantly, quercetin exerts its tumor suppressive effect through mechanisms like: inhibition of DNA topoisomerase I/II, release of cytochrome c, activation of caspase 3, and heat shock protein 27 (Badziul et al. 2014). Furthermore, Yuan and colleagues (2014) reported that quercetin is a potent modulator of P-gp, and their study showed that quercetin from 25 to 100 μmol/L reversed gene-encoded P-gp-mediated MDR in KB/VCR oral

cancer resistant cells by inhibiting its expression. Similarly, Chen et al. (2018) confirmed the potential role of quercetin and ABC transporter-mediated MDR in BEL/5-FU hepatocellular carcinoma cells. Evidently, their study showed that quercetin increased the sensitivity of a resistant cell line to chemotherapeutic drugs with a significant increase in rhodamine and Adriamycin drug accumulation.

The biological activity of carotenoids as reported by previous studies indicated that they exhibit anticancer properties through cell cycle arrest, growth factor inhibition transduction, stimulation of anti-oncogene proteins, and apoptotic mechanism induction (Garattini et al. 2007; Yu et al. 2011). The carotenes, xanthophylls, and retinoids class of carotenoids have a high affinity to a P-gp transporter and are thus used as a competitive inhibitor for the transporter (Gyemant et al. 2006). This was apparent in the findings of Eid et al. (2012) using MDR-resistant colon and leukemia cells. Eid and colleagues confirmed that the five carotenoids (β-carotene, crocin, retinoic acid, canthaxanthin, and fucoxanthin) studied competitively inhibit the P-gp activity in both the colon and leukemic cell line. These compounds increased drug accumulation and efficacy in the resistant cells and reversed the MDR effect of the chemotherapeutic drugs in a synergistic fashion. Likewise, many naturally occurring isothiocyanates display anticarcinogenic activity because they reduce the activation of carcinogens and increase their detoxification (Wu et al. 2009). Recent studies show that phenethyl isothiocyanate, a natural compound found in cruciferous vegetables, can suppress cancer stem cell properties in vitro and in a xenograft model. Yun and colleagues (2017) revealed that ABCG2 as well as pluripotent-associated transcription factors in epithelial cellular adhesion molecule (EpCAM)-positive NCCIT, a pluripotent stem cell line established by Shinichi Teshima (National Cancer Institute, Tokyo, Japan), human embryonic carcinoma cells, such as octamer-binding transcription (Oct4), sex-determining region Y-box (Sox-2), and NANOG were downregulated by phenethyl isothiocyanate. Previous studies have reported that cancer stem cells exhibit drug resistance through the expression of ABCG2, which closely correlates with the expression of pluripotency factors. Thus, isocyanate compounds are useful in targeting cancer stem cells, which are a source of tumor initiating cells and contribute in drug resistance.

2.5 CONCLUSION AND FUTURE PROSPECTS

The ability of cancer cells to develop resistance to chemotherapeutic agents seems to be a continuous process with a substantial effect on therapeutic outcome and limited efficacy. These shortfalls make natural products to be in the forefront of becoming a very important alternative source of treatment for resistant cancer cells, generally, because of their lower cost, toxicity, and natural abundance within our environment. Many publications and reports have documented the antiproliferative effect of plant extracts against breast, lung, colon cancer, etc., while others have also shown the important pharmacological applications of these extracts against several human diseases. From all these reports, it is evident that medicinal plants can be a rich source in potential anticancer compounds. Hence, it is necessary to consider and look toward the use of new molecules from nature in drug development with an unexploited mode of action to fight against cancer drug resistance.

ACKNOWLEDGMENTS

The South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation of South Africa (Grant No 98337) supports this work.

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