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Phytochemicals are the promising tools towards drug-resistant cancers

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ABSTRACT

Cancer cells rapidly acquire drug (single/multi) resistance. In this regard, continuous efforts are necessary to better understand the drug resistance mechanisms along with or aiming to boost of discovery of sufficient and new anticancer drugs. Plants have been found one of the pioneer sources of modern medicines. This review reports on potential phytochemicals acting against drug resistant cancer cells. A search was made in the scientific databases such as *PubMed*, *Science Direct*, *Web of Science*, *Scopus* and *Google Scholar* for published articles to date (December 2016) with a number of keywords covering phytochemicals or their derivatives and preparations acting against chemoresistant cancer cells. The results suggest that, a number of phytochemicals and their derivatives or preparations have been found to show sensitivity towards various drug resistant cancer cells under the main molecular mechanisms: oxidative stress, mitochondrial dysfunction, apoptosis and anti-proliferative effects. Some of them were also seen to act *via* adenosine triphosphate binding cassette transporters, epidermal growth factor receptor, tumor suppressor protein p53, and topoisomerase dependent pathways. In conclusion, phytochemicals may be one of the promising therapeutic candidates in the treatment of chemo-resistant cancers.

Keywords: cancer cells; drug resistance; phytochemicals; resistance reversal activity.

RESUMO

As células de cânceres diversos adquirem rapidamente resistência aos tratamentos farmacológicos (único/múltiplo). A este respeito, esforços contínuos são necessários para entender melhor os mecanismos de resistência a medicamentos com o objetivo de aumentar a descoberta de novos fármacos anticancerígenos. Nesta perspectiva, as plantas constituem importantes fontes para a descoberta de fármacos inovadores. Esta revisão aborda os possíveis fitoquímicos que tem atividade no tratamento de células cancerígenas resistentes a alguns dos fármacos em uso. A pesquisa foi realizada nas bases de dados científicas *PubMed, Science Direct, Web of Science, Scopus* e *Google Scholar* para artigos publicados até dezembro de 2016 com uma série de palavras-chave abrangendo fitoquímicos ou seus derivados e formulações que atuam em células de câncer resistentes. Os resultados sugerem que uma série de fitoquímicos e seus derivados ou formulações destes têm maior ação em relação a várias células cancerígenas resistentes a fármacos sob os principais mecanismos moleculares: estresse oxidativo, disfunção mitocondrial, apoptose e efeitos antiproliferativos. Em conclusão, os fitoquímicos podem ser candidatos terapêuticos promissores no tratamento de câncer resistentes as terapias convencionais.

Palavras-chave: células cancerígenas; resistência à droga; fitoquímicos; atividade de reversão de resistência.

1. INTRODUCTION

Till date, cancer is recognized as a critical public health problem and lethal cause of death throughout the world. The number of new cancer cases may reach 15 million every year by 2020 worldwide, 70% of which will be in developing countries (VOROBIOF; ABRATT, 2007), thus an awareness of this impending epidemic is a priority today, and all possible resources should be mobilized to both prevent and effective cancer treatment.

Cancer is coined by the accumulation of multiple genetic and epigenetic alterations, leading to abnormal expression of genes involved in physiological and pathological processes (HOLMES et al., 2007; ISLAM, 2016a). Cancer cells may rapidly acquire drug resistance or multi-drug resistance (DR/MDR), mainly due to the presence of adenosine triphosphate binding cassette (ABC) transporters, and P-glycoprotein (Pgp/MDR1/ABCB1) (SHEN et al., 2011), the oncogene epidermal growth factor receptor (EGFR) (EFFERTH et al., 2003) and the deletions or inactivation of tumor suppressor gene protein 53 (p53) (EL-DEIRY, 1997).

Nowadays, the plant's secondary metabolites have been gaining much attention due to their indispensable role in the treatment of diseases and health promotion. Plants are the pioneer for the sources of new cytotoxic agents. It is doubtless that, the use of chemotherapies to combats DR still remains a challenging issue (EICHHORN; EFFERTH, 2012). This review focuses the role of overcominh chemoresistant (DR/MDR) cancers by the plant-based constituents and their derivatives.

2. METHODOLOGY

A search was made in the *PubMed*, *Science Direct*, *Web of Science*, *Scopus* and *Google Scholar* databases with the keyword "phytochemicals" then followed by 'alkaloids', 'glycosides', 'flavonoids', 'saponins', 'tannins', 'plant sugars', 'steroids', 'phenols/polyphenols', 'essential oils', 'terpenoids', 'monoterpenes', 'diterpenes', 'triterpenes', 'quinones', pairing with 'cancers', 'cell line', 'drug resistance/multi-drug resistance' and 'drug resistant/multi-drug resistant cancer cells'. The inclusion and exclusion criteria have been given in **Box 1**.

Box 1. Inclusion and exclusion criteria of phytochemicals acting against drug/multi-drug resistant cancer cells

Inclusion criteria:
1. Studies carried out *in vitro*, *ex vivo* or *in vivo* with phytochemicals, their derivatives or preparations in single or multi-drug resistant cancer cells or cell lines.
2. Phytochemicals/derivatives/preparations, co-treated with other substances (including drugs or chemicals/biochemicals).
3. Studies with or without proposing activity mechanisms.

Exclusion criteria:
1. Studies with extracts without phytochemical analysis.
2. Studies with chemicals other than the plant-based.

3. FINDINGS

To date (December 2016), a total 2095 records were seen. Among them, 1701 were discarded after reading the titles, while 191 by data duplication. Abstracts and contents were read about 203 articles, from where 53 falls into the acceptable criteria in this study.

It should be mentioned that, this study follows the following cutoff points for the phytochemicals/derivatives/preparations acting against DR/MDR cancer cells/cell lines: Significant or strong cytotoxicity: IC_{50} <20 µg/mL; moderate cytotoxicity: IC_{50} 20 to <50 µg/mL; low cytotoxicity: IC_{50} 50 to <200 µg/mL; no cytotoxicity: IC_{50} >200 µg/mL.

Cancer cell drug resistance

Most of the chemotherapies in cancer act of chronic induction of reactive oxygen species (ROS) (RENSCHLER, 2004). Although, ROS play important physiological roles in our body, but excess production can trigger oxidative damage to the cellular substances such as membranes, organelles, carbohydrates, proteins, lipids, genetic materials (DNA/RNA). Furthermore, ROS can trigger inflammation and some chronic human diseases, including aging, cancer, cardiovascular and neurological diseases. However, our body has antioxidant (e.g. – catalase, superoxide dismutage, glutathione) as well as a number of repair systems (ISLAM, 2016b). These two systems may also counteract and protect the cancer cells from anticancer drug-induced damaging effects, especially those acts *via* a ROS inducing pathway. In this context, the antioxidant system mediated reduction in the efficacy of the chemotherapies and a chance of escaping of the cancer cells are two major concerns, despite the defense is crucial for non-cancerous or normal cells.

The overexpression of ABC transporters is known for MDR and failure of cancer chemotherapy (SZAK´ACS et al., 2006). P-Glycoprotein 1 (also called permeability glycoprotein, P-gp or Pgp) is an ATP-dependent efflux pump with broad substrate and evolved as a defense mechanism against harmful substances during evolution of life. The P-gp is encoded by the multidrug resistance gene 1 (*MDR1*), also known as ATP-binding cassette subfamily B member 1 (*ABCB1*) or cluster of differentiation 243 (CD243) and function as an important protein of the cell membrane to pump many foreign substances out of the cells (SHEN et al., 2011).

Upon activation from an inactive monomeric form, the EGFR undergoes a transition to an active homodimer that stimulates its intrinsic intracellular protein-tyrosine kinase activity (YARDEN; SCHLESSINGER, 1987). Through phosphorylation and several signal transduction cascades (e.g. - MAPK, Akt, and JNK pathways), EGFR leads to DNA synthesis, and cell proliferation (ODA et al., 2005). Thus, mutations in EGFR may be associated with many cancers (WALKER et al., 2009).

The p53, encoded by the *TP53* gene, is crucial in multicellular organisms, where it regulates the cell cycle and functions as a tumor suppressor; prevents cancer. Moreover, p53 has been described as “the guardian of the genome” because of its role in conserving stability (MATLASHEWSKI et al., 1984). On the other hand, the topoisomerase (Topo) controls the changes in DNA structure by catalyzing the breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle (MITSCHER, 2005).

In cancer, DR (both primary and acquired resistance) can be caused by the alterations of drug metabolism or modifications to the drug targets. However, the development of resistance to one drug can lead to resistance to other drugs (WILSON et al., 2006; ULLAH, 2008). The loss of drug transporters can lead to resistance to structurally diverse compounds that utilize same transporter systems. In contrast, an elevation of the transporters may influence the efficacy of other compounds, including toxic chemicals/biochemicals and non-anticancer molecules (NOBILI et al., 2012). Mainly, the entrance of drugs into the cells depends on the chemical nature of the drugs and the receptors, which they bind to and transmit their effects (GOTTESMAN, 2002). The resistance can result from mutations that modify the activity or reduce the expression of the surface receptors and transporters. For examples, mutations or reduced expression of the extracellular receptor smoothened (Kasper and Toftgard 2013), nucleoside or folate transporters (DAMARAJU et al., 2003; LONGO-SORBELLO; BERTINO, 2001) and so on.

To date, in human a total 48 ABC transporters have been identified. Among them, P-gp (*MDR1* gene product), multi-drug resistance-associated protein 1 (MRP1) and mitoxantrone resistance protein [MXR; also known as breast cancer resistance protein (BCRP) or placenta ABC protein (ABC- P)], have been demonstrated for a number of cancer chemo-resistance. The P-gp resistance occurs towards the hydrophobic anti-cancer drugs (GOTTESMAN et al., 2002), while MRP1 towards the negatively charged drugs, especially those are modified by the conjugation of glutathione (GSH), glucuronic acid or sulfate (BORST et al., 2000) and the MXR to the topoisomerase I inhibitors (GOTTESMAN, 2002). The conjugation with GSH mainly renders the drug substrates for ABC transporters which enhances drug efflux (ISHIKAWA; ALI-OSMAN, 1993).

However, some drugs may need metabolic activation, thus mutations of the enzymes may cause an inactivation of such drugs, leading to the development of resistance (SAMPATH et al., 2006). Mutations at the gatekeeper residues of the kinase domain as well as oncogenes to which cancer cells are addicted; disable drug binding and may grow up DR (GIOELI, 2011; WONG; LEE, 2012). Moreover, mutations in the apoptotic proteins, such as p53, or activating anti-apoptotic proteins are also known to cause DR in cancers (TEICHER, 2006).

Phytochemicals found to sensitive towards DR/MDR cancer cells/cell lines

Sinocalycanchinensin E isolated from the leaves of *Sinocalycanthus chinensis* enhanced cytotoxicity towards MDR KB cells (KASHIWADA et al., 2011). Nine triterpenes and a triterpene glucoside isolated from the methanol extract of the *Dysoxylum cumingianum* were also found to act against MDR KB-C2 cells (KURIMOTO et al., 2011). In a recent study, PEG-PE and vitamin E co-loaded with curcumin synergistically acted against MDR SK-OV-3TR cells (ABOUZEID et al., 2014)

The phytochemicals, galanals A and B, naringenin, and kaempferol-3,7,4’-trimethylether isolated from *Aframomum polyanthum* and *A. arundinaceum* showed MDR reversal activity towards leukemia CEM/ADR5000, breast adenocarcinoma MDA-MB-231/*BCRP*, glioblastoma multiforme U87MG.Δ*EGFR*, CCRF-CEM, MDA-MB-231, and U87MG cells (KUETE et al., 2014a). The bicyclic sesquiterpene ester jaeschkeanadiol *p*-hydroxybenzoate (from *Ferula hermonis*) was also found to act against CEM/ADR5000 cells (KUETE et al., 2012a). The phytochemicals 3,4',5-trihydroxy-6″,6″-dimethylpyrano[2,3-g]flavones and isotetrandrine derived from the methanol extract of *Xylopia aethiopica* exhibited significant cytoxicity towards CCRF-CEM, U87MG.Δ*EGFR* and MDA-MB-231-pcDNA cells within the IC_{50} values 1.45 to 18.60 µM (KUETE et al., 2015a). Artocarpesin and cycloartocarpesin and one chalcone, isobavachalcone exhibited cytotoxicity against HCT116 (p53(-/-), CCRF-CEM, U87MG.Δ*EGFR*, CEM/ADR5000 cells as well as HCT116 (p53(+/+) cells between the IC_{50} values 0.20 and 195.12 µM (KUETE et al., 2015b).

The elatunic acid, an ursolic acid-type compound, isolated from the plant *Omphalocarpum elatum* showed a low to moderate cytotoxic effects towards CEM/ADR5000 and CCRF-CEM cells (IC_{50}: 16.60 and 67.91 µM, respectively) (SANDJO et al., 2014), while the triterpene-saponin α-hederin from *Polyscias fulva* towards a number of doxorubicin-resistant cancer cell lines, including CEM/ADR5000, MDA-MB-231/*BCRP*, glioblastoma multiforme U87MG.Δ*EGFR*, CCRF-CEM, MDA-MB231, and U87MG cells (KUETE et al., 2014b).

The candidone and 4-hydroxy-2,6-di-(3’,4’-dimethoxyphenyl)-3,7dioxabicyclo-octane isolated from the active fractions of *Echinops giganteus* were found to sensitive towards HL60AR and HCT116 (*p53*−/−) cells (IC_{50}: 32 to 39 µg/mL (KUETE et al., 2013a), while futokadsurin B from *Uapaca togoensis,* showed strong cytotoxic effects on CEM/ADR5000 and CCRF-CEM cells (KUETE et al., 2014c).

In a study, the flavonoids gancaonin Q, 6-prenylapigenin, 6,8-diprenyleriodictyol, and 4-hydroxylonchocarpin isolated from the genus *Dorstenia* were found to inhibit the proliferation of CCRF-CEM and CEM/ADR5000 cells (KUETE et al., 2011). The neobavaisoflavone, sigmoidin H, and isoneorautenol isoflavonoids from *Erythrina excelsa* and *E. senegalensis* were found to act against CCRF-CEM, MDA-MB-231/*BCRP*, HCT116 (*p53*+/+), *BCRP*-transfected MDA-MB-231 and U87MG.Δ*EGFR* cells (IC_{50}: 2.67 to 9.89 μM) (KUETE et al., 2014e). On the other hand, the xanthones, namely, 8-hydroxycudraxanthone G and morusignin I from *Garcinia nobilis* and cudraxanthone I from *Milicia excels* exerted an anti-proliferative effect on MDA-MB-231, HCT116 (*p53*+/+) and U87MG.Δ*EGFR* cells (KUETE et al., 2014f).

Xanthone V1 isolated from *Vismia laurentii* was found to act against CCRF-CEM (4.9 µg/mL) and CEM/ADR5000 cells (KUETE et al., 2011). However, the activity was more prominent towards CCRF-CEM cells. 17β-hydroxywithanolides exhibited a significant cytotoxic effect against metastatic castration-resistant PC cells (XU et al., 2015).

Benzophenones 2,2',5,6'-tetrahydroxybenzophenone and isogarcinol from *Hypericum lanceolatum*, and isoxanthochymol, and guttiferone E isolated from the *G. punctata* exerted an anti-proliferative effect towards U87MG.Δ*EGFR* cells. However, isogarcinol and isoxanthochymol were found more hypersensitive towards MDA-MB-231/*BCRP* cells, while guttiferone E towards HCT116 (*p53*−/−) cells (KUETE et al., 2013b). In a study, 4'-hydroxy-2',6'-dimethoxychalcone isolated from *Polygonum limbatum* strongly inhibited the BCRP transfectant MDA-MB-231 (6.48 µM) and the p53-knockout HCT116 cells (6.27 µM) (KUETE et al., 2014g). It was also found to sensitive against CEM/ADR5000, MDA-MB-231/*BCRP*, p53-knockout HCT116 and U87MG.Δ*EGFR* cells (KUETE et al., 2014g). The naphthyl butenone guieranone A (from *Guiera senegalensis*) was also found hypersensitive towards CCRF-CEM and CEM/ADR5000 cells with IC_{50} values below 10 µM (KUETE et al., 2012a).

A cinnamate derivative obtained from *Erythrina excelsa* called *para*-hydroperoxycoumaroate of nonadecyl or excelsaperoxide exhibited significant cytotoxic activity against CEM/ADR5000 (IC_{50}: 1.07 µM), CCRF-CEM cells (IC_{50}:1.02 µM), MDA-MB-231 cells (IC_{50}: 3.22 µM) and HCT116 (*p53*+/+) (IC_{50}: 57.77 µM) cells (KWAMOU et al., 2014). An acridone alkaloid arborinin isolated from *Uapaca togoensis* displayed strong cytotoxicity against CEM/ADR5000, CCRFCEM, MDA-MB-231/*BCRP*, MDA-MB-231 and U87MG.Δ*EGFR* cells (KUETE et al., 2014c).

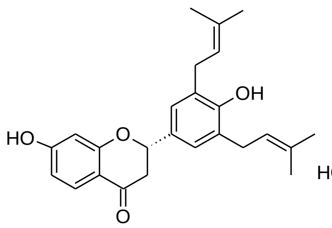
Four alkaloids namely benzophenanthridines, buesgenine and isofagaridine, and two fluoroquinolones, maculine and kokusaginine, isolated from the aerial part of the *Zanthoxylum buesgenii* showed anti-proliferative effects on a panel of DR cancer cell lines, especially buesgenine and isofagaridine were found more sensitive towards CCRF-CEM cells (IC_{50}s: 24 and 0.30 µM, respectively) (SANDJO et al., 2014).

2-(penta-1,3-diynyl)-5-(4-hydroxybut-1-ynyl)-thiophene isolated from the roots of *Echinops giganteus* demonstrated a broad spectrum of cytotoxic activities in DR cancer cells within IC_{50} range of 19 to 38 µg/mL (KUETE et al., 2013a). Thymoquinone, the vastly studied *Nigella sativa* quinone component was found to act against MDR MCF-7/TOPO cells, where a synergistic cytotoxic activity was also seen with the chemotherapeutic drug doxorubicin (EFFENBERGER-NEIDNICHT; SCHOBERT, 2011).

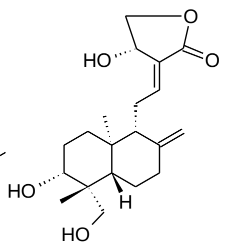
On the other hand, euphomelliferine and euphomelliferene A isolated from *Euphorbia mellifera* were also reported to show an MDR reversing activity in a dose-dependent manner in MDR1 gene-transfected mouse (L5178Y MDR) and human colon adenocarcinoma (COLO 320) cells (VALENTE et al., 2012). Examples of some other MDR reversal diterpenes are – jatrophanes (LU et al., 2014; RÉDEI et al., 2015) lathyrol (JIAO et al., 2015) and diterpenes from *Euphorbia* sp. (WIŚNIEWSKI et al., 2016).

The phytochemicals furoquinoline montrofoline and four acridones namely 1-hydroxy-4-methoxy-10-methylacridone, norevoxanthine, evoxanthine, 1,3-dimethoxy-10-methylacridone were also evident to act against HCT116 (p53(-/-), MDA-MB-231-pcDNA, gliobastoma U87MG.Δ*EGFR*, CCRF-CEM, MDA-MB-231/*BCRP*, CEM/ADR5000, CCRF-CEM and CEM/ADR5000 cells within the IC_{50} values 0.20 to 195.12 µM (KUETE et al., 2015c). Furthermore, the phenolic compounds caffeic acid, rosmarinic acid, lithospermic acid, luteolin-7-O-glucuronide, luteolin-7-O-rutinoside, eriodictiol-7-O-rutinoside, and arbutin were reported to act against adriamycin-resistant MCF-7/Adr (BERDOWSKA et al., 2013).

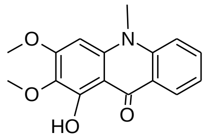
A number of phytochemicals were also reported to exert synergistic effects on DR/MDR cancer cells. For examples, andrographolide, epigallocatechin-3-gallate, chlorophyllin, colchicines, curcumin and paclitaxel produced marked synergistic effects in cisplatin resistant human ovarian cancer cell line A2780(cisR) (YUNOS et al., 2011), while alkaloids (glaucine, harmine, and sanguinarine), phenolics (epigallocatechin-3-gallate and thymol), and terpenoids (menthol, aromadendrene, β-sitosterol-O-glucoside, and β-carotene), alone or in combination with the saponin digitonin were found to act towards MDR Caco-2 and CEM/ADR5000 cells (EID et al., 2012, 2015). Anethole and curcumin were applied in binary combination with platinum drugs cisplatin and oxaliplatin, where a significant synergistic cytotoxicity was observed towards the epithelial ovarian cancer cell lines A2780(cisR) (cisplatin-resistant) and A2780(ZD0473R) (ZD0473-resistant) (NESSA et al., 2012). In a recent study, capsaicin and curcumin were found to act against cisplatin-resistant A2780 (A2780(cisR)) and ZD0473-resistnat A2780 (A2780(ZD0473R)) cancer cell lines, where they efficiently enhanced the drug efficacy (ARZUMAN et al., 2016). Some important DR/MDR cancer reversal phytochemicals have been shown in **Figure 1**.



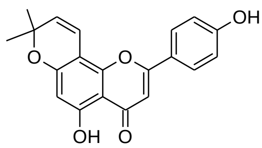
Abyssinone IV



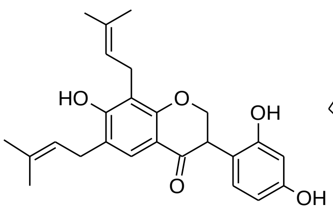
Andrographolide



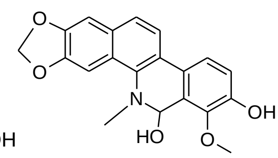
Arborinin



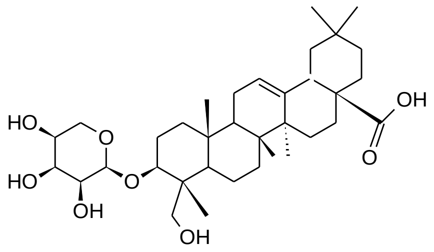
Atalantoflavone



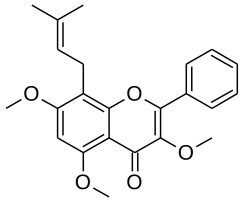
Bidwillon A



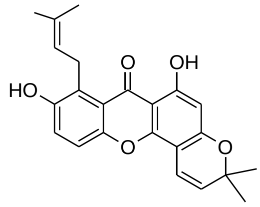
Buesgenine



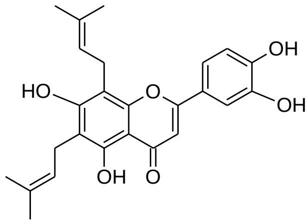
δ–Hederin



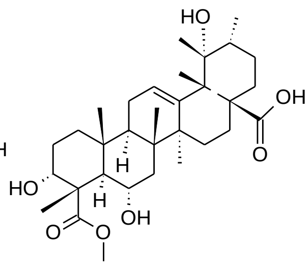
Candidone



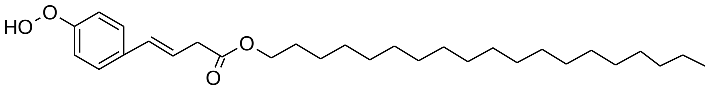
Cudraxanthone I



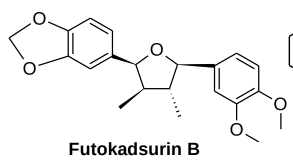
6,8-diprenyleriodictyol



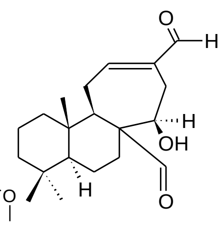
Elatunic acid



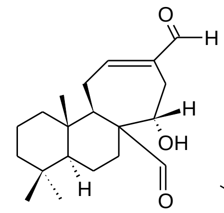
Excelsaperoxide



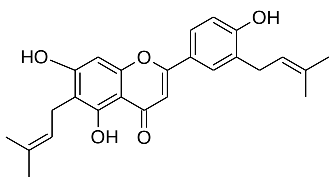
Futokadsurin B



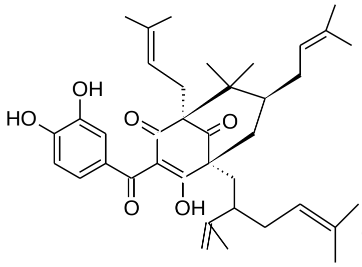
Galanal A



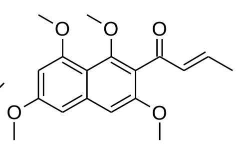
Galanal B



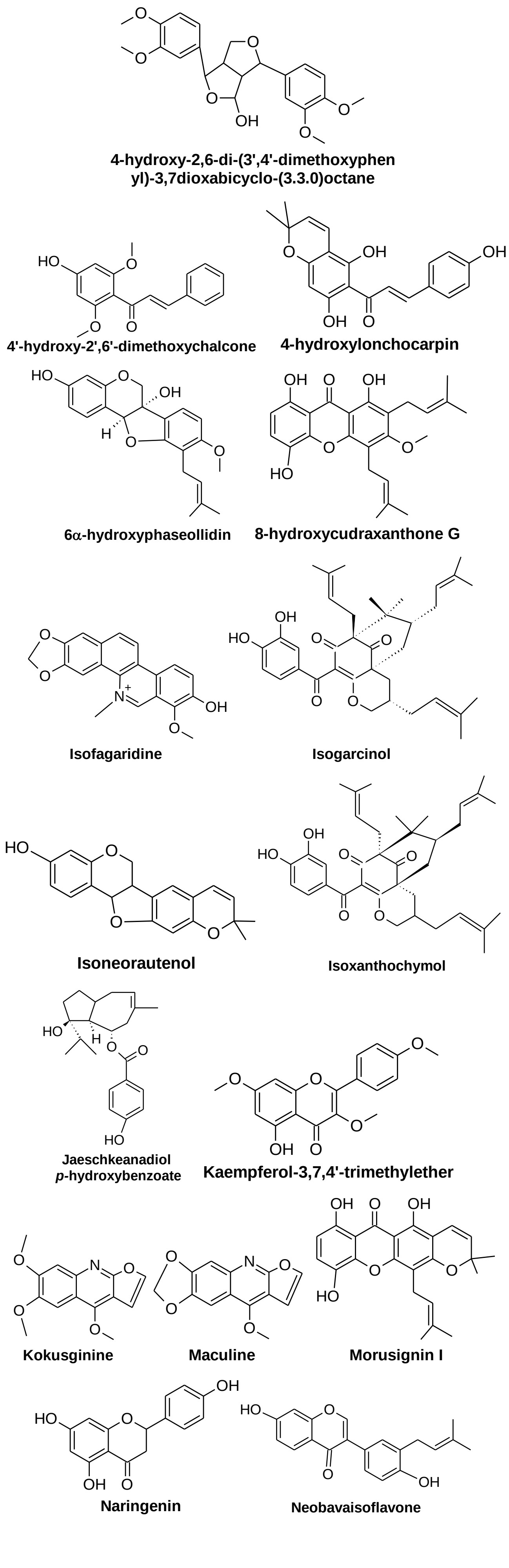
Gancaonin Q



Guttiferone E



Guieranone A



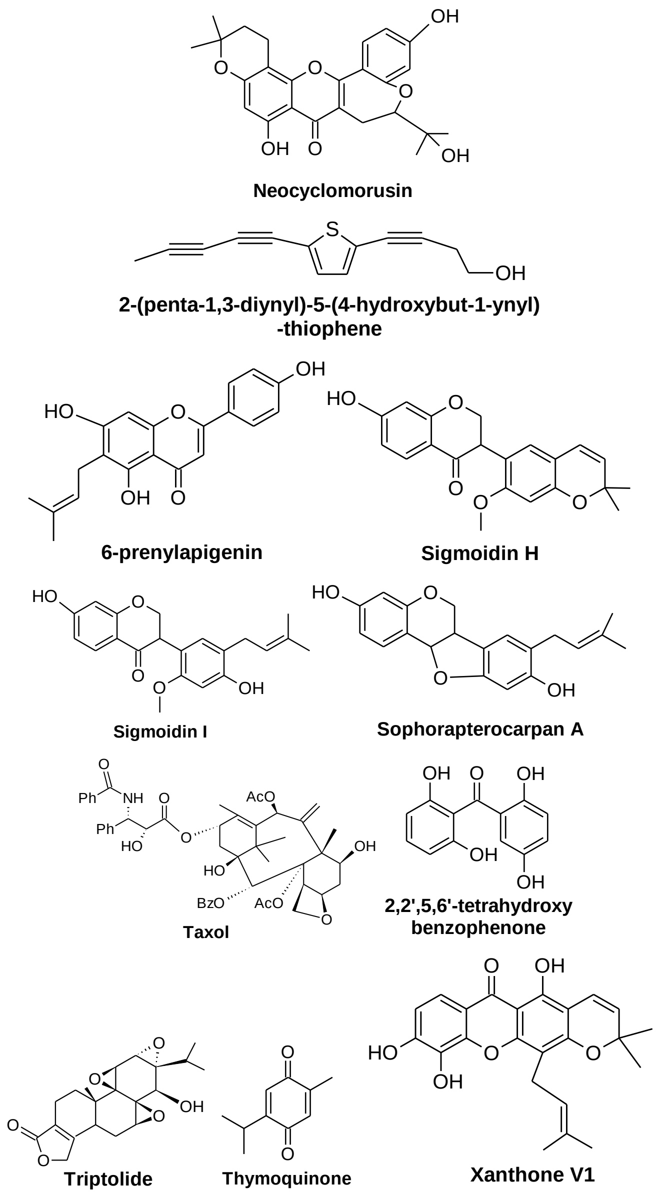


Figure 1. Anticancer drug resistance reversing phytochemicals and their derivatives.

Molecular mechanisms of phytochemicals/derivatives/preparations in DR/MDR cancer cells

In a study, fifty-eight ecdysteroids, herbal analogues were reported to act against MDR1/A retrovirus in a mouse model *via* ABCB1 efflux pump (MARTINS et al., 2012). The antioxidant phytochemical resveratrol in doxorubicin-resistant breast cancer (MCF-7/adr) markedly enhanced cytotoxicity. In the latter case, the combination treatment (resveratrol + doxorubicin) significantly increased the cellular accumulation of doxorubicin by down-regulating the expression of ABC transporter genes, MDR1, and MRP1 (KIM *ET AL.*, 2014). Four guanidine alkaloids (i.e., galegine, nitensidine A, pterogynidine, and pterogynine) isolated from *P. nitens*; among them nitensidine A was also found as is a novel substrate for ABCB1 in MDR CEM/ADR5000 cells (TAJIMA et al., 2014).

On the other hand, the phenanthroindolizidine alkaloids, (-)-10beta-antofine N-oxide and (-)-10β, 13aα-14β-hydroxyantofine *N*-oxide, and a novel alkaloid, (-)-10β,13aα-secoantofine N-oxide, isolated from the aerial parts of *Cynanchum vincetoxicum* were reported to act *via* P-gp (P-170) efflux pump in MDR KB-V1 cancer cell line (STAERK et al., 2000). The paclitaxel (PTX) nanosuspension coated with TPGS also evident act against MDR H460 human lung cancer cells *via* P-gp pathway (GAO et al., 2014). In a study, β-sitosterol was found to act *via* ABCB1 and P-gp expression pathways in MCF7 and MDR NCI/ADR-RES cells, respectively (RUBIS et al., 2010). Moreover, quercetin and rutin exerted an anti-resistant effect *via* P-gp transport function in a number of chemo-resistant cancer cell lines (MOHANA et al., 2016). In a study, sixteen macrocyclic diterpenes isolated from *Euphorbia* sp. showed an MDR-reversal activity *via* P-gp dependent efflux inhibition pathway in MDR human colon adenocarcinoma cells (COLO 320 MDR) (REIS et al., 2012). The phytochemicals abyssinone IV, sigmoidin I, atalantoflavone, sophorapterocarpan A, bidwillon A, neocyclomorusin, 6*α*-hydroxyphaseollidin, neobavaisoflavone, were reported to act to impart a cytotoxic effect *via* P-gp-dependent pathway in doxorubicin-resistant CEM/ADR5000, HCT116 (*p53*−/−) and U87MG.Δ*EGFR* cells (KUETE et al., 2014d).

Isogarcinol, isoxanthochymol and guttiferone E were evident to induce apoptosis (KUETE et al., 2013b), while abyssinone IV, sophorapterocarpan A, 6’-hydroxyphaseollidin, 4’-hydroxy-2’,6’-dimethoxychalcone, guieranoneA and isoneorautenol for cell cycle arrest at G0/G1 phase. The compounds, sigmoidin I, cudraxanthone I and arborinin arrested cell cycle at G0/G1 and S phases (KUETE et al., 2112; KUETE et al., 2014c,d,e,g). Moreover, xanthone V1 and 2-acetylfuro-1,4-naphthoquinone are also evident to arrest cell cycle at S phase in CCRF-CEM cells (KUETE et al., 2011). In a study, a caspase-dependent apoptotic cell death was seen with the isogarcinol, isoxanthochymol, guttiferone E in CCRF-CEM cells (KUETE et al., 2013b). The phytochemicals xanthone V1, isoneorautenol and cudraxanthone I are also reported for their high activation of caspases-3/7, while moderate of caspases-8 and -9 (KUETE et al., 2011; KUETE et al., 2014e,f). On the other hand, 6’-hydroxyphaseollidin exhibited a low activation of caspases-3/7, -8, and -9 (KUETE et al., 2014e). Withaferin A, a steroidal lactone derived from several genera of the *Solanaceae* plant was found to inhibit the growth of temozolomide (TMZ) -resistant GBM cells as a monotherapy and in combination with TMZ, Withaferin A arrested the cell cycle at G2/M phase and inhibited the cell proliferation. Moreover, it induced an apoptotic cell death *via* intrinsic and extrinsic apoptotic pathways (GROGAN et al., 2014).

In a number of studies, isogarcinol, isoxanthochymol, guttiferone E, abyssinone IV, sigmoidin I, 6’-hydroxyphaseollidin, 4’-hydroxy-2’,6’-dimethoxychalcone and cudraxanthone I strongly disrupted mitochondrial membrane potential (MMP) in CCRF-CEM cells in a dose-dependent manner (KUETE et al., 2011; KUETE et al., 2014d,f,g). Moreover, 3,4',5-trihydroxy-6″,6″-dimethylpyrano[2,3-g]flavone induced apoptosis by the disruption of the MMP, while isotetrandrine by the overproduction of ROS in CCRF-CEM cells (KUETE et al., 2015a). In another study, Kuete et al (2015b) also found that, the cycloartocarpesin and one chalcone, isobavachalcone induced apoptotic cell death in CCRF-CEM leukemia cells *via* caspase activation and the disruption of MMP. The diterpene, triptolide showed an apoptotic cell death by regulating the ROS generation in mitochondrial pathways in the DDP-resistant HNE1/DDP nasopharyngeal cancer (NPC) cells (WANG et al., 2015). However, triptolide was also found to reverse the taxol-resistant activity in lung adenocarcinoma cell line by inhibiting the nuclear factor kappa B (NF-κB) signaling pathway (JIANG et al., 2016). According to Zhang et al (2016), a high expression of TXNDC17 (thioredoxin domain containing 17) may be linked to the taxol resistance in colorectal cancer cells. Acridone alkaloid 1,3-dimethoxy-10-methylacridone also evident to induce apoptosis in CCRF-CEM leukemia cells *via* overproduction of ROS (KUETE et al., 2015c). Plumbagin ferrocene and (p-cymene)Ru(II) conjugates were found to increase in ROS levels and cause cell death in MDR KB-V1/Vbl cervix carcinoma cells (SPOERLEIN-GUETTLER et al., 2014)

Furthermore, guieranone A in CCRF-CEM cells, caused an arrest of the cell cycle at G2/M and interfered DNA damage checkpoint regulation and ATM signaling pathways. The two most upregulated genes were detected as: *HSPA6* (heat shock 70 kDa protein 6) and *HIST1H2BD* (histone cluster 1, H2bd) (KUETE et al., 2012b).

In some studies, the bitter diterpene lactone andrographolide from *Andrographis paniculata* inhibited androgen-stimulated and castration-resistant human prostate cancer (CRPC) cells, where it significantly decreased the androgen receptor expression as well as interleukin (IL)-6 expression (CHUN et al., 2010; LIU et al., 2011). Karmakar et al (2016) demonstrated that, a pimarane diterpene isolated from *Boesenbergia pandurata* exerted an apoptotic cell death by up-regulating DR4, DR5, p53, Fas, CHOP, Bak, and cleavage of caspases-3, -8, and -9, along with a downregulation of Bcl-2, c-FLIP, and GSK-3β in TRAIL-resistant AGS cells.

Esulatin M showed a strong MDR-selective anti-proliferative activity against EPG85-257RDB and EPP85-181RDB cells (IC_{50} of 1.8 and 4.8 µM, respectively), while epoxywelwitschene and esulatin M induced apoptosis *via* caspase-3 activation in mouse T-lymphoma MDR1-transfected cell, gastric (EPG85-257) and pancreatic (EPP85-181) human cancer cells and their drug-selected counterparts (EPG85-257RDB, EPG85-257RNOV, EPP85-181RDB, EPP85-181RNOV) (REIS et al., 2016). The alkaloid jonquailine from *Narcissus jonquilla* also found to exert a synergistic anti-proliferative effect with paclitaxel in chemo-resistant lung cancer cells (MASI et al., 2015).

4. CONCLUSIONS

Cancer drug resistance continues to be a major impediment in medical oncology, due to its multi-dimensional modes. Clinically, resistance can arise prior to and/or as a result of cancer therapy. Therefore, the design of anti-cancer drugs that are fully effective necessitates a better understanding of the mechanisms by which cancer cells elude treatment.

Doubtless, the use of medicinal plants is antique and they are independent of their ethnopharmacological relevance. Many of them are already known for their sources of potential anticancer phytochemicals. This review also summarizes a number of important phytochemicals that are acting against chemo-resistant cancer cells. Interestingly, a number of phytochemicals and their derivatives are found, acting through various pathways against chemo-resistant cancer cells. More researches are necessary to understand the exact action mechanism of each phytochemical, undergoing encounter the DR/MDR cancers, aiming to meet the challenge of successful cancer treatment.

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CONFLICT OF INTEREST

None declared.

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