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Original Research

Natural agents' role in cancer chemo-resistance prevention and treatment: molecular mechanisms and therapeutic prospects

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Abstract

Cancer is a leading cause of morbidity and mortality worldwide, necessitating exploring novel preventive and therapeutic strategies. Over the years, the potential of natural agents in cancer prevention and treatment has garnered considerable attention. This review highlights the current understanding of the molecular mechanical bases underlying the role of natural agents and their therapeutic potential in combating cancer. The molecular mechanisms through which these natural agents exert their anti-cancer activities are elucidated, encompassing modulation of signaling pathways involved in cell proliferation, apoptosis, angiogenesis, metastasis, and immune response. Additionally, the review delves into the emerging research on the epigenetic modifications induced by natural agents, providing a deeper insight into their anti-cancer properties.

Keywords: anti-cancer; natural products; molecular

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INTRODUCTION

It is well known that cancer is the second cause of death globally after cardiovascular diseases. In 2017, 1.7 million people were diagnosed with cancer in the USA, and 600.000 of them died as a consequence.[1] Ninety percent of cancer-related deaths are due to developing drug resistance, leading to ineffective chemotherapeutic agents.[2]

This inefficacy can be defined as the capacity of cancer cells to reduce the potency and efficacy of chemotherapeutic agents.[3] Certain forms of cancer, such as renal and hepatocellular carcinoma cells, develop resistance. Cells can resist chemotherapeutic drugs without prior exposure. This intrinsic resistance is unsatisfactory in the first treatment.[4,5] In certain instances, cancer cells may initially demonstrate a favorable response to chemotherapy but subsequently exhibit an insufficient reaction due to the emergence of resistance (commonly referred to as acquired resistance).[3] Prior research has demonstrated that the development of drug resistance in cancer can occur through intricate mechanisms, such as the utilization of ATP-binding cassette (ABC) transporters to facilitate drug efflux, as observed in cell lines and animal models,[6] altering the proteins expression,[7,8] drug detoxification,[9] augmenting repair mechanisms in DNA,[10] apoptosis evasion,[1] and/or changes in the tumor microenvironment[11] Preclinical and clinical studies demonstrated that the host's microbiota can, in fact, alter chemotherapy and immunotherapy responses. Thus modifying the gut microbiota can facilitate overcoming medication resistance, improving cancer treatment, and restoring healthy microbiota[12]

This called for the need for investigating innovative approaches to overcoming anticancer drug resistance. Consequently, extensive research was conducted in this realm exploring the potential utilization of various approaches including drugs

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derived from natural phytochemical recourses to overcome anticancer drug resistance.[13] Additionally, using natural products derived from medicinal plants and other natural sources has shown great potential as a viable and economically efficient strategy.[14-16]

Therefore, this review aims to highlight the current understanding of the molecular mechanical bases underlying the role of natural agents and their therapeutic potential in combating cancer.

Mechanistic Underpinnings of Chemotherapy Resistance in Cancer

The phenomenon of chemotherapy resistance represents a significant challenge in cancer treatment. Malignant cells can potentially acquire mechanisms that enable them to evade therapeutic interventions. Gaining a comprehensive understanding of these pathways may facilitate the development of novel medications utilizing innovative targeting strategies, thereby offering significant clinical implications. The present section provides an analysis of medication resistance mechanisms that are clinically relevant.

Drug Efflux

Drug efflux is a prominent mechanism contributing to chemotherapy resistance. It involves the active transport of drugs out of the intracellular environment through energy-dependent pumps.[17,18] The overexpression of the multidrug efflux pumps is one of the leading causes of chemotherapy failure due to their ability to actively expel drugs from cancer cells, thereby reducing intracellular drug concentration and diminishing their cytotoxic effects, potentiating the cell's capability to evade the treatment**.**[19-22] This phenomenon may exhibit either intrinsic or acquired characteristics, indicating its presence before the cellular intervention or after drug administration.[1]

ABC transporter family are sophisticated transmembrane transporter proteins that were found to be direct drug efflux transporters.[23] In human beings, a total of 48 ABC transporters have been identified. Using a phylogenetic analysis approach, these transporters can be categorized into seven distinct subdivisions, namely ABCA through ABCG. ABC transporters depend on ATP hydrolysis to pump substrates out of cells. ABCB1, ABCG2, and ABCC1 are the most well-known ABC transporters linked to cancer multidrug resistance. ABCB1 and ABCG2 were linked with multidrug resistance in vitro. However, their in vivo association with chemoresistance in cancer patients is still ambiguous. Hence neither can be used as predictive markers.[1,23-25] Moreover, the existing body of literature suggests that they play a role in the transportation of various endogenous compounds, specifically lipids, as well as exogenous substances including toxins and pharmaceuticals.[26] These transporters are differentiated from classical selective transporters due to their ability to interact with a wide range of structurally and chemically diverse substrates, exceeding 200 in number. This characteristic is known as promiscuity.

Furthermore, their impact on tumor biology depends not solely on their capacity to remove cytotoxic drugs from cells. Besides regulating lipid export and maintaining lipid homeostasis, this group of 48 transporters also facilitates the liberation of bioactive lipids, specifically phospholipids, and sphingolipids. These free lipids subsequently activate signaling cascades involved in cellular processes such as proliferation, migration, and tumorigenesis.[27-31] Several transporters are known to play a significant role in acquiring multidrug resistance (MDR) characteristics in cancer chemotherapies. Notable examples include ABCB1, ABCC1, and ABCG2, along with various other transporters ,[23]which will be briefly discussed below.

ABCB1, or MDR1 or P-glycoprotein (P-gp), is a widely studied transporter linked to drug resistance in various tumor types, including leukemia, multiple myeloma, colorectal, kidney, and lung cancers.[27-30] A positive correlation has been observed between the overexpression of P-gp in cancer cells and their heightened resistance to various chemotherapeutic agents.[29,32-34] Thus, overexpression of ABCB1 potentiates the cell competence and hinders chemotherapy.[1] Furthermore, the efflux of drugs from the cell is linked to ATP hydrolysis and the transporter's conformational alterations.[35] This transporter has the capability to bind and transport a diverse range of drugs.

The upregulation of ABCC1, also called multidrug resistance-associated protein-1 (MRP1), is a significant contributor to the ineffectiveness of drugs in various types of cancer malignancies. ABCC1 is a 190 kDa glycophosphoprotein identified in a multidrug-resistant lung cancer cell line that did not overexpress ABCB1. It is believed that ABCC1 both induces an inflammatory response and protects cells from oxidative stress, xenobiotics, and endogenous toxic metabolites. Nevertheless, in ovarian cancer, for example, elevated ABCC1 expression contributes to disease progression and drug resistance. There was an observed upregulation of ABCC1 in both the untreated and treated samples, suggesting a potential involvement of ABCC1 in both intrinsic and acquired resistance. Comparably, a heightened level of ABCC1 transcripts was detected in ovarian cancer tissue before the administration of chemotherapy, in contrast to healthy ovarian tissue. Furthermore, it is important to mention that in vitro studies have demonstrated that the suppression of the ABCC1 gene resulted in heightened responsiveness to different chemotherapeutic agents and reduced cell proliferation in various types of malignancies.[36-40]

The ABCC1 transporter has the ability to expel various types of anticancer drugs, including vinca alkaloids, a limited number of kinase inhibitors, and methotrexate.[41] This particular transporter is also responsible for actively transporting organic anionic compounds conjugated with either glutathione (GSH), glucuronide, or sulfate. In addition to the detoxification enzymes specific to certain drugs, glutathione S-transferase (GST) demonstrates a broad detoxifying effect. GST plays a role in the detoxification process of various anticancer medications. This is achieved through the binding of a glutathione molecule to the medication, resulting in its inactivation and enhanced affinity to specific ABC transporters. Notably, these transporters primarily belong to the ABCC and ABCG families.[42-45] Thus, the use of peptidomimetic glutathione conjugate of ethacrynic

acid (EA) was able to inhibit the efflux of MRP1- transported drugs in ovarian cancer cells (overexpress MRP1).[27,46-48]

The Breast Cancer Resistance Protein (BCRP), also called ABCG2, is recognized as a primary efflux transporter for breast cancer. The expression of ABCG2 has been observed in cancer stem cells (CSCs) that are positive for CD133 in human colorectal tumors. As a result, it is regarded as a marker for malignancies associated with such CSCs.[49,50] ABCG2 was also found to be overexpressed in CD133+ CRC stem-like cells. Moreover, the downregulation of ABCG2 expression increases the apoptosis rate of CD133+ CRC-SCs significantly after chemotherapy.[8] In addition, the elimination of ABCG2 by siRNA was reported to drastically improve the chemotherapy efficacy of LS174T and CD133+ CRC cells.[51,52] The upregulation of ABCG2 has been observed to be linked with different types of malignancies.[53,54] ABCG2 has the ability to transport a diverse range of anticancer medications, including those with both positive and negative charges. ABCG2 is also referred to as Mitoxantrone Resistance Protein (MXR), which is responsible for Mitoxantrone efflux from malignant cells. It induces drug resistance by efficiently transporting a vast array of anticancer drugs, including genotoxic agents and novel Tyrosine Kinase inhibitors (e.g. Gefitinib and Imatinib)., Epipodophyllotoxin, Mitoxantrone, Camptothecins, Bisantrene, Anthracyclines, and Flavopiridol**.**[49,55]

In addition, it has been demonstrated that the upregulation of ABCC2 and ABCC3 plays a crucial role in conferring resistance to various cytotoxic agents, including Methotrexate, Cisplatin, Doxorubicin, and Etoposide. ABC transporters mediate multidrug resistance to various chemotherapeutics. ABCB1, ABCC2, and ABCG2 are also linked to chemoresistance. ABCB1, ABCC2, and ABCG2 substrates include anticancer medicines including Doxorubicin, Cisplatin, and 5-Fluorouracil, reducing cancer cell bioavailability. Many ABCB1, ABCC2, and ABCG2 substrates overlap, increasing cancer chemotherapy resistance. Inhibitors of these transporters can be utilized as chemosensitizers. Quercetin for instance was found to downregulate ABCB1 expression in Doxorubicin-resistant breast cancer MCF-7 cells, enhancing the effect of Doxorubicin, Paclitaxel, and Vincristine. Moreover, in breast cancer MCF-7 and MDA-231 cells, Quercetin downregulated Doxorubicin effluxers ABCC1 and ABCG2. It was also reported that Quercetin downregulated ABCB1, ABCC1, and ABCC2 expression, sensitizing the cells to 5-Fluorouracil, Mitomycin C, and Doxorubicin in the multidrug-resistant human hepatocellular carcinoma model BEL/5-FU. The efflux pump activity of these transporters was reduced by Quercetin, as expressed by the rise in Rhodamine-123 and Doxorubicin intracellular accumulation following Quercetin treatment [56-58]. They were found to increase chemotherapy resistance in some types of cancers.[57,59,60] Thus, a comprehensive comprehension of ABC transporters encompassing their structural, physiological, overexpression, and mutational aspects holds significant potential in developing efficacious anticancer therapeutics.

Drug detoxification

The detoxification of drugs is considered one of the prominent mechanisms to antagonize chemotherapy treatment. As it is well known, this process involves two main pathways. The first pathway (Phase I) is mediated by cytochrome P450 enzymes (CYP450), encompassing hydrolysis and oxidation-reduction reactions. CYP450 oxidases are key to drug metabolism. They metabolize anticancer medicines. Therefore, their high expression in many malignancies causes rapid turnover and drug removal before reaching the target.[20,61,62] The Phase II pathway comprises conjugation reactions, including glutathionylation, glucuronidation, acetylation, methylation, and sulfonation.[63] Phase II is considered to be a complementary stage to phase I, as its primary objective is to enhance the hydrophilic properties of the parent drug or phase I metabolite. This modification is crucial in facilitating the excretion of the drug or metabolite.[20]

Furthermore, ABC efflux transporters translocate phase II conjugated outside the cell.[42,43] As an example, the prodrug Irinotecan, which functions as a topoisomerase-1 inhibitor, undergoes hepatic metabolism facilitated by carboxylesterases, resulting in the formation of the active compound 7-ethyl-10-hydroxycamptothecin (SN-38). Subsequently, SN-38 undergoes glucuronidation and is actively transported out of the cell via ATP-binding cassette (ABC) transporters.[64] The concurrent operation of detoxification mechanisms and efflux transporters substantially diminishes the chemotherapeutic efficacy.[65] CYPs primarily expressed in the liver (constituting 90% of the body) have been shown to be conserved in cancer cells, and examined in malignancies and cancer cell lines. Therefore, CYPs may play a role in anticancer drug detoxification and biotransformation. Numerous studies highlight the corresponding substrate specificities of the CYP3A and ABCB1 (ATP-binding cassette B1) transporters. This combination of mechanisms may have led to decreasing the concentration of active pharmaceuticals in systemic circulation and target cells and thus to chemotherapy drug resistance.[66]

Glutathionylation is nother significant pathway for drug resistance conjugation, which is facilitated by the GSH-GST system.[63] Glutathione S-transferases (GSTs) are a group of enzymes that facilitate the conjugation of glutathione (GSH) to chemotherapy drugs. This process enhances the hydrophilicity of the drugs, thereby facilitating their efflux from the cell.[42,43] In the catalysis of GST P1-1, most chemotherapy drugs can bind to glutathione (GSH) to form adducts, which could be pumped out of the cells by using multidrug-resistant proteins reducing the drug retention time and resulting in reduced anticancer effectiveness in addition to severe clinical multidrug resistance in cancer cells.[67] Additionally, there have been reports indicating a proportional increase in the levels of GSH and GST with the progression of cancer stages. Nonetheless, an interindividual variability among patients was also observed, limiting this finding's clinical implication.[68] It is noteworthy to mention that a positive correlation has been examined between the expression level of the GSTπ protein and the development of drug resistance in various neoplastic conditions.[69-72]

A study has reported a correlation between the polymorphism of the GST gene and the occurrence of tumors at the genetic level.[73] GST gene polymorphism can exacerbate the aggregation of reactive metabolites in the body, thereby increasing the

likelihood of their interaction with biomolecules in the cells, triggering the oncogenesis process[74] and the efficiency of chemotherapy.[75,76]

Regrettably, a number of chemotherapeutic agents serve as substrates for detoxification mechanisms. Thus, directing attention towards the machinery within this domain may aid in surmounting the challenge of resistance.

Apoptosis inhibition

Preventing cell demise is a critical characteristic of cancer. The principal objective of anticancer drugs is to trigger programmed cell death, or apoptosis.[77] As a result, any modifications to the apoptosis system could lead to resistance to drugs.[20] Based on existing research, promoting apoptosis can make cancer cells more susceptible to chemotherapeutic drugs like 5-FU, DOX, and ActD. The process of evoking apoptosis can therefore assist in mitigating chemoresistance.[78] Two primary pathways facilitate apoptosis: the extrinsic and intrinsic pathways.[77] The extrinsic pathway activation occurs when the tumor necrosis factor family binds to their specific receptors located on the cell's surface. This event leads to caspase-8 activation, consequently triggering cellular apoptosis.[79] The initiation of the intrinsic pathways is governed by mitochondrial factors, specifically an imbalance between pro-apoptotic proteins such as BAX and BAK, and anti-apoptotic proteins such as BCL-2, BCL-XL, BCLw.[80-82] The mobilization of pro-apoptotic signaling entities primes the mitochondrial outer membrane to become permeable, triggering the release of cytochrome c and a cascade of apoptotic reactions mediated by caspases.[77]

The imbalance between pro-apoptotic and anti-apoptotic entities also serves as a critical factor in the onset of therapeutic resistance in cancer treatments.[83] In recent decades, cancer research has concentrated on medications and radiotherapy to accelerate tumor cell death, reduce tumor volume, and stop invasion. Oncology medications target several survival-promoting pathways, yet the basic apoptosis pathway induces apoptosis. BCL-2 gene identification in follicular lymphoma patients can inhibit cancer growth by increasing apoptosis. FDA also approved a BCL-2-targeted medication that regulates cancer cell proliferation and promotes apoptosis. A leukemia/non-solid tumor clinical trial used selective Bcl-2 drugs. Some solid cancers were treated with Bcl-xL inhibitors and chemotherapy. In several cancers, the inhibitor of apoptosis (IAP) proteins limit caspase activation and promote tumor cell survival, worsening prognosis.[84] Accordingly, the imbalance in cellular apoptosis regulation, characterized by the overexpression of anti-apoptotic proteins or the suppression or disruption of pro-apoptotic proteins production is a key trait of cancer cells.[83,85,86] It has been noted in various cancer types, including breast cancer, acute myeloid leukemia, and non-Hodgkins lymphoma, that there is a positive correlation between the increased expression of anti-apoptotic proteins and the capability of cancer cells to evade therapeutic interventions.[87-89] Through proteomic analysis, it was found that cells resistant to ABT-199 had higher expression of pro-growth and anti-apoptotic proteins compared to their progenitor cells. At the same time, ONO-7475 was observed to reduce these proteins in both parent and resistant cells [90]. Presumably, increased Bcl-2 and Akt levels inhibit the release of cytochrome c from the mitochondria, subsequently discouraging the apoptotic cascade.[86,91] The activation of Akt leads to the phosphorylation of NFκB, which obstructs apoptotic processes, thereby facilitating cancer cell survival. Both Akt and NFκB activate Bcl-2's inhibitory function, enhancing cellular resistance.[92] In clinical practice, developing targeted therapies to modulate pro- or anti-apoptotic protein levels may provide a potential solution for overcoming drug resistance in cancer, thereby improving clinical outcomes.

Improved DNA damage repair

Many chemotherapeutic agents, including platinum-based drugs, alkylating substances, and anthracyclines, primarily function by inducing DNA damage in cancer cells.[93] However, the effectiveness of this approach can be compromised by the cell's DNA repair responses, which can lower drug efficiency and contribute to resistance.[94,95] A variety of DNA repair mechanisms are known, such as direct reversal, mismatch repair (MMR), nucleotide excision repair (NER), base excision repair (BER), homologous recombination (HR), and nonhomologous end joining (NHEJ).[94,96, 97] including, direct reversal, mismatch repair (MMR), nucleotide excision repair The path of DNA restoration is influenced by several factors, including tissue location, the nature of the DNA-drug adduct, and the proteins involved.[20,93,96] For example, the DNA repair endonuclease XPF and the DNA excision repair protein ERCC1 are crucial in NER and inter-strand crosslink repair pathways.[98] Research has demonstrated a positive link between the overexpression of these proteins and the development of significant drug resistance, such as resistance to platinum-based drugs.[99,100]

Contrastingly, studies have reported that patients with ERCC1-negative non-small cell lung and breast tumors experienced a substantial reduction in mortality rate when treated with cisplatin-based chemotherapy compared to those with ERCC1-positive tumors.[101,102] Another instance is the resistance to alkylating chemotherapeutic agents, which was significantly associated with the overexpression of the O6-methylguanine DNA methyltransferase (MGMT) repair enzyme. Patients with glioblastoma demonstrating elevated MGMT levels exhibited poorer treatment results and higher mortality rates compared to those with lower expression levels.[103] Consequently, such proteins may serve as prognostic markers and promising therapeutic targets for various anticancer drugs.

Epigenetic alterations

In addition to previously discussed resistance strategies, epigenetic modifications represent one of the key mechanisms. These modifications primarily influence the gene expression and functionality of cells, without necessarily inducing mutations in the DNA sequence.[104,105] Epigenetic changes are hereditary genomic modifications that don't lead to a change in the DNA sequence. Such changes can arise from various mechanisms like covalent DNA modification (for example, methylation), alteration of histone proteins, or gene silencing mediated by micro-RNA (miRNA).[106] Epigenetic modifications can manifest in different forms, such as alterations related to

noncoding RNA.[1,107]

The process of DNA methylation is utilized in cellular division, wherein a methyl-group is covalently affixed to DNA cytosine through the action of DNA methyltransferases.[108] This is an essential epigenetic mechanism where DNA methyltransferases add a methyl (CH3) group to cytosines in position 5. Methylation can either stimulate or suppress the transcription of various genes, thereby regulating several cellular functions.[109] The phenomenon of hypermethylation has been noted to affect a significant number of cancer genes, leading to the suppression of tumor suppressor genes through transcriptional silencing. This is particularly evident in the CpG promoter islands of tumor suppressor genes.[110,111] In addition, several multigene panels have been clinically validated. Methylation commonly silences well-established tumor suppressor genes like CDKN2A, hMLH1, and MGMT. In addition to these, three genes associated with tumor advancement - CSF2, DIS3L2, and OAF - were examined in a study involving 120 patients with colorectal cancer. There was a noticeable correlation between the count of hypermethylated genes and disease progression tracked over five years [112]. One notable example is the substantial involvement of gene promoter hypermethylation in the manifestation of cisplatin resistance in cells of ovarian cancer.[110,113]

On the other hand, it is well-established that demethylation or hypomethylation mechanisms significantly impact the chemotherapeutic efficacy of cancer cells and enhance the activation of oncogenes. In the context of esophageal squamous cancer cells, it has been observed that hypomethylation of the ABCB1 promoter leads to an upregulation of the ABCB1 efflux transporter. This upregulation subsequently contributes to the amplification of drug resistance.[114] Furthermore, it has been revealed that the process of DNA demethylation and alterations in histone structures within the promoter region contribute to the upregulation of the protein known as thymosin β4 (Tβ4). The observed enhancement in drug resistance in a hepatocellular carcinoma (HCC) cell line is attributed to the augmentation resulting from treatment with the VEGFR inhibitor sorafenib.[115] A separate investigation exhibited that the inhibition of DNA methylation and histone modifications in cells affected by acute lymphoblastic leukemia resulted in the reversal of disease recurrence and the restoration of chemosensitivity.[116,117] As Therefore, the exploration and intervention of these resistance mechanisms could potentially offer favorable opportunities in the field of cancer therapy, as evidenced by their effectiveness in addressing resistant-heterogeneous multiple myeloma.[118]

Furthermore, epigenetic changes can also manifest as chromatin reorganization and alterations related to noncoding RNAs, which include microRNAs (miRNAs) and long noncoding RNAs (lncRNAs).[119,120] MiRNAs play a curial role in modulating the gene expression post-transcriptionally and protein synthesis.[121] On the other hand, LncRNAs lncRNAs can interact with chromatin-modifying proteins to induce structural changes in the chromatin. This can either permit or hinder the binding of transcription factors and other proteins to the DNA, which in turn can activate or repress gene expression.[119,120] DNA methyltransferase inhibitor have been used as a strategy to reverse the hypermethylation status of certain genes and overcome chemoresistance. In pediatric acute lymphoblastic leukemia (ALL), for instance, studies have shown that DNMT inhibitors can restore the expression of genes preferentially silenced during relapse, thereby improving treatment response and patient outcomes.[122] Both these noncoding RNAs contribute to chemoresistance by modulating protein synthesis. Multiple studies have demonstrated the upregulation and oncogenic potential of microRNA (miRNA) and long non-coding RNA (lncRNA) in diverse cancer types, including lymphoma, lung, breast, stomach, colon, and pancreatic cancer.[121,123-125] Hence, these epigenetic modifications could be considered potential future targets and could play a part in the hallmarks of cancer.

ATP-Mediated resistance

Chemotherapy resistance can be brought about by ATP-based pathways, which can be either inside or outside the cell. Research suggests that ATP levels inside cancer cells are typically higher than those inside healthy cells from the same source. This increase in ATP within the cell is primarily due to a boost in glycolytic metabolism via a process known as the Warburg effect.[126] This effect is a common trait observed in nearly all forms of cancer.[127,128] Furthermore, it has been reported that cancer cells resistant to drugs have higher levels of ATP within them compared to other tumor cells from the same tissue. This increased ATP is necessary for these cells to survive under conditions harmful to the cell.[129,130] This excess intracellular ATP (iATP) pool supports cancer cell growth and helps them survive metabolic stress, as shown by experiments. The activity of the efflux pump in ABC transporters, the phosphorylation of PDGFR, and the activation of the Akt-mTOR and Raf-MEK pathways are all increased, which in turn enhances resistance to a range of chemotherapy drugs and targeted tyrosine kinase medications. Cancer cells that are drug-resistant have higher ATP levels than their drug-sensitive counterparts. Elevated intracellular ATP levels, as well as ATP internalization via macropinocytosis, lead to enhanced movement and invasion by upregulating EMT-TFs and their activities.

Cancer cells exhibit heightened intracellular ATP (iATP) levels due to the Warburg effect, which involves glucose transport and aerobic glycolysis. Notably, cancer cells resistant to treatment have even higher iATP levels than their original, non-resistant counterparts. This elevated ATP content aids in the formation and maintenance of resistance. Experimental data suggest that this increased iATP pool enables tumor cells to proliferate and survive metabolic stress. Resistance to various chemotherapeutic drugs and targeted tyrosine kinase medications is also facilitated by increased iATP. This happens through the upregulation of ABC transporters' efflux pump activity, the phosphorylation of PDGFR, and the activation of the Akt-mTOR and Raf-MEK pathways. Resistant cancer cells have a greater ATP content than cells sensitive to drugs. Furthermore, by increasing the activity of EMT-TFs, the internalization of ATP (eATP) via macropinocytosis, and iATP levels, migration and invasion are enhanced.[131,132] For instance, Zhou et al.'s study found that chemoresistant colon cancer cell lines express double the amount of iATP compared

to non-resistant cells.[129,132] Conversely, the study found that sensitivity to chemotherapy increased when iATP levels were reduced and glycolysis was inhibited in the resistant cells, implying that controlling these elements can be crucial for managing chemoresistance.[129] The introduction of ATP directly into cancer cells in colon cancer cases was shown to induce a transformation from drug-sensitive to drug-resistant cells, while depleting ATP by inhibiting glycolysis restored their sensitivity to chemotherapy. This underscores that iATP levels play a critical role in determining chemoresistance.[132]

In addition to producing high levels of intracellular ATP (iATP), cancer cells can significantly uptake extracellular ATP (eATP), further increasing iATP levels, thereby enhancing drug resistance and cancer cell survival.[133] Studies show that the eATP levels in many types of cancer are 1000 to 10,000 times higher than in normal cells of the same origin.[133,134] This uptake of eATP mainly occurs via the process of micropinocytosis.[134-137] Upon internalization into the cancer cell, adenosine triphosphate (ATP) enhances the functionality of the drug efflux pathway, specifically via ATP-binding cassette (ABC) transporters. This phenomenon leads to a decrease in intracellular drug concentration, thereby facilitating the continued presence of cancer cells.[133] In addition, the presence of elevated intracellular adenosine triphosphate (iATP) levels creates a competitive environment with tyrosine kinase inhibitors (TKIs) at the binding site of receptor tyrosine kinases (RTKs). This competition leads to the activation of phosphorylation and subsequent initiation of cell signaling cascades.[138] The augmentation of ATP internalization additionally promotes the efflux of TKIs (as well as chemotherapy drugs) from the cell through the efflux transporter, consequently reducing the intracellular accumulation of TKIs and augmenting the activity of receptor tyrosine kinases (RTKs), cellular machinery, and resistance.[133] Wang et al. (year) further demonstrated that drug resistance in cancer cells is facilitated by the capacity of extracellular ATP molecules to augment the activity and upregulation of efflux-ABC-transporters.[133] eATP enhances cancer cell proliferation, migration, invasion, and therapy resistance in several cancer cell lines. Following macropinocytosis, a characteristic feature of cancer metabolism, eATP stimulates a variety of activities in cancer cells both intracellularly and extracellularly in laboratory and animal models. The internalization of eATP results in a rise in iATP levels.

Lung cancer cells have been found to absorb extracellular ATP and proteins via macropinocytosis to survive in low-energy conditions. Lung cancer exhibits high levels of extracellular ATP. Various studies have proved that non-small cell lung cancer cells can absorb this extracellular ATP, increasing intracellular ATP levels. This process fosters cancer cell proliferation and drug resistance. ATP plays a key role in controlling ABC transporters, and it has been observed that drug-resistant cancer cells possess higher ATP levels. Interestingly, when cancer cells lose ATP, their sensitivity to chemotherapy increases. Conversely, elevated intracellular ATP levels can make cells that were previously sensitive to drugs resistant to them. Extracellular ATP amplifies the activity of ABC transporters, leading to an increase in drug expulsion. It also boosts the tumor microenvironment (TME). Cancer cells absorb extracellular ATP via macropinocytosis, resulting in an unusually high intracellular ATP concentration that fosters resistance to multiple chemotherapy treatments.[55] Given these observations, focusing on strategies to block or inhibit the absorption of eATP and ABC transporters' expression or activity could significantly enhance tumor cells' sensitivity to anti-cancer drugs.

Targets of natural agent in the treatment of cancer that is resistant to chemotherapy

The phenomenon of a specific form of cancer exhibiting resistance to multiple pharmaceutical agents is commonly referred to as the emergence of multidrug resistance (MDR).[139] A potential approach for mitigating drug resistance involves targeting the underlying mechanisms that contribute to its development. The present comprehension of these overarching mechanisms encompasses enhanced drug efflux, diminished drug influx, drug inactivation, repair of drug-induced damage, modifications in drug targets, and evasion of apoptosis. One instance of a particular mechanism involves the upregulation of resistance transporters or genes that have the ability to augment the efflux of drugs.[140]

The development of MDR in cancer cells is related to drug efflux, which is facilitated by membrane transport proteins.[141] The overexpression of ATP-binding cassette (ABC) membrane transport proteins is a major factor contributing to resistance and chemotherapy failure in several types of cancer.[142-144]

An increased efflux, or expulsion, of chemotherapeutic drugs from cancer cells results in decreased intracellular drug concentrations by actively pumping drugs out of the cells. Drug efflux transporters are primarily implicated in developing multidrug resistance (MDR) in cancer cells [145, 146] The aforementioned membrane transport proteins possess the capacity to eliminate pharmaceutical substances from cellular environments and facilitate their subsequent redistribution. This redistribution process lowers drug concentrations within cellular organelles to levels below those required to cause cell death, which further amplifies drug resistance. Several proteins known to be associated with MDR include P-gp, MRP, BCRP, and LRP.[146] **(Figure 1).**

P-Glycoprotein

Permeability-glycoprotein (P-gp) or multidrug resistance protein-1 (MDR-1) is an ATP-binding cassette (ABC) glycoprotein that is encoded by the ABCB1 gene in humans.[145] ATP binding to the cytoplasmic part of the cell membrane transporter glycoprotein activates the ATP-binding domains. Substrate efflux arises from the following hydrolysis of ATP, which alters the shape necessary for transporter functioning.[145] P-gp can bind drugs penetrating the plasma membrane.[141,145,147] It maintains physiological homeostasis by protecting cells from xenobiotics and cellular toxicants.[148,149] P-gp expression differs between cancers. P-gp expression is highest in colon, pancreas, liver, adrenal glands, and kidneys cancers. P-gp expression is moderate in soft tissue carcinomas, neuroblastomas, and hematological malignancies. P-gp levels rise after chemotherapy resistance in lung, breast, esophageal, and

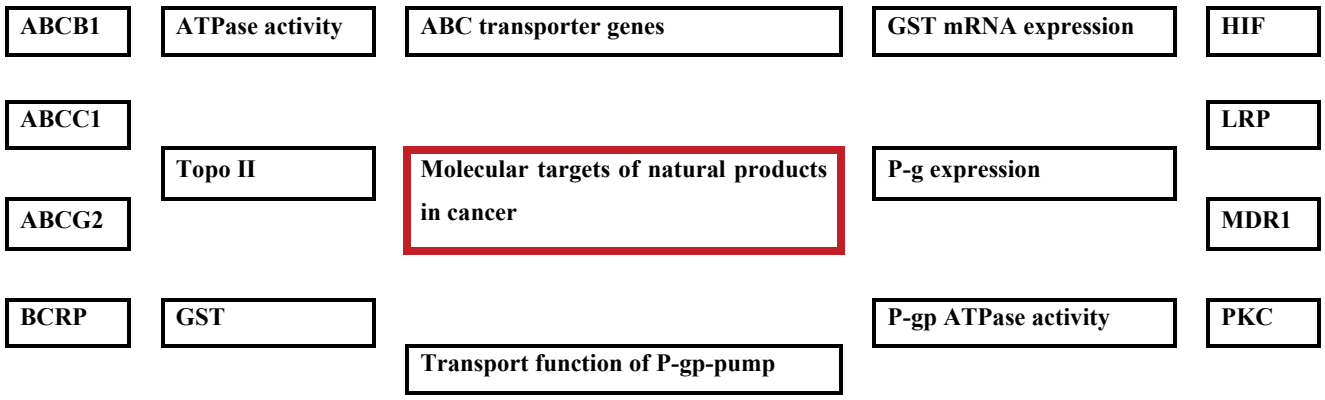

Figure 1. Molecular targets of natural agents in cancer

ovarian cancers.[145,150] Overexpression of P-gp is typically linked to MDR as they lowers intracellular drug concentration.[146,150] Multiple generations of P-gp inhibitors were created to circumvent MDR and enhance the efficacy of chemotherapy in MDR malignancies.[143,145,148,151] MDR chemosensitizers or P-gp modulators with cytotoxic drugs, efflux pump substrates, may restore efficacy in resistant tumor cells.[152]

First-generation P-gp inhibitors are weak, non-selective, and low-affinity. To reverse MDR, high doses of these inhibitors cause toxic adverse effects. Second-generation P-gp inhibitors are more selective yet hinder chemotherapeutic drug metabolism and excretion. Third-generation P-gp inhibitors solved the shortcomings of second-generation, namely cytochrome P450 interaction.[145] The initial three iterations exhibited unanticipated toxicities, non-specific inhibition, and unforeseen interactions in terms of pharmacokinetics between chemotherapeutic agents and potential P-gp inhibitors. Researchers are employing alternative approaches in developing fourth-generation P-gp inhibitors derived from natural compounds, aiming to enhance their safety profile.[148,151,153,154]

Stemofoline, a plant alkaloid from Stemona bukilli, has been shown to raise the intracellular accumulation of P-gp substrates and increase the sensitivity of MDR leukemic cells to chemotherapy (calcein AM and rhodamine 123). According to western blot research, it does not affect P-gp expression.[155] Chang et al. examined wilforine, a sesquiterpene pyridine alkaloid, and P-gp expression and function. Wilforine re-sensitized MDR cancer cells to chemotherapeutic medicines while suppressing P-gp efflux in a concentration-dependent manner.[156] Another study suggests that natural sesquiterpene lactones tenulin and isotenulin may be synergistic MDR cancer treatments. By increasing P-gp ATPase transporter activity, this study inhibits P-gp activity.[157] In addition, doxorubicin reduced P-gp function in human colon cancer (Caco-2) and leukemia cell lines when administered with non-toxic polyphenols like epigallocatechin gallate (EGCG), tannic acid, and curcumin.[158] Furthermore, the western blot results indicate a decrease in the level of P-glycoprotein subsequent to the administration of curcumin treatment in the drug-resistant K562/DOX cell line of chronic myeloid leukemia. Additionally, this treatment improves the cells' responsiveness to chemotherapy.[159] Further, a reduction in P-gp expression was observed in A2780/Taxol cells that exhibited resistance following the co-administration of curcumin and piperine via solid lipid nanoparticles.[160]

According to Teng et al. (2020), caffeic acid exhibits potential as a natural product for mitigating cancer MDR. The compound was found to impede the efflux of P-gp by binding to specific residues, namely GLU74 and TRY117, in human cervical cells (KB/VIN).[161] A recent study has indicated that quercetin exhibits a dose and time-dependent impact on the expression of P-gp in cervical cell lines, specifically HeLa and SiHa. Based on the findings from the western blot analysis, it was observed that the co-treatment group, consisting of both quercetin and cisplatin, exhibited reduced levels of P-gp expression in comparison to the groups treated with each drug individually.[162] Besides, other studies have shown quercetin downregulation on P-gp efflux function.[163-165] Kaempferol, a naturally occurring flavonoid, can counteract MDR in HepG2 and N1S1 liver cancer cells through downregulating P- overexpression.[166] By inhibiting the expression of P-gp, the natural compound emodin has demonstrated anticancer properties and increased chemotherapy sensitivity in lung cancer cell lines (A549 and H460).[167] Furthermore, it exhibited the ability to counteract drug resistance and augment the susceptibility of cisplatin in A549/DDP cells.[168] Ecteinascidin 74, a naturally occurring substance derived from Caribbean Sea squirts (Ecteinascidia turbinate), inhibits P-gp expression at nanmolar concentrations. Cervical cells that overexpressed P-gp also collected more doxorubicin/vincristine.[169] Sophocarpidine from Sophora flavescens, vincristine, and Adriamycin all inhibited P-gp expression in KBV200 cells. [146] Piperine is an alkaloid found in the plant Piper nigrum, also known as black pepper. P-glycoprotein, breast cancer resistance protein, multidrug resistance-associated proteins, and ATP-binding cassette transporter genes, specifically ABCB1, ABCG2, and ABCC1, were shown to have lower expression. This process has the ability to overcome multidrug resistance in cancer cells.[170-173]

The modulation of P-gp in resistant cancer cell lines (KB-vin and NCI-H460/MX20) and the concentration-dependent stimulation of basal ATPase activity by β-carotene have been documented in previous studies.[150,170] The compound Schisandrin A (also known as Deoxyschizandrin), obtained

from Fructus Schizandrae, exhibited the ability to counteract resistance to DOX that P-gp facilitated in MCF-7/DOX cells. This was achieved by inhibiting P-gp, Stat3, and NF-κB signaling pathways.[174] Salvia miltiorrhiza's tanshinone microemulsion can also reverse K562/ADM cells' drug resistance by blocking the P-gp efflux pump and enhancing chemotherapeutic drug accumulation.[147] Magnolia officinali bark contains honokiol and magnolol. They suppressed P-gp in NCI/ADR-RES cells and increased P-gp substrate (calcein) accumulation in cells. In U937/ADR cells, magnolol reverses MDR by suppressing NF-KB, p65, and MDR1 and P-gp expression.[146,175] Cepharanthine, coumarins, cycloalkanes, and euphocharacins A-L work as P-gp inhibitors in different cancer cell lines.[170] Other phytochemicals that inhibit P-gp are available in Table 1.

Multidrug Resistance Proteins

The transmembrane transporters known as Multidrug resistance proteins (MRPs) are categorized under subfamily C in the ABC transporter superfamily. It is widely recognized that they facilitate the active removal of diverse substrates, thereby resulting in multidrug resistance (MDR). The MRP family comprises 13 members, designated as MRP1 through MRP13. The ABCC2 gene is responsible for encoding the Multidrug Resistance Associated Protein-1 (MRP-1) in the human body. The phenomenon of drug resistance in various cancers has been extensively investigated due to its significant implications. MRP1 is characterized by its unique attribute of being a basolateral transporter. The aforementioned statement suggests that the activity of MRP1 leads to the translocation of substances into subepithelial cells located under the basement membrane. The transporter mechanism inhibits the drug's absorption and facilitates the efflux from the intracellular environment.[145] MRP-1 demonstrated a substrate preference for negatively charged compounds, including endogenous, chemotherapeutics, and natural products.[145,147,150] This suggests that the transportation mechanism of MRP1 differs from that of P-gp.[145]

The gene encoding for MRP1 exhibits ubiquitous expression across various tissues in the body, such as the lungs, testes, skeletal muscles, and cardiac muscles. Therefore, it is widely distributed in numerous types of tumors, such as breast cancer, and serves a significant function in MDR. A potential approach to address MDR caused by MRPs is to impede the activity of these transporters.[145,176] Multiple MRP inhibitors alter MRPs to re-sensitize cancer chemotherapy medicines.[177] Inhibitors of the MRP1 have demonstrated the ability to counteract drug resistance and enhance the sensitivity of drug-naïve cancer cells to anticancer medications.[176] Natural compounds impede MRPs efflux. Resveratrol, a polyphenol molecule found in many fruits and vegetables, has impacted MRP1 and P-gp function in multidrug-resistant human colon cancer and increased doxorubicin cytotoxicity.[178]

The administration of curcumin to MCF-7 breast cancer cells that have developed tamoxifen resistance has been observed to augment the cells' responsiveness to tamoxifen while concurrently impeding the activity of MDR proteins, specifically through the reduction of MRP2 mRNA expression.[179] Curcumin also reversed cisplatin chemo-resistance in SiHa cervical cancer cells by downregulating MRP1 and P-gp1 expression (Roy and Mukherjee 2014). Quercetin, a natural polyphenol, modulates efflux transporters and other pharmacological actions. It lowered drug efflux transporter expression in triple negative breast cancer cells. (MDA-MB-231).[180] EGCG, a polyphenolic catechin in green tea, affects 5-fluorouracil resistance by suppressing MDR-related proteins in gastric and colorectal cancer cells.[181,182] 7,3',4'-trihydrox The BCRP transporter is classified as a half-ABC transporter due to its possession of a single ATP-binding cassette and six transmembrane domains. There exists a hypothesis suggesting that the functionality of BCRP may necessitate the formation of a homodimer or homooligomer. Yisoflavone (THIF) represents the primary metabolite derived from daidzein. When the combination of THIF and adriamycin was administered, it was observed that the mRNA expression levels of P-gp, MPR1, and MRP2 were comparatively lower than those observed when adriamycin was administered alone [146]. Besides, strychnine decreased MRP's gene expression but not P-gp[146] (Table 1).

Table 1. A comprehensive list of natural products and their associated mechanisms of inhibition

Mechanism of inhibition	Substances
↓ The utilization of [3 H] azidopine photoaffinity labeling in the context of P-gp research implies a potential direct interaction between azidopine and the substrate binding site of P-gp.	Silymarin
↓ ABC transporter genes (ABCB1, ABCG2, and ABCC1)	Piperine
↓ ABCB1	Taxifolin
↓ ABCG2	Epigallocatechin gallate,Berberine (isolated from ancient Chinese herb Coptis chinensis French),Marsdenia tenacissima.
↓ ABCG2 and ABCC1	Curcumin
↓ ABCG2-mediated efflux	Tenacigenin B: P8, P26 and P27
↓ ATPase activity	Catechin,Green tea catechins
↓ ATP-binding cassette transporters	Yu Ping Feng San, Astragali Radix, Atractylodis Macrocephalea Rhizoma, Saposhnikoviae Radix

↓ BCRP	Harmine, Acacetin, Apigenin, Biochanin A, Chrysin, Diosmetin, Genistein, Kaempferol, Luteolin, Naringenin-7-glucosid Quercetin, Silymarin, Tangeretin, Curcumin, Protopanaxatriol ginsenosides 20S-ginsenoside Ginsenoside Rb1 Ginsenoside Rg3 Cannabinoids, Hypericin and hyperforin, Piperine, Terpenoids, 3'-4'-7-Trimethoxyflavone, 6-Prenylchrysin, Eupatin, Daizein, Hesperetin, Plumbagin, Resveratrol, Rotenoids, Stilbenoids, Tectochrysin, Tetrahydrocurcumin Gypenoside, Fumitremorgin C, Tryprostatin A, Terrein, Lamellarin O, Secalonic acid D, Reserpine and yohimbine (isolated from Rauwolfia serpentine), Kaempferide, Daidzein, Tanshinone IIA (isolated from Salvia miltiorrhiza), Heterotheca inuloides Cass, Kanglaite(isolated from Coix lacryma-jobi).
↓ binding of [3 H] azidopine to P-gp	Ginsenoside Rg_3
↓ Calcein efflux	Myricetin
↓ gene and protein expression of MRP	Strychnine
↓ GST	Fucoxanthin,Yu Ping Feng San, Fisetin
↓ GST mRNA expression	Resveratrol
↓ GSTπ	Curcumin, Ginger phytochemicals, Emodin, Oridonin, Chinese herbal supplement energy and nourish lung
↓ HIF-1α	Apigenin, Epigallocatechin gallate, Quercetin, Curcumin, Resveratrol, Emodin, Nuciferine.
↓ LRP	Protopanaxatriol, ginsenosides,20S-ginsenoside,Ginsenoside Rb1, Ginsenoside Rg3, Tetrandrine (dried root of Stephania tetrandra),Paeonol (extracted from the dry velamen of peony or any part of Cynanchum paniculatum), Oridonin, Peimine, Shen-qi-jian-wei Tang
↓ MDR1	Glau,Green tea catechins, Epigallocatechin gallate, Quercetin, Protopanaxatriol ginsenosides 20S-ginsenoside Ginsenoside Rb1 Ginsenoside Rg3 Bisdemethoxycurcumin,Honokiol and magnolol (isolated from Magnolia officinali), Schisandrin A (Deoxyschizandrin),Triptolide Three hydroxyl soy isoflavone,Paeonol (extracted from the dry velamen of peony or any part of Cynanchum paniculatum and derivatives of epimedium),Allicin Shen-qi-jian-wei Tang,Heterotheca inuloides Cass,Kanglaite, Astragalus membranaceus polysaccharides Astragaloside II, another component from A. membranaceus.
↓ MDR1 and MRP1 genes	Glaucine
↓ MDR1 gene	Saikosaponin D
↓ MDR1 gene expression	Berbamine,O-(4-ethoxyl-butyl)- berbamine, Staurosporine
↓ MDR1 mRNA	Antofine,Tetramethylpyrazine,Gravacridonetriol,Curcumin, Antofine, Ephedrine, Vauqueline, Gravacridonetriol, Clitocine Sulfinosine,Praeruptorin A (extracted from Radix Peucedani).
↓ MDR1 mRNA expression	Pyranocoumarins
↓ mRNA expression of MRP, MDR1, and MRP2	7,3',4'-trihydroxyisoflavone
↓ mRNA expression of P-gp, MRP1, MRP2, and MRP3	Xanthohumol (derived from Humulus lupulus)
↓ MRP1	Glaucine, Acacetin, Apigenin, Biochanin A, Chalcone, Genistein, Kaempferol, Luteolin, Morin, Nobiletin (found in citrus fruit), Phloretin, Curcumin, Matairesinol (found in soybean (Glycine max), Glycyrrhetinic acid (Enoxolone)(Licorice), Protopanaxatriol ginsenosides 20S-ginsenoside Ginsenoside Rb1 Ginsenoside Rg3, Tenacigenin B: P8, P26 and P27, Tenacigenin B: P2, P3 and P6, Glaucine Schisandrin B (Sch B), Ginger phytochemicals (6-Gingerol, 10- Gingerol) Ginger phytochemicals (6-gingerol, 10-gingerol, 4-shogaol, 6-shogaol, 10-shogaol, and 6-dehydrogingerdione) Cepharanthine, Ginkgo biloba extract, Kaempferia parviflora extracts, Three hydroxyl soy isoflavone, Emodin, Gypenoside, Baicalin, Cinobufacini, Wogonin, Aposterol A, Fumitremorgin C, Secalonic acid D, Silybin (isolated from Silybum marianum), Sophoraisoflavone A, Tanshinone IIA (isolated from Salvia miltiorrhiza), Marsdenia tenacissima, Heterotheca inuloides Cass.
↓ MRP1 and MRP2 activity	Myricetin
↓ MRP1 and MRP2 activity (inhibited calcein efflux)	Robinetin
↓ MRP1 protein expression	Triptolide
↓ MRP1, 4 and 5	Quercetin
↓ MRP1, MRP2, MRP3	Tetramethylpyrazine,Xanthohumol(derived from Humulus lupulus).
↓ MRP1-mediated drug transport	Quercetin
↓ MRP1-mediated drug transport	Silymarin
↓ MRP2	Tryptanthrin,Three hydroxyl soy isoflavone,Kanglaite (isolated from Coix lacryma-jobi).
↓ MRPs	Guggulsterone, Baicalein and derivatives, Cannabinoids, Piperine, (Paeonol (extracted from the dry velamen of peony or any part of Cynanchum paniculatum) Beta-Elemene (isolated from Aeruginous Turmeric rhizome)), (As2O3, or white arsenic Arsenic Trioxide), Sodium norcantharidate, Brucea Javanica, Hyaluronate Oligomers, Jew ear.

↓ P-g expression	Dauriporphine, GlaucinHernandezine, Antofine, Tryptanthrin, Lobeline (from Lobelia inflate), Tetramethylpyrazine, Danshensu and tetramethylpyrazine (from the Chinese herbs), Acrimarine E, 2-Methoxycitpressine I, Capsaicin (extracted from Capsicum annuum), Amorphigenin, Apigenin, Ampelopsin, Biochanin A, Catechin, Chalcone, Chrysin, Green tea catechins (EGCG, ECG, CG), Epicatechin gallate, Epigallocatechin gallate, Formononetin, Glabridin, (3, 3', 4', 5, 6, 7, 8-Heptamethoxy-vone), Kaempferol, Mori, Naringenin, Nobiletin (found in citrus fruit), Phloretin, Procyanidine, Quercetin, Rotenone, Tangeretin, Curcumin, Matairesinol (found in soybean (Glycine max)), Sesamin, Gomisin A, Schisandrol A, Ginkgolic acid, beta-Amyrin, Glycyrrhetinic acid (Enoxolone) (Licorice), Obacunone, Oleanolic acid, Uvaol, Alisol B 23-acetate, Ginsenoside Rg3, Protopanaxatriol ginsenosides 20S-ginsenoside Ginsenoside Rb1 Ginsenoside Rg3, Tenacigenin B: P8, P26 and P27, Tenacigenin B: P2, P3 and P6 Tenacigenin B: P1, P4, P5, P9 and P28, Aurochrome, Diepoxycarotene, Mutatochrome, Glaucine, Fangchinoline, Tetrandrine (dried root of Stephania tetrandra), Matrine, Antofine, Ephedrine, Indole-3-carbinol, Staurosporine, Vauqueline, Clitocine, Sulfinosine, Bisdemethoxycurcumin, Honokiol and magnolol (isolated from Magnolia officinali), Schisandrin A (Deoxyschizandrin), Pyranocoumarins, Ginger phytochemicals (6-Gingerol, 10- Gingerol), Alisma orientalis, Piper methysticum, Guggulsterone, Phenolic diterpenes, Vincristine, 5-Bromotetrandrine, Abietane diterpene, Amooranin, Baicalein and derivatives, Bitter melon extract, Bufalin, Cannabinoids, β-Carotene, Catechins, Cepharanthine, Coumarins, Cycloartanes, Didehydrostemofolines, Eudesmin, Euphocharacins A-L, Ginkgo biloba extract, Grapefruit juice extracts, Hapalosin, Hypericin and hyperforin, (Isoquinoline alkaloid, isotetrandrine), Isostemofoline, Jatrophanes, Kaempferia parviflora extracts, Kavalactones, Ningalin B and derivatives, Opiates, Piperine, Polyoxypregnanes, Sesquiterpenes, Tenulin, Sinensetin, Taxane derivatives, Terpenoids, Tetrandine, Vitamin E TPGS, Resveratrol, Ligustrazine, Sophocarpidine, Ecteinascidin, Ecteinascidin 743, Paeonol (extracted from the dry velamen of peony or any part of Cynanchum paniculatum), (3', 4', 5', 5, 7-pentamethoxyflavone (PMF) and derivatives of epimedium), Osthole (isolated from Fructus Cnidii), Praeruptorin A (extracted from Radix Peucedani), Diphyllin, Emodin, Psoralen, Gypenoside, Allicin, Taccalonolide A and B (extracted from Tacca chantrieri), Oridonin, Ursolic acid (found in Rosmarinus officinalis), Sipholenol A (found in sponge Callyspongia siphonella), Cantharidin (extracted from Mylabris phalerata Pallas or Mylabris cichorii L), Beta-Elemene (isolated from Aeruginous Turmeric rhizome), (As2O3, or white arsenic Arsenic Trioxide), Artemisinin, Artesunate, Baicalin, Berberine (isolated from ancient Chinese herb Coptis chinensis French), (Carnosic acid (Rosemary) Chelerythrine), Gambogic acid, Neferine, Oxymatrine, Sodium norcantharidate, Brucea Javanica, Cinobufacini, Grape seed polyphenols, Hyaluronate Oligomers, Jew ear, Radix notoginseng, Rhizoma pinelliae, Realgar, Thallus laminariae, Dihydroptychantol A (isolated from A. angusta), Riccardin F (isolated from P. intermedium), Riccardin D, Andrographolid, Parthenolide, (Rhei Rhizoma, Scutellariae Radix, Poria, Zizyphi Fructus, Zingiberis Rhizoma, Asiasari Radix, Sophorae Radix (Herbal extract)), Tripterygium wilfordii, Shenghe Powder (consisting of Radix codonopsis pilosulae, Radix pseudostellariae, Radix scrophulariae, Rhizoma atractylodis macrocephalae, and additional 6 herbs), Icaritin, Icariin, Sesquiterpene ester 1, Celafolin A-1, Celorbicol ester, Demethoxycurcumin, Euphomelliferine, Euphodendroidin D, Pepluanin A, Sipholenone E, Siphonellinol D, GUT-70 (From C. Brasiliense), Lamellarin I, Wogonin, Aposterol A, Fumitremorgin C, Lamellarin O, Secalonic acid D, Quinine and its isomer quinidine, Reserpine and yohimbine (isolated from Rauwolfia serpentine), Bromocriptine ergot alkaloid, β-Sitosterol-O-glucoside, cardiotonic steroid 3, Menthol, Aromadendrene, Citronellal, Citronellol, Carnosol, Limonin, Kaempferide, Diosmin tanshinone microemulsion, tea polyphenol, Stemocurtisine, Stemofoline, Oxystemokerrine, amurensin G (from Vitis amurensis), Sakuranetin, Floretin, Fisetin, Silybin (isolated from Silybum marianum), LANGDU a traditional herbal medicine, Tanshinone IIA (isolated from Salvia miltiorrhiza), Auraptene(Grapefruit), Nimbolide, Marsdenia tenacissima, taxifolin, Saikosaponin D, (Astragalus membranaceus polysaccharides Astragaloside II, another component from A. membranaceus), Wilforine, (Boswellia serrata extracts 3- O-acetyl-11-keto-β-boswellic acid (AKBA), the major active ingredient of the gum resin from Boswellia serrata and Boswellia carteri Birdw), Pervilleine F, Ellipticine, cnidiadin, Conferone, Rivulobirin A, Dicamphanoyl khellactone (DCK), Cannabidiol Taccalonolides A, Jolkinol B, Portlanquinol, Dihydro-β-agarofuran, pentadeca-(8, 13)-dien-11-yn-2-one, Silibinin, Nirtetralin, Cordycepin.
↓ P-gp ATPase activity	Silymarin, Chlorogenic acid, Agnuside, Picroside-II, Santonin, Acteoside (Verbascosine)
↓ P-gp-mediated cellular efflux	Silymarin
↓ P-gp-mediated drug efflux	Clausarin
↓ PKC	Quercetin
↓ PKC	Schisandrin A (Deoxyschizandrin)
↓ PKC-α and –ζ	Curcumin
↓ Topo II	Riccardin D
↓ Topo II**α**	Curcumin
↓ Topo II**β**	Emodin
↓ Transport function of P-gp-pump	Algerian propolis

Breast Cancer Resistance Protein (BCRP)

The BCRP is an integral component of the ATP-binding cassette (ABC) transporters belonging to the ABCG subfamily. In humans, the BCRP is encoded by the ABCG2 gene. The initial detection of this phenomenon occurred in a human breast cancer cell line that exhibited resistance to drugs and was subjected to a combination treatment of mitoxantrone and tariquidar, a substance that inhibits P-glycoprotein. The functionality of BCRP is dependent on dimerization, as it is a half-transporter.[145,150] The BCRP protein is categorized as a half-ABC transporter because it possesses a solitary ATP-binding cassette and six transmembrane domains. The probable action mechanism of BCRP involves forming a homodimer or homooligomer.[183,184] The BCRP protein is primarily found

in the cellular membranes of multiple organs, including the gastrointestinal tract, liver, kidney, brain, endothelium, mammary tissue, testis, and placenta. The main purpose of this mechanism is to facilitate the active transportation of a wide variety of both endogenous and exogenous substances, such as sulfate conjugates, taxanes, carcinogens, glutamate folates, and porphyrins, from within the cells to the extracellular environment.[185,186] In addition, it is imperative to note that the BCRP plays a crucial role in facilitating intercellular processes such as drug absorption, metabolism, excretion, and toxicity.[145] BCRP's function as a drug efflux transporter contributes to MDR and has been extensively investigated. Overexpression of BCRP has been considered one of the sources of MDR in various hematopoietic and solid tumors.186 Besides being present in cell membranes, BCRP is also detected in intracellular vesicles. The vesicles typically exhibit drug retention; however, the BCRP swiftly expels the drugs.[145] The BCRP efflux transporter is identified as an additional factor contributing to the escalation of drug resistance. The expression of BCRP is notably elevated in the side-population cells of breast cancer. These cells exhibit characteristics similar to stem cells and demonstrate a high degree of resistance to chemotherapy. the efflux of anticancer drugs.[145] There exists a notable association between elevated ABCG2 expression and unfavorable prognosis among individuals diagnosed with leukemia.[187]

The BCRP efflux transporter is identified as a contributing factor to the escalation of drug resistance, providing an additional rationale for this phenomenon. Breast cancer side-population cells exhibit a high expression of BCRP. These cells exhibit characteristics similar to stem cells and demonstrate high resistance to chemotherapy.[145] Regrettably, the development of clinically effective inhibitors targeting BCRP has been limited. Hence, there remains a requirement for developing novel and targeted inhibitors of the BCRP to enhance the efficacy and overall success of pharmacological interventions.[184,186] Harmine, a β-carboline alkaloid, has been historically employed in traditional medicine for its potential application in anticancer therapy.[188] The compound was recognized as a BCRP inhibitor in the MDA-MB-231 breast cancer cell line, exhibiting BCRP overexpression. The study demonstrated that while the P-gp over-expressing CEM/ADR5000 cells remained unaffected, the resistance of methotrexate and cisplatin in MDA-MB-231 cells was successfully reversed.[169,170,175] The flavonoid compound Acacetin, which exhibits mild estrogenic activity, has been found to possess potent reversal activity against BCRP-mediated drug resistance in K562 cells that have been transduced with BCRP.[170,175] Moreover, many flavonoids such as apigenin, biochanin A and chrysin reversed BCRP-mediated drug resistances.[175,189] Biochanin A is an antimutagenic isoflavone that is present in red clover. It inhibited the MDR-associated proteins p-gp, MRP1, and BCRP.[169,170,175] Other flavonoids, including diosmetin, genistein, kaempferol, luteolin, naringenin-7-glucoside, and quercetin, have been reported to inhibit BCRP activity.[175] Tangeretin, a natural polymehoxyflavone, inhibited BCRP potently and suppressed MDR markers significantly.[169,175] (Table 1)

Lung Resistance Protein (LRP)

LRP is a transmembrane protein encoded by the LRP gene.[145] The human major vault protein (MVP or VAULT1), known as LRP, is primarily found in nuclear pore complexes and plays a role in facilitating bidirectional nucleocytoplasmic transport of molecules. The expression of LRP is typically observed in the bone marrow. There is a correlation between elevated or positive expression levels and unfavorable outcomes in leukemia, as well as various types of solid tumors.[190] The initial identification of this phenomenon occurred in the SW-1573 cell line, which is associated with non-small cell lung cancer. The protein is localized within the cytoplasm as well as the nuclear membrane of tumor cells. These vaults' involvement in MDR could be attributed to their ability to regulate the transport of drugs between the nucleus and cytoplasm. The phenomenon of LRP has been observed to result in the development of resistance to a variety of drugs, such as doxorubicin, vincristine, cisplatin, carboplatin, and epipodophyllotoxin.[145,146] LRP, unlike MRP and P-gp, does not belong to the ABC superfamily of transporter proteins. Its transmembrane transport domain lacks the ATP-binding site of ABC transporters. It transports the nucleus and cytoplasm, not the cell membrane.[147] The downregulation of LRP has been found to be effective in overcoming chemotherapeutic resistance in various natural products. Ginsenoside Rg3 represents one of the primary ginsenosides obtained from the ginseng plant. The compound has been observed to impede the growth of tumor cells in both animal models and cell cultures. Additionally, it specifically targets MDR factors, in cells that exhibit resistance to treatment.[191-193] Peimine, a Fritillaria alkaloid, reversed MDR in A549/cisplatin-resistant lung cancer cells by suppressing of ERCC1 mRNA and LRP expression.[194] Paeonol, a natural phenolic compound, has been identified as a mediator in the inhibition of LRP, P-gp, and MRP in cells exhibiting multidrug resistance.[146]

Protein kinase C (PKC)

PKC is a class of serine/threonine kinases dependent on phospholipids and primarily located in the cytoplasm. This kinase family comprises at least 12 isozymes.[195,196] These isozymes classified into three main groups.[197,198] Tumorigenesis and drug resistance are associated with interrupting PKC regulation.[195] Inhibiting PKC has been demonstrated to improve drug resistance and conventional chemotherapy cytotoxic activity in preclinical trials.[196,199,200] Compared to normal cells, MDR tumor cell lines upregulated PKC in the cytosol and nucleus [201-204]. The activity of PKC is controlled by several phosphorylation reactions and the binding of cofactors.[205] PKC isozymes may be activated by Ca^{+2}, diacylglycerol (DAG), and phospholipids.[206] A positive association was observed in MDR cancer cell lines between elevated transduction signaling of PKCs, specifically cPKC and nPKC, and the increased phosphorylation of P-gp, along with the induction of intracellular MDR phenotypes.[196,207,208] Plant-derived compounds blocking PKCs can reverse MDR in cancer cells.[9] Polyphenolic curcumin suppressed PKC-α and – in breast cancer cell lines (MCF-7 and MDA-MB-231), sensitizing tumor cells to chemotherapeutic treatments.[209] Flavonoids like quercetin also inhibited PKC signal transduction in hepatocellular carcinoma.[210] Russo et al. have found that activation of PKCα by quercetin induced apoptosis in CD95-resistant cell lines.[211]

Glutathione transferase (GSTs)

GSTs are a class of multifunctional enzymes recognized as phase II metabolic enzymes, which function as cellular detoxification agents. The reducing agent, glutathione, is conjugated with xenobiotics and endogenous molecules, converting these substances into more water-soluble compounds. This process facilitates their excretion.[212] The GST family encompasses various classes of isozymes, namely α, Σ, Z, Ω μ, π, and θ, which play a pivotal role in the conjugation process of a diverse array of substance. [213,214] Furthermore, it has been observed that an elevated intracellular concentration of GSTs is correlated with the acquisition of MDR in cancer cells.[215-217] The reducing activity of GSTs facilitates drug resistance in tumor cells by detoxifying the drugs, reducing cells' sensitivity to chemotherapy.[214,218] Multiple studies have demonstrated a correlation between the overexpression of GSTs and the development of resistance to chemotherapy in diverse cancer types, including lung cancer,[219-221] breast cancer,[222-224] brain,[225, 226] and gastric cancer.[227,228] Numerous natural and synthetic inhibitors of GST have been extensively studied in order to regulate multidrug resistance in cancer cells.[212] Curcumin has been known for its reducing, anti-inflammatory, and chemopreventive activity.[214,229] It affects MDR markers by inhibiting GSTπ in the non-small cell lung carcinoma cell line (NCI-H460/R).[230] Besides, it decreased drug resistance in melanoma cells by downregulating GST and MRP1.[231] Emodin is a natural anthraquinone in several herbal medicines.[232] Through many pathways, it exhibited a reversal effect on multidrug-resistant promyelocytic leukemia (HL-60/ADR cells) and human oral squamous carcinoma (KBV200 cells). One was the reduction of GSTπ.[233,234] Recent research has also stated the inhibitory activity of emodin and quercetin on GSTπ to overcome MDR in tumor cells.[235] Additionally, it was observed that fisetin, a flavonol compound derived from plants, exhibited a significant decrease in the expression of GST in colorectal adenocarcinoma cells (Caco-2). This finding suggests that fisetin holds potential as a chemosensitizer for GST modulation in the context of MDR.[236] Yu Ping Feng San (YPFS) is a widely recognized traditional Chinese herbal formulation that consists of three key ingredients: Astragali Radix, Saposhnikoviae Radix, and Atractylodis Macrocephalea Rhizoma. Du et al. conducted an investigation into the impact of YPFS on cisplatin-resistant lung cancer, specifically A549/DDP cells. The intervention resulted in a decrease in MDR-associated proteins and enzymes, specifically ATP-binding cassette transporters and GST isozymes.[237] A combination of Chinese herbal ingredients known as Supplement Energy and Nourish Lung (SENL) was utilized in a study involving multidrug resistant human lung adenocarcinoma A549/DDP cells. The SENL mixture comprises ginsenoside Rg1, ginsenoside Rb1, ginsenoside Rg3, astragaloside IV, ophiopogonin D, and tetrandrine. The expression of GSTπ was diminished and the resistance to cisplatin in lung cancer xenografts was reversed.[238] In addition, the active constituents of ginger, namely 6-gingerol, 10-gingerol, 4-shogaol, 6-shogaol, 10-shogaol, and 6-dehydrogingerdione, demonstrated inhibitory effects on GSTπ and MRP1 in prostate cancer cells that were resistant to docetaxel treatment (PC3R).[239] According to another study, it has been suggested that oridonin, a tetracyclic diterpenoid derived from Rabdosia labtea, has exhibited the ability to induce apoptotic markers in gemcitabine-resistant PANC-1 pancreatic cancer cells. The expression of GSTπ and lipoprotein receptor protein 1 (LRP1) has been repressed.[240] Resveratrol, a type of natural phenol, has been observed to exert a regulatory effect on multidrug resistance in tumor cells. The management of doxorubicin resistance The application of resveratrol to Caco-2 cells resulted in a noteworthy decrease in the expression of GST mRNA, as well as the expression of MDR markers.[178] Dietary carotenoids, notably fucoxanthin (FUC) from brown seaweeds, have antioxidant properties and increase cancer cell sensitivity to chemotherapies.[241,242] In their study, Eid et al. investigated the impact of FUC on the augmentation of doxorubicin efficacy and the facilitation of apoptosis. This was achieved through the upregulation of caspases and p53, as well as the downregulation of GST, CYP3A4, and PXR in cancer cells that exhibited resistance to treatment.[222]

Topoisomerases

DNA Topoisomerases (Topo) enzymes are present and perform their functions within the cellular nucleus. The topoisomerase enzyme is responsible for modulating the topology of DNA, thereby regulating DNA repair, replication, transcription, and chromosomal segregation mechanisms.[243] Two distinct classes of topoisomerases exist, namely topo I and topo II, each with unique functions. The relaxation of DNA supercoiling is accomplished through the cleavage of individual DNA strands, which is facilitated by topo I. On the other hand, topo II is responsible for separating double-stranded DNA.[244,245] Cell-cycle arrest and apoptosis are observed upon inhibiting a specific topoisomerase. However, blocking the two types can considerably affect the cancer cells cytotoxicity cells.[246,247] Due to its high expression in numerous cancer cells, Topo II has emerged as a promising target for novel chemotherapy.[248] Topoisomerase II has two main isoforms, namely topo IIα and topo Iiβ [249, 250]. The high expression of Topo II in rapidly proliferating cancer cells is due to its pivotal involvement in cellular growth. Conversely, Topoisomerase II remains present in quiescent cells across various tissue types throughout the entirety of the cell cycle.[250,251] Topoisomerase II inhibitors are a category of highly effective chemotherapeutic agents, which comprise doxorubicin, teniposide, and etoposide.[250] The utilization of these medications may result in significant adverse effects due to their insufficient selectivity and the possibility of drug resistance caused by enzyme gene mutations or dysregulation of their expression in cancer cells.[215,250,252,253] Thus, a promising area of chemotherapeutic research is the search for novel phytochemicals that target the enzyme topoisomerase. Several secondary metabolites, including alkaloids, flavonoids, and triterpenes, exhibit an impact on topoisomerase enzymes triterpenes.[246,254-257] Emodin, a natural product, has been observed to exhibit reversal of multidrug resistance in promyelocytic leukemia (HL-60/ADR cells). Furthermore, it was observed that the administration of this substance resulted in a reduction in the expression of MDR proteins, namely topoisomerase II (topo II) and multidrug resistance-associated protein 1 (MRP1), while simultaneously

enhancing the intracellular accumulation of Adriamycin and Daunorubicin.233 Human oral squamous carcinoma cells with resistance have also shown similar effect.[234] Curcumin also downregulated topo II in human NCI-H460/R cells.[230] Chinese liverwort produces macrocyclic bisbibenzyl riccardin D. Topoisomerase II inhibition and P-gp downregulation caused leukemia cells to apoptose and reduce MDR.[258]

The Hypoxia-Inducible Factor

Hypoxia commonly arises within rapidly proliferating cancer cells. The attainment of efficacious cancer chemotherapy poses a substantial challenge.[259, 260] The phenomenon of tumor hypoxia has been widely recognized as a stimulant for the upregulation of numerous genes that exhibit a strong correlation with the development of drug resistance. [261] The hypoxia-inducible factor-1 (HIF-1) is a transcription factor that consists of two subunits, namely α and β, and is sensitive to changes in oxygen levels.[261-263] According to reports, there exists a correlation between chemoresistance and the elevated expression of HIF-1α in various types of cancer, such as ovarian cancer, hepatocellular carcinoma, glioblastoma, and colorectal cancer.[264-267] HIF-1α also activates over 60 genes involved in tumor growth, metastasis, cellular metabolism, apoptosis, and poor prognosis.[268,269] HIF-1α employs diverse mechanisms to facilitate the development of drug resistance in tumors, including regulating MDR-associated proteins such as p-gp and MRP .[270, 271] Natural products and their derivatives represent a plentiful and reliable reservoir of resistance reversal agents that are both safe and efficacious. [272] The green tea polyphenol Epigallocatechin-3-gallate (EGCG) is one of the MDR reversal modulators. [272, 273] Wen et al. suggested that downregulating HIF-1α and p-gp in doxorubicin-resistant human hepatocellular carcinoma cells (BEL-7404/DOX) with the EGCG derivative could reduce drug resistance. [272] Furthermore, the inhibitory effect of apigenin, a specific flavonoid compound, on HIF-1α has been observed to successfully reverse the resistance to paclitaxel in hypoxic-liver tumor cells.[274] It is noteworthy that quercetin demonstrated the ability to suppress HIF-1α and MDR1, thereby augmenting the cytotoxic efficacy of doxorubicin and gemcitabine in cells afflicted with pancreatic and liver cancer. [275] In contrast, the downregulation of HIF-1α protein expression by resveratrol inhibited the development of resistance to doxorubicin in MCF-7 cells under hypoxic conditions.[276] Nuciferine, an aromatic alkaloid derived from lotus leaves, has demonstrated properties with potential therapeutic applications in the areas of anti-inflammatory, antioxidant, and anticancer activities .[277-279] In recent research, the utilization of nuciferine has been observed in drug-resistant tumor cells, demonstrating its capacity to modulate MDR proteins while concurrently mitigating the activation of Nrf2 and HIF-1α .[280] The modulation of HIF-1α by curcumin has also been documented in previous studie.[281]

CONCLUSIONS

The utilization of natural products is gaining traction as a potential avenue for the development of efficacious anticancer agents. The abundance of sources for these products results in a significant range of targets and mechanisms of action. The presence of a wide range of variations has prompted researchers to contemplate the potential of natural substances as remedies for drug resistance in cancer. Several natural compounds can target cancer medication resistance systems and cause tumor regression. In preclinical and clinical trials, some natural substances have shown medicinal potential. Nevertheless, the utilization of natural products as a conventional treatment for drug resistance remains constrained. Additional research is required to investigate the potential of utilizing natural products in conjunction with therapeutic interventions as a means of surmounting drug resistance.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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ABBREVIATIONS

ABCG: ATP-binding cassette subfamily G member

BCRP: Breast cancer resistance protein

GST: Glutathione transferases

HIF: Hypoxia-Inducible Factor

LRP: lung resistance-related protein

MDR: Multidrug resistance protein

P-g: Permeability-glycoprotein

PKC: Protein kinase C

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