Research Progress of Naturally Originated Potential Drugs on Reversing Drug Resistance in Malignant Tumors

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Deng *et al.*: Role of Natural Active Ingredients in Reversing Drug Resistance

Cancer chemotherapy is considered to be an effective strategy to delay the occurrence, development and recurrence of tumors. However, multi-drug resistance is the main cause of treatment failure and recurrence in tumor patients, and the primary limiting factor for tumor cure. It is clinically pointed out that drug combination chemotherapy can improve the success rate of chemotherapy, but about 50 % of tumor cells are still resistant to drugs, which leads to chemotherapy failure. The mechanism of drug resistance to traditional chemotherapy drugs, targeted therapy drugs and immunotherapy drugs is complex. Reversing chemotherapy drug resistance and mastering the mechanism of drug resistance are challenges in cancer research. To solve the problem of multi-drug resistance in tumors and improve the efficiency of chemotherapy better, this paper reviews the potential pharmacological mechanism and research progress of natural active ingredients (including alkaloids, flavonoids, sesquiterpenoids, diterpenoids, triterpenoids, coumarins, lignans and natural biarylpolyphenols, etc.) in reversing chemotherapy drug resistance based on available relevant literature.

Key words: Natural medicine, chemotherapy, malignant tumor, drug resistance

Cancer is a serious threat to public health and a reliable survey from 2020 shows that occurrence of cancer worldwide reached 19.29 million, and the deaths caused by cancer was 9.96 million in 2020[1]. Drug resistance and metastasis of malignant tumors are the main causes of cancer death, which is also a challenge in cancer treatment. More than 90 % of cancer deaths are attributed to drug resistance[2]. Cancer chemoprevention strategies can delay tumorigenesis, minimize tumor progression and reduce recurrence. However, tumor treatment failure and recurrence are often limited by drug resistance[3]. The solution to single-agent chemotherapy resistance is drug combination chemotherapy. This combination chemotherapy involves using combination of different doses with different intensities of chemotherapeutic drugs, which improves the success rate of chemotherapy and becomes an example of tumor treatment. However, clinical practice has found that only about 50 % of tumor cells are sensitive to drugs, and more than 50 % of tumor cells are still resistant to drugs, resulting in chemotherapy failure. Tumor drug resistance is divided into intrinsic resistance and acquired resistance. According to the drug resistance spectrum, acquired resistance is divided into Primary-Drug Resistance (PDR) and Multi-Drug Resistance (MDR). MDR is a phenomenon of cross-drug resistance, in which the drug resistance is caused by a certain drug that induces mechanisms on other drugs with different structures[4]. MDR can lead to unsuccessful treatment with some combination drugs. Medical researchers still need to find and develop drugs with tumor MDR reversal effect. Natural medicine refers to natural medicinal substances, natural extracts, and compounds derived from natural raw materials and used under the guidance of modern medical theory. It has the advantages of abundant resources, diverse compound structures, multi-targets, high selectivity, low toxicity and low side effects. It can exert anti-tumor and anti-viral activities and is an important source for the continuous development and application of therapeutic drugs[5,6]. Research on natural drugs have attracted many researchers for the prevention and treatment of malignant tumors, and it has been preliminarily confirmed that alkaloids, flavonoids, sesquiterpenoids, diterpenoids, triterpenes, coumarins, lignans and natural biaryl polyphenols are effective in reversing

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drug resistance of malignant tumors these years. Based on the relevant literature, this paper reviews the potential pharmacological mechanisms and research progress of natural drug components in reversal of drug resistance in malignant tumors, to provide a reference for the clinical reversal of drug resistance and optimization of treatment options.

FORMATION MECHANISM OF MDR

The formation mechanism of MDR is complex, which mainly includes transmembrane transporters such as Permeability-glycoprotein (P-glycoprotein), MDR Protein (MRP) and Lung Resistance Protein (LRP) mediated drug effective mechanism, abnormal enzyme activity mediated MDR, enhancement of Deoxyribonucleic Acid (DNA) repair function, increased apoptotic resistance, increased protein kinase C activity, MRP overexpression, etc.[7]. The main mechanism of cancer MDR is shown in fig. 1, and the key signaling pathways to overcome MDR through the regulation of natural drug derived components are shown in fig. 2.

The MDR mechanism of tumors is different to traditional chemotherapy drugs, targeted therapy drugs and immunotherapy drugs. The MDR mechanism of the tumor against traditional chemotherapy drugs includes abnormal expression of Adenosine Triphosphate (ATP)-Binding Cassette (ABC) transporter, apoptosis-induced chemical resistance, autophagy-induced chemical resistance, enhanced DNA damage repair ability, and the regulation of tumor microenvironment and platelet by non-coding Ribonucleic Acid (RNA) on MDR[8]. The MDR mechanism of tumor response to targeted therapeutic agents includes targeted mutations in tumor stem cells such as Threonine 790 Methionine (T790M) and Human Epidermal growth factor Receptor 2 (HER2) amplification and changes in the Autophagy Lysosomal Pathway (ALP) signaling pathway[9]. The MDR mechanisms of tumor response to immunotherapy drugs include tumor antigen deficiency, alteration of antigen presentation mechanism, loss of soft and hard junction of Human Leukocyte Antigens (HLA) expression, alteration of Mitogen-Activated Protein Kinase (MAPK) pathway and Phosphoinositide 3-Kinase (PI3K)/Protein kinase B (Akt)-Beta (β)-catenin signaling pathway, loss of T cell function, and induces downregulation of tumor antigen presentation, inadequate cell recognition and the development of escaped mutant variants in cancer[10,11].

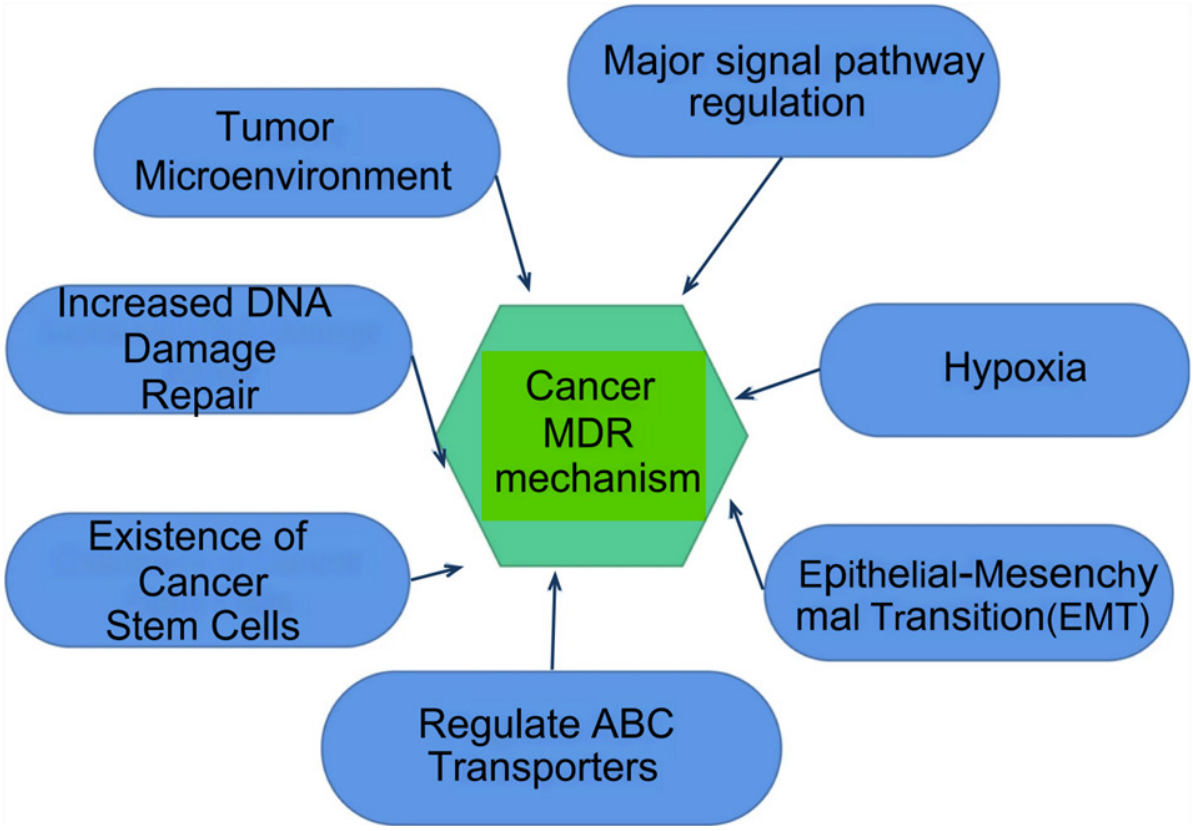

Fig. 1: Mechanism of cancer MDR

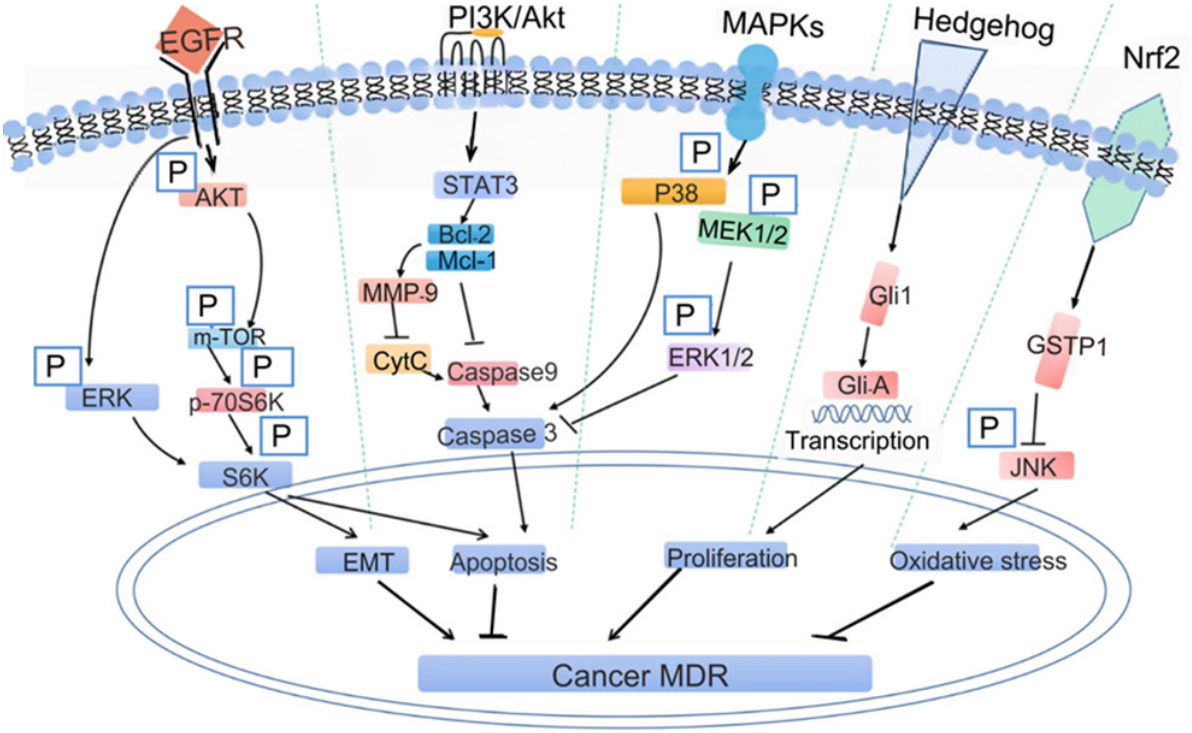

Fig. 2: The key signaling pathways to overcome MDR through the regulation of natural drug derived components

NATURAL MEDICINE AND ITS RESEARCH APPLICATION

Nature contains many natural products with diverse structures and novel activities. Natural active ingredients are derived from the chemical components and metabolites of animals, plants and microorganisms, including polysaccharides, amino acids, antibiotics, alkaloids, flavonoids, terpenoids, saponins and other chemical components. These compounds are rich in species and structure, which have strong medicinal potential and are important resources for drug development. These chemical components have different degrees of efficacy in reducing injuries or relieving diseases. According to statistics, between 1981 and 2010, 34 % of the United States Food and Drug Administration (US FDA) approved drugs derived from natural products or their derivatives[12]. Medical researchers have devoted themselves to the task of reversing the drug resistance of malignant tumors by using active ingredients such as alkaloids, flavonoids, sesquiterpenoids, diterpenoids, triterpenoids, coumarins, lignans, and natural biaryl polyphenols, and obtained satisfactory results.

Alkaloids:

Alkaloids are a class of nitrogen-containing organic compounds that are mostly alkaline. They are mainly distributed in natural plants such as Chinese herbal medicine pepper, *Lobelia chinensis*, and so on. They have anti-viral, anti-bacterial, anti-inflammatory, anti-arrhythmic, anti-tumor and other biological activities[13]. Among them, anti-tumor activity has attracted much attention. There are many alkaloids with anti-tumor activity, such as vinblastine isolated from primrose, Paclitaxel (PTX) isolated from *Taxus chinensis*, and camptothecin isolated from *Camptotheca acuminata*. At the same time, researchers have also found some alkaloids with MDR reversal activity in the chemical composition of natural drugs.

Sugisawa *et al.*[14] studied the reversal effect of new effective ABC subfamily B member 1 (ABCB1) regulator of phenyl ethyl isoquinoline alkaloids on MDR of cancer cells. They found that phenyl ethyl isoquinoline alkaloids screened by fluorescence was a novel ABCB1 inhibitor showing a significantly enhanced reversal of ABCB1-mediated MDR effects. Moreover, the compound reversed tumor resistance to PTX without significantly increasing toxicity in ABCB1-overexpressed KB-V1 cell xenografts. The over-expression of ABC transporters cause tumor MDR, leading to the failure of chemotherapy. As the main active components, the *Uncaria* alkaloids are isolated from *Uncaria rhynchophylla*. In the analysis of the MDR reversal activity of rhynchophylline, isorhynchophylline, corynoxeine, isocorynoxeine, hirsutine, hirsuteine and other *Uncaria* alkaloids, Huang *et al.*[15] found that when combined with

Adriamycin (ADR), they all showed a strong reversal effect on tumor MDR. Ricinine is a dibenzyl isoquinoline alkaloid previously having a variety of anti-cancer effects. Kadioglu *et al.*[16] analyzed the action mode of the bisbenzylisoquinoline alkaloid of lotus (from the *Nelumbo nucifera*) on MDR tumor cells. Consistent with P-glycoprotein inhibition experiments, liensinine may allocate P-glycoprotein drug binding bags and prevent Rhodamine 123 (R123) binding, in which liensinine increases the uptake of R123. DCZ0358 is a novel alkaloid compound with a strong cytotoxic effect on Bortezomib (BTZ) resistant multiple myeloma cells *in vitro* and *in vivo*. A study indicates that DCZ0358 can successfully combat BTZ resistance in multiple myeloma cells[17]. DCZ0358's anti-myeloma activity was related to inhibiting cell proliferation, promoting cell apoptosis through the caspase-mediated apoptotic pathway, and inducing G0/G1 phase arrest by down-regulating cyclin D1, Cyclin-Dependent Kinase 4 (CDK4) and CDK6. Besides, DCZ0358 inhibited the Janus Kinase 2/ Signal Transducer and Activator of Transcription 3 (JAK2/STAT3) signaling pathway.

Matrine is obtained from the dried root of the leguminous plant *Sophora flavescens*. Based on different concentrations and time of administration (i.e., dose-time dependent), this compound can inhibit the proliferation of liver cancer, acting on multiple signaling pathways, affecting the expression of tumor-related proteins, interfering with the energy metabolism of Hepatocellular carcinoma cell line (HepG2)[18]. Li *et al.*[19] showed that by promoting autophagy, matrine reversed the resistance of K562/ADR cells to ADR and vincristine. In addition, Chen *et al.*[20] studied the reversal effect of matrine on chemotherapy-resistant leukemia K562/ADR cells and found that matrine had powerful reversal properties, which could enhance the cytotoxicity of cancer drugs on K562/ADR cells and the apoptosis rate induced by Doxorubicin (DOX).

Flavonoids:

The flavonoid structure contains two benzene rings connected by three carbon atoms. Flavonoids mainly distributed in vascular plants such as cucumbers, wheat and soybeans and have anti-inflammatory, anti-oxidation, anti-tumor, and treatment of cardiovascular diseases. At present, flavonoids have been proven to prevent MDR to cancer by regulating different pathways[21].

Breast Cancer Resistance Protein (BCRP) is a key target of novel resistance reversal drugs. To find new potential BCRP inhibitors, Petersen *et al.*[22] studied the inhibitory activity of crude extracts from leaves of *Eremophila galeate*, an Australian specialty plant, on Human colorectal adenocarcinoma cell line parental (HT29par) and HT29 cells overexpressing BCRP (HT29-SN38) cells. Dye accumulation experiments showed that 5,3',5'-trihydroxy-3,6,7,4'-tetramethoxyflavone inhibited BCRP. Docking studies showed that this component and SN-38 bound to a BCRP site, suggesting that this flavonoid component acts synergistically with SN-38, where the flavonoid is a BCRP effector pump inhibitor. Both flavonoids and isoflavones can kill or re-sensitize conventional chemotherapy drugs to resistant cancer cells. A study pointed out that these flavonoids negatively regulate MDR rather than specifically regulate target proteins[23]. Kan *et al.*[24] showed that in the absence of poisoning or animal death, Flavonoid Monomer (FM04) co-administration with PTX could directly modulate P-glycoprotein-mediated PTX resistance, resulting in a 56 % reduction in tumor volume. This study demonstrated that flavonoid FM04 (Half maximal effective concentration EC_{50}=83 nm) was not only be used as an effective inhibitor to reverse P-glycoprotein-mediated PTX resistance, but also improve the oral bioavailability of PTX.

Dihydromyricetin, a flavonoid compound, was confirmed to have a reverse effect on Human gastric cancer cell line (SGC7901)/5-Fluorouracil (5-FU) cell multiple drug resistance[25]. *Euryops pectinatus* L. flower extract contains a large number of flavonoids, which can inhibit P-glycoprotein and reverse cancer cell MDR[26]. Flavonoids have strong application potential in cancer clinical medical research. Quercetin is a photogenic flavonoid found in plant parts such as fruits, vegetables and grains. Lu *et al.*[27] found that quercetin enhances Docetaxel (DTX) sensitivity to prostate cancer cells in the presence of androgen receptor and PI3K/Akt signaling pathway.

Sesquiterpenoids, diterpenes, and triterpenes:

Sesquiterpene is an important secondary metabolite in nature and composed of three isoprenes end to end. Although the parent nucleus

of sesquiterpenoids contains only 15 carbon atoms, they have various structure types and complex stereo structures due to the complex metabolic process in plants. Its basic pharmacological effects include anti-tumor, anti-inflammation and anti-fungal. The pharmacological activities of diterpenoids and triterpenoids are mainly anti-tumor, anti-inflammatory, anti-viral and anti-bacterial, etc. For example, the famous anti-tumor drug PTX is diterpenoids.

Liu *et al.*[28] confirmed in their study that Dihydroartemisinin (DHA) may reverse MDR of human oral squamous cell KBv200 cells by promoting Reactive Oxygen Species (ROS) production and inhibiting MAPK pathway. Liu *et al.*[29] found that the Forkhead box P3 (FOXP3) gene was highly expressed in Chronic Myeloid Leukemia (CML) K562/ADR-resistant cell lines. Artesunate can inhibit FOXP3 gene expression, increase intracellular ADR concentration of K562/ADR, and reverse MDR in a dose-dependent manner. The research data of Yang *et al.*[30] shows that vinyl diterpenes may be a kind of high-affinity P-glycoprotein substrates, and are explants by P-glycoprotein monomers to reverse MDR.

Liu *et al.*[31] identified EM-E-11-4, a lathyrane-type diterpenoid with multiple action mechanisms and confirmed that EM-E-11-4 could be a promising new PTX resistance reversal agent, especially for tumor patients with high P-glycoprotein expression. The application of triterpenoids to reverse MDR in tumor cells has also made progress. Yazdani *et al.*[32] confirmed that triterpenes, as a cytotoxic and chemical sensitizer, can overcome the MDR of cancer cells. Saikosaponin b2 is a triterpenoid component of *Bupleurum chinense*. Studies have shown that saikosaponin b2 enhances liver targeting of anti-cancer drugs by inhibiting MDR-related drug transporters[33]. Saikosaponin b2 increases *Narcissus* efflux in Human Embryonic Kidney (HEK) 293 cells mainly by enhancing MRP1 activity. Saikosaponin b2 enhances MRP2 function and increases cisplatin effluence in Buffalo Rat Liver (BRL) 3A cells by up-regulating MRP2 gene expression, but it has little effect on the P-glycoprotein of normal cells. Saikosaponin b2 increased the Organic Cation Transporter 2 (OCT2) activity of OCT2-HEK293 cells by increasing OCT2 protein and micro RNA (mRNA) expression.

Coumarins:

As a kind of natural component of phenyl propyl, coumarins are widely distributed in plants and have functions such as plant growth regulation, photosensitivity, antibacterial and antiviral. In recent years, researchers have also found that some coumarins had the potential to reverse MDR.

Al-abbas *et al.*[34] found that coumarins combined with DOX induce cell death in drug-resistant Acute Myelogenous Leukemia (AML). Their data also showed that coumarin combined with DOX resulted in significant apoptotic cell death compared with DOX and coumarin alone. These results suggest that coumarin combined therapy may be a good choice to overcome drug resistance in AML patients. Psoralen (PSO) belongs to coumarin compounds. A study shows that PSO-loaded Lipid-Polymer hybrid Nanoparticles (P-LPNs) enhance ADR efficacy in multidrug-resistant HepG2 cells[35]. In those cells, P-LPNs increased the cytotoxicity of DOX by 17 times compared with free DOX. P-LPNs can enhance DOX cytotoxicity and lead to apoptosis of HepG2/ADR cells by increasing cytochrome C release, enhancing caspase-3 cleavage. Wang *et al.*[36] utilized Transferrin (Tf) to encapsulate DOX (Tf-M-DOX/PSO) and modified micelles reversed MDR in leukemia cells, and it found that this treated Tf exhibited higher uptake in K562/DOX cells compared to other nano micelles. In addition, when exposed to the treated Tf, the cytotoxicity was 2.8 and 1.6 times higher than that of unmodified DOX and DOX-loaded Tf-nano micelles, respectively. The treated Tf strongly promotes the apoptosis of K562/DOX cells. In the end, when cells are exposed to Tf-M-DOX/PSO, the reversal of drug resistance is associated with the inhibition of P-glycoprotein expression. Tf-M-DOX/PSO nano beams showed a reversal of MDR and make cellular uptake and delivery release active.

Lignans and natural biaryl polyphenols:

Lignans are natural products produced by the oxidation polymerization of phenylpropyl, which widely exists in plants. Lignans have various structures, and their main activities include anti-tumor, liver protection, antioxidant, antiviral and central nervous system regulation[37]. Natural polyphenols become a kind of promising compound solving P-glycoprotein-related MDR. Teng *et al.*[38] confirmed that cinnamon overcomes

cancer MDR through allosteric regulation of human P-glycoprotein at drug-binding sites and ATPase-binding sites. Natural polyphenols, such as ellagic acid, ellagic acid derivatives and *Schisandra*, can enhance MDR cell lines to conventional anti-cancer drugs sensitivity[39]. Studies have shown that microemulsion co-loaded with schisandrin A-DTX improves the efficacy of oesophagal cancer treatment by defeating MDR[40]. This study found that the apoptosis rate of EC109/DDR cells treated with a microemulsion system (SD-ME) co-loaded with DTX and schizandrin A was better than that of DTX alone and increased by a factor of 20. Lignans are one of the potential natural compounds to reverse MDR in tumor cells. Researchers expected to find more novel MDR-reversing drugs in these compounds.

DEVELOPMENT STATUS AND PROBLEMS OF NATURAL DRUGS

The goal of developing natural drugs to reverse drug resistance in malignant tumors is firm, but the process is strenuous. For example, modern pharmacological studies have confirmed that the active ingredient sinecatechins extracted from green tea not only inhibit Human Papillomavirus (HPV) and tumor growth but also enhances the body's immune ability. It is the first plant medicine approved by the US FDA. However, the content of catechins with a clear structure in sinecatechins was 85 %, the content of other components was 2.5 %, and the content of unknown components was only 7.5 %. In 2014, the Research and Development (R&D) company completed two multi-center, randomized, double-blind, parallel, controlled phase III clinical trials[41], making the natural drugs against cancer a step forward.

However, there are few problems in the research and development of natural drugs, such as the low content and complex structure of the extracted active ingredients, which increases the difficulty of subsequent drug synthesis. Although some natural medicines are therapeutic, they have serious side effects. Studying about the active ingredients of natural medicines is an important part of the transformation and development of natural medicines. With the rapid development of medicinal chemistry, synthetic biology, and other disciplines, biosynthesis methods are becoming more and more reasonable, and the problem of developing natural drug research has been reduced. At present, although only two botanical drugs have been approved by the US FDA[42], each successful registration is an important milestone in the US drug development market, which can provide a favorable reference for the subsequent development of botanical drugs.

CONCLUSION

Natural medicine has its unique advantages and has always been the focus of researchers. Compounds with MDR reversal activity found in natural medicines include many types of natural products such as alkaloids, flavonoids, sesquiterpenoids, diterpenoids, triterpenoids, coumarins, lignans and natural biaryl polyphenols, and have their structural characteristics. Natural drugs have great potential in the reversal of MDR in tumor cells. Different active ingredients of natural drugs achieve the reversal effect of MDR in tumor cells through P-glycoprotein, drug effervescent mechanism, MRP over-expression and other ways. However, there are few studies on this aspect, most of which remain at the molecular or animal experimental level. The composition of natural medicine is complex, and all of them are composed of a variety of bioactive chemical components. Therefore, its action mechanism may be a combination of a single pathway or multiple pathways. In the future, it is necessary to deepen clinical pharmacological research and strengthen the depth of research, to find multi-target and multi-effect natural drugs, and to promote the process of natural drugs in cancer prevention and treatment.

Conflict of interests:

The authors declared no conflict of interests.

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