MINI-REVIEW

Biotransformation, a Promising Technology for Anti-cancer Drug Development

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Abstract

With the high morbidity and mortality caused by cancer, finding new and more effective anti-cancer drugs is very urgent. In current research, biotransformation plays a vital role in the research and development of cancer drugs and has obtained some achievements. In this review, we have summarized four applications as follows: to exploit novel anti-cancer drugs, to improve existing anti-cancer drugs, to broaden limited anti-cancer drug resources and to investigate correlative mechanisms. Three different groups of important anti-cancer compounds were assessed to clarify the current practical applications of biotransformation in the development of anti-cancer drugs.

Keywords: Biotransformation - anti-cancer drugs - development - practical application

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Introduction

Cancer is among the leading cause of death in the world and the low treatment rate has led to huge inquietude for human beings. In China, new cancer cases are over 2.82 million and deaths caused by cancer are approximately 1.96 million each year. Apart from the aforementioned, new cancer cases and death toll will continue to increase to 3.88 million and 2.76 million respectively by 2020 (Ferlay et al., 2008). What is alarming is that the percentage of cancer cases diagnosed in less developed countries is projected to increase from approximately 56% to more than 60% of the total cancer population from 2008 to 2030. This increase is due to the high cancer incidences and prolonged life expectancy of the human population (Ahmedin et al., 2010). With the high morbidity and mortality caused by cancer, finding more effective anti-cancer drugs is thus of great importance.

In current research, traditional chemical synthesis and natural medicine separation technology are the two main methods contributing to the development of anti-cancer drugs. However, traditional chemical synthesis uses a lot of organic solvents, such as acetone, pentane, chloroform etc, which possess corrosive, toxic and carcinogenicity, and they also can cause environmental pollution and menace human health (Eric, 2004). Natural medicine separation technology mainly focuses on the existing natural medicine but the workload incurred is extensive (Chen et al., 2006). Therefore, some scientists have developed a prerequisite for the development of new reactions and technologies so as to reduce waste generation and solvent usage, minimize energy input, improve safety, and attain material and cost efficiency (Ran et al., 2008; Cheng et al., 2010). Biotransformation is one of the technologies which has basically fulfill those requirements. Biotransformation is a chemical reaction that is catalyzed by whole cells (microorganisms, plant cells, animal cells), or by isolated enzymes due to high stereo- or regioselectivity combined with the high product purity and high enantiomeric excesses (Hiltrud; Emily, 2010). Therefore, in order to accomplish a perfect and specific biotransformation, it is necessary to find certain biocatalysts (whole cells and solitary enzymes) to support this reaction. Biotransformation is increasingly welcomed in anti-cancer drugs research area because of its three features which are far better than the traditional chemical synthesis and natural medicine separation technology: Firstly, the application of biotransformation has proved that some compounds activity increases while toxicity decreases after being transformed through biotransformation. Zhu converted camptothecin (strong side-effect compound) into 10-hydroxycamptothecin (lower side-effect and better activity compound) successfully through this method (Zhu et al., 1978). Secondly, irregardless of the nature of the catalysts, whether a whole cell or isolated enzyme, enzyme catalysis reaction is the basic reaction in biotransformation. Thus, this kind of reaction is of high sensitivity and specificity.

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Furthermore, the output is always higher and byproduct is usually fewer in biotransformation than that of chemical synthesis. For example, Samuel chemical synthesized a well-recognized anti-cancer drug taxol successfully and the synthesis process includes 26 synthesis schemes and 107 intermediate products (Samuel et al., 1996). However, taxol can also be directly isolated from *Pestalotiopsis microspora*, an endophytic fungus of *Taxus wallachiana*, when cultured for 2-3 weeks (Gary et al., 1996). Finally, biotransformation process is a mild and ecologically harmless reaction (normal pressure, low temperature, neutral pH), which is an important requirement for sustainability (Kathryn et al., 2001). The chemical synthesis of taxol requires OsO_4, CH_2Cl_2, Tf_2O, NaH, $LiAlH_4$, H_2O_2, etc, which are corrosive and toxic chemicals, and occasionally a temperature of 78°C(Samuel et al., 1996). Whereas taxol biotransformation only require fungus to be kept at 26°C for a period of 2-3 weeks (Gary et al., 1996).

With the advantages of biotransformation, application of it in the field of researching anti-cancer drugs is gaining popularity. In this review, we have summarized the four applications and three different groups of important anti-cancer compounds that would be shown so as to clarify the current practical application of biotransformation in the development of anti-cancer drugs fields.

Main application of biotransformation

To exploit novel anti-cancer drugs

Seeking novel anti-cancer drugs for cancer treatment has increasingly become a mission for some scientists. Therefore, searching for more desirable ways to look for these excellent anti-cancer drugs in an unknown world is the center of attention. The emergence of biotransformation is of promising breakthrough. Most scholars are interested in finding novel anti-cancer compounds from rare microorganisms. It is an easy way to find them because many complex biotransformation processes that takes place *in vivo* of microorganisms so as to produce many specific and novel metabolites which may show good bioactivities. For instance, many secondary metabolites of marine microorganisms are bioactive natural products which show pharmacological activity for anti-cancer. Marinamide (Compound 1;shown in the Figure 1) and its methyl este (Compound 2) are pyrrolyl 1-isoquinolone alkaloids, which are produced by co-cultures of two marine-derived mangrove endophytic fungi from the South China Sea coast and they have cytotoxic activity against HepG2, 95-D, MGC832 and HeLa tumour cell lines (Zhu et al., 2013). Anthracenedione derivative 1403P-3 (Compound 4) is a novel anthracenedione derivative isolated from the secondary metabolites of endophytic fungus from the South China Sea and it can induce apoptosis in KB and KBv200 cells via reactive oxygen species-independent mitochondrial pathway and death receptor pathway (Zhang et al., 2007), induction of apoptosis in human breast cancer cells (MDA-MB-435) by blocking Akt activation (Yuan et al., 2011). Neoechinulin A (Compound 6) comes from marine-derived fungus *Microsporum* sp. and can induce apoptosis in human cervical carcinoma HeLa cells (Isuru et al., 2013). Furthermore, some bacteria and fungi, from land or fresh water, are also the source of locating novel anti-cancer compounds. Compound 3 (shown in the Figure 1) is obtained from a freshwater-derived fungal strain *Chaetomium* sp. YMF 1.02105 shows cytotoxic activities against A549, Raji, HepG2, MCF-7, and HL-60 cell lines (Shen et al., 2012). Compound 7 is isolated from the fungus *Neosartorya pseudofischeri* S.W. Peterson has inhibitory activity in human glioblastoma, breast, melanoma and esophageal cancer cell lines (Amnat et al., 2012). Pycnidione (Compound 5), a small tropolone first isolated from the fermented broth of *Theissenia rogersii* 92031201 can induce cell cycle arrest and apoptosis in A549 human lung cancer cells (Hsiao et al., 2012). These instances are not enough to stand for the contributions of secondary metabolites of microorganisms to our anti-cancer research but can only briefly state the efficiency of locating novel anti-cancer compounds from microorganisms.

To improve existing anti-cancer drugs

As far as we know, a large number of anti-cancer drugs are not good enough to treat cancers because of the high rates of side effects and low rates of curative effects. Biotransformation is an alternative tool in the structural modification of complex natural products in achieving higher activity and lower toxicity of some anti-cancer drugs due to its great capability of catalyzing novel reactions and its region- and stereo-selectivity (Sergio, 2001). An example can be found in camptothecin which is a renowned anti-cancer compound that can be extracted from Nyssaceae arbo (Wen et al., 2005). It is worth mentioning that camptothecin is not a perfect and inexhaustible compound in cancer treatment because of the side-effect on gastrointestinal system and bone marrow, and moderate solubility in aqueous media (Zhu et al., 1978; Kehrer et al., 2001; Li et al., 2006). However, 10-hydroxycamptothecin, which can also be extracted from Nyssaceae arbo exists at a low content of 0.001% but shows higher anti-cancer activity and lower side-effect

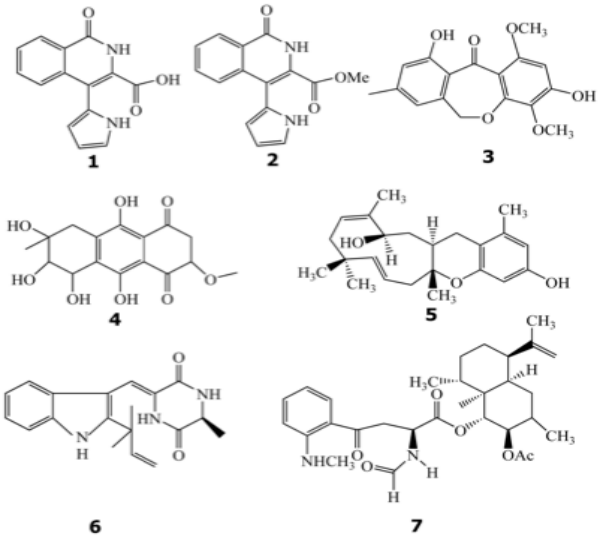

Figure 1. The Structures of Some Novel Anti-cancer Compounds

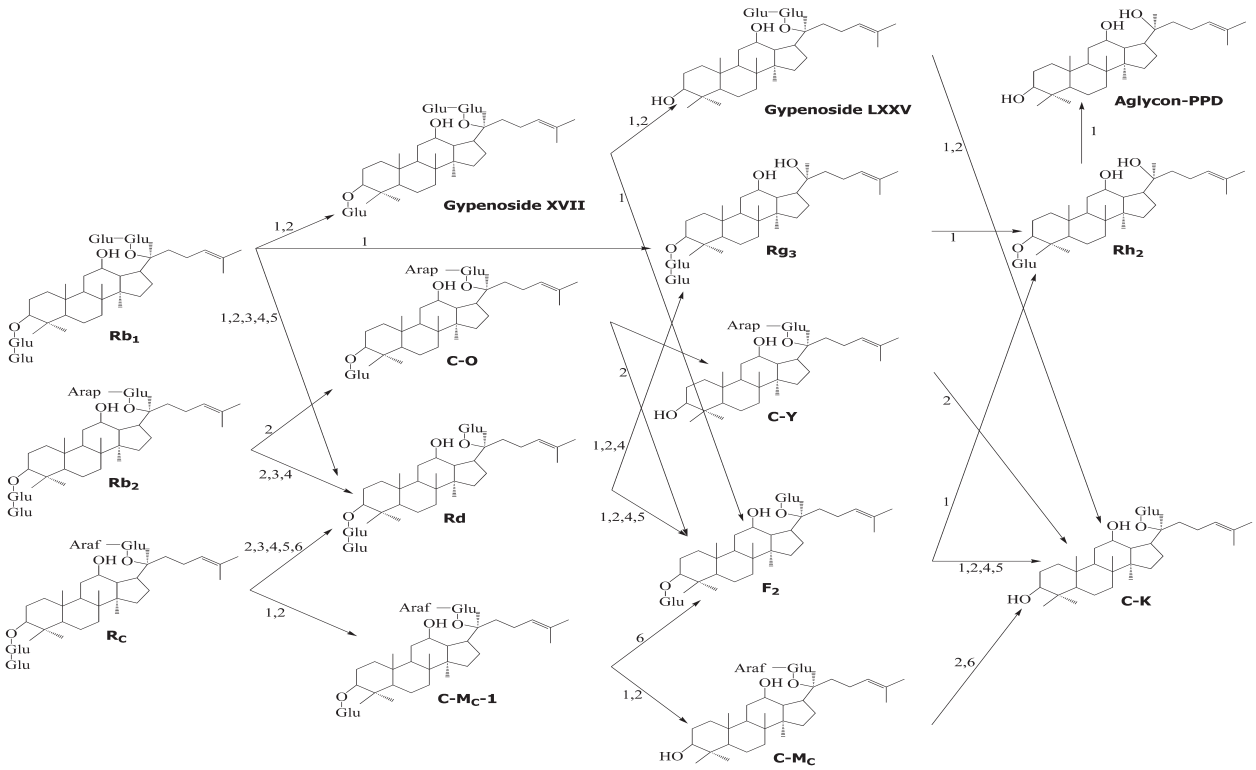

Figure 2. The Key Pathways of Ginsenosides Biotransformation and Their Structures. 1, β-glucosidase; 2, β-glycosodase; 3, Cellulase; 4, Lactas; 5, β-glactosodase; 6, α-L-arabinofuranosidase. C-Mc-1 compound Mc-1, C-Y compound Y, C-Mc compound Mc, C-K compound K

compared to camptothecin. Therefore, it is necessary to convert camptothecin into 10-hydroxycamptothecin by biotransformation. In 1978, Zhu found that *aspergillus* T-36 strain has a good ability in converting camptothecin into 10-hydroxycamptothecin and the yield is over 10% (Zhu et al., 1978). An increasing number of camptothecin derivatives have been found since then (Kehrer et al., 2001). In addition, in order to find much better active anti-cancer drugs, some scholars focus on finding good anti-cancer drugs' analogues or metabolites which would have better anti-cancer activities so as to create more choices to meet the vast demands in clinical requirements. For instance, 20(S)-Protopanaxatriol, a glycone of ginsenosides, was found in human blood as a final metabolite after oral administration of ginseng extract and shown the action to mediate the anti-cancer effects (Hideo et al., 2002). Chen converted 20(S)-protopanaxatriol by *Absidia corymbifera* and obtained four anti-cancer compounds (7β-hydroxyl-20(S)-protopanaxatriol, 7β, 15α-dihydroxyl-20(S)-protopanaxatriolby, 29-hydroxyl-20(S)-protopanaxatriol, 28-hydroxyl-20(S)-protopanaxatriol) that show the more potent inhibitory effects against DU-145 and PC-3 cell lines than the substrate (Chen et al., 2013).

To broaden limited anti-cancer drugs resources

Recently, although a large number of novel anti-cancer drugs have been found, the resources have become the key challenge for researchers. Some scholars try to synthesize these compounds chemically, which is not an easy and environmental friendly method in producing abundant products. Due to the advantages of biotransformation that we have mentioned earlier, biotransformation has become a popular method in producing some anti-cancer drugs that suffers from a limited supply of resource. One kind of the key catalysts are endophytic fungi which grow within their plant hosts without causing apparent disease symptoms. They are also a novel resource of anti-cancer leader and can be used to produce anti-cancer drugs which can be isolated from their hosts (Sheela, 2012). Vinblastine and vincristine belong to indole alkaloid and they are isolated from catharanthus roseus which is a famous anti-cancer herbal medicine (Igor et al., 2005). They are commonly used to treat acute lymphoblastic leukemia, Hodgkin's and non-hodgkin's lymphoma, bronchial lung cancer, etc (Norikazu et al., 2008). However, 12-15 tons are required to produce 1 oz of vinblastine which proves that resources is the important factor limiting its clinical application (Taha et al., 2009). Fortunately, many scholars found that some endophytic fungi can also produce vinblastine. For instance, Zhang found an endophytic fungus named *Fusarium oxysporum* which can be isolated from the phloem of catharanthus roseus and the fungus can produce vincristine (Zhang et al., 2000). Not only can the natural anti-cancer compounds be produced by biotransformation method, but some other anti-cancer compounds, which are the metabolites, can also be produced by biocatalysts. Rare ginsenosides (ginsenoside F_2, Rg_3, Rh_2, compound K) which are the metabolites of ginseng, are hard to be obtained from ginseng but their anti-cancer activities is excellent and exact (Noh et al., 2009). In order to solve problem of limited resource, many kinds of fungi, bacteria and yeasts are used to produce rare ginsenosides and extensive details will be mentioned in later paragraphs.

To Investigate correlative mechanism

Investigating correlative mechanism is an important

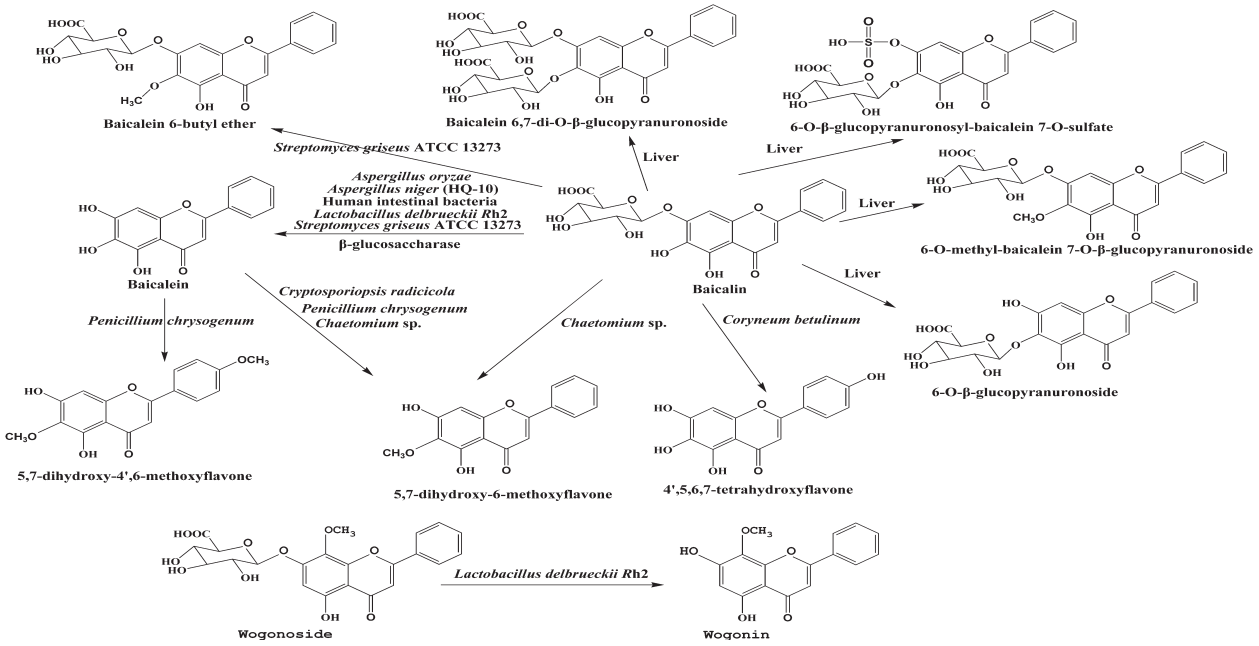

Figure 3. Main Biotransformation Pathways of Baicalein and Wogonin

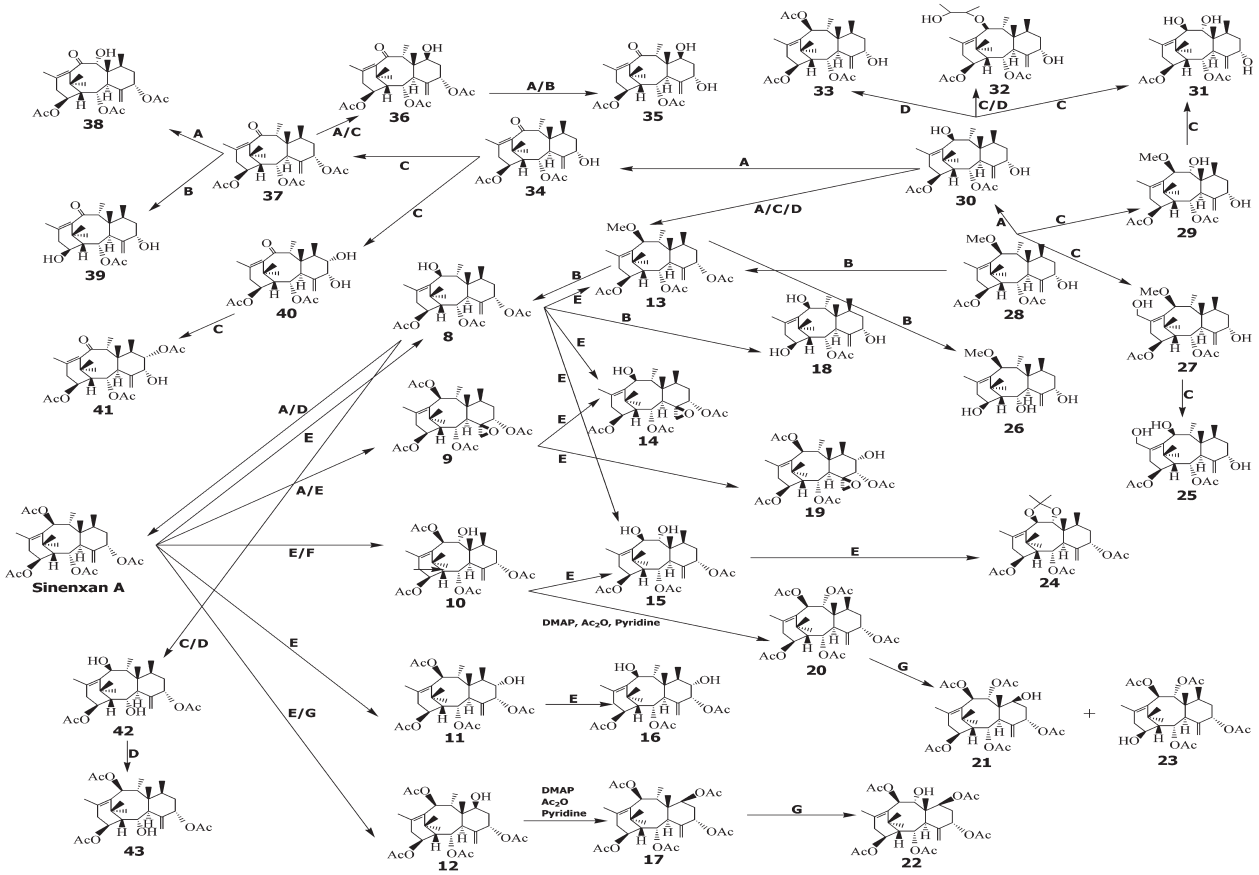

Figure 4. The proposal biotransformation pathways of Sinenxan A. A, Streptomyces *Griseus* CACC 200300; B, *Nocardia purpurea*; C, *Cunninghamella echinulata* CGMCC 3.3400; D, *Aspergillus niger* CGMCC 3.1858; E, *Mucor genevensis*; G, *Ginkgo* Cell Cultures

work for every researcher. Only by knowing the mechanism of treating cancer via anti-cancer drugs can we efficiently apply them in clinical treatment. Also, only by understanding the mechanism of catalysts reaction producing anti-cancer drugs can we apply catalysts to produce drugs more comprehensively. Although there are many methods used for investigating mechanisms, including genetic engineering, proteomics engineering, metabonomics engineering etc. Biotransformation is also a very good method in exploring the mechanism of anti-cancer drugs. On the one hand, some scientists focus on investigating the mechanisms of anti-cancer drugs in treating cancer. One method used by some experts is that using some microorganisms or enzymes, which are isolated from tumor tissue, to bio-convert certain anti-cancer drugs in vitro so as to investigate the anti-cancer mechanism.

Table 1. Microorganisms Used to Produce Rare Ginsenosides During 2012-2013.4

Microorganisms	Reference
Esteya vermicola CNU 120806	(Jingang et al., 2012)
Flavobacterium johnsoniae	(Hao et al., 2012)
Leu.mesenteroides	(Su et al., 2012)
Lb. delbrueckii	(Su et al., 2012)
Cladosporium cladosporioides	(Lunpeng et al., 2012)
Microbacterium esteraromaticum	(Lin-Hu et al., 2012) (Lin-Hu et al., 2013)
Leuconostoc sp. 22-3	(Jin-Kwang et al., 2013)
Chryseobacterium yeoncheonense sp. nov.	(Van-An et al., 2013)
Sphingomonas	(Xue-Feng et al., 2013)
Actinosynnema mirum	(Chang-Hao et al., 2013)
Nocardioides panaciterrulae sp. nov.	(Jin-Kwang, Qing-Mei et al., 2013)
Lactobacillus paralimentarius	(Lin-Hu, Yeon-Ju et al., 2013)
Penicillium oxalicum sp. 68	(Juan et al., 2013)

For example, resveratrol is a cancer preventative agent that is found in red wine, and piceatannol is a closely related stilbene that has anti-leukaemic activity and also a tyrosine kinase inhibitor. Potter successfully converted resveratrol into piceatannol by the cytochrome P450 enzyme CYP1B1 which is overexpressed in a wide variety of human tumours and catalyses aromatic hydroxylation reactions. This observation demonstrates that a natural dietary cancer preventative agent, resveratrol, can be converted to piceatannol with known anti-cancer activity by P450 enzyme CYP1B1 so as to have the effect of anti-cancer (Potter et al., 2002). On the other hand, others focus their full attention on researching the pathways of biotransformation so as to explore the mechanisms of microorganisms and enzymes how to producing anti-cancer compounds. In this review, we have summarized three vital anti-cancer drugs biotransformation pathways (Figure 2, Figure 3, Figure 4).

Typical anti-cancer drugs paragons with biotransformation

Biotransformation can be applied to each phase of anti-cancer cancer drugs research. After many years of efforts by a variety of scientists, some typical anti-cancer drugs have obtained gratifying achievements in the development of anti-cancer drugs via biotransformation. They are ginsenosides, baicalein and wogonin, taxol and analogues.

Ginsenosides

Ginsenosides, which are glycosides with steroids or triterpenes as aglycons, are an important class of physiologically active compounds found in many herbs such as Panax ginseng, Panax quinquefolium and Pseudo-ginseng. Over 60 kinds of ginsenosides have been isolated from ginseng so far (Qi et al., 2011). Among which, ginsenoside Rb_1, Rb_2, Rc, Rd, Re, Rg_1 are the majority chemicals in ginseng that can be produced by hydrolyzing the sugar moieties whereas ginsenoside F_2, Rg_3, Rh_2, compound K(CK) are rare ginsenosides and are present at low concentrations or absent in ginseng (Noh et al., 2009) (the structures of key ginseng saponins are shown in Figure 2). However, recent research has proved that these rare ginsenosides show relatively strong activities on anti-cancer. For example, ginsenosides Rh_2 can against human pancreatic, Colorectal, leukemia cancer cells (Li et al., 2011; Tang et al., 2013; Chung et al., 2013); ginsenosides Rg_3 can against human prostate, colon, breast, gastric cancer cells (Sun et al., 2010; Yuan et al., 2010; Chen et al., 2011; Kim et al., 2011; Pan et al., 2012); ginsenosides F_2 can against glioblastoma, breast cancer cells (Ji et al., 2012; Trang et al., 2012); ginsenosides compound K can against human lung adenocarcinoma, hepatoma, colorectal cancer cells (Wang et al., 2012; Li et al., 2013) . Hence, these rare ginsenosides would develop into excellent anti-cancer drugs.

However, due to the lack of resources of these rare ginsenosides, their development and utilization is limited. To solve this scarcity problem, an increasing number of scholars have paid full attention on researching ways to obtain these rare ginsenosides by biotransformation. Different scholars deal with this problem differently. Some scholars do their best to find novel microorganisms which can transform the majority ginsenosides to rare ginsenosides, including fungi, bacteria and yeast. About 30 species of microorganisms applied to obtain rare ginsenosides has been summarized by Park et al. (2010). After two years of development, the quantity has grown to about 50, and the new microorganisms that have been used to produce rare ginsenosides which are shown in Table 1. Ginsenoside Rb_1 is the main substrate of obtaining rare ginsenosides, followed by ginsenoside Rb_2 and Rc. Other scholars focus their attention on finding appropriate bio-enzyme as they research on the biotransformation of rare ginsenoside. They focus on the purification and characterization of the new bio-enzyme, the reaction conditions and results in the reaction system, such as pH, temperature, time, substrate concentration and yield. The resources of bio-enzyme contain natural bio-enzyme and recombination natural bio-enzyme, such as recombinant ginsenoside hydrolyzing glycosidase cloned from *Sanguibacter keddieii* (Kim et al., 2012) and β-glucosidase from *Microbacterium esteraromaticum* (Quan et al., 2012). The bio-enzymes used in the biotransformation of rare ginsenosides includeβ-glucosidase, β-glycosodase, Cellulase, Lactas, β-glactosodase and α-L-arabinofuranosidase. But the main enzymes are β-glucosidase and β-glycosodase which are good at hydrolyzing glucosidic bond on the ginsenoside. Some other scholars always focus on the pathway of rare ginsenosides biotransformation. The pathways of ginsenosides biotransformation have been summarized by Park et al. (2010). However, as research continues, the information has been renewed and some details are summarized in Figure 2 (An et al., 2010; Yan et al., 2010; Hou et al., 2012; Lee et al., 2013). All in all, recent research reports prove that resolving rare ginsenosides limited resource problem through biotransformation technology is developing at a top speed and the method is advantageous and feasible.

Baicalein and Wogonin

When it comes to baicalein and wogonin (the structure

shown in Figure 3), Scutellariae Radix needs to be introduced. Scutellariae Radix is a famous traditional Chinese medicine that is commonly used in clinical practice for over two thousand years. Baicalin and wogonoside are the major compounds that have good anti-cancer activity found in Scutellariae Radix. Recent research has reported that baicalin and wogonoside are insoluble in water and hard to be absorbed. However, it is found that baicalein and wogonin are the metabolites of baicalin and wogonoside respectively and can easily be absorbed by digestive tract and its bioavailability is also better than baicalin and wogonoside (Che et al., 2001; Lai et al., 2003). In addition, more scholars found that baicalein and wogonin show strong anti-cancer activities on different kind of cancers cells, such as ovarian, ESCC, bladder, oral, colon, pancreatic, breast, bronchial, colorectal, glioma, lung, cervical cancer cells and the activities are better than baicalin (Zhao et al., 2010; Lan et al., 2011; Huang et al., 2012; Cheng et al., 2012; Kim, Kim et al., 2012; Chen et al., 2013; Zhang et al., 2013; Yang et al., 2013) .

However, the content of baicalein and wogonin is very minimal in Scutellariae Radix, and are hard to obtain in natural conditions. Recently, an increasing number of scholars come to recognize the significance of transforming baicalin into baicalein or wogonin by biotransformation which may be a good method in dealing with the problem imposed by limited resources. For instance, baicalin can be transformed into baicalein by *Aspergillus oryza*e (He et al., 2007), human intestinal bacteria (Liu et al., 2007), *Lactobacillus delbrueckii* Rh_2 (Seock et al., 2011) and *Streptomyces griseus* ATCC 13273 (Wang et al., 2005). It can also be converted into baicalein by *Aspergillus niger* (HQ-10) and the conversion ratio was over 92%, which is an excellent way to produce baicalein (Wang et al., 2009). The biotransformation mechanism of baicalein convert to baicalein is the hydrolysis of β-glucosaccharase. In addition, *Lactobacillus delbrueckii* Rh_2 can convert wogonoside into wogonin (Seock et al., 2011). Moreover, baicalin also can be converted by liver, *Chaetomium sp*., *Coryneum betulinum, Cryptosporiopsis radicicola, Penicillium chrysogenum* and *Chaetomium sp*. and can obtain many novel compounts (ABE et al., 1990; Edyta et al., 2007). More details can be found in Figure 3.

Taxol and Analogues

Taxol was first isolated from the bark of yew trees and exists at a limited concentration of 0.01%-0.05% (Mansukhlal et al., 1971; Nicholas et al., 1992). In addition, yew tree is one of the endangered plants which distribute in the south of China and United Nations has banned logging them. However, Taxol plays an integral role in anti-cancer drugs area as well as its analogues. FDA (Food and Drug Administration) has approved of it since 1992 (David et al., 1994) as it is a potent and excellent anti-cancer drug which can against breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer and prostate cancer, and it is also well-recognized globally. Taxol and analogues can against to cancer through inducing and promoting tubulin polymerization, inhibition of microtubule depolymerization and termination of mitosis (Jean et al., 2004). Recently, many novel taxane formulations have been approved by FDA , such as cabazitaxel that specializes in treating prostate and breast cancer was approved in 2010, and nab-paclitaxel specializing in prostate and breast, NSCLC, pancreas, ovarian cancer was approved in 2005 (Jean et al., 2012).

In the past decades, expanding and finding new sources of taxol has become a hot research field. At present, biotransformation technology has shown specific superiority in researching and developing taxol and its analogues at high speed. In order to better develop these excellent anti-cancer compounds, scientists focus mainly on two aspects: finding novel producing endophytic fungi and finding better taxol analogues. On the one hand, some scholars are interested in finding novel endophytic fungi which can produce taxol. In 1993, the first taxol and analogues producing endophytic fungus *Taxomyces andreanae* was discovered in *Taxus brevifolia* (Stierle et al., 1993). After which, more endophytic fungi were found in different laboratories and the types of taxol-producing endophytic fungi were summarized by Zhou in 2010 (Zhou et al., 2010). About 30 taxol-producing endophytic fungi were found from 2001 to 2009 and the highest yield of endophytic fungi was IFBC-Z38 (1000 μg/L) which may be a good fungus and can produce toxol in taxol-producing factories (Zhou et al., 2010). Furthermore, the reaction conditions in the bioconversion system and the detection methods are among the important factors, which would be taken into account by researchers. After 2010, the research is still ongoing. At present, screening for higher or better taxol producing fungi by genetic techniques (Zhang et al., 2011; Zhao et al., 2011; Mohammad et al., 2012) or by immunoassay technique (Sreekanth et al., 2011) has become a more active research area. On the other hand, a large number of scholars has devoted their time in finding taxol analogues which may have better anti-cancer activities, such as RP 56976 (taxotere) which is 2.5-fold more potent than taxol in J774.2 and P388 cells and at least 5-fold more potent in taxol-resistant cells (Israel et al., 1991). IDN5109 is a new taxane which is highly active against the two human ovarian carcinoma xenografts 1A9 and HOC18 and shows significant activity on the paclitaxel-resistant MNB-PTX1 xenograft (Nicoletti et al., 2000). Moreover, a perfect example can be found in Sinenxan A (2α,5α,10β,14β-tetra-acetoxy-4(20),11-taxadiene) which is a kind of toxid isolated from the callus cultures of *Taxus spp*. in high yields (Zhan et al., 2005). Because of the abundant resources and the specific chemistry structure, it has become a hot compound researched through biotransformation technologies. Recently, about 40 compounds are obtained from the process in bioconversion of Sinenxan A by *Ginkgo Cell Cultures, Mucor genevensis, Cunninghamella echinulata* CGMCC 3.3400, *Streptomyces griseus* CACC 200300, *Nocardia purpurea* and *Aspergillus niger* CGMCC 3.1858 (Lin et al., 2007; Dan et al., 2011; Liu et al., 2012). The reactions that occur exhibit diversity, including selective hydroxylation, epoxidation, oxidation, demethylation, acetylation, deacety-lation, and O-alkylation. In order to make us understand more proposal biotransformation

pathways of Sinenxan A, this review summarized it in Figure 4. It is worth pointing that among these compounds, five compounds (Sinenxan A, compound 8, compound 9, compound 13 (Lin et al., 2007) and compound 43 (Liu et al., 2012) proved to have better multi-drug resistant tumor reversal activities. Especially, compound 9 has possessed about two-fold activity as verapamil. What you can know from this review is that biotransformation applied to research taxol and analogues have made some achievements and the research will continue.

Conclusion and Prospect

To sum up, with the advance development of technology, multidisciplinary association for anti-cancer drugs research has become a leading trend. From the foregoing, biotransformation has begun on obtaining a few good attempts in anti-cancer drugs discovery. It is worth mentioning that biotransformation is a green technology and process in developing anti-cancer drugs which is far better than traditional chemical synthesis. It is also an effective method in obtaining novel or rare anti-cancer compounds which are difficult to synthesize in laboratories. Furthermore, it is a convenient way in producing certain anti-cancer drugs as researchers can ensure the substrates and have control over the optimal conditions required for the necessary reaction. What we have to stress is that biotransformation is not an independent technology as it depends highly on the traditional chemical synthesis and modern separation technologies, such as CO_2 technology, membrane separation technology, high-speed counter-current chromatography, high-performance capillary electrophoresis etc (Chen et al., 2009). In addition, introducing some advanced technologies to develop and broaden biotransformation technology is essential. As such, some scholars try to introduce genetic technology to design some recombinases which serve as a better enzyme in producing higher yield products or in creating certain recombinant bacteria to produce required products (Kim et al., 2012; Quan et al., 2012; Quan et al., 2012).

However, there is still a long way for biotransformation technology as an emerging important tool in cancer treatment. Firstly, although there are many kinds of enzymes and microorganisms, the biotransformation reaction and related mechanisms of these are still unclear, which means there are future development prospects. Secondly, some existing biotransformation parameters need further investigation and optimization so as to enhance the production of anti-cancer drugs. Finally, it is necessary to point out that the products of biotransformation are not always useful. When biotransformation results in metabolites of lower toxicity, the process is known as detoxification. In many cases, however, the metabolites are more toxic than the parent substance. This is known as bioactivation. Occasionally, biotransformation can produce an unusually reactive metabolite that may interact with cellular macromolecules which can lead to detrimental health problems, for example, cancer or birth defects. An example of this is the biotransformation of vinyl chloride to vinyl chloride epoxide, which covalently binds to DNA and RNA, a step leading to liver cancer (Emily, 2010). Even so, as a promising useful technique, it is thus necessary to pay close attention to its upcoming potential great achievements in anti-cancer drugs discovery.

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