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The Underlying Mechanisms of Chinese Herbal Medicine-Induced Apoptotic Cell Death in Human Cancer

Feiyu Chen, Zhangfeng Zhong, Hor Yue Tan, Ning Wang and Yibin Feng

Abstract

The high incidence of cancer is a global burden. Cancer cells acquire immortality, which results in loss of control in cell proliferation and population expansion. Cancer cells undergo a series of genomic instability, leading to mutated amplification or deletion of certain genes that strictly control the cell fate. Programmed cell death is a mechanism of cell fate control that is aberrantly regulated in cancer cells. Apoptosis is the major form of programmed cell death regulated by both intrinsic and extrinsic pathways. Discovering effective and specific alternative solutions that can reprogram apoptosis in cancer cells is always a challenge. Chinese herbal medicine has captured increasing attention from both researchers and manufacturers, as evidenced by observable curative effects from previous clinical experience. Hence, to clarify and reinforce the understanding of the effect of Chinese medicine on cancer, in this chapter, we will retrospectively review the latest 5 years of literature and summarize the mode of action of Chinese herbal medicine on apoptotic cell death in cancer. Both Chinese medicine-induced intrinsic and extrinsic mechanisms of apoptosis will be discussed, and common compounds from Chinese medicine with druggable potential as novel apoptosis-inducing agents will be highlighted.

Keywords: cell apoptosis, Chinese herbal medicine, programmed cell death, intrinsic and extrinsic pathways, human cancer

1. Introduction

Programmed cell death is a tight process mediated by an intracellular program, whereby damaged or harmful cells and their organelles are recycled or disposed of. The regulated cell death occurs along with morphological alterations. Biologists have employed such morphotypes from functional and biochemical perspectives to classify cell death routines. As provided by the Nomenclature Committee on Cell Death, three major widely accepted definitions of terms include apoptosis, autophagy, and necrosis [1]. Among them, apoptosis involves plasma membrane blebbing, cytoplasmic shrinkage, nuclear fragmentation, and chromatin condensation. The process ends up with formation of apoptotic bodies that are being taken

up by phagocytic cells [1]. Apoptosis has been orchestrated in detail as two basic mechanism-oriented classifications: intrinsic pathway and extrinsic pathway.

Intrinsic apoptosis is initiated by multiple exogenous and endogenous stimuli such as stress, DNA damage, and chemotherapy, whereby cytochrome c is increasingly released from the mitochondria to the cytosol. Irreversible mitochondrial outer membrane permeabilization (MOMP) hence occurs, followed by caspase-3 activation that mainly promotes the typical apoptosis features [2]. In striking contrast, extrinsic apoptotic pathway is a modality of cell death driven by extracellular microenvironmental perturbations, which are normally two types of plasma membrane receptors: (1) death receptors consisting of a type of tumor necrosis factor (TNF) receptor FAS and TNF-related apoptosis-inducing ligand (TRAIL) receptors. The activation occurs when they bind to the cognate ligands; (2) dependence receptors such as NTN1, whose presence of elevated level relies on the drop in the levels of their specific ligands below a specific threshold. The process is then propagated by caspase-8 and executed mainly by caspase-3 [3] (**Figure 1**).

To our knowledge, programmed cell death provides an important function in metazoan cells to eliminate the toxic accumulation of superfluous cells and organelles and thereby to sustain the homeostatic cellular life. Due to loss of control of cancer cells in proliferation and expansion, a major focus has been placed on the association between defective regulation of apoptosis and immortality property of cancer cells. A large body of experimental evidence has unveiled that the defect in the physiological mechanism of apoptosis may promote tumorigenesis, while regulated apoptosis contributes to the recovery from diseases. For example, MOMP is one of the most common phenomena observed which is mediated by a variety of protein interactions of B-cell lymphoma 2 protein (Bcl-2) family, representing a total of 25 pro- and anti-apoptotic proteins. During the life of the cell, the balance of Bcl-2 family proteins partly determines cellular health. Besides the presence of decreased levels of pro-apoptotic proteins, the activation of anti-apoptotic family members is an important mechanism of apoptosis disequilibrium in cancer. Cellular inhibitors of apoptosis proteins (IAPs) represent a family of evolutionarily

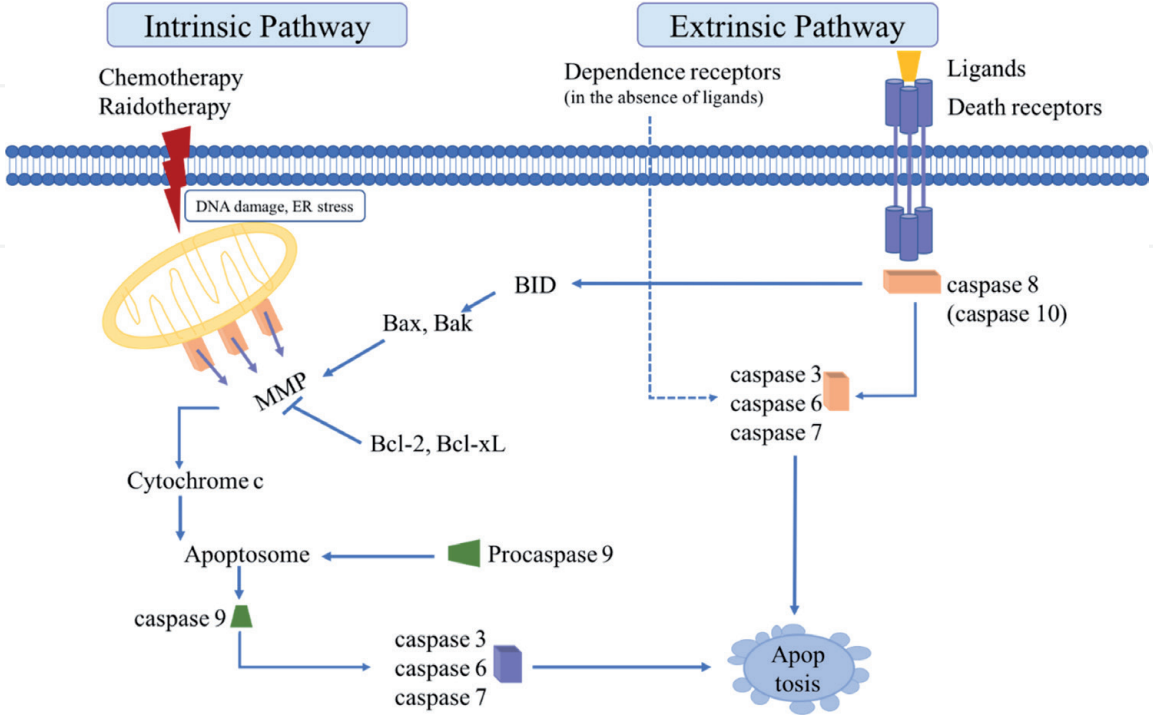


Figure 1.
Intrinsic and extrinsic pathways of apoptosis.

conserved apoptosis suppressors, which are known to be dysregulated in many cancers; that said, cancer cells might use the disequilibrium to retard apoptotic processes or stay in an apoptosis-resistant state [4, 5].

Therefore, seeking for sensitive and specific treatments that can restore the perturbation of apoptosis to a state of equilibrium in cancer cells is a challenge. Previous studies have focused on Chinese herbal medicine for its employment for centuries in the treatment of patients as well as its positive effects on tumors. Rather than focusing on the ablation of tumors per se, Chinese medicine focuses on correcting the imbalance of apoptosis. Evidence has been accumulating over decades that natural compounds of herbal medicine or formula are responsible for correcting apoptotic disequilibriums or resetting of apoptotic thresholds. A range of signaling pathways have been involved in the favorable effects of Chinese medicine in the treatment of cancers. As the domain continues to develop and novel molecular mechanisms are still being characterized, we have retrieved the latest 5 years of literature related to tumor apoptosis in response to herbal medicine. We also present literature on natural compounds from Chinese medicine with druggable potential as novel apoptosis-inducing agents.

2. Chinese herbal medicine that induces intrinsic apoptosis in human cancers

The intrinsic apoptosis pathway is driven by intercellular and extracellular perturbations such as oxidative stress, DNA damage, and chemo- and radiotherapies, which result in mitochondrial dysfunction and release of cytochrome c in the cytoplasm. Initiator caspase-9 is then activated, and executioner caspase-3 precipitates the apoptotic process. During this process, Bcl-2 family proteins which are involved in the activation of intrinsic apoptosis have been identified to play a role by either activating pro-apoptotic pathways that cause the subsequent efflux of cytochrome c or inhibit cytochrome c release. Pro-apoptotic proteins include Bax, Bid, and Bad, among others. The other subtype presenting anti-apoptotic activity contains Bcl-2 and Bcl-xL. When procaspase-9 forms, the caspase cascade will be in turn activated and caspase-2, caspase-8, caspase-9, and caspase-10 initiate the process of apoptosis, while caspase-6, caspase-7, and mainly caspase-3 precipitate the cell apoptosis. This is totally different from extrinsic apoptosis, which is mediated by death receptors. As membrane receptors such as Fas, TNF receptors will interact with corresponding ligands to recruit relevant adaptor proteins, followed by the recruitment of a series of downstream factors, in particular caspase-8, which is the critical mediator to activate the caspase cascade [6, 7] (**Figure 1**).

Evidence has been accumulating, across the last few decades, that dysfunctional apoptosis in cancer partly leads to the immortality property of cancer cells [6]. With well-reported observations of good curative effects on multiple cancers as well as clinical application of centuries, attention has been extensively attracted to Chinese herbal medicine. Substantial laboratory evidence has unveiled that Chinese herbal medicine is able to recover the defective apoptosis via intrinsic apoptotic pathway, which eventually is in favor of tumor suppression (**Table 1**). Interestingly, Chinese herbal medicine that only involves the regulation of the extrinsic pathway has been rarely reported.

Osteosarcoma is a type of cancer existing in a bone. Most cases occur among children and adolescents. Polyphyllin I (PPI) is extracted from *Paris polyphylla* rhizomes, which has been used for centuries in China for the treatment of infectious diseases and cancer. In osteosarcoma cells, PPI has been shown to activate unfolded protein response (UPR)/endoplasmic reticulum (ER) stress pathway, followed by

Name of Chinese herbal medicine	Cancer type	Mechanism of action	Ref.
<i>Paris polyphylla</i> Smith var. <i>yunnanensis</i> (polyphyllin I)	Osteosarcoma	UPR and ER stress	[8, 9]
<i>Salvia miltiorrhiza</i> (tanshinone IIA)	Osteosarcoma	Bcl-2 regulation	[10]
	Cervical cancer	ER stress	[11]
<i>Epimedium</i> (icaritin)	Cervical cancer	ROS stress	[12]
Chinese bayberry (flavonoids)	Ovarian cancer	Bcl-2 regulation	[13]
<i>Psoralea corylifolia</i>	Breast cancer	Bcl-2 regulation	[14]
<i>Pueraria</i> (6"-O-xyloside)	Colon cancer	Bcl-2 regulation	[16]
<i>Ornithogalum caudatum</i> Ait (OSW-1)	Colon cancer	Cytochrome c release	[17]
<i>Ginkgo biloba</i> (ginkgolic acids)	Colon cancer	ROS stress	[18]
<i>Macleaya cordata</i> (sanguinarine)	Colorectal cancer	Bax regulation	[20]
<i>Cordyceps sinensis</i> (cordycepin)	Pancreatic cancer	Bcl-2 regulation	[22]
<i>Angelica sinensis</i> (N-butylidenephthalide)	Gastric cancer	MMP	[23]
<i>Lonicera japonica</i> (luteolin)	Gastric cancer	Bax, Bcl-2 regulation	[24]
<i>Tripterygium wilfordii</i> (celastrol)	Liver cancer	ER stress	[27]
	HCC	Bax, Bcl-2 regulation	[28]
<i>Polygoni multiflora</i> (ethanolic extract)	HCC	MMP	[29]
<i>Brucea javanica</i> (dehydrobruceine B)	Lung cancer	MMP	[30]
<i>Catharanthus roseus</i> (cathachunine)	Leukemia	ROS stress	[31]
<i>Pulsatilla chinensis</i> (saponins)	Leukemia	MMP	[32]
<i>Coptidis rhizoma</i> (berberine)	Melanoma	Bax, Bcl-2 regulation	[33]
	HCC	Cytochrome c release	[34]

UPR, unfolded protein response; ER, endoplasmic reticulum; Bcl-2, B-cell lymphoma 2 protein; ROS, reactive oxygen species; Bax, Bcl-2-associated X protein; MMP, mitochondrial membrane potential; HCC, hepatocellular carcinoma.

Table 1.
Chinese herbal medicines that induce intrinsic apoptosis in human cancer.

descending levels of anti-apoptotic proteins as well as ascending expressions of pro-apoptotic proteins [8, 9]. With regard to osteosarcoma, tanshinone IIA (Tan IIA) is one of the main phytochemical ingredients isolated from the roots of *Salvia miltiorrhiza* (Danshen). Exposure of osteosarcoma cells to Tan IIA caused in vivo tumor suppression and apoptosis induction in osteosarcoma cells. Huang et al. investigated the mechanism of its inhibitory effect and found that Tan IIA treatment elicited significant activation of caspase cascade by Bcl-2 family modulation, as evidenced by a remarkable increase in the fission protein Drp1 and a decrease in mitochondrial fusion proteins Mfn1/2 and Opa1. The study concluded that mitochondrial dysfunction in combination with dynamic change was involved in apoptosis of primary malignant bone tumors treated by Tan IIA [10]. More so, Tan IIA exhibited strong inhibitory effects on cervical carcinoma CaSki cells through promoting caspase cascades, whereas the phosphorylation of p38 and JNK signaling was activated. Comprehensive proteomics revealed the global protein changes and

the network analysis confirming that Tan IIA administration activated ER stress signaling cascade that eventually resulted in mitochondrial-related apoptosis [11].

Cervical cancer is the fourth most common female malignancy in the world. Despite preventive vaccines against human papillomavirus (HPV) which are now commercially available and which have been shown to be safe and effective, there are still a large number of women, in particular in low- and middle-income countries, who are less likely to have access to HPV vaccines or screening of cervical cancer due to geographical, economic, and political barriers. Icaritin, a native compound derived from the Chinese herb *Epimedium*, was demonstrated to be effective in repressing growth of human cervical cancer cells such as HeLa and SiHa. The levels of pro-apoptotic protein Bax and activated caspase-3 and caspase-9 enzymes were upregulated, with concomitant downregulated levels of anti-apoptotic proteins Bcl-2 and XIAP. The changeable expression of these proteins had implications in remarkable induction of apoptosis in icaritin-treated cancer cells, which suggested that cancer cell death via induction of extensive oxidative DNA damage was promoted by icaritin-induced ROS overload that rendered activation of the intrinsic apoptotic pathway [12].

Ovarian cancer and breast cancer are malignancies that commonly occur in females. The treatment with Chinese bayberry leaf flavonoids increased the expression of cleaved caspase-3 and caspase-7, which induced intrinsic apoptosis with the activation of Erk-dependent caspase-9, as well as increased expression of the pro-apoptotic proteins Bad and Bax and decreased levels of anti-apoptotic proteins Bcl-xL and Bcl-2 [13]. Bakuchiol is an active constituent of Chinese herb *Psoralea corylifolia* which induced disturbed mitochondrial membrane potential in MCF-7 cells. Bakuchiol-induced apoptosis was associated with increased expression of caspase family and Bcl-2 family proteins, suggesting that bakuchiol may induce apoptosis via the intrinsic apoptotic pathway [14]. Another study evaluated the function of *Paeonia suffruticosa* in triple-negative breast cancer cells. Bcl-2 expression was found to be decreased, while Bax levels remained relatively constant. Small decrease in Fas ligand levels was observed in parallel with a lack of increase in caspase-8 activity. The extract was able to induce intrinsic apoptosis which meant it possessed the potential ability of reducing cancer burden [15].

Colon cancer is worldwide and is considered the third most commonly diagnosed cancer clinically. To identify novel specific and effective therapeutic strategies for colon cancer is extremely essential. Natural products have gained increasing attention lately. Puerarin 6"-O-xyloside (PRX), a natural compound, is derived primarily from the root of the *Pueraria*. PRX was found to significantly upregulate cleaved caspase-3, cleaved caspase-9, Bcl-2, Bcl-2-associated X proteins, and phosphorylated c-Jun terminal kinase and downregulate expression levels of matrix metalloproteinase-3, metalloproteinase-9, and vascular endothelial growth factor. The study suggested that PRX exerted antitumor activity against colon cancer cell lines and the anticancer mechanisms of PRX may be associated with the induction of mitochondria-mediated intrinsic apoptosis, which provides a scientific basis for the clinical use of PRX in the treatment of colon cancer [16]. As a natural compound, *Ornithogalum caudatum* Ait is primarily used as an anti-inflammatory and antitumor agent in Chinese folk medicine. It was shown that with low toxicity on normal colonic cells, an isolated compound OSW-1 suppressed colon cancer cells in vitro via intrinsic apoptotic pathway, whereby it increased cellular calcium, changed mitochondrial membrane potential, disrupted mitochondrial morphology, and led to the release of cytochrome c and the activation of caspase-3 [17]. Ginkgolic acids (GA), a botanical drug extracted from the seed coat of *Ginkgo biloba* L., possess various bioactive properties. The findings, for the first time, illustrated that GA suppressed colon cancer cell proliferation, migration, and invasion

ability. Ginkgolic acids (GA) proved to trigger intrinsic apoptosis as evidenced by the release of cytochrome c. Autophagy modulation mediated by ROS generation was also observed in GA-treated colon cancer cells, elucidating that GA might be a potential agent for colon cancer therapy [18].

Colorectal cancer and colon cancer are clearly related and often used interchangeably. These two terms are often believed to be the subset of the other or even the same thing. In truth, despite similarities, there is still variation including sex predilection, anatomy, disease recurrence, surgery, and invasion of nearby tissues, not the least of which are the development ways of the two diseases. *Macleaya cordata* is originally described in Ben Cao Shi Yi in Tang dynasty and is commonly used in the treatment of various diseases for thousands of years [19]. Sanguinarine is a major bioactive component of *Macleaya cordata*. Sanguinarine was shown to decrease the tumor size of implanted colorectal BALB/c-nu mice model via the intrinsic apoptosis pathway with significant increased cleavage of caspase-3 and poly(ADP-ribose) polymerase (PARP) in orthotopical colorectal carcinoma. In vitro experiments found that sanguinarine could increase mitochondrial ROS and trigger mitochondrial membrane potential (MMP) in multiple colorectal cancer cell lines. Furthermore, intrinsic apoptosis induced by sanguinarine was demonstrated to be Bax-dependent [20]. Cordycepin is one of the main native constituents extracted from the traditional Chinese herbal remedy *Cordyceps sinensis* and *Cordyceps militaris*. It has been extensively used as food, health supplement, and herbal formulas from ancient times for health care [21]. Recent evidence demonstrated that cordycepin has anti-inflammatory and antitumor activities. In human MIA PaCa-2 and Capan-1 pancreatic cancer cells, cordycepin was found to inhibit cell viability, proliferation, and colony formation ability and induce cell cycle arrest and early apoptosis in a dose- and time-dependent manner, while the same effect was observed in in vivo experiments. Further, the expression levels of Bax, cleaved caspase-3, cleaved caspase-9, and cleaved PARP were upregulated, and Bcl-2 proteins were downregulated. The study suggested that either in vivo or in vitro the intrinsic apoptotic pathway mediated by mitochondria was involved in the cordycepin's antitumor capacity [22].

Despite the fact that the incidence of gastric cancer has declined across the globe over the past century, there is still a startling lack of effective therapeutics. *Angelica sinensis* (Danggui) is one of the most famous medical herbs widely used in China. Liao et al. investigated the function of a bioactive compound N-butyldenephthalide (BP) from Danggui in gastric cancer. The results showed that BP inhibited gastric cancer cell proliferation and induced apoptosis through activating mitochondrial apoptotic pathway. These data provide the basis for a novel therapeutic approach toward the management of gastric cancer [23]. Another active component named luteolin from a traditional Chinese medicine exhibits potent antitumor properties. The molecular events occurring in the process of tumor inhibition and the signal transduction pathways involved were explored by Lu et al. They found increasing levels of caspase-3, caspase-9, and cytochrome c in response to luteolin as well as an increased ratio of Bax to Bcl-2, suggesting that luteolin induced apoptosis through the intrinsic pathway [24].

Globally, liver cancer ranks as the sixth most common form of cancer. With the growing prevalence of liver cancer, it remains a major killer worldwide. Patients' status is dismayingly unsatisfying unless liver cancer is caught early and specific therapeutic methods are being discovered [25]. Celastrol is a pharmacologically active compound originally identified from the root bark of the Chinese herb "Thunder of God Vine" (*Tripterygium wilfordii* and *Celastrus regelii*). Since old times it has been used as a natural remedy for inflammatory conditions and autoimmune diseases [26]. Investigators demonstrated the inhibitory effects of celastrol on

liver cancer HepG2 and Bel7402 cell lines. Induction of ER stress and UPR occurred in cells exposed to celastrol, which subsequently activated the intrinsic apoptotic pathway. They also reported that celastrol repressed H22 tumor growth in mice model via ER stress induction [27]. Another report aimed to evaluate the antitumor effects of celastrol against diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) in rats. In addition, the underlying mechanism was explored, and the data showed that celastrol activated the intrinsic mitochondrial apoptosis pathway, inhibited anti-apoptotic Bcl-2 and Bcl-xL, and induced pro-apoptotic Bax, cytochrome c, PARP, and caspases [28]. Zhiheshouwu (*Polygoni Multiflori Radix Praeparata*) is a Chinese medicinal herb exhibiting inhibitory effects on cancer cells. The study investigated the function of Zhiheshouwu ethanolic extract (HSWE) and revealed the decreased mitochondrial membrane potential in HSWE-treated Bel-7402 cells. The authors concluded that HSWE induced intrinsic apoptosis in hepatocellular carcinoma cells on the basis of the evidence that mitochondrial injury is characterized as an intrinsic apoptotic cell death mechanism [29].

Lung cancer has been one of the leading causes of mortality in this era. With the etiologic factors of lung cancer being more complex such as environmental pollution, industrialization, and urbanization, cases of lung cancer increase across the world and account for nearly 20% of cancer-caused deaths. Studies on the new ways of diagnosis and treatment have played an important role in the tertiary prevention of lung cancer. *Brucea javanica* is an effective traditional medicine listed in Chinese Pharmacopeia. It has long been used as a commercially available agent for cancer treatment in practice. Dehydrobruceine B (DHB) is an active ingredient isolated from *Brucea javanica*. Since the loss of MMP, the release of cytochrome c into cytosol and the cleavage of caspase-9, caspase-3, and PARP were observed in lung cancer cells exposed to DHB. Researchers suggested that DHB-induced apoptosis was mediated through mitochondrial intrinsic pathway [30].

Leukemia is a group of life-threatening malignant disorders which often originate in the blood and bone marrow. The acute leukemia is more prevalent among adolescent and young adult population. *Catharanthus roseus*, a species of flowering plants, consists of dimeric indole alkaloids with significant antitumor activities. The induction of apoptosis by cathachunine occurred along with the regulation of Bcl-2 protein family members. The observations further indicated that cathachunine triggered ROS-dependent mitochondria-mediated intrinsic pathway in human HL60 and K562 leukemia cells, which provided evidence for a natural source of an antitumor agent [31].

Total saponins isolated from *Pulsatilla chinensis* has been identified to induce the apoptosis of solid cancer cells. The rhizoma of the plant has virtually been used as Chinese herbal remedy for thousands of years. 23-Hydroxybetulinic acid, one of natural compounds from total saponins, upregulated Bax, cytochrome c, cleaved caspase-9, and caspase-3 expressions and downregulated Bcl-2 and survivin levels, suggesting that saponins induced intrinsic apoptosis via disrupting mitochondrial membrane potential [32].

Coptidis rhizoma (CR) has been used in clinical practice from thousands of years ago. A large body of research has placed attention on *Coptidis rhizoma* as well as its extracts and major active chemical constituents. Berberine, the most famous natural ingredient from CR, has been shown to have anticancer activities against multiple cancers. Recent work investigated the effects of berberine in human melanoma and reported that exposure of CR to human melanoma cells triggered significant suppression of anti-apoptotic proteins including Bcl-2, Mcl-1, and Bcl-w while upregulating the expression of pro-apoptotic proteins Bax and Bak [33]. As berberine is one of the most active molecules from traditional Chinese medicine, to better understand the natural product, our group has conducted

several investigations over the years. Although berberine-induced cell death has been extensively demonstrated in cancer, the underlying death mechanisms still remain obscure. Exposure of hepatocellular carcinoma HepG2 and MHCC97-L cells to berberine increased Bax expression, permeable transition pore formation, cytochrome c release to cytosol, and subsequent execution of the caspase-3 and caspase-9 [34]. Tumor suppressor p53 plays an important role in cancer inhibition. It was verified to be involved in berberine's antitumor action [35, 36]. Our group found that human HCC cell miR-23a was upregulated upon berberine treatment, and the upregulation of miR-23a could be blocked by inhibiting p53 expression. The study suggested that miR-23a may be involved in regulating the antitumor effect of berberine in HCC through p53-dependent mechanisms [37]. Baicalin is a natural flavonoid from several medicinal herbs such as *Scutellaria baicalensis* Georgi. We speculated that tumor-associated macrophages (TAM) had a key role in HCC. Our findings revealed that TAM repolarisation contributed to suppressive function of baicalin on HCC and autophagy-associated activation of RelB/p52 was essential in the process [38]. Huanglianjiedu decoction (HLJDD) has been well documented for the treatment of heat and dampness-related diseases thousands of years ago. As clinical practice requires more specific and safe Chinese herbal formula, our group members explored the inhibitory effect of this formula in HCC suppression. The results showed the involvement of eEF2 inhibition in its mode of action [39].

3. Both intrinsic and extrinsic apoptotic pathways involved in Chinese herbal medicine-induced apoptosis in human cancers

From a molecular standpoint, extrinsic apoptosis and intrinsic apoptosis are strikingly different. But on the whole, the two pathways are sometimes related. Receptor trimerization can lead to recruitments of several death domains and subsequent recruitment and activation of caspase-8 and caspase-10, which then either activate the intrinsic apoptotic pathway through cleavage of the BID or initiate extrinsic apoptosis directly by activating executioner caspase-3, caspase-6, and caspase-7 to induce efficient cell death (**Figure 1**). Previous efforts have reported that both intrinsic and extrinsic apoptoses may coexist when cancer cells were exposed to Chinese herbal medicine (**Table 2**).

Butein is a subtype of chalcones, which is widely biosynthesized in plants. Butein has been identified to be extractable from Chinese herbal medicine and possess different pharmacological activities. Recent works reported that butein owned abilities of inhibiting proliferation and inducing apoptosis both in vivo and in vitro. A finding suggested that butein could decrease cervical cancer cell viability via pro-apoptotic effect, which involved inhibition of IAP proteins and activation of both extrinsic and intrinsic pro-apoptotic pathways. Therefore, butein may be applicable for cervical cancer treatment [40]. *Tetragium hemsleyanum*, named Sanyeqing in Chinese, has long been used as a folk medicine to overcome cancer. A recent study prepared petroleum ether fractions (PEF) of Sanyeqing and aimed to investigate the possible mechanisms by which PEF presented antitumor activity against HeLa cells. Caspase-9 and caspase-3 were activated, and mitochondrial membrane potential decreased after PEF treatment. In addition, PEF administration was involved in the extrinsic apoptotic pathway indicated by the activation of caspase-8 [41]. The same observations were found in ovarian cancer cells upon exposure to butein. Increased levels of cytochrome c, caspase-3, caspase-8, and caspase-9 in two types of ovarian cancer cells, with concomitant downregulated levels of Bcl-2 and Bcl-xL and upregulated proteins Bax and Bad, suggested that both extrinsic and intrinsic pathways were involved in butein-induced apoptosis [42]. To treat ovarian cancer,

Name of Chinese herbal medicine (active constituent)	Cancer type	Mechanism of action	Ref.
<i>Dalbergia odorifera</i> , <i>Caragana jubata</i> , <i>Rhus verniciflua</i> , <i>Semecarpus anacardium</i> (butein)	Cervical cancer	IAP; Fas	[40]
<i>Tetrastigma hemsleyanum</i> (petroleum ether fraction)	Cervical cancer	MMP; Fas	[41]
<i>Dalbergia odorifera</i> , <i>Caragana jubata</i> , <i>Rhus verniciflua</i> , <i>Semecarpus anacardium</i> (butein)	Ovarian cancer	Bcl-2, Bcl-xL; Fas	[42]
Chinese bayberry (prodelphinidins)	Ovarian cancer	Bcl-2, Bcl-xL; DR5, Fas	[43]
<i>Sanguisorbæ</i> (ziyuglycoside I)	Breast cancer	Bax, Bcl-2; Fas	[44]
<i>Paeonia moutan</i> (paeonol)	Prostate cancer	Bax, Bcl-2, caspase-9; caspase-8	[45]
<i>Ginkgo biloba</i> (exocarp extracts)	Lewis lung cancer	Bax, Bcl-2; Fas, p-p38	[46]
<i>Labiatae</i> (<i>Scutellaria barbata</i> D)	Lung cancer	Cytochrome c; Fas	[47]
<i>Anisomeles indica</i> (ovatodiolide)	Lung cancer	PUMA, Bax; DR5	[48]
<i>Curcuma</i> (curcuminoids)	Lung cancer	MMP, Fas	[49]
	Head and neck squamous cell	Caspase-9; caspase-8	[50]
	Leukemia	Bcl-2; FasL	[51]
<i>Tripterygium wilfordii</i> (celastrol)	Liver cancer	Caspase-9; caspase-8	[52]
	Mantle cell lymphoma	Caspase-9; caspase-8	[53]
<i>Licorice</i> (licochalcone B)	Oral squamous cell carcinoma	ROS; DR4	[54]
	Skin cancer	Sp1; Fas	[55]
<i>Magnolia officinalis</i> (honokiol)	Glioblastoma	Bax, Bcl-2, caspase-9; caspase-8, Fas	[56]
<i>Allium sativum</i> (allicin)	Glioblastoma	MMP; Fas	[57]
<i>Phellinus linteus</i> (hispolon)	Leukemia	Bax, Bcl-2, caspase-9; caspase-8	[58]
<i>Jujube</i> (extracts of jujube seed)	Leukemia	Caspase-9; caspase-8	[59]
<i>Cordyceps kyushuensis</i> Kob (aqueous extracts)	Leukemia	Bcl-2; Fas	[60]

IAP, inhibitor of apoptosis; MMP, mitochondrial membrane potential; Bcl-2, B-cell lymphoma 2 protein; Bcl-xL, B-cell lymphoma-extra large; DR5, death receptor 5; PUMA, p53-upregulated modulator of apoptosis; FasL, Fas ligand; DR4, death receptor 4; Sp1, specificity protein 1; Bax, Bcl-2-associated X protein.

Table 2.
Chinese herbal medicines that induce both intrinsic and extrinsic apoptosis in human cancer.

increasing herbal medicines have been studied. Chinese bayberry leaves are rich in prodelphinidins. Since the isolation and purification of prodelphinidins are difficult, the association between the degree of prodelphinidin polymerization and their anti-carcinogenic activity remains ambiguous. Recent findings reported that apoptosis was executed through the intrinsic pathway by upregulating the expression of pro-apoptotic proteins including p53-upregulated modulator of apoptosis (PUMA), Bax, and Bcl-2-associated agonists of cell death. The extrinsic pathway was also observed in the apoptotic process as evidenced by upregulation of death receptor 5 (DR5) and Fas expression [43]. Triple-negative breast cancer (TNBC) is currently considered

as one of the most severe malignancies due to poor prognosis and aggressive clinical behavior. Recent work explored the cytotoxic effect of ziyuglycoside I, the major component extracted from *Sanguisorbae Radix*, on a type of TNBC cell line. The results showed that ziyuglycoside I triggered apoptosis of MDA-MB-231 cells in a dose-dependent fashion, as evaluated by the elevated expression of p53 and p21 and upregulated Bax/Bcl-2 ratio, suggesting that these effects were mediated through mitochondrial-initiated and Fas/FasL-initiated apoptotic pathways [44]. Paeonol (Pae) is a main active ingredient from the root bark of *Paeonia moutan*. Numerous reports indicated that Pae effectively restrained several types of cancer lines. A study lately reported that Pae inhibited cancer cell proliferation in prostate cancer. Moreover, the study showed that antiproliferative effects of Pae may be closely related to the activation of extrinsic and intrinsic apoptotic pathways [45].

Ginkgo biloba is known as an edible traditional Chinese medicine. The extracts prepared from the exocarp of *Ginkgo biloba* (GBEE) have been identified to possess capabilities of antitumor, antiaging, and immune promotion, among others. Lewis lung cancer cells were used as a cell model to detect the effect of GBEE, and results showed that Bax/Bcl-2 ratio and the release of cytochrome c from the mitochondria to cytosol increased. In addition, GBEE upregulated the cleaved caspase-3 protein expression as well as the protein levels of Fas, FasL, and p-p38. These data suggested that GBEE induced apoptosis in Lewis lung cancer cells via death receptor-mediated extrinsic pathways and mitochondrial-mediated intrinsic pathways [46]. *Scutellaria barbata* D. Don (SB) is a well-known anti-inflammatory compound isolated from dried whole plant of *Labiatae*. Chen et al. reported that the antitumor mechanism of SB was mediated by P38/SIRT1-regulated cell apoptosis, which involved mitochondrial- and Fas/FasL-mediated pathways [47]. With regard to lung cancer, ovatodiolide, extracted from medicinal herb *Anisomeles indica*, was also explored due to its effective antibacterial and anti-inflammatory properties. Recent work investigated the antitumor activity of ovatodiolide, in which the mechanism was characterized by elevated levels of PUMA, Bax, and DR5 proteins, decreased expressions of Bcl-2 and Mcl-1, as well as activation of caspase-8, caspase-9, and caspase-3 [48]. Curcuminoids, a mixture of curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC), are a primarily natural phenolic compound purified from *Curcuma* species. The study found that BDMC decreased the levels of MMP and promoted caspase-3, caspase-8, and caspase-9 activation while upregulating the levels of Fas ligand and Fas. These results suggested that BDMC triggered cell apoptosis via extrinsic and intrinsic signaling pathways [49]. Another group also examined the anticancer activity of curcumin against head and neck squamous cell. Treatment of FaDu and Cal27 cells with curcumin increased caspase-9 and caspase-8 protein expression, which meant that intrinsic and extrinsic apoptotic pathways were both activated by curcumin in the treatment of head and neck squamous cell carcinoma [50]. Besides, curcumin function was also investigated in leukemia cells. The results of PCR and Western blotting analysis showed that curcumin increased the FasL level; inhibited Bcl-2, NF- κ B, and ERK expression; and activated P38 MAPK, JNK, and caspase-3. This study demonstrated that curcumin played its role not only through intrinsic but also through extrinsic apoptosis pathways [51].

Celastrrol is an active ingredient derived from *Tripterygium Wilfordii*, a type of traditional Chinese medicinal herb, which has been reviewed for the treatment of liver cancer as stated above. As of now, celastrrol has gained great interest due to its potential anti-inflammatory and antitumor properties in many cancers. For instance, the long-term survival of osteosarcoma has stagnated over decades; exposure of osteosarcoma to celastrrol resulted in the activation of caspase-3, caspase-8, and caspase-9, which suggested that celastrrol-induced apoptosis was mediated by extrinsic and intrinsic pathways [52]. Another report demonstrated

that celastrol treatment markedly inhibited mantle cell lymphoma cells proliferation by stimulating apoptosis via extrinsic and intrinsic pathways while exerting minimal cytotoxic effects on normal cells. The results provided support for the clinical use of celastrol [53]. Licochalcone B (Lico B) belongs to retrochalcone family and is normally isolated from the roots of Chinese *licorice*, which has long been used in China with a variety of pharmacological properties such as antioxidant, anti-inflammatory, and antibacterial. The underlying mechanism by which Lico B plays a part in oral squamous cell carcinoma (OSCC) has been elucidated by Oh et al. They reported that exposure of Lico B to oral cancer cells induced upregulation of Bax as well as downregulation of Bid, Bcl-xL, and Mcl-1. The loss of MMP led to the release of cytochrome c. Furthermore, Lico B promoted the generation of ROS, which in turn induced DR4, DR5, and CHOP. Thereby, it is suggested that Lico B triggered apoptotic cell death via intrinsic and extrinsic pathways [54]. Lico B was also investigated in human skin cancer cells. Lico B induced apoptotic cell death through the modulation of specificity protein 1 and apoptotic proteins including death receptors, critical factors of the extrinsic pathway. Based on these facts, conclusions could be made that Lico B treatment resulted in extrinsic and intrinsic apoptotic cell death [55]. A natural bioactive compound honokiol that was isolated from the *Magnolia officinalis* exhibited potent inhibitory activity against multiple human cancer cells. Zhang et al. for the first time reported that the antineoplastic effect of honokiol on glioblastoma cells was mediated through caspase-dependent apoptosis that involved intrinsic and extrinsic signaling pathways [56]. Following treatment with allicin, the expression levels of Fas/FasL increased and Bcl-2 protein significantly decreased in glioblastoma cells, at both mRNA and protein levels. The data demonstrated that allicin induced glioma cell apoptosis by both extrinsic Fas/FasL-mediated and intrinsic mitochondrial pathways [57]. Hispolon was extracted from *Phellinus linteus* and has been demonstrated to show strong anticancer, anti-inflammatory, antioxidant activities. A study reported that exposure of human NB4 leukemia cells to hispolon resulted in upregulated expressions of apoptosis-related proteins, including the cleavage form of caspase-3, caspase-8, and caspase-9, the increased ratio of Bax/Bcl-2, and cytochrome c, with concomitant increased levels of Fas and FasL. Therefore, it was demonstrated that both extrinsic and intrinsic apoptotic pathways were involved in human leukemia cells treated with hispolon [58]. *Jujube* (Zǎo) is well known as a type of snack and has long been used as a supplement in gynaecopathia. Seeds of *jujube* exhibit antineoplastic effects and have been used in Chinese medicine for centuries. Recent work found that extracts of *jujube* seed could increase caspase-8 and caspase-9 activities in human Jurkat leukemia T cells through extrinsic and intrinsic apoptosis pathways [59]. Zhao and colleagues measured the antitumor activity of aqueous extracts of *Cordyceps kyushuensis* Kob (AECK), which is a type of entomogenous fungi. The group reported the upregulated amount of Ca^{2+} and downregulated expression of Bcl-2, which indicated that AECK triggered intrinsic apoptosis. Meanwhile, AECK gave rise to extrinsic apoptosis via elevating the level of Fas death receptor in U937 cells [60].

4. Chinese herbal medicine that is favorable in reducing the drug resistance in human cancers

Despite significant improvements in cancer treatment and emergence of a substantial number of novel therapeutics, cure rates for most malignancies remain suboptimal. Treatment resistance is less likely predicted for individual patients and is being the largest obstacle to the success of recovery. The most targeted therapies and chemotherapeutics for cancer disrupt cancer cells via the generation of

pro-death signaling molecules and subsequent initiation of programmed cell death. Based on facts mentioned previously, defects in apoptotic pathways that make tumor cells fail to die are believed to be one of the reasons for resistance acquisition. Successfully targeting apoptotic pathways with Chinese herbal medicines may shed a new light on cancer therapy (**Table 3**).

Pterostilbene is a natural polyphenolic compound chemically related to resveratrol, which has received FDA GRAS status in 2007. Pterostilbene exhibits antitumor, antioxidant, and anti-inflammatory activities and is primarily found in blueberries, almonds, grape leaves, and vines. Effects of pterostilbene on cisplatin-resistant oral cancer cells and the mode of action were explored by researchers. By using pan-caspase inhibitor and directly testing DNA breakage of human oral CAR cells, pterostilbene was found to trigger caspase-dependent apoptosis, suggesting that intrinsic apoptotic cascade was involved in the effect of pterostilbene in oral cancer [61]. A heat-sensitive sesquiterpene named furanodiene is extractable from the essential oil of *Rhizoma Curcumae*. In doxorubicin-resistant MCF-7 cells, furanodiene was identified to preferentially cause apoptotic cell death by interfering with abnormal intrinsic- and extrinsic-dependent pathways [62]. As depicted in the introduction part, TRAIL has a specific antineoplastic property against malignancies. You and colleagues studied the function of trichosanthin, a kind of traditional Chinese medicine isolated from the root of *Trichosanthes*, on TRAIL resistance by using non-small cell lung cancer TRAIL-resistant cells. The results showed that the expression levels of extrinsic and intrinsic apoptotic proteins were modulated. They concluded that trichosanthin rendered apoptosis by augmenting the sensitivity of TRAIL-resistant cells through upregulating DR4 and DR5 [63]. Oxaliplatin is an effective alternative treatment of HCC after sorafenib treatment failure. The combination treatment of oxaliplatin and huaier was verified to exhibit remarkable synergistic antineoplastic effect through inhibition of expression of apoptosis-related proteins and Yes-associated protein (YAP), which was demonstrated to reduce the chemotherapeutic sensitivity of oxaliplatin. As such, huaier was considered to enhance the oxaliplatin sensitivity by modulating Yap as well as apoptotic processes [64]. Chinese people have used milky sap or the aboveground part of *Euphorbia lunulata* to treat cancerous ailments since old times. The specific

Name of Chinese herbal medicine (active constituent)	Cancer type	Resistant drugs	Ref.
Blueberry (pterostilbene)	Oral cancer	Cisplatin	[61]
<i>Curcumae</i> (furanodiene)	Breast cancer	Doxorubicin	[62]
<i>Trichosanthes</i> (trichosanthin)	Non-small cell lung cancer	TRAIL	[63]
Huaier (extracts)	Hepatocellular carcinoma	Oxaliplatin	[64]
<i>Euphorbia lunulate</i> (extracts)	Gastric cancer	TRAIL	[65]
<i>Tanshinone</i> (tanshinone IIA)	Gastric	Doxorubicin	[66]
Wild mushroom (clitocine)	Colon cancer	TRAIL	[67]
<i>Curcuma longa</i> (curcumin)	Oral cancer	Cisplatin	[68]
<i>Tripterygium wilfordii</i> (celastrol)	Oral cancer	Vincristine	[69]
Houpo (honokiol)	Glioma cancer	Temozolomide	[70]

TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

Table 3.
Chinese herbal medicines that reduce drug resistance in human cancer.

mode of action remains obscure and was lately elucidated by researchers. Fu et al. observed that *Euphorbia lunulata* extract significantly increased activities of apoptotic indexes including caspase-3, caspase-8, caspase-9, and Bax while downregulating Bcl-2 expression, suggesting that both extrinsic and intrinsic pathways are involved in the mechanism of apoptosis induction [65]. Tanshinone IIA has been verified to be effective for cancer suppression in osteosarcoma cells and cervical carcinoma cells, which has been reviewed in detail in the preceding part of the text. With regard to gastric cancer, it was found that tanshinone IIA reinforced antineoplastic effect in doxorubicin-resistant gastric cancer cell lines SNU-719R and SNU-610R. The inhibition of multidrug resistance-associated protein 1 was verified to increase apoptosis and induce autophagic cell death, which contributed to the potent anticancer effect of tanshinone IIA in doxorubicin-resistant gastric cancer cells [66]. Clitocine is a naturally occurring compound purified from wild mushroom and has been recently demonstrated as an apoptosis initiator in multidrug-resistant human cancer cells. A study recently found that clitocine treatment dramatically enhanced TRAIL lethality via induction of apoptosis in resistant human colon cancer cells. The disruption of the binding between Mcl-1 and Bak and mitochondrial translocation of Bax mediated by clitocine were identified as the key underlying mechanism, which in turn generated MMP. These findings indicated that clitocine was an effective adjuvant alternative in TRAIL-based cancer therapy [67]. The combination of Chinese herbal medicines with standard therapeutics has been increasingly popular for the potentiation of curative effects. Curcumin is extractable from a broad range of traditional Chinese herbs and has long been used in clinic for its capabilities of tumor inhibition. A group in the field found that compared with single treatment, combination treatment of curcumin and cetuximab dramatically induced the activation of caspase-3 and caspase-9, which are critical factors in apoptosis process [68]. Besides, another type of herb, celastrol, was studied in oral cancer. It was also studied in liver cancer, osteosarcoma, and mantle cell lymphoma as reviewed in the preceding text. Here the authors reported that exposure to celastrol led to upregulated expression of cleaved caspase-3, caspase-8, caspase-9, and PARP and downregulated expression of Bcl-2, suggesting that celastrol exerted antitumor capacity in multidrug-resistant oral cancer cells via intrinsic and extrinsic pathways [69]. Honokiol is one of the main physiologically bioactive constituents of the traditional Chinese medicine *Houpo*. A recent study showed that exposure of human U87 MG glioma cells to honokiol significantly enhanced temozolomide-induced apoptotic insults to glioma cells via an intrinsic mitochondrion-dependent mechanism, as evidenced by the enhanced activity of caspase-9 without affecting Fas and caspase-8 expression. In addition, honokiol enhanced the changes of temozolomide-induced regulation in Bax translocation, MMP, mitochondrial complex I enzyme activity, intracellular ROS level, and cytochrome c release. All these data suggested the therapeutic potential of honokiol to attenuate temozolomide-induced side effects [70].

5. Derivatives of compounds from Chinese herbal medicine that are explored for cancer treatment

Substantial native compounds are identified to possess inhibitory effects against multiple cancers. To provide therapeutic alternatives for cancer therapy and develop more efficient and specific cancer treatments, more similar compounds are being produced from naturally occurring constituents of medicinal herbs (Table 4).

Name of Chinese herbal medicine (active constituent)	Cancer type	Derivatives	Ref.
<i>Artemisia annua</i> (artemisinin)	Prostate, lung, cervical, ovarian, and breast cancers	Dihydroartemisinin	[71]
<i>Ardisia gigantifolia</i> (triterpenoid saponin)	Breast cancer	AG36	[72]
<i>Pulsatilla</i> (<i>Pulsatilla saponin D</i>)	Non-small cell lung cancer	Compound 14	[73]
Genera <i>Hypericum</i> and <i>Garcinia</i> (guttiferone)	Leukemia	Compound 2	[74]
<i>Citrus reticulata</i> (benzofuran)	Chondrosarcoma	BL-038	[75]
<i>Isodon rudescens</i> (oridonin)	Esophagus cancer	Compound 19	[76]
White birch (betulinic acid)	Prostate, gastric, and melanotic cancers	Compound 3k	[77]

Table 4.
Derivatives of compounds from Chinese herbal medicines for cancer treatment.

The natural extract artemisinin has been gaining great attention in the medical field since Chinese scientist Tu Youyou was granted Nobel prize for his discovery of artemisinin. A study lately reported that derivatives of artemisinin have great antineoplastic activities. Researchers synthesized dihydroartemisinin (DHA) and applied it in the management of tumor cell lines including PC-3, A549, HeLa, OVCAR-3, and MCF-7. The results showed that combination of DHA and doxorubicin markedly regulated the caspase cascade through the intrinsic apoptotic pathway. DHA and doxorubicin also had a significant favorable effect in vivo. This study suggested that DHA might be a potential therapeutic agent against several types of cancer [71]. AG36 is the biotransformation product of triterpenoid saponin from *Ardisia gigantifolia* Stapf. The antitumor activity and underlying molecular mechanisms of AG36 against human breast cancer cells including cell lines MCF-7, MDA-MB-231, and SK-BR-3 were investigated. Researchers found that compared with control group, the ratio of Bax/Bcl-2 and the release of cytochrome c into cytoplasm were dramatically upregulated. Western blot analysis showed that the death receptor-related proteins Fas/FasL, TNFR1, and DR5 were modulated in different breast cancer cells. This study provided a novel idea that AG36 could be used as a clinical medication against human breast cancer with regulation of extrinsic death receptor and intrinsic mitochondrial pathways [72]. A total of 17 derivatives was synthesized on the basis of molecular formula of pulsatilla saponin D. The study indicated that compound 14 induced typical cell cycle arrest and apoptosis in lung cancer A549 cells, and western blot assay suggested the involvement of both intrinsic and extrinsic apoptosis pathways in the mode of action. These data indicated that compound 14 was a potential candidate for developing new anti-lung cancer agents in the future [73]. A team recently synthesized three different types of polycyclic polyprenylated acylphloroglucinol (PPAP). Compound 2 was found to activate the intrinsic pathway by reducing the expression of anti-apoptotic protein Bcl-2 while enhancing the pro-apoptotic protein Bax. Moreover, caspase-3 and PPRP1 levels were upregulated. The present results suggested that compound 2 may merit further development as a potential antileukemia agent [74]. BL-038, the novel benzofuran derivative, has been evaluated for its antitumor activity in human chondrosarcoma cells. Chondrosarcoma is a highly malignant cartilage-forming bone tumor that is intrinsically resistant to conventional chemotherapy or radiotherapy. Recent research reported that intrinsic apoptosis response was elicited by BL-038 with

the observation of release of cytochrome c, activation of caspase-9 and caspase-3, as well as the cleavage of PARP [75]. *Isodon rudescens* is well known for its antibacterial and antitumor activities and has also been regarded as a traditional green tea for centuries. Oridonin is the major bioactive ent-kaurane diterpenoid of this medicinal tea. Herein, 22 novel derivatives of oridonin were designed and synthesized. Among these compounds, compound 19 was reported to induce MOMP, which was probably involved in the intrinsic apoptotic pathway [76]. A total of 25 derivatives of betulinic acid was synthesized at C-28 position after structural modifications. The antitumor activities of these new products against human cancer cell lines including MGC-803, PC3, Bcap-37, A375, and MCF-7 were evaluated. Most of the derivatives possessed significant antiproliferative capacities. In addition, the study indicated that the apoptosis of MGC-803 cells induced by compound 3 k was mediated by mitochondrial intrinsic pathway [77]. Natural compounds have promising activities but are also quickly metabolized in the human body, leading to limited therapeutic outcomes especially in the treatment of cancer. The compound n-butylidenephthalide (BP) is isolated from *Angelica sinensis*, which has long been used as a traditional Chinese herb to treat anemia and gynecological dysfunctions. However, BP is quickly metabolized by the liver within 24 h; here an investigation prepared BP through encapsulation with a novel polycationic liposome containing polyethylenimine (PEI) and polyethylene glycol complex (LPPC) in melanoma cells. The results demonstrated that compared with BP alone treatment, BP/LPPC presented higher cytotoxicity in B16/F10 melanoma cells. BP/LPPC-treated cells showed an increase in subG1 percentage and TUNEL positive apoptotic morphology through induction of extrinsic and intrinsic apoptosis pathways [78].

6. Conclusions and perspectives

Dysregulation of programmed cell death acts as a natural barrier in survival and dissemination of cancer cells, whereas, malignant cells evolve many tricks to modify or generate some key modulators to evade programmed cell death. Apoptosis is one of the primary programmed cell death mechanisms, and extensive reports have identified intrinsic and extrinsic apoptosis pathways in cells. Its role in tumor proliferation is rather complex as different apoptotic pathways may cross talk or coexist in cancer. The decision taken by a cell to undergo apoptosis is regulated by various factors such as exogenous or endogenous damage.

For a long time, complementary medicine, in particular traditional Chinese medicine, has been extensively employed in practice due to good outcomes for patients in the treatment of either serious diseases or ailments. Recent attention has increasingly focused on the function of Chinese medicine on cancer and relevant molecular mechanisms. Chinese medicinal herbs may be of great value in the management of malignancies. This review retrospectively documented experimental data and precise effects of various herbs on tumor biology, especially the roles of apoptotic pathways in modulatory processes. Chinese herbal medicine serves to correct internal disequilibriums via the modulation of apoptosis and eventually contributes to cancer repression.

As the field of Chinese herbal medicine develops rapidly and apoptosis is not the only type of programmed cell death, which has expanded to include autophagy, and necrosis, among others, novel mechanisms of action that may be favorable in oncotherapy are still being characterized. We anticipate a major focus will be placed on other programmed cell death mechanisms as well as investigating potential functions of Chinese herbal medicines in such death pathways.

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