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Review

Traditional Chinese medicine targeting apoptotic mechanisms for esophageal cancer therapy

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Esophageal cancer is one of the most common types of cancer in the world, and it demonstrates a distinct geographical distribution pattern in China. In the last decade, inducing apoptosis with traditional Chinese medicine (TCM) has become an active area in both fundamental and clinical research on cancer therapy. In this review, we summarize the molecular mechanisms by which TCM induces apoptosis in esophageal cancer cells. These mechanisms are generally related but not limited to targeting the extrinsic death receptor pathway, the intrinsic mitochondrial pathway, and the endoplasmic reticulum (ER) stress pathway. By using different monomers and composite prescriptions of TCM, it is possible to modulate the ratio of Bcl-2/Bax, regulate the expression of caspase proteases and mitochondrial transmembrane potential, increase the expression of Fas and p53, down-regulate NF-κB pathway and the expression of Chop and survivin, and block cell cycle progression.

Keywords: traditional Chinese medicine (TCM); esophageal cancer; apoptosis

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Introduction

Esophageal cancer is one of the most common malignant tumors in the world, and it is globally ranked 8th and 6th for morbidity and mortality, respectively[1]. Esophageal cancer has distinct regional distribution patterns, with the highest morbidity and mortality rates in China[2]. Cellular apoptosis, also known as "programmed cell death", was first defined by Kerr in 1972 according to morphological features of apoptotic cells[3]. Apoptosis, a biological process in which multiple factors involve the induction of programed cell death, has been shown to be an attractive strategy and one of the effective ways to block cancer growth and progression. Inducing apoptosis with traditional Chinese medicine (TCM) is an active areas of research in the current attempts to find more effective therapies for cancer treatment. The mechanisms, however, involved in TCM-induced apoptosis are complicated and remain to be unraveled. Here, we summarize recent advances in aspects of using TCM to induce apoptosis in therapeutic settings and present the challenges of using TCM as a promising alternative option for cancer therapy.

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Apoptotic pathways as therapeutic targets in esophageal cancer cells

Apoptotic pathways can generally be categorized into signaling via the: (1) extrinsic death receptor pathway, (2) intrinsic mitochondrial pathway, and (3) endoplasmic reticulum stress pathway (Figure 1). Interaction of the death receptor with its natural ligand (such as CD95L, TRAIL or TNFα) or with an agonist (such as specific antibodies against APO-1) triggers a sequential activation of caspase-8 and -3, eventually leading to apoptosis. Intrinsic death signals, such as radiation, viral infections and serum/growth factor withdrawal, will directly or indirectly trigger the mitochondrial pathway, resulting in the release of cytochrome C (Cyt-C) from the mitochondria and the formation of the apoptosome complex, which consists of Apaf-1, caspase-9 and Cyt-C. The endoplasmic reticulum (ER) is the functional cellular organelle that is fundamental for biosynthesis, folding and posttranslational modifications of proteins destined for the secretory pathway. The ER is precisely regulated by oxidizing and Ca^{2+}-flux. Hypoxia, ER-Ca^{2+} depletion, reactive oxidative injury, or hypoglycemia will impact ER homeostasis and disrupt proper protein folding, which could lead to ultimate dysfunction of protein folding. The resulting 'ER stress' also triggers apoptosis via ATF/PERK-CHOP/UPR signaling. TCM can induce programmed cell death via individual extrinsic, intrinsic, or ER-mediated apoptosis, or a combination

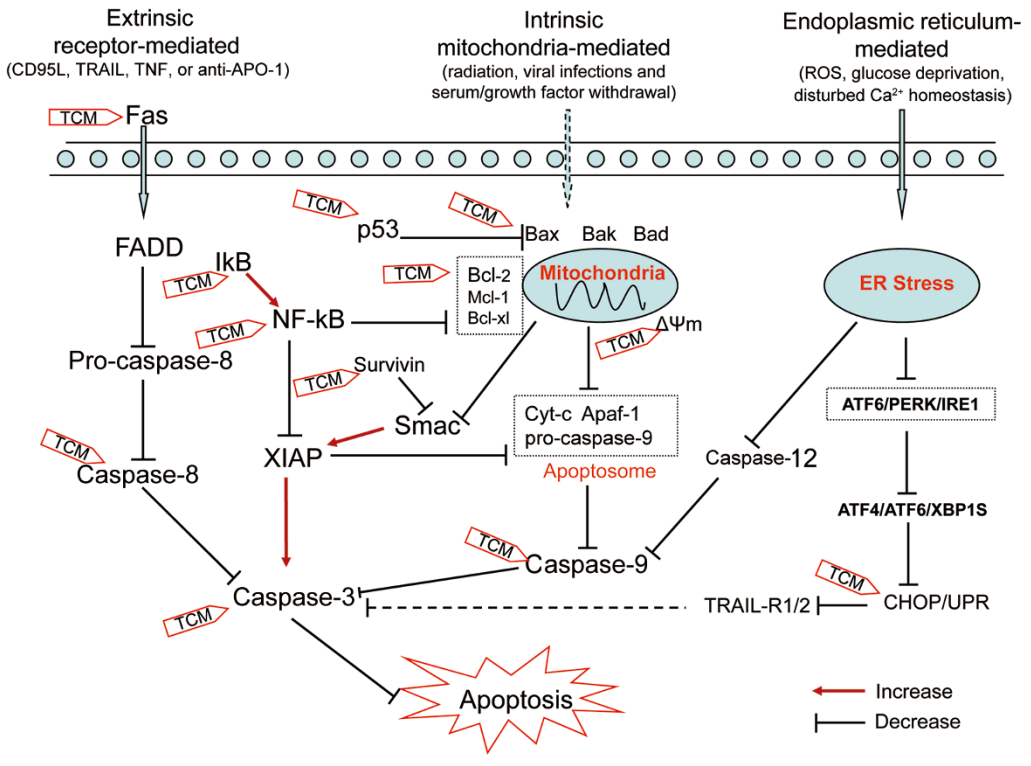

Figure 1. Schematic description of the mechanisms of induction of apoptosis by traditional Chinese medicine (TCM). FADD, Fas-related death domain structure protein.

of two or more apoptotic pathways.

Induction of apoptosis by the mitochondrial pathway

Mitochondria control the life and death of cells in an aerobic environment, and they are the organelles that generate ATP. The mitochondrion is the hub for regulating apoptosis and the intrinsic apoptotic pathway can be triggered by a variety of stimuli, eventually leading to the cascade reaction of the caspase family.

Induction of apoptosis by an alteration in the Bcl-2/Bax ratio

The Bcl-2 family is one of the most studied apoptosis gene groups to date. Bcl-2 family proteins can be divided into anti-apoptotic proteins, including Bcl-2 and Bcl-xL, and apoptosis promoting proteins, including Bax and Bak. The Bcl-2 gene is an important negative regulator of apoptosis[4]. Bcl-2 prolongs survival time of cancer cells by inhibiting apoptosis. On the other hand, the Bax gene is a member of the Bcl family, and it does not directly induce apoptosis but accelerates death signals[5]. Although how Bcl-2 precisely regulates apoptosis is not clear, it is generally agreed that: (1) Bcl-2 adjusts the Ca^{2+} balance between the ER and mitochondria, and maintains a lower Ca^{2+} pool inside the mitochondria to resist apoptosis[6]; (2) Bcl-2 inhibits the release of Cyt-C from mitochondria and thus suppresses apoptosis[7]; and (3) Bcl-2 also restrains the release of a secondary mitochondria-derived activator of caspase/direct IAP-binding protein[8]. Studies have confirmed that Solanum Lyratum Thunb induces apoptosis in EC-9706 human esophageal cancer cells, probably through down-regulating Bcl-2 expression and up-regulating Bax expression[9, 10]. Wang *et al* reported that Gecko alcohol extract (GAE) induces apoptosis in EC-9706 cells, and increases Bax protein and the Bax/Bcl-2 ratio, but not Bcl-2[11]. AiDi, a unique composite prescription of proprietary Chinese medicine, effectively reduces toxicity and enhances the efficacy of chemotherapy drugs[12]. Lu *et al* reported that AiDi enhances chemotherapy in esophageal cancers by decreasing the expression of Bcl-xL and increasing the expression of Bax[13]. Other TCMs, such as Acanthopanax saponins[14], matrine[15] and lutein[16], were also reported to induce apoptosis in esophageal cancer cells by inhibiting the expression of Bcl-2 and Bax, or changing the Bax/Bcl-2 ratio.

Induction of apoptosis by regulating the expression of caspase proteases

Caspases-1 to -11 belong to the protease family that contains proteolytic activity. Caspase-3 is one of the most important components in the family because it is the central node in the process of the protease cascade[17, 18]. Caspase family members mediate the mitochondrial and death receptor apoptotic pathways. With stimulation from various apoptotic signals, mitochondria release Cyt-C and other active proteins to the cytoplasm to activate downstream pro-caspase-9. In the death receptor pathway, the death-inducing signaling complex (Fas/FADD/caspase-8) activates pro-caspase-8, leading to the activation of caspase-3 in the downstream cascade and degrada-

tion of substrates to eventual apoptosis. Lei *et al* found that ethanol extract from Forsythia Suspensa leaf (FSEE) induces apoptosis of TE-13 cells, increases cleaved caspase-3 and caspase-9 dose-dependently. This is probably done via an endogenous dependence on caspases[19]. Similarly, Guo *et al* found that the n-butyl alcohol of Actinidia arguta significantly enhanced the expression of caspase-3 and caspase-9, thus promoting apoptosis in Eca-109 cells, with minimal impact on the expression of caspase-8[20]. It is evident that multiple TCMs induce apoptosis in esophageal cancer cells via the caspase-3 cascade, such TCMs include oxymatrine (an active extract from Sophora)[21], casticin (a major active ingredient from Fructus Viticis)[22], and pterostilbene (transformed from resveratrol)[23]. Recently, norcantharidin[24] and ginsenoside Rh2[25] were reported to up-regulate the expression of caspase-3 and caspase-8, leading to apoptosis in esophageal cancer cells.

Induction of apoptosis by decreasing the mitochondrial transmembrane potential

The mitochondrion is the site of ATP synthesis. Alteration in the mitochondrial transmembrane potential (ΔΨm) is directly involved in the regulation of apoptosis. A decrease in ΔΨm induces Cyto-C release and activates the caspase protease family, resulting in a reaction cascade of apoptosis and irreversible apoptotic processes. Liu *et al* found that the ΔΨm of EC-9706 esophageal cancer cells was gradually reduced and caspase-3 protein expression gradually increased with artesunate (Art)[26], thus initiating the intrinsic mitochondrial apoptotic pathway and activating caspase-3 protein. Xin *et al* found that esophageal cancer cells treated with oridonin for two hours demonstrated adaptive proliferation of mitochondria. Treatment for four hours caused mitochondria to appear swollen with outer membrane breaks, eight hours of treatment led to typical apoptotic changes in the nuclei and, after 24 h of treatment, the inner ΔΨm decreased[27]. Deguelin also induces apoptosis via adjusting the ΔΨm in esophageal cancer cells[28].

Induction of apoptosis by the death receptor pathway

The death receptor pathway is also known as the extrinsic apoptotic pathway that mediates the extracellular signal to trigger apoptosis. There are at least 8 types of death receptors on the surface of mammalian cells: Fas, TNFR1, TNFR2, DR3, DR4, DR5, DcR1 and DcR2, and all of them belong to the family of tumor necrosis factor alpha receptors. TCMs induce apoptosis by targeting the genes of the Fas and NF-κB pathways.

Induction of apoptosis by increasing the expression of Fas

Fas, also called APO-1 (CD95 molecules), is a type I membrane protein. It exists mainly in the form of a membrane receptor and plays a role in signal transduction in cellular apoptosis. Fas combines with Fas ligand (FasL), and then interacts with Fas-related death domain structure protein (FADD), to form the FasL-Fas-FADD death-inducing signaling complex (DISC), leading to pro-caspase-8 activation in the cytoplasm. The activated pro-caspase-8 then activates downstream components of the caspase cascade, resulting in eventual apoptosis. It was reported that GAE induces apoptosis in Eca-109 esophageal cancer cells by increasing protein expression of Fas and caspase-3[29]. Xu *et al* found that norcantharidin inhibits the growth of Eca-109 cells in a dose- and time-dependent manner by significantly increasing the protein expression of Fas, caspase-8 and caspase-3, whereas the expression of cellular FADD-like interleukin-1β converting enzyme inhibitory protein (c-FLIP) is decreased[24]. The same study found that Solanum Lyratum Thunb induced apoptosis of esophageal cancer cells by enhancing *fas* gene expression[10].

Induction of apoptosis by down-regulating the NF-κB pathway

Nuclear factor-kappa B (NF-κB) is a transcription factor with multi-dimensional functions, and it is critical for the development of a variety of cancers[30]. Many stimuli trigger the degradation of I kappa alpha B (IκBα) via phosphorylation. It drives the dissociated NF-κB into the nucleus to expose its nuclear recognition sites to promote the transcription of NF-κB-regulated genes. Dong *et al* showed apoptosis in correlation with increasing curcumenol concentrations and decreasing NF-κB expression levels[31]. Tian *et al* reported that curcumin inhibits the phosphorylation of IκBα and down-regulates activation of the NF-κB signaling pathway, leading to reduced proliferation of EC9706 and Eca109 esophageal squamous cell lines[32]. Parthenolide (PN) can also suppress the proliferation of esophageal cancer cells EC9706 and induce cell apoptosis. The anti-tumoral mechanism of PN may contribute to the suppression of NF-κB[33].

Induction of apoptosis by the endoplasmic reticulum stress pathway

In addition to the two classic apoptotic pathways, there is a newer apoptotic pathway known as the ER pathway, which was discovered in recent years[34, 35]. Currently, three categories of ER stress have been identified: (1) transcription activation of the CAAT/enhancer binding protein homologous protein (CHOP)/GADD153 gene; (2) activation of the JNK pathway; and (3) activation of the caspase-12 pathway, which is distinct from the ER pathway[36]. Cao *et al* studied the effect of oxymatrine injectionon protein expression associated with the ER pathway for apoptosis in an esophageal carcinoma xenograft mouse model[37]. They found a significant decrease in tumor volume 21 days after oxymatrine injection. While apoptosis was induced, the expression of binding immunoglobulin protein (BIP) was reduced and CHOP was increased significantly, leading to the hypothesis that inhibition of BIP and induction of CHOP contributes to apoptosis.

Other mechanisms

Induction of apoptosis by down-regulating the expression of survivin

Survivin is a member of the inhibitors of apoptosis protein (IAP) family. Its overexpression significantly reduces apoptosis[38]. Survivin controls caspase protease activity through direct inhibition of expression and separation of caspase-3 and caspase-7[39, 40]. In esophageal cancer, survivin expression is

significantly higher than in normal tissue, suggesting that it is an important indicator for recurrence, metastasis and prognosis of esophageal cancer[41, 42]. Wu *et al* found that the expression of survivin protein is gradually decreased and caspase-3 protein gradually increased with increasing concentrations of tetrandrine (Tet)[43], suggesting that this may be one of the mechanisms for inducing apoptosis in Eca-109 cells. Cox-2 is a critical rate-limiting enzyme in the process of prostaglandin synthesis and is highly expressed in the development of multiple cancers. Cox-2 inhibits tumor cell apoptosis mainly by increasing the expression of survivin[44, 45]. Zhang *et al* found that sinomenine, the active ingredient of orientvine, represses the expression of Cox-2 and survivin *in vitro*, and inhibits cell proliferation and enhances apoptosis of Eca-109 cells[46]. Thus, it was speculated that sinomenine reduces survivin expression and enhances apoptosis through inhibiting Cox-2 expression, leading to the suppression of downstream signal transduction pathways. Liu *et al* also found that paeonol (Pae) inhibits the growth of nude mouse xenograft tumors and induces apoptosis of Eca-109 *in vivo*[47]. The mechanism might be associated with down-regulation of the expression of Cox-2, Bcl-2 and survivin. The active ingredients of Cortex Periplocae inhibit expression of survivin protein, induce apoptosis of Eca-109 cells and inhibit xenograft tumor growth in nude mice[48, 49]. These studies suggested that survivin is one of the major target proteins for TCMs to induce apoptosis in esophageal cancer cells.

Induction of apoptosis by enhancing p53 expression

The p53 gene is predominantly involved in the apoptosis protease activating factor-1(APAF-1)/caspase-9 pathway, death receptor pathway and downstream caspase cascade events. Multiple factors such as Bax, PIG, CD95, DR5 and IGF-BP3 regulate apoptosis by modulating the p53 gene[50]. Zheng *et al* found that the oral composite prescription of Dihuang Guanshi Tong (composition: Rehmannia Root, Chinese Yam, Dogwood Fruit, Oriental Water Plantain, Moutan Bar, Poria, Subprostrate Sophora Root, and Rubescens) promotes apoptosis of esophageal cancer cells after radiotherapy, possibly by inhibiting the expression of p53 protein and decreasing the expression of Bcl-2 protein[51]. Tonglian Decoction composite prescription (composition: Spreading Hedyotis Herb, Peach Seed, Safflower, Bugbane Rhizome, Areca Seed, Barbed Skullcap Herb) significantly increases p53 expression in esophageal cancer cells and decreases survivin protein in cancerous tissue. In combination with microwave thermal therapy, Tonglian Decoction resulted in efficacy that is better than microwave thermal therapy alone[52].

Induction of apoptosis by blocking the cell cycle

As early as the late 1990s, researchers proposed that cancer is a disease of disorders in the cell cycle[53]. Tumor cells undergo G_1, S, G_2, and M phases, and then enter a relatively quiescent G_0 phase before a cell starts a new G_1 phase. The normal transition of the cell cycle depends on the fine regulation from cyclins and associated cyclin-dependent kinases(CDKs). TCM treatment could lead to the blockade of cell proliferation and eventual induction of apoptosis via blocking cell cycle progression (Figure 2).

Cyclins

Cyclin D and cyclin E are the cell cycle proteins of the G_1 phase, of which cyclin D1 has been the most studied. Cyclin D1 is overexpressed in esophageal squamous carcinoma[54, 55], and increases in its expression matches the progression from

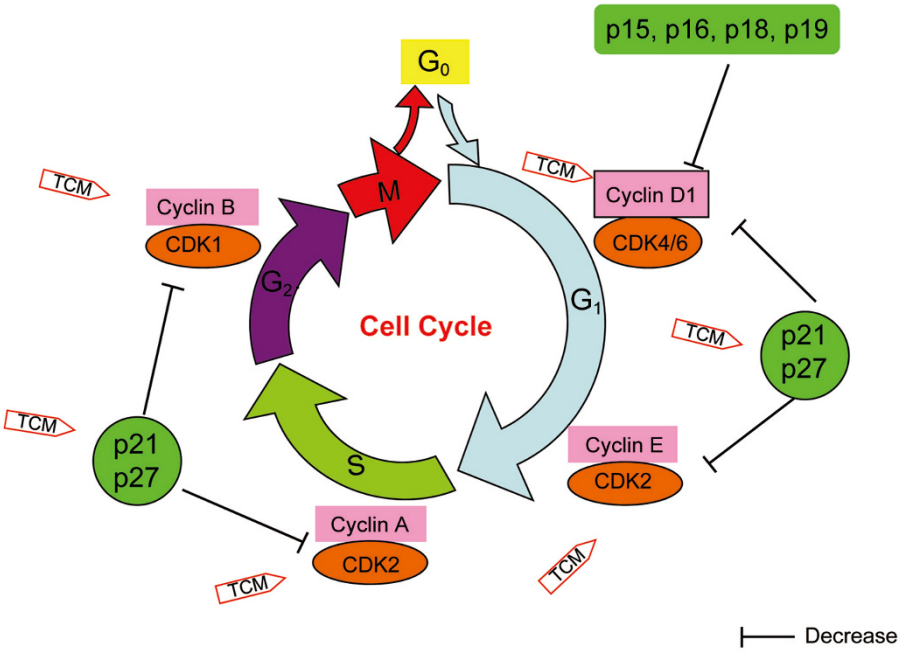

Figure 2. TCM induction of apoptosis by blocking the cell cycle.

a normal squamous epithelium to atypical hyperplasia to squamous carcinoma tissue. Cyclin B regulates the G_2-M transition and induction of cell mitosis. Cyclin B1 is aberrantly expressed in esophageal cancers and is significantly related to clinic-pathological parameters such as tumor grade, stage, lymph node metastasis and survival rate[56, 57]. Liu *et al* found that baohuoside-1, which is extracted from Cortex Periplocae, reduces the G_0/G_1 phase ratio and increases the G_2/M phase ratio of Eca-109 cells through the down-regulation of cyclin B1 expression[58]. Others also found that baohuoside-I induces apoptosis of Eca-109 cells by downregulating the expression of cyclin D1 mRNA and protein[59]. Zhang *et al* found that the extract from walnut green seedcase induces apoptosis in EC-9706 and KYSE510 esophageal cancer cell lines, which may be related to inhibition of cyclin D1 expression[60]. Curcuminextracted from Curcuma Longa is a phenolic pigment, and it was found to induce cell cycle arrest at the G_0/G_1 phase and inhibit proliferation of esophageal cancer cells by down-regulating the expression of cyclin D1 and cyclin E dose-dependently[61]. Zhang *et al* demonstrated that three flavones (luteolin; chrysin; and apigenin) and three flavonols (quercetin; kaempfero; and myricetin) can block the G_2/M phase in multiple human esophageal cancer cell lines (squamous cancer cell KYSE-510 and adenocarcinoma line OE33)[62]. These authors analyzed the expression of cell cycle regulation genes in the presence of luteolin and quercetin. Luteolin induces the expression of $p21^{wafl}$ and inhibits cyclin B1 expression in KYSE-510 cells, while quercetin induces the expression of GADD45p and 14-3-3σ, and inhibits cyclin B1 expression in OE33 cells. These results suggest that G_2/M cyclins are the potential targets of flavones and flavonols in esophageal cancer cells.

Cyclin-dependent kinases (CDKs)

CDKs are the proteins directly involved in cell cycle regulation. Several recent studies showed that CDKs are targets to prevent tumor formation and progression via inhibiting the expression of CDK2 and/or CDK4[63, 64]. CDK2 and CDK4 combine with cyclin E and cyclin D, respectively, and then form complexes of CDK-cyclins. Such complexes promote the phosphorylation of genes such as retinoblastoma (Rb), leading to inactivation of Rb and aberrant tumor cell growth. Shang *et al* found that ethyl acetate extract from Cortex Periplocae (CPEA) could induce apoptosis and block cell cycle progression in TE-13 esophageal cancer cells, via down-regulation of CDK4[65]. Periplocin from Cortex Periplocae also inhibits the proliferation of TE-13 esophageal cancer cells and arrests the cell cycle in the G_0/G_1 phase, with CDK4 downregulation but not CDK2[66]. However, the mechanism for this differential inhibition is still unknown.

Cyclin-dependent kinase inhibitors (CKIs)

Members of the CipPKip family, ie, p21 and p27, are negative regulators of the cell cycle. The proteins p21 and p27 inhibit the activity of CDKs via binding with CDKs. These factors prevent Rb phosphorylation and induce cell cycle arrest, and thus are important regulators of the cell cycle and cellular division. The p27 expression level is low in esophageal cancers and other malignant tumors[67]. Chen *et al* treated Eca-109 cells with ursolic acid (UA) and this resulted in increased apoptosis and cells in the G_0/G_1 phase and decreased S-phase cells in a dose-dependent manner, and up-regulated expression of p21[68]. Expression of p21 was found to be negatively associated with differentiation of esophageal carcinoma and invasion status, but its expression in early esophageal cancer was lower than that of normal esophageal mucosa. Thus, p21 expression could serve as a biomarker to predict esophageal cancer early events, biological behavior and prognosis[69, 70]. Li *et al* found that ginenoside-Rh2 (GS-Rh2) could block Eca-109 cells in the G_0/G_1 phase[71]. GS-Rh2 not only enhances p21 gene expression but also modulates the expression of cyclin E and CDK2, thus suppressing esophageal cancer cell proliferation and inducing apoptosis.

Summary

In summary, TCM induces apoptosis via multiple pathways (Table 1). In TCM terminology, TCM regimes mainly promote blood circulation, remove blood stasis, and clear away heat and toxic materials. Based on the ancient TCM literature and our current clinical practice, we propose that deficiency of stomach-Yin is the basic pathogenic mechanism for esophageal cancer development, and it should be corrected with Ganrun Ruyang as its therapeutic guidance. We therefore developed a Qigesan composite prescription (composition: Coastal Glehnia Root; Dan-shen Root; Poria; Fritillary Bulb; Turmeric Root; Villous Amomum Fruit; Lotus Leaf) on the basis of Qigefang (compositions: Coastal Glehnia Root, Dan-shen Root, Poria, Fritillary Bulb, Turmeric Root, Villous Amomum Fruit, Scorpion; Chinese Yam) from the ancient literature Medicine Comprehended and applied in our clinical practice, and we obtained significant responses in pilot studies in esophageal patients with middle and advanced stage diseases. We have studied the mechanism of Qigefang in enhancing homogeneity adhesion in esophageal cancer cells, inhibiting the proliferation and migration of tumor cells, and inhibiting pulmonary metastasis in mice[72-74]. Our team is currently investigating the apoptotic mechanism of anti-cancer action for Qigefang in treating esophageal cancers.

Challenges and prospects

Induction of apoptosis is one of the effective strategies in anti-tumor treatment. Recently, TCM has gradually moved into the era of molecular biology research. However, by examining the mechanisms by which TCM induces apoptosis in esophageal cancer cells, we identified a number of challenges in characterizing the anti-cancer efficacy from either a monomer or composite of TCM. The majority of research was carried out *in vitro*, without *in vivo* study to support and validate the results. Most studies have only revealed the effect on the expression of genes or proteins with TCM induction of apoptosis of esophageal cancer cells, but there has been no in-depth study of signaling pathways and relevant mechanisms. Further, the molecular mechanism studies have focused on

Table 1. Summary of TCMs and apoptotic pathway targets.

Apoptotic pathway targets	Traditional Chinese Medicine
Bcl-2, Bax	Solanum Lyratum Thunb[9, 10], Gecko alcohol extract[11], AiDi[13], Acanthopanax saponins[14], Matrine[15], Lutein[16], Ethanol extract from Forsythia Suspensa leaf[19], Actinidia arguta[20], Casticin[22], Pterostilbene[23], Deguelin[28], Paeonol[47], Oral liquid Dihuang Guanshi Tong[51], Ursolic acid[68]
Caspase-3, Caspase-8, Caspase-9	Ethanol extract from Forsythia Suspensa leaf[19], Actinidia arguta[20], Oxymatrine[21], Casticin[22], Pterostilbene[23], Norcantharidin[24], Ginsenoside Rh2[25], Artesunate[26], Gecko alcohol extract[29], Tetrandrine[43]
CDK2, CDK4	Ethyl acetate from Cortex Periplocae[65], Periplocin[66], Ginenoside-Rh2[71]
CHOP	Oxymatrine Injection[37]
Cyclin B, Cyclin D, Cyclin E	Curcumin[32], Baohuoside-1[58, 59], Extracts from Walnut green seedcase[60], Curcumin[61], Flavones (luteolin, chrysin, and apigenin) and Flavonols (quercetin, kaempferol, and myricetin)[62], Ginenoside-Rh2[71].
Fas	Solanum Lyratum Thunb[10], Norcantharidin[24], Gecko alcohol extract[29]
NF-κB	Curcumenol[31], Curcumin[32], Parthenolide[33]
p21, p27	Flavones (luteolin, chrysin, and apigenin) and Flavonols (quercetin, kaempferol, and myricetin)[62], Ursolic acid[68], Ginenoside-Rh2[71]
p53	Oral liquid Dihuang Guanshi Tong[51], Tonglian Decoction[52]
Survivin	Solanum Lyratum Thunb[9], Oxymatrine[21], Tetrandrine[43], Sinomenine[46], Paeonol[47], Cortex Periplocae[48, 49], Tonglian Decoction[52], Baohuoside-I[59]
ΔΨm	Artesunate[26], Oridonin[27], Deguelin[28]

CDK, cyclin-dependent kinases; CHOP, CAAT/enhancer binding protein homologous protein; NF-κB, nuclear factor kappa B; ΔΨm, inner mitochondrial membrane potential.

some aspects of apoptotic induction without a comprehensive and systemic characterization. Lastly, composite prescriptions of TCM are complicated and are significantly less appreciated and recognized internationally. All of these factors have resulted in the current situation in which TCM studies focus more on the monomer or active ingredients, and studies focusing on composite prescriptions are lacking. Clinically, TCM treatments are predominantly given as composite prescription therapies under the guidance of TCM theory. Thus, establishing valid experimental standards and evaluation criteria, either for *in vitro* or for *in vivo* TCM studies, will be fundamental for advancing research using TCM as an alternative option for cancer treatment. To date, there is a global transition from chemical synthetic drugs to natural medicine. Relevant anti-tumor mechanisms and drug research within TCM have become focuses of research. Future studies should emphasize TCM composite prescriptions, guided by Chinese medicine theory. With in-depth research on molecular mechanisms, TCM will be a viable choice of anti-cancer treatment, and such therapies possess advantages including multiple targeting, less therapeutic resistance, curative effects, fewer side effects, a wide supply and significantly lower cost.

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Abbreviations

ΔΨm, Inner mitochondrial membrane potential; ATF, activating transcription factor; CDK, cyclin-dependent kinases; CHOP, CAAT/enhancer binding protein homologous protein; FADD, Fas associated death domain; IkBa, I kappa B alpha; NF-kB, nuclear factor kappa B; PERK, pancreatic ER kinase (PKR)-like ER kinase; ROS, reactive oxygen species; Smac, second mitochondria-derived activator of caspases; TRAIL, tumor necrosis factor related apoptosis inducing ligand; TCM, Traditional Chinese medicine; UPR, unfolded protein response; XIAP, X-linked inhibitor of apoptosis proteins.

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