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Chinese herbal medicine exhibits anticancer properties via eight cancer hallmarks

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ABSTRACT

Chinese herbal medicine (CHM) is the key component of health care in China for the past 5,000 years. It has extensively influenced the healthcare industry not only in China but also in neighboring countries. The use of CHM to treat human diseases, especially cancer, is keep growing. Furthermore, millions of money were invested to study the role of CHM in cancer cure. In the last decade, researchers together with CHM practitioners tried to bridge the gap to understand each other's perspective to find the effectiveness of CHM in treating cancer. The mechanism of CHM in treating cancer is best understood via the theory of cancer hallmark proposed by Hanahan and Weinberg, which describes functional, molecular, and biological traits of specific cancer. The eight hallmarks of cancer are inhibiting proliferative signaling, inducing growth suppressors, inducing cell death, inhibiting replicative immortality, antiangiogenesis, inhibition of invasion and metastasis, energy metabolism, and immune destructive. The information is extracted from electronic resources (PubMed, Wiley, Springer, and ScienceDirect). This article reviews the antitumor activity of CHM against various cancers through each of the eight cancer hallmarks. It is hoped that this article would provide essential knowledge in cancer treatment by CHM.

INTRODUCTION

Cancer is a phenomenon when abnormal cells begin to grow out of control and end up in spreading to a distant region. Worldwide, the incidence of cancers is among the leading causes of morbidity and mortality, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012. The number of new cases expected to increase to 22 million within the next two decades (Stewart and Wild, 2014). Anticancer drugs are an important means to mitigate the impact of cancer mortality. Cancer treatment can be categorized into conventional (chemotherapy, radiation therapy, and surgery) and modern therapies (molecularly targeted therapy and immunotherapy). Lately, a holistic way of cancer treatment receives equal attention to treat this deadly disease. As such, the Chinese herbal medicine (CHM) plays a significant role in cancer treatment. Asian countries such as China, Japan, and Korea have been using CHM for thousands of years mainly because they are naturally available and less toxic to normal cells (Mishra and Tiwari, 2011).

A very long history of CHM practice in cancer therapy has started in the last 2,000 years. An important proof was documented first in the classical works, such as *The Yellow Emperor's Inner Canon* and *The Classic of Medical Problems* (Liu *et al*., 2015; Wang, 2003). CHM practitioners follow merely the same approach to treat or manage cancer patients. The treatment is focused on strengthening body resistance, eliminating pathogens, and treating both the manifestation and root cause. Apart from that, they also practice treating the same disease with different methods and treating different diseases with the same method based on symptoms and signs. For example, treating patients with the common cold is not identical in CHM principle. Common cold is usually further divided into two types of syndrome: either caused by wind heat or wind cold. Herbs, pungent in flavor and cool in property, can relieve the wind heat, whereas herbs, pungent in flavor and warm in property, relieves wind cold. Next, chronic dysentery and prolapse of the rectum and uterus are two different

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diseases, but both exhibit the same syndrome of sinking Middle-Qi. Therefore, according to the CHM concept, both can be treated with identical therapeutic to elevate Middle-Qi (Chan and Lee, 2002). These concepts of diagnosis and treatments have been proved by clinical practice (Liu *et al*., 2015).

Many CHM-derived anticancer drugs have been used in Western medicine. Between 1940 and 2014, around 49% of approved cancer chemotherapeutic drugs are derived from natural products (Newman and Cragg, 2016). Vinblastine, vincristine, paclitaxel, camptothecin, and epipodophyllotoxin are few examples of plant-derived CHMs that have been used in Western medicine (Pereira *et al*., 2012). Millions of people around the world have been accepting and using CHM. It is not only used as standalone therapy but often used as an adjuvant or in combination with other therapies to improve health. Undoubtedly, CHM is a valuable resource to discover novel anticancer agents.

ROLE OF CHM IN TREATING VARIOUS DISEASES

CHM utilizes a unique approach by combining the advantages of physiological and holistic theories. Its prime method to heal patients is by modulating and exploiting interactions between the patients and their environment. Therefore, it is important to understand the patient's environment and herbal formulae in CHM perspectives. In this holistic approach, the human's health system is explained based on ancient theory "Qi," which said that the life force energy is carried in the body via meridians. Qi is said to be responsible for physiological functions. Any disruption in Qi ultimately results in disharmony in the body such as disruptions to homeostasis and diseases. In the event of disruption in Qi, CHM aims to address these imbalances to enable the body to heal itself (Li and Zhao, 2012).

The principle of CHM explains that herbal formulae consist of four elements. First, the monarch (Jun) that aims at the cardinal pathological of a disease. Second, the minister (Chen) that helps monarch to treat secondary symptoms. Next, assistant (Zuo) and servant (Shi) both are mainly coordinate the formulae, facilitate the first two elements, and decrease their side effects. All the elements eventually help each other to maintain harmonious of body to achieve an ideal therapeutic outcome (Zhou *et al*., 2016).

CHM was used in various diseases such as hypertension (Lu *et al*., 2007), coronary heart (Jian *et al*., 2010), and rheumatoid arthritis (Lu *et al*., 2010) or biomedical conditions such as neuroendocrine–immune network (Li *et al*., 2007) including cancer for more than hundred years. Today, there are many options available to treat cancer including surgery, radiation, chemotherapy, immunotherapy, hormonal therapy, targeted therapy, and many more. Among them, herbal medicine is emerging as an important alternative therapy in cancer treatment. This ancient therapy not only plays a key role in prevention but also has been reported to enhance pain management and to improve the lifespan (Ritenbaugh *et al*., 2012).

A special characteristic of CHM is utilizing the precision medicine concept. The ideology of this treatment is based on the right patient, right diagnosis, and right treatment with the right amount of drug to treat the disease efficiently. Even though this concept is well established in CHM practice, its role as precision medicine was only emerged recently worldwide. A great evolution started when President Obama announced the launch of new Precision Medicine Initiative (Fox, 2015) in the State of the Union address, in which he has mentioned that every patient is unique, and it is essential that they are tailored with individual treatment. Currently, efforts are taken to evaluate CHM's efficacy in cancer treatment by utilizing pharmaceutical-based approaches to reveal the mode of actions at molecular levels.

MODE OF ACTION: HOW CHM REGRESSES CANCER

A large number of studies show that the multitargeted nature of CHM may comprise multiple herbs and components acting simultaneously on multiple cellular mechanisms and molecular targets that derived from its biological compounds (Yoo *et al*., 2018). CHM contains many active compounds that can target the eight hallmarks of cancer. The eight hallmarks of cancer shown in Figure 1 are inhibiting proliferative signaling, inducing growth suppressors, inducing cell death, inhibiting replicative immortality, antiangiogenesis, inhibition of invasion and metastasis, energy metabolism, and immune destructive (Hanahan and Weinberg, 2011).

Antiangiogenesis

Angiogenesis is a process to form a new blood vascular system around the cells and tissues. When normal cells require nutrient and oxygen to remove metabolic waste products, angiogenesis will occur. In the normal human body, during embryogenesis, formation of new endothelial cells and surrounded vascular allows sprouting of new vessels from the existing ones. Angiogenesis is constitutively activated in normal cells during wound healing and female menstrual cycle. However, in highly proliferative cancer cells, angiogenesis is always activated to support neoplastic growth and tumor progression (Hanahan and Folkman, 1996).

Angiogenesis in tumor environment ensures continuous supply of nutrient and oxygen and elimination of carbon dioxide and waste materials from neoplastic cells. Pro- and antiangiogenesis factors from tumor microenvironment control the formation of vascularization. As shown in Figure 2, binding of pro-angiogenesis factors to cell receptors induces growth, proliferation, and formation of tubules, whereas binding of antiangiogenesis factors activates caspases, which leads to apoptotic cell death. The well-known angiogenesis inducer is vascular endothelial growth factor (VEGF). Basic fibroblast growth factor (bFGF and FGF2), angiogenin, transforming growth factor (TGF)-α, TGF-β, tumor necrosis factor (TNF)-α, platelet-derived endothelial growth factor, granulocyte colony-stimulating factor, placental growth factor, interleukin-8, hepatocyte growth factor, and epidermal growth factors are among other commonly listed inducers (Mousa and Davis, 2016). Negative regulators such as thrombospondin, angiostatin, endostatin, interferon, platelet factor 4, prolactin 16-kd fragment, and tissue inhibitor of metalloproteinase-1, -2, and -3 also play a critical role in controlling angiogenesis (Nishida *et al*., 2006). When tumor cells demand nutrient and oxygen, angiogenesis is activated; angiogenic activators are upregulated, whereas negative regulators will be downregulated. A balance between these two types of markers is vital to control vascular homeostasis or angiogenesis.

CHM inhibits cancer development and progression by altering tumor microenvironment and by directly inhibiting angiogenesis and lymphangiogenesis. Extract from *Ginkgo*

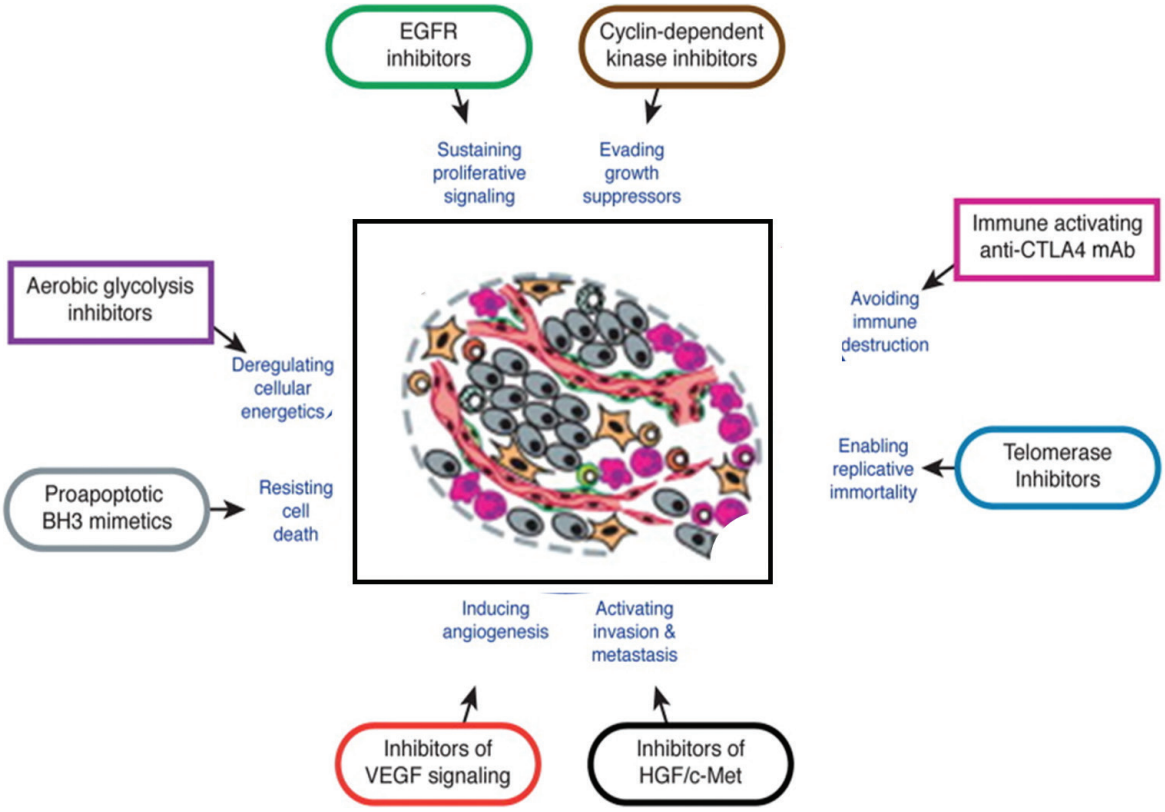

Figure 1. The hallmarks of cancer. This illustration encompasses the eight hallmarks of cancer proposed by Hanahan and Weinberg in 2011 (Hanahan and Weinberg, 2011).

biloba was reported to show inhibitory effects in *in vitro* and *in vivo* against multiple cancers such as ovarian (Ye *et al*., 2007), breast (Papadopoulos *et al*., 2000), hepatocellular (Chao and Chu, 2004), and oral (Kim *et al*., 2005). *Scutellaria barbata* D. Don is another CHM that proved to suppress angiogenesis in colon cancer by downregulating VEGF-α (Wei *et al*., 2011). It has been used in clinical trials, revealed to be safe and well-tolerated, and showed promising clinical evidence against metastatic breast cancer patients (Perez *et al*., 2010). The Yangzheng Xiaoji (YZXJ) capsule, derived from a CHM formula, exhibited anticancer actions on primary hepatic carcinoma (Zhang *et al*., 2009). This capsule contains the following 16 ingredients: *Panax ginseng C.A. Mey.*, *Astragalus membranaceus* (*Fisch.*) *Bge.var. mongholicus* (*Bge.*) *Hsiao, Ligustrum lucidum Ait.*, *Curcuma phaeocaulis Val.*, *Ganodema lucidum*, *Gynostemma pentaphylla* (*Thunb) Mak*, *Atractylodes macrocephala Koidz*., *S. barbata D. Don, Oldenlandia diffusa* (*Willd.*) *Roxb., Poria cocos, Duchesnea indica Focke, Solanum lyratum Thunb., Artemisia scoparia* (*Bge.*) *Ki., Cynanchum paniculatum Kitag*, *Eupolyphaga sinensis Walker,* and *Gallus domesticus Brisson*. YZXJ was demonstrated to inhibit angiogenesis by directly targeting endothelial cells and significantly affect endothelial tubule formation, migration, and cell matrix attachment (Jiang *et al*., 2012). Ginsenoside Rg3, a pure compound extracted from *ginseng* (Lu *et al*., 2009; Zheng *et al*., 2014), showed an antiangiogenic effect in colorectal cancer. It was executed by downregulating the expression of 22 pro-angiogenic-related genes (Tang *et al*., 2017). The antiangiogenesis effect of Rg3 was also reported in glioblastoma (Sun *et al*., 2016).

Inhibit invasion and metastasis

Tumor microenvironment is made up of complex non-malignant cells such as endothelial, pericytes, fibroblasts, and immune cells that surround cancer cells (Jia *et al*., 2012). The tumor environment largely depends on signals including tumor promoter and tumor suppressor produced from these various cells. CHM has been shown to control tumor environment by inhibiting tumor-promoting signals while inducing the production of cytokines to suppress tumor development. Matrix metalloproteinases (MMPs) are enzymes that activate tumor microenvironment to undergo metastasis, spreading of tumor cells from the primary sites. Highly expressed MMPs often result in poor clinical outcome due to cell invasiveness and metastasis (Sherman-Baust *et al*., 2003). Several studies showed CHM's ability to inhibit MMP expression in cancer environment upon treatment. A standard formulation of Si-Jun-Zi-Tang (composed of four Chinese herbs: *ginseng* root, *A. macrocephala*, licorice root, and poria root) with the addition of *Myristica fragrans* and five-leaf akebia fruit (known as Yi-Qi-Fu-Sheng) has shown to initiate ERK1/2-dependent inhibition of MMP-2/9 expression. By selectively targeting ERK phosphorylation, this decoction modulates the REK/Mitogen-activated protein kinases (MAPK) pathway and its downstream factors (Deng *et al*., 2013). Other Chinese herbs that can promote anti-invasiveness by controlling the inhibition and regression of MMPs are Mu BieZi (*Momordica cochinchinensis*) (Zheng *et al*., 2014). Artemisinin, which is an active compound from Chinese wormwood (*Artemisia absinthium*), acts by lowering both VEGF and its receptors (Efferth *et al*., 2002), turmeric (*Curcuma longa*)

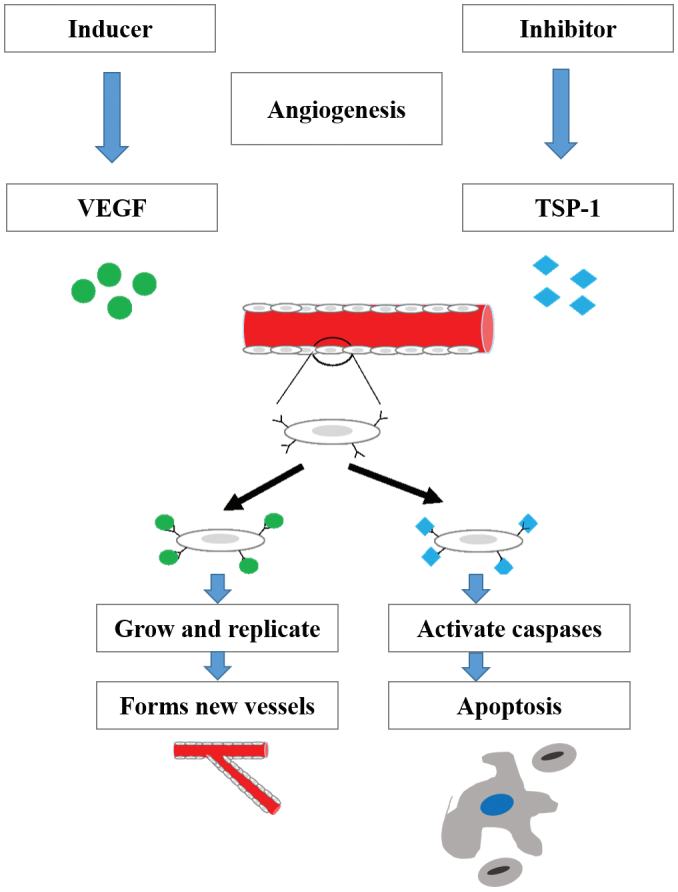

Figure 2. Role of pro- and antiangiogenesis factors on vascularization. VEGF binds to its receptors on endothelial cells to initiate a break through existing blood vessels, grow and migrate to form new blood vessels. Binding of inhibitors to the receptors triggers the activation of caspases to activate apoptosis.

(Arbiser *et al*., 1998), and *Scutellaria Baicalensis* (Yance *et al*., 2006).

Antiproliferative signaling

Proliferation is a natural phenomenon in normal cells to rapidly reproduce cells, tissues, or organism. An uncontrolled cell division increases the proliferation rate to form malignant tumor. Proliferation has become an important event of cancer development and progression. Cell-cycle mechanism is a process where cells actively divide in several phases. Each phase of the cell cycle is tightly regulated, and the damaged cells are immediately removed before entering the next phase to avoid genetic mutation. Dysregulated expression of cell-cycle proteins (Rb, CDKs, and CDK inhibitors) promotes uncontrolled cell proliferation. Apart from cell-cycle proteins, there are other proteins such as Akt, PI3-kinase, and Rat sarcoma involved in directing the proliferation and constitutive activation of multiple signaling pathways (Hanahan and Weinberg, 2011; Liebermann *et al*., 2007; Wang *et al*., 2015). A number of studies have shown that the dysfunction of cell-cycle regulation and proliferation receptors often results in cancer progression (Hsu *et al*., 2013). Therefore, a compound that can stop excessive proliferation leads to inhibition of cancer development. Previous studies reported that CHM-based compounds and decoctions can act as antiproliferative agents in cancer treatment. For example, Xiaoji Decoction (composed of *Coriolus Versicolor*, *Psoralea Corylifolia* L., *Hedyotis Diffusa*, *Astragalus Mongholicus*, Scorpion, Centipede, and Rhubarb) inhibits proliferation of lung cancer cell line via Akt pathway by upregulating the expression of Bcl-2-associated death promoter and caspase-9 (Chai *et al*., 2014). *M. cochinchinensis* seeds were also reported to have antiproliferative activity on various human lung cancer cell lines, such as A549, H1264, H1299, and Calu-6 (Yu *et al*., 2017). *Marsdenia tenacissima* extract inhibits proliferation of esophageal carcinoma via MAPK pathway (Fan *et al*., 2015). A synergistic combination of *Rosa roxburghii* Tratt and *Fagopyrum cymosum* significantly inhibits proliferation and activates apoptosis against human esophageal squamous carcinoma CaEs-17. The protein expression level of Ki-67 and Bcl-2 was greatly decreased, whereas the expression of Bax was markedly increased (Liu *et al*., 2012). Bufalin, an active compound extracted from the dried toad skin, induces G2/M phase arrest in liver cancer (Hsu *et al*., 2013). Apart from common cancers, CHMs also have shown to affect the proliferation of gastric cancer cell lines. Sanpi Pingwei formula was reported to inhibit proliferation as well as induce apoptosis in SGC-7901 gastric cell line. This formula targets the main channel such as Bax, p53, and Bcl-2. Upregulation of p53 and a decrease in Bcl-2 levels control proliferation upon treatment (Dang *et al*., 2013). Similarly, upon exposure of arsenic sulfide, the main component of realgar, a CHM was showed to induce apoptosis in AGS gastric cells by targeting p53 expression (Zhang *et al*., 2014). Jianpi Huayu decoction, a Chinese medicine formula, inhibited proliferation in SW480 colorectal cells by inducing G_0/G1-phase cell-cycle arrest and apoptosis. Besides, this decoction also enhanced the expression of p27, cleaved poly (ADP-ribose) polymerase, cleaved caspase-3, and Bax while reducing the level of Bcl-2 and various cyclins (Xi *et al*., 2015). *Emodin*, a natural compound extracted from various Chinese herbal plants, including *Rheum officinale* and *Polygonum cuspidatum* (Ma and Li, 2012), inhibits proliferation of colorectal cancer cell line LOVO by inducing mitochondrial-mediated apoptosis via upregulating expression of Bax and downregulating Bcl-2 expression (Ma and Li, 2014). Figure 3 shows the summary of reported antiproliferative actions of CHM.

Antigrowth suppressor

Many programs in cancer cells help in proliferation to ensure the formation of tumor without interruption. When these programs are negatively regulating cell proliferation, it will control cancer progression and ultimately prevent tumor formation. These programs are mainly activated by tumor suppressor proteins. They play important roles in suppressing uncontrolled proliferation, immortality, and tumorgenicity. The two main tumor suppressors are retinoblastoma susceptibility gene (RB) and p53 proteins. RB is a negative regulator of the cell cycle that inhibits both G_1 and S-phase progression (Bartek *et al*., 1997). RB (unphosphorylated or hypo-phosphorylated) suppresses cell cycle progression by binding to transcription factors such as E2f1 (transcription factor 1) to inhibit their activation. The phosphorylation of RB-E2f1 complex leads to dissociation and consequently enters S-phase (Cobrinik *et al*., 2005; Martin and Gerd, 2017). Apart from controlling cell cycle regulation, RB also controls other cellular

processes such as differentiation (Lipinski *et al*., 1999), senescence (Dasgupta *et al*., 2006), and apoptosis (Chau and Wang, 2003).

p53, a tumor suppressor, controls various genetic expression, cell proliferation, and modulation of signal transduction pathway. During DNA damage in a cell, p53 will be accumulated to initiate cell arrest and trigger apoptosis to control abnormal cell proliferation. Besides, p53 is also involved in DNA repair to prevent the accumulation of mutation and suppresses tumor development (O'Neil and Rose, 2006). Other examples of tumor suppressors include phosphatase and tensin homolog (PTEN) (phosphatase and tensin homolog on chromosome 10), p21WAF1, p27KIP1, and adenomatosis polyposis coli (APC) (adenomatosis polyposis coli). As shown in Figure 4, the accumulation of p53 induces p21WAF1/p27KIP1 to initiate cell cycle arrest, whereas APC a multidomain

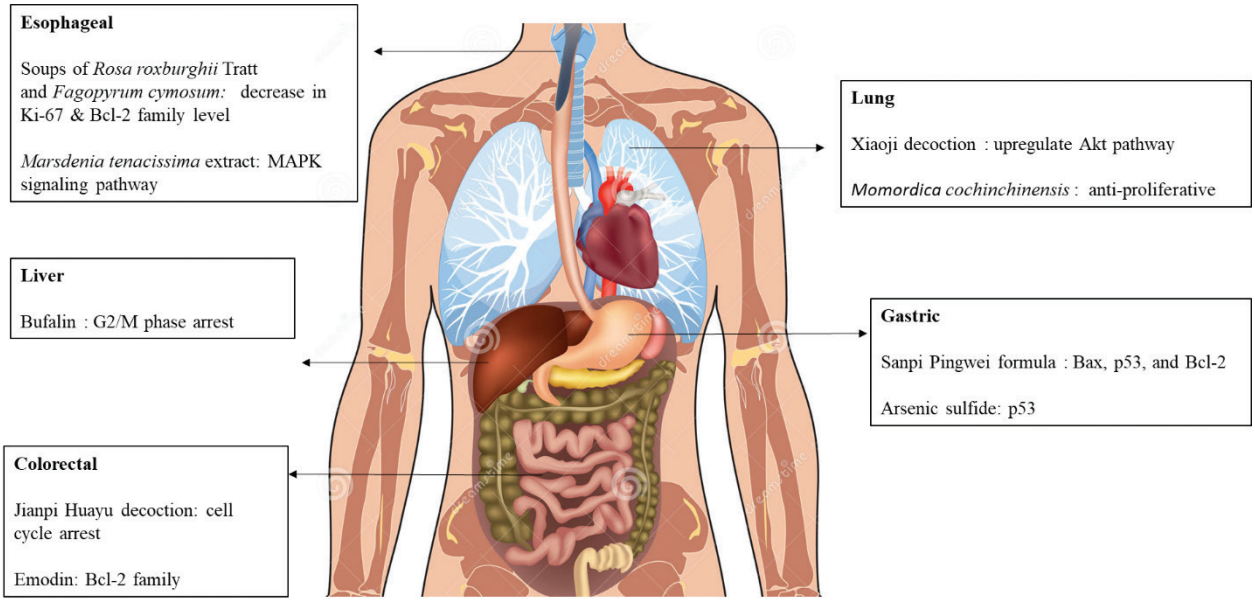

Figure 3. Antiproliferative actions of CHM against human cancers and its targets.

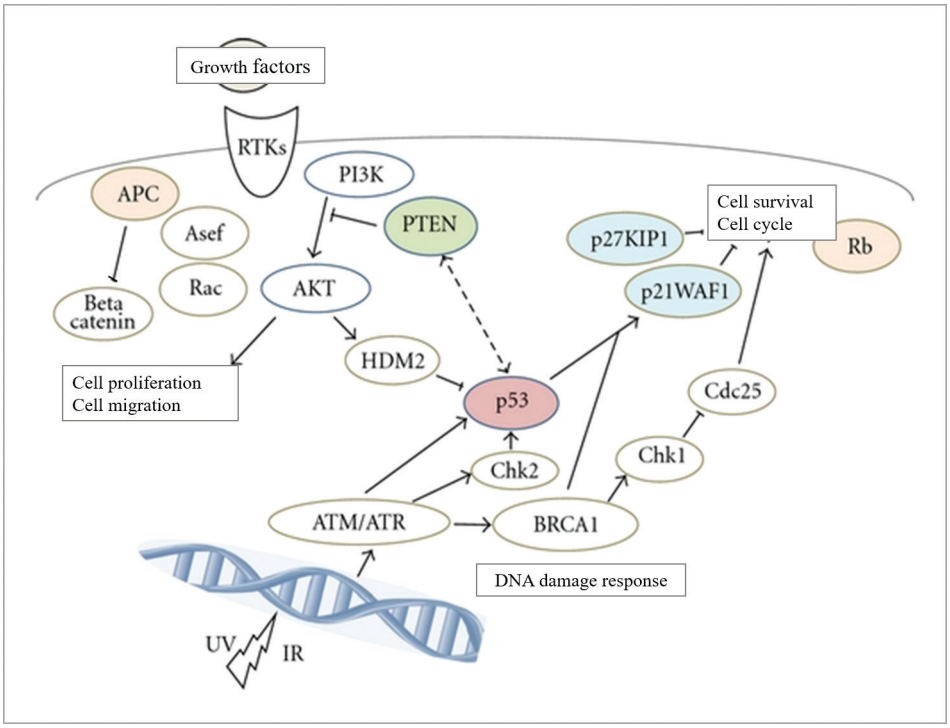

Figure 4. Schematic representation of tumor suppressor signaling including p53, Rb, APC, p21WAF1/p27KIP1, and PTEN. Examples of molecules known to act on cell proliferation and cell survival via the regulatory pathways are shown (Adapted from Kitagishi *et al*., 2012).

protein, through which it binds to various binding proteins such as beta-catenin, Asef, and Rac, leads to the prevention of cancer cell overgrowth (Kitagishi *et al*., 2012).

Several studies revealed the role of CHM in tumor suppression. Chinese herbal formula, Yangyinjiedu, inhibits the proliferation of lung cancer cell lines (95-D, A549, H460, and H1975) by inducing cell cycle arrest and senescence via an elevated level of p53 (Zheng *et al*., 2017). *Kanglaite* (KLT), an extract from Coix seed, induces apoptosis of tumor cell by increasing the mRNA level of p53 (Lu *et al*., 2008). Honokial, a component of oriental herb *Magnolia officinalis*, significantly reduces the level of Rb protein in prostate cancer cells (Hahm *et al*., 2007). It also reduces the PTEN protein level in adipocyte cancer by controlling angiogenic activity (Liu *et al*., 2008). Similarly, *Acanthopanax gracilistylus* inhibits the proliferation of MT-2, Raji, HL-60, TMK-1, and HSC-2 through cell cycle arrest accompanied by a decreased phosphorylated level of pRb (Shan *et al*., 2000). Liposome-encapsulated curcumin and resveratrol in combination reported to effectively inhibit cell growth and to induce apoptosis. The finding also confirms that the cell death of prostate cancer was due to the loss of PTEN suppressor (Narayanan *et al*., 2009). Carnosol, a constituent from rosemary herb, has shown to prevent APC-associated intestinal tumorigenesis by increasing E-cadherin-mediated adhesion and suppression of beta-catenin tyrosine phosphorylation (Moran *et al*., 2005). APC-mediated suppression was also reported in human cervical cancer cells such as Caski and HeLa on exposure with trichosanthin. Trichosanthin is a main bioactive component from CHM, the root tuber of *Trichosanthes kirilowii* Maxim. In a study done by Huang (Huang *et al*., 2012), trichosanthin showed to inhibit DNA methyltransferase and restore the expression of methylation-silenced tumor suppressor genes. Therefore, it was categorized as potentially useful demethylation agent for the clinical treatment of human cervical cancer. An extract of *Magnolia* inhibits the proliferation of urinary cancer cells via G1 cell cycle arrest. Post-treatment and expression of p21WAF1 and p27KIP1 were reported to be upregulated. They were also believed to interact with cell cycle proteins, CDKs, and nuclear antigens to form complex, which trigger the prevention of cell proliferation. Similarly, baicalin, a flavonoid compound extracted from the root of *S. baicalensis* Georgi, reported to inhibit the proliferation of prostate cancer cells such as PC-3 and LN-CaP by activating the expression of cyclin-dependent kinase inhibitor, p27KIP1. Table 1 shows the role of CHM and active compound as a tumor suppressor.

Cell death

In early 2018, Galluzzi (Galluzzi *et al*., 2018) highlighted 14 different types of cell death such as intrinsic apoptosis, extrinsic apoptosis, mitochondrial permeability transition – driven necrosis, necroptosis, ferroptosis, pyroptosis, parthanatos, entotic, NETotic, lysosome-dependent, autophagy-dependent, immunogenic, cellular senescence, and mitotic catastrophe. Among them, three major cell deaths are apoptosis, autophagy, and necrosis. The role of CHM against these cell deaths will be discussed in this session.

Apoptosis has taken the central stage as the principal mechanism of programmed cell death (PCD). PCD basically refers to its strong genetic controls (Daniel and Korsmeyer, 2004) where it ends up in the disintegration of cellular components and engulfment by surrounding cells. Apoptosis is a biochemical event involving cell membrane blebbing, shrinkage, chromatin condensation, and nucleosomal fragmentation (Kroemer *et al*., 2008). Apoptosis is classified as a major mechanism of chemotherapy-induced cell death. Therefore, cytotoxic agents/drugs that target this pathway are the main focus of many preclinical discovery investigations. Apoptosis can be further divided into intrinsic and extrinsic apoptosis. These two pathways are controlled by its own initiator caspases (intrinsic apoptosis govern by caspase-9 and extrinsic apoptosis initiated by caspase-8) and follow similar execution pathways via caspase 3.

Ursolic acid is an active ingredient found in several CHMs, such as *O. diffusa* (Willd.) Roxb. and *L. lucidum* W.T. Aiton. It was showed to induce cancer cell death via caspase-dependent pathway in prostate cancer cells (Kwon *et al*., 2010). This active compound has elevated caspase-9 and caspase-3 levels in prostate cancer cells. In general, the activation of intrinsic apoptosis involves the release of cytochrome-c from mitochondria, apaf-1, and apoptosome formation before it enters into the cascade of caspase activation. Other CHMs such as *Aloe emodin* (Dong *et al*., 2010), artemisinins (Chen *et al*., 2017), arsenic trioxide (Lam *et al*., 2005), baicalin (Peng *et al*., 2015), hesperetin (Palit *et al*., 2015), and matrine (Zhang *et al*., 2012) were also reported to induce mitochondrial-mediated apoptosis.

While intrinsic apoptosis mediated by internal organelle (mitochondria), external apoptosis involves the binding of death ligands (Fas and FasL) at cellular membrane to facilitate apoptosis. Oridonin (Kang *et al*., 2010), polyphenols from green tea (Oz *et al*., 2010; Tsukamoto *et al*., 2012), and glycyrrhizin (Haghshenas *et al*., 2014) are the examples of CHM, which target cancer cell death via this pathway.

Autophagy is also a genetically controlled cell death and classified under PCD. It is activated during essential nutrient starvation such as carbon and amino acid, resulting in intracellular component degradation. During autophagy, autophagosomes in cytoplasm combine with the key organelle, lysosome. On fusion, the release of lysosomal hydrolases allows the degradation of misfolded proteins and organelles (Shintani *et al*., 2004). The presence of beclin one protein indicates the activation of autophagy. Anticancer drug combination of Sun-Bai Pi extract with commercial drug cisplatin was reported to synergistically kill non-small cell lung cancer and allows rapid low-dose cancer cell elimination via autophagy cell death (Tseng *et al*., 2016).

Next, necrosis is most likely controlled by signal transduction pathways and catabolic mechanisms. Its features include translucent cytoplasm, swollen organelles, dilatation of nuclear membrane, chromatin condensation, and increased cell volume (Vandenabeele *et al*., 2010). In cancer cell, imbalance of intracellular calcium flux, reactive oxygen species (ROS) generation, and activation of non-apoptotic proteases influence each other to activate necrosis. Cell dying via necrotic death initiates pro-inflammatory signals to release inflammatory cytokines and spill their content during lyses. Due to this, necrosis is considered to be a more harmful way for a cell to die compared with apoptosis. However, very less CHMs were reported to induce necrotic cell death. Shikonin from *Lithospermum erythrorhizon* Siebold was showed to induce necrosis in MCF-7 and HEK293 cells (Han *et al*., 2007; Han *et al*., 2009). Interestingly, Han (Han

Table 1. The role of CHM and active compound as tumour suppressor.

Tumour suppressor genes	CHM & active compound	Plant source/part	Cancer type	Cell line	Mechanism of action	Reference
p53	*S. baicalensis*	Root	Lung	A549,	Cell growth arrest	(Gao *et al*., 2011)
				SK-LU-1	Apoptosis	
				SK-MES-1		
	Gleditsia sinensis	Thorn	Colon	HCT116	Cell growth	(Lee *et al*., 2010)
					Cell cycle arrest	
	KLT	*Coix* seed	Non-small-cell lung cancer	A549	Apoptosis	(Lu *et al*., 2010)
	Ginsenoside	*Ginseng* root	Colorectal	HCT116 SW480	Bax protein and	(Li *et al*., 2011)
					induces cell death	
	Thymoquinone	Black seed	Colorectal	HCT-116	Apoptosis	(Gali-Muhtasib *et al*., 2004)
Rb	Honokiol	*M. officinalis*	Prostate	PC-3	Cell cycle arrest	(Hahm *et al*., 2007)
				LNCaP		
	A. gracilistylus	Dried barks	Leukemia	MT-2	Inhibit proliferation via cell cycle arrest	(Shan *et al*., 2000)
				Raji		
				HL-60		
			Stomach	TMK-1		
			Oral	HSC-2		
	Licochalcone	root	Prostate	PC-3	Anti-proliferation	(Fu *et al*., 2004)
			Gastric	MKN-28	Reduces expression of transcription factor E2F; cyclins D1, Cdk4, and Cdk6. inhibits phosphorylation of S780	(Xiao *et al*., 2011)
				AGS		
				MKN-45		
	Zyflamend	Rosemary, turmeric, ginger, holy basil, green tea, hu zhang, Chinese goldthread, barberry, oregano, baikal skullcap	Prostate	PC-3	Anti-inflammatory	(Yang *et al*., 2007)
PTEN	Honokiol	*Magnolia* species	Adipocytes	3T3-L1	Angiogenic activity	(Liu *et al*., 2008)
						(Yang *et al*., 2008)
			Breast	BT-474		
	Curcumin and resveratrol	Turmeric	Prostate	PTEN-CaP8	Apoptosis	(Narayanan *et al*., 2009)
		Japanese knotweed				
	Rosemary extract	Rosemary herb	Myeloid cell	K562	Repress PTEN expression	(Yoshida *et al*., 2011)
p21WAF1 p27KIP1	Aqueous extract of *Magnolia*	*Magnolia officinalis*	Urinary cancer	5637	Anti-proliferation	(Lee *et al*., 2007)
					G1 cell cycle arrest	
	Baicalin	Root of *S. baicalensis Georgi*	Prostate cancer	LNCaP	Apoptosis	(Dong *et al*., 2010)
				PC3	Anti-proliferation	
	G. sinensis	Thorns	Vascular smooth muscle cells	VSMC	Cell cycle arrest	(Lee *et al*., 2012)
	Saussurea involucratat	Aerial part including flower	Prostate	PC-3	G1 phase cell cycle arrest and apoptosis	(Way *et al*., 2010)
APC	Tichosanthin	*T. kirilowii* Maximowicz	Cervical	HeLa	Demethylation	(Huang *et al*., 2012)
	Carnosol	Rosemary	Intestinal cancer	C57BL/6J/Min/+ (Min/+) mouse	Enhance E-cadherin-mediated adhesion	(Moran *et al*., 2005)
					Suppress beta-catenin tyrosine phosphorylation	

et al., 2009) further stated the presence of necrostatin-1 (Nec-1), a specific necroptosis inhibitor, that can revert back necrosis to apoptosis. This switch mode is associated with Bax translocation partially due to the conversion of mitochondrial inner membrane permeability to outer membranes. Their data also suggested that apoptosis and necroptosis may function as reciprocal backup mechanisms of cellular demise. Similarly, a synergistic combination of 5-FU with gambogenic acid against human lung cancer cells A549 was reported to induce a typical cellular necrotic death which was primarily necroptosis and posteriorly apoptosis (Su *et al*., 2014).

Inhibit replicative immortality

Normal cells are going through a limited number of growth and division. The cell cycle consists of four distinct stages: M, G_o, S, and G1 inclusive of two proliferation barriers: senescence and crisis. Under certain conditions, when normal cells skip these barriers, it reaches immortalized state. In normal cells, telomeres at the end of chromosome protect the DNA from instability and damages. When telomeres shorten progressively with each cell division, it damages the DNA. Therefore, successive cell division is correlated with the length of telomeric DNA. Telomerase is highly expressed in the majority of immortalized cells, and telomere repeat segment is added to the end of the DNA that helps to increase the cell cycle division which eventually will increase the resistance to cell death. In a nutshell, the activation of telomerase enzyme leads to the extension of telomere that could block apoptosis and promotes proliferation and tumor oncogenesis (Shay *et al*., 2011). It was reported that telomerase activity and malignancy have a close association. Therefore, targeting telomerase activity can be a promising cancer treatment.

Several studies have reported the use of CHM in targeting telomerase activity. Matrine, one of the main components extracted from a Chinese herb, *Sophora flavescens* Ait. (Leguminosae), was reported to have a significant effect on the inhibition of proliferation by suppressing telomerase activity in K562 cells (Zhang *et al*., 2001). In 2009, Wang (Wang *et al*., 2009) found that epigallocatechin gallate (EGCG), a major component of polyphenols in green tea, inhibits telomerase activity. They found that EGCG inhibited cell growth and induced apoptosis with an increase of caspase-3 activity and downregulation of telomerase activity in a dose-dependent manner in Hep-2 cells. A further study revealed that EGCG directly inhibited the catalytic subunit of telomerase that blocks the transcription of telomerase reverse transcriptase (Meeran *et al*., 2010). The inhibition of telomerase activity was also observed in allicin (major compound found in crushed garlic)-treated gastric cancer SGC-7901 cells (Sun *et al*., 2003).

Immune destructive

In cancer initiation and progression, failure of host immune system plays a crucial role. A weaker immune system fails to recognize and eliminate the majority of neoplastic cells, thus resulting in progression and spreading to other organs. Repetitive chemotherapy and radiotherapy can also impair the immune system followed by bone marrow suppression (Fromenti *et al*., 2009; Meir *et al*., 2017).

In general, natural compounds inclusive of CHMs are believed to regulate the human immune system. They can enhance the immune response against the tumor, may suppress immune inhibitory responses, shift the immune system balance, and restore/reverse the impaired immune system to its normal condition (Haddad *et al*., 2005). During the activation of immune system, an increase in inflammatory T cells and natural killer T cells can be observed, whereas the reduction of regulatory T cells and myeloid-derived suppressor cells can also be seen. Apart from that, CHM also regulates cytokine productions such as IFN-α, IL-2, IL-6, and IFN-γ to fight against tumor cells (Ma *et al*., 2008; Peng *et al*., 2013; Xiao *et al*., 2015).

The ability of CHMs in regulating patient's immune system is not new. Research findings proved that polysaccharide content found in CHM plays a main role to activate immune response. For example, treatment with *Momordica charantia* polysaccharide (Fang *et al*., 2012), *Lycium barbarum* polysaccharide, *G. lucidum* polysaccharides (Xu *et al*., 2011), and *Acanthopanax senticosus* polysaccharide and lentinan strengthen the immune system to inhibit tumor growth (Huyan *et al*., 2014). Next, *Radix Astragali* (RA), a popular CHM, is obtained from the dried root of *A. membranaceus Bge. Var. mongholicus*. The main active compounds of RA are polysaccharides (6.83%–13.48%), saponins (1.96%–3.58%), and flavonoids (0.75%–1.49%) (Jung *et al*., 2016). It has been used as a tonic and known to enhance immune function by activating macrophages and natural killer cells (Cho *et al*., 2007). Apart from that, RA also shows immunomodulatory properties in combination with chemotherapy and radiotherapy (Monograph, 2003). *Ginseng* is a famous CHM that highly used among Asian. It shows anticancer and anti-inflammatory properties and reduces cancer occurrence in gastric, liver, pancreatic, and colon by controlling host immune system (Hofseth and Wargovich, 2007; Yun and Choi, 1995).

Energy metabolism

Energy metabolism in normal cells occurs in aerobic and anaerobic conditions. In aerobic condition, the presence of oxygen allows glucose breakdown to pyruvate in the cytoplasm. Later, pyruvate with the help of oxygen breaks down in mitochondria to release carbon dioxide and 36 molecules of adenosine triphosphate (ATP). This phenomenon is known as oxidative phosphorylation. In anaerobic condition, normal cells undergo anaerobic glycolysis in the cytoplasm, where glucose converted to pyruvate then lactate. Anaerobic glycolysis produces less energy, which is only 2-ATP. In conclusion, normal cells select oxidative phosphorylation in the presence of oxygen to release high energy, whereas uses anaerobic glycolysis in the absence of oxygen to release less energy. Interestingly, this is not the norm in cancer cells (Fig. 5). Energy metabolism in cancer cells does not depend on aerobic or anaerobic conditions. Proliferative tissues or tumor consumes glucose to produce pyruvate and then converts it to mostly lactate even in the presence of ample of oxygen (DeBerardinis *et al*., 2008; Warburg, 1956). Cancer cell adaptation to this pathway is known as the Warburg effect or aerobic glycolysis which is critical for tumor cell growth, proliferation, angiogenesis, and stress resistance. As one of the hallmarks of cancer, active aerobic glycolysis by cancer cells has been utilized in the clinical sector as a means of diagnosis and monitoring cancer treatment response in positron emission

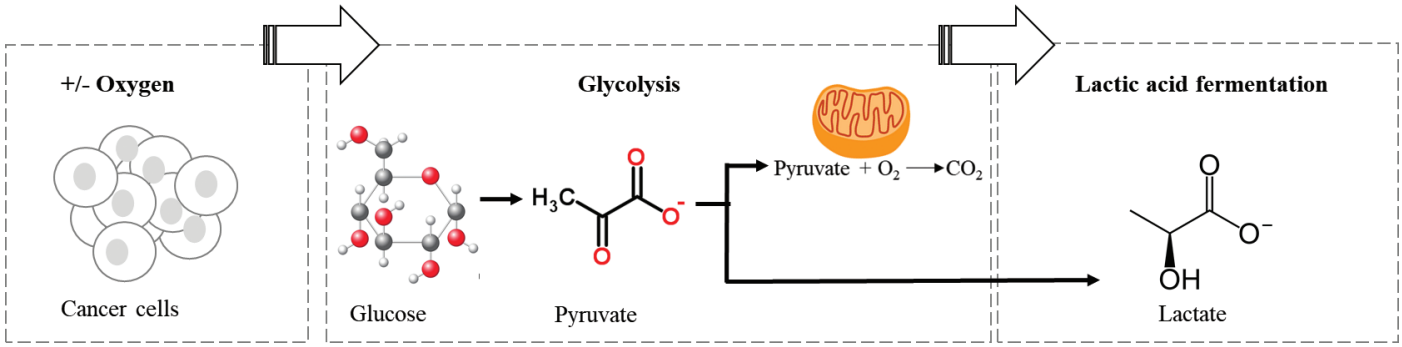

Figure 5. Schematics of aerobic glycolysis – ''Warburg effect." To enable rapid proliferation, cancer cells favor high levels of glucose uptake and lactate production.

Table 2. List of CHM that inhibits cancer metabolic expression-Warburg effect.

Compound	CHM	Type of Cancer	Metabolite regulation	Mechanism	Reference
Berberine	*Berberis* species	Breast	Mitochondrial OXPHOS	Regulate ACC and ACL pathway; Inhibit phosphorylation of PKM2 & PFKP	Tan *et al*., 2014
Ginsenoside 20(S)-Rg3	*Panax ginseng*	Ovarian	Glycolysis	Targets the STAT3/HK2 pathway	Li *et al*., 2015
Apigenin	*A. graveolensvar*. dulce	Breast	HIF-1α inhibitor	Downregulating VEGF inactivated the PI3K/Akt pathway	Semenza, 2009
		Ovarian			Choi and Kim, 2009
		Prostate			Li *et al*., 2009
		Lung			Shukla and Gupta, 2006
Chrysin	*Oroxylum indicum* (L.) Vent	Prostate	Decreased HIF-1α expression	Apoptosis	Samarghandian *et al*., 2011
		Thyroid			Phan *et al*., 2011
		Leukemia			Khoo *et al*., 2010
Shikonin	*L. erythrorhizon*	Leukemia	ROS deregulation and OXPHOS uncoupling	Apoptosis	Wiench *et al*., 2012
Wogonin	*S. baicalensis* (Huang qin)	Colon	Glucose uptake	Inhibits PI3K/Akt signaling pathway	Wang *et al*., 2014

tomography, positron emission tomography scan (Sotgia *et al*., 2011).

Metabolic adaptation of tumor cells is regulated by a number of oncogenes and tumor suppressors including Myc (Lewis *et al*., 1997), hypoxia-inducible factor, HIF-1α (Kim *et al*., 2006), p 53 (Bensinger and Christofk, 2012), and PI3K/Akt/mTOR signaling pathway (Elstrom *et al*., 2014). Interrupting any of the above could lead to metabolism blockade followed by cell death.

The distinct phenomena of energy production in cancer cell via aerobic glycolysis open the door to target this metabolism and its related critical enzymes such as glucose transporter GLUT1, HK, PFKFB3, mTORC1, and OXPHOS to be exploited as targets for cancer therapy. By controlling/preventing aerobic glycolysis, cancer cells can undergo starvation, and the inhibition of proliferation can be reached. Subsequently, cancer progression can be prevented. As such, the role of CHM in the development of glycolysis-based therapeutic interventions for cancer is focused in this session.

Apigenin, a plant flavonoid compound isolated from *Apium graveolensvar*. Dulce, acts as a HIF-1α inhibitor (Semenza, 2009). This active compound showed to inhibit proliferation and to induce apoptosis in various cancers including breast (Choi and Kim, 2009), ovarian (Li *et al*., 2009), prostate (Shukla and Gupta, 2006), and lung (Lu *et al*., 2010). Apigenin was reported to inactivate PI3K/Akt pathway in prostate cancer cells (Shukla and Gupta, 2007) and reduce HIF-α stability via PI3K/Akt/GSK-3 β pathway (Mirzoeva *et al*., 2008). Apart from this, Chrysin (Fu *et al*., 2004), EGCG (Tachibana, 2009), and curcumin (Bae *et al*., 2006) are among other reported CHM-derived pure compounds that could control aerobic glycolysis by inhibiting HIF-1α expression.

Expression of c-Myc oncogene is upregulated in the majority of human cancers including breast, colon, bladder, and prostate cancers (Dang *et al*., 2009). Overexpression of c-Myc is also linked to increase in many glucose metabolism enzyme genes, such as GLUT1, HK2 (Kim *et al*., 2007), phosphofructokinase, enolase 1, lactate dehydrogenase A, mitochondrial ROS, and pyruvate dehydrogenase kinase, thus stimulating the Warburg effect (Lewis *et al*., 1997; Shim *et al*., 1997). Table 2 shows the various CHMs in targeting the Warburg effect.

CHINESE HERBAL MEDICINES UNDER CLINICAL TRIAL

CHM has become an important and growing part of public healthcare around the world. Initially, its importance was overlooked due to the lack of scientific evidence to evaluate safety and efficacy. In this review, we have highlighted the mechanism

Table 3. Completed clinical trials of CHM in cancer.

	Title	Study results	Conditions	Interventions	Locations
1	Compound Herbal Formula (TPE-1) for Leukopenia and Cancer-related Fatigue in breast Cancer Patients with Radiotherapy	No results available	• Breast cancer • Radiotherapy • Chinese herbal medicine	• Drug: CHM decoction	Taiwan
2	Clinical Trial on Palliative Cancer Patients with Constipation	No results available	• Constipation	• Drug: CHM • Drug: Placebo	Hong Kong
3	Safety and Pharmacokinetics of Jin Fu Kang in Comb w/Docetaxel for Patients w/Non-Small Cell Lung Cancer	No results available	• Non-small cell lung cancer	• Drug: Docetaxel • Drug: Jin Fu Kang	United States
4	A Phase II Multicenter, Randomized, Placebo Controlled, Double Blinded Clinical Study of KD018 as a Modulator of Irinotecan chemo-therapy in Patients with Metastatic Colorectal Cancer	Results available	• Colorectal neoplasms	• Drug: KD018 • Drug: Irinotecan • Drug: Placebo	United States
5	Sho-Saiko-To Following Removal of Liver Cancer by Embolization in Treating Patients with Liver Cancer That Cannot Be Surgically Removed	No results available	• Liver cancer	• Dietary Supplement: Sho-saiko-to	United States
6	Life Quality and Mental State in Patients with Breast Cancer	No results available	• Breast cancer	• Other: Individualized complementary • medicine treatment • Other: Individualized usual care	Italy
7	Cross Sectional Study of Constipation in Advanced Cancer Patients	No results available	• Palliative care • Constipation • Traditional Chinese medicine		Hong Kong
8	Combination Chemotherapy After Surgery with or Without Chinese Herbal Therapy to Treat Symptoms in Women with Breast Cancer	No results available	• Breast cancer • Drug/Agent Toxicity by Tissue/Organ	• Dietary Supplement: Chinese herbs • Drug: cyclophosphamide • Drug: doxorubicin hydrochloride • Procedure: adjuvant therapy	United States
9	Study of TLBZT Based Herbal Therapy Plus Chemotherapy for Metastatic Colorectal Cancer	No results available	• Metastatic colorectal cancer	• Drug: Chemotherapy • Drug: Herbal therapy	China
10	Chinese Herbal Medicine for Immune Reconstitution Following HSCT in Acute Leukemia Patients	No results available	• Acute leukemia	• Dietary Supplement: Sheng-Yu-Tang	Taiwan
11	Herbal Therapy in Treating Women with Metastatic Breast Cancer	No results available	• Breast cancer	• Drug: herba *S. barbata* • Other: herba *S. Barbatae* (HSB)	United States
12	Treatment of Anal HSIL Through Use of a Chinese Herbal Topical Cream	Results available	• Anus neoplasms	• Drug: AIJP • Drug: Placebo	United States
13	Traditional Chinese Medicine in the Supportive Management of Anaemic and Cytopenic (Leukopenia, hrombocytopenia) Haematological Disorders	No results available	• Myelodysplastic Syndrome (MDS) • Aplastic anaemia (AA) • Myelofibrosis (MF) • Thalassemia intermedia	• Drug: Chinese herbal concoction twice a day for 6 months	Singapore

ClinicalTrials.gov Search Results 06/18/2019.

behind the potential use of CHM in inhibiting cancer development. However, to further widen their acceptance globally and to promote herbal medicines into conventional medical practices, clinical trials of these medicinal plants are encouraged. As such, Table 3 shows the completed clinical trials of CHM in breast, lung, anal, leukemia, liver, and colorectal cancers (http://clinicaltrials.gov/). Among the listed 13 completed clinical studies, only two studies were shown to have available results. A phase II study was carried out from 2008 to 2018 to investigate the mechanism and efficacy of CHM as an adjunct to chemotherapy in the treatment of patients with metastatic colorectal cancer. In the CHM, KD018 is an oral form of a spray-dried aqueous extract composed of Huang Qin Tang herbal mixture (*Glycyrrhiza uralensis* Fisch, *Paeonia lactiflora* Pall, *S. baicalensis* Georgi, and *Ziziphus jujube* Mill), which have been used against gastrointestinal (GI) infectious symptoms including diarrhea and nausea/vomiting. A therapeutic use of KD018 was tested for its potential activity in reducing chemotherapy-induced toxicity, especially diarrhea. The CHM was shown to decrease GI toxicity induced by the chemotherapeutic drug CPT-11 (irinotecan) and increase the antitumor activity of irinotecan while decreasing weight loss caused by irinotecan (Lam *et al*., 2010). Next, phase II study on anal high-grade squamous

intraepithelial lesions (HSIL) through the use of a Chinese herbal topical cream by the University of California was carried out from 2008 to 2012. This CHM that consists of Arnebia Indigo Jade Pearl (AIJP) was applied as a noninvasive topical cream for the treatment of precancerous anal lesions caused by human papillomavirus to prevent their progression to anal cancer.

With the growing scientific evidence on the safety and efficacy of CHM in clinical trial, CHM-based drugs can be confidently used to treat cancer. With more clinical trials on CHM conducted, this may allow the integration of CHM into the current conventional healthcare systems.

Perspectives

CHM has the potential to develop anticancer drug against the deadliest disease, cancer. CHM's ability to significantly target all the hallmarks of cancer proves the millennia-old Chinese medicine's efficacy to work against various cancers. While in the beginning, it was only prescribed by CHM practitioner without any standard protocol to prepare and was not well documented, thus missing of scientific evidence that made it not well received by conventional medicine. Over the decades, tremendous efforts and intellectual contributions have been given to reveal the mode of action and mechanism behind its effectiveness. For example, with modern scientific techniques including isolation, extraction, active compound detection, biological assays, RNA, and DNA extractions, *in vitro* and *in vivo* analysis made it possible for a better understanding of CHM and its role to treat this malignancy. However, a number of limitations and challenges have existed, which reduces the progress of studies on the use of CHM in cancer treatment. Most importantly, there was a great controversy about CHM use of complex/whole mixture in contrast to isolate bioactive single compounds. In mixture, hundreds of compounds might work together synergistically to enhance therapeutic effect, and also, this could enable the treatment with less or no side effects. For the same scenario, there are chances to have unstable and unreactive compounds present in the composite mixture. By isolating active compounds, the mechanism of action for treatment could be clearly revealed and understood. Next, mostly, CHM knowledge and preparation techniques are inherited, and based on the reports provided by ancient physicians, many of which lack the standardized procedure and criteria. This definitely sets a drawback for CHM to be well-accepted and confidently used as a treatment regime. It is necessary to introduce a holistic strategy and evidence-based approaches to further study CHM.

CONFLICT OF INTEREST

Authors declared that there are no conflicts of interest.

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