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Review

Anticancer effects of traditional Chinese herbs with phlegm-eliminating properties – An overview

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ABSTRACT

Ethonopharmacological relevance: Cancer is considered to be the second leading cause of human death. It is unsatisfactory that in the past decades, the treatment for cancer has not progressed as fast as it was expected, as only 50% of newly diagnosed patients could be cured even today. The development of cancer is a multifactorial process, involving tumor cells themselves, the interactions between tumor cells and their microenvironments, as well as the interactions between tumor cells and the host's immunity. Focusing on any single goal may bring limited benefits.

Aim and methods of the study: Phlegm-eliminating herbs, which can reduce phlegm and eliminate pathological metabolites, are commonly used to treat cancer in China. However, the underlying molecular targets and efficacy of herbal medicines in cancer treatment still remain unclear. In this study, we reviewed the potential anticancer mechanisms of some phlegm-eliminating herbs and their active ingredients from the articles through such scientific databases as MEDLINE, PubMed, and Google Scholar.

Results: We found that the anticancer mechanisms of phlegm-eliminating herbs and ingredients include inducing apoptosis, anti-proliferation, preventing tumor invasion and metastasis, and reducing resistance to chemotherapy. In addition, some phlegm-eliminating herbs and their ingredients have anti-inflammatory and anti-metabolic syndrome effects.

Conclusions: We suggest that the phlegm-eliminating herbs and ingredients are potential candidates for anticancer treatment and cancer prevention by playing a comprehensive role.

Contents

Abbreviations: AMPK, AMP-activated protein kinase; ACC, acetyl-CoAcarboxylase; COX, cyclooxygenase; CDK, cyclin-dependent kinase; CaMK, Ca2+/calmodulin-dependent protein kinase; CPT, Cholinephosphotransferase; Egr, early growth response gene; ERK, extracellular signal-related kinase; GSH-Px, Glutathione peroxidase; HDL-C, High Density Lipoprotein Cholesterol; hTERT, human telomerase reverse transcriptase; HPV, human papillomavirus; iNOS, inducible nitric oxide synthase; IL, interleukin; JNK, c-Jun N-terminal kinase; K-ras, Kirsten RAS; LDL-C, low density lipoprotein-cholesterol; MAPK, mitogen-activated protein kinases; MCP, Membrane cofactor protein; MDA, malondialdehyde, multidrug resistance; MMP, matrix metalloproteinase; NO, nitrie oxide; NF-κB, nuclear factor-kappaB; NK, nature killer cell; PARP, poly ADP-ribose polymerase; PCNA, proliferating cell nuclear antigen; P-gP, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PL, phospholipid; p-Rb, phosphorylated retinoblastoma protein; PRDX, peroxiredoxin; ROS, reactive oxygen species; SOD, Superoxide Dismutase; STAT, signal transducer and activator of transcription; TG, triglyceride; TC, cholesterol total; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

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1. Introduction

Cancer is considered to be the second leading cause of human death. It is unsatisfactory that in the past decades, the treatment for cancer has not progressed as fast as it was expected, as only 50% of newly diagnosed patients could be cured even today (Arends, 2010). Pathogenesis of cancer relates to proliferation, apoptosis, inflammation, internal environment, etc. (Wolchok and Chan, 2014). It is a complex process involving a multitude of factors including tumor cells themselves, the interactions between tumor cells and their microenvironments, as well as the interactions between tumor cells and the host's immunity. Focusing on any single goal may bring limited benefits such as targeted treatment drugs. The mechanisms of cancer should be further studied. Some studies have indicated that there are common molecular properties and biological programs among cancer, inflammation, and metabolic diseases, which may contribute to the epidemiological connections between cancer and other particular diseases (Hirsch et al., 2010).

According to the theories on traditional Chinese medicine (TCM), phlegm refers not only to phlegm in the respiratory tract but also to the pathological metabolites in vivo. It plays an important role in the occurrence and development of cancer (Shi et al., 2012). TCM proposes that tumors result from the interactions among phlegm obstruction, qi stagnation, blood stasis and heat. Phlegm obstruction is believed to play a dominant role in tumor formation. TCM holds that phlegm, which results from the abnormal transformation of fluid-humor, is a pathologic metabolite that can be produced by diseases and other factors that are related to fluid-humor. For example, qi deficiency contributes to the accumulation of dampness into phlegm, and qi stagnation causes water retention, which in turn results in the production of phlegm. In addition, heat can boil fluid-humor, which condenses into phlegm. When phlegm is coagulated through the malfunctioning of fluid-humor, it further blocks meridians and collaterals, thus slowing down the circulation of qi, blood, and fluid-humor. Over time, the abnormal fluid-humor coagulates into a tumor.

Studies have increasingly demonstrated the effectiveness of herbs in treating cancers (Kaefer and Milner, 2008). Conventionally, phlegm-eliminating herbs, with the function of transforming phlegm, are commonly used to dissolve phlegm caused by common cold and internal diseases. They are also useful for epilepsy, wind stroke, and cancer. Recently, modern pharmacological studies have indicated that many of these herbs or bioactive spices are likely to contain anticancer active ingredients.

In the current review, the potential anticancer mechanisms and clinical trials regarding the phlegm-eliminating herbs are summarized. Peer-reviewed articles were selected through the scientific databases MEDLINE, PubMed, and Google Scholar with the keywords including herb, cancer, phlegm, TCM, and phytochemical.

2. Anticancer activities of phlegm-eliminating herbs in vitro

Pharmacological studies have revealed that some phlegm-eliminating herbs contain active ingredients, the antitumor effects of which are reflected in many aspects such as induction of apoptosis, prevention of invasion and metastasis, and the reduction of resistance to chemotherapeutic drug (Table 1).

2.1. Apoptosis-inducing and anti-proliferative effects

Disorder of apoptosis is one of the key characteristics of tumor cells. Caspase and cell cycle arrest are important in apoptosis. Induction of apoptosis in tumor cell is an important aspect of most antitumor studies (Debatin, 1999). With regard to induction, many ingredients of phlegm-eliminating herbs are likely to play a role.

Citrus reticulata Blanco is one of the most important TCM herbs for eliminating phlegm. With the effect on circulating qi, drying dampness and transforming phlegm, it is used to treat cough and cancer in TCM practice. Current studies have indicated that the extracts or constituents of *C. reticulata* Blanco have anticancer effects on several tumor cell lines (Silalahi, 2002; Arias and Ramon-Laca, 2005), and its mechanism involving induction of apoptosis was demonstrated on human leukemic HL-60 (Hirano et al., 1995), gastric cancer (Kim et al., 2005; Lee et al., 2012b), colorectal cancer (Zheng et al., 2002), and lung cancer cells (Xiao et al., 2009). It is believed that the main active ingredients of *C. reticulata* Blanco are flavonoids, particularly polymethoxyflavones (PMFs), which are reported to have a role in inducing an increased level of intracellular Ca^{2+} and thus activating Ca^{2+}-dependent apoptotic proteases, and modulating key signaling proteins related to cell proliferation and apoptosis (Sergeev et al., 2007; Qiu et al., 2010). Similarly, *Platycodon grandiflorus* (Jacq.) A. DC., a common food and medicine in China, Korea and Japan, is another TCM herb for eliminating phlegm. As it is an expectorant and has anti-inflammatory effects, it is used to treat cough with profuse sputum, pharyngitis, etc. As reported, the extract of *P. grandiflorus* (Jacq.) A. DC. can induce apoptosis in SKOV-3 human ovarian tumor cells (Hu et al., 2010), while platycodon D from the roots of *P. grandiflorus* (Jacq.) A. DC. has the similar effect on inducing apoptosis in MCF-7 human breast tumor cells (Yu and Kim, 2010) and U937 human leukemia cells (Shin et al., 2009). The possible mechanism is associated with the production of reactive oxygen species, activation of caspase-3, mitochondrial-dependent pathway, etc. *Laminaria japonica* Aresch is widely used to treat thyroid tumor, lymph node tuberculosis, etc. in China and Japan, due to its effects of softening hardness and dissipating bind. According to the previous studies, glycoprotein, a constituent of *L. japonica* Aresch could induce cell apoptosis via multiple pathways such as the Fas signaling pathway, the mitochondrial pathway, cell cycle arrest, downregulation of telomerase activity, prostaglandin E2 synthesis, etc. (Go et al., 2010; Han et al., 2011).

Overall, these data suggest that many types of phlegm-eliminating herbs or their ingredients can induce apoptosis of several tumor cells, while some other herbs and some spices can inhibit special tumor cells. *Fritillaria ussuriensis* Maxim., with heat-clearing, phlegm-transforming effects, is usually used to treat cough in TCM practice. One study has indicated that verticinone from the bulbus of *F. ussuriensis* Maxim., has an effect on inducing apoptosis in malignant human oral keratinocytes through a caspase pathway mediated by mitochondrial damage and G0/G1 cell cycle arrest (Yun et al., 2008).

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