Journal of Ethnopharmacology 138 (2011) 652–661

Contents lists available at SciVerse ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

Are there new therapeutic options for treating lung cancer based on herbal medicines and their metabolites?

Soo-Jin Jeong, Wonil Koh, Bonglee Kim, Sung-Hoon Kim*

Cancer Preventive Material Development Research Center, College of Oriental Medicine, Kyung Hee University, 130-701, Republic of Korea

ARTICLE INFO

Article history:
Received 21 June 2011
Received in revised form 10 October 2011
Accepted 11 October 2011
Available online 18 October 2011

Keywords:
Herbal medicine
Phytochemical
Lung cancer
Molecular targets
Apoptosis
Angiogenesis

ABSTRACT

Ethonopharmacological relevance: Lung cancer is one of the most lethal cancers in terms of mortality and incidence worldwide. Despite intensive research and investigation, treatment of lung cancer is still unsatisfactory due to adverse effects and multidrug resistance. Recently, herbal drugs have been recognized as one of attractive approaches for lung cancer therapy with little side effects. Furthermore, there are evidences that various herbal medicines have proven to be useful and effective in sensitizing conventional agents, prolonging survival time, preventing side effects of chemotherapy, and improving quality of life (QoL) in lung cancer patients.

Aim and methods of the study: Nevertheless, the underlying molecular targets and efficacy of herbal medicines in lung cancer treatment still remain unclear. Thus, we reviewed traditionally used herbal medicines and their phytochemicals with antitumor activity against lung cancer from peer-reviewed papers through Scientific Database Medline, Scopus and Google scholar.

Conclusions: We suggest that herbal medicines and phytochemicals can be useful anti-cancer agents for lung cancer treatment by targeting molecular signaling involved in the regulation of angiogenesis, metastasis and severe side effects, only provided quality control and reproducibility issues were solved.

Contents

1. Introduction 653
2. Anti-lung cancer effects and molecular regulation of herbal medicines *in vitro* 653
   2.1. Apoptosis and herbal medicines 653
   2.2. Inhibitory effects of herbal medicines on angiogenesis and metastasis *in vitro* 656
   2.3. Herbal medicines as multidrug resistance (MDR) reversal agents 656
   2.4. Reactive oxygen species (ROS) and lung cancer therapy 657
3. Anti-lung cancer activities of herbal medicines *in vivo* 657
4. Clinical trials of herbal medicines for the treatment of lung cancer 658
   4.1. Herbal medicines as combination therapy with conventional chemotherapy 658
   4.2. Herbal medicines for improved quality of life in lung cancer patients 658
   4.3. Herbal medicines for adverse effects of conventional intervention 658

Abbreviations: BBSKE, 1,2-[bis (1,2-benzisoselenazolone-3 (2H)-ketone)] ethane; bFGF, basic fibroblast growth factor; CAM, complementary and alternative medicine; COX, cyclooxygenase; CREB, cAMP response element-binding; CRP, clinical radiographic physiologic; DHA, dihydroartemisinin; DPPH, 1,1-diphenyl-2-hydrazyl; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; ERK, extracellular signal-related kinase; FD, feiyanning decoction; GSP, grape seed proanthocyanidin; HUVEC, human umbilical vein endothelial cell; MDR, multidrug resistance; MK, monacolin K; MMP, matrix metalloproteinase; MRP, MDR-associated protein; NF-κB, nuclear factor-kappaB; NP, navelbine and cisplatin; NSCLC, non-small cell lung cancer; PAI, plasminogen activator inhibitor; PARP, poly (ADP)-ribose polymerase; PDGF, platelet-derived growth factor; PFS, progression free survival; p-gp, p-glycoprotein; QoL, quality of life; RCT, randomized-controlled trial; ROS, reactive oxygen species; RTOG, Radiation Therapy Oncology Group; SCLC, small cell lung cancer; SENL, Supplement energy and nourish lung; SM, solamargine; TCS, trichosanthin; TGF, tumor growth factor; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; UA, ursolic acid; VEGF, vascular endothelial growth factor.

* Corresponding author at: Cancer Preventive Material Development Research Center, College of Oriental Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul 131-701, Republic of Korea. Tel.: +82 2 961 9233; fax: +82 2 964 1064.
E-mail address: sungkim7@khu.ac.kr (S.-H. Kim).

0378-8741/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jep.2011.10.018

4.4. Limitations and challenges of current clinical trials with herbal medicines 658
5. Conclusions 659
Acknowledgement 659
References 659

1. Introduction

Lung cancer, the leading one of cancer-related deaths worldwide, is divided into two major types such as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The most risk factor for lung cancer is cigarette smoking. Furthermore, lung cancer can be induced by chemical exposure to arsenic, beryllium, cadium, vinyl chloride, and nickel chromates. The occurrence of lung cancer in non-smokers is frequently attributed to a combination of genetic factors (Gorlova et al., 2007), radon gas (Catelinois et al., 2006), and air pollution (Kabir et al., 2007). Because lung cancer does not generally exhibit any significant symptoms until the cancer initiates metastasis to other organs, early diagnosis is a key factor for improving the survival of lung cancer patients.

Therapeutic approaches to lung cancer, such as chemotherapy, radiotherapy, and surgery have been widely used. For treatment of SCLC, cisplatin, etoposide (Murray and Turrisi, 2006), and celecoxib (Aruajo et al., 2009) are generally utilized, whereas anthracycline, doxorubicin, epirubicin, topotecan, irinotecan, paclitaxel, and gemcitabine are applied either alone or in combination with others (Azim and Ganti, 2007). For treatment of NSCLC, cisplatin and carboplatin are often used in combination with other anti-cancer agents such as gemcitabine, paclitaxel, docetaxel, etoposide, or vinorelbine (Clegg et al., 2002). Nonetheless, because this standard chemotherapy often limited survival benefit due to severe toxicity (Broker and Giaccone, 2002), recent reports suggested that antitumor herbal medicines and their phytochemicals with little toxicity are attractive for lung cancer therapy. In traditional medicine, several herbal plants such as *Platycodon grandiflorum* (Campanulaceae), *Morus alba* (Moraceae), *Prunus armenica* (Rosaceae) and *Rhus verniciflua* (Anacardiaceae), *Perilla frutescens* (Labiatae), *Stemona japonica* (Stemonaceae), *Tussilago farfara* (Compositae) and *Draba nemorosa* (Brassicaceae) have been frequently used for lung diseases including cancer as folk remedies and medicines. Previously, 130 Chinese herbal medicines possessing anti-lung cancer effects were classified into five subgroups based on their action: (1) clearing heat and toxin, (2) resolving Dampness and Phlegm, (3) regulating blood and Qi, (4) reinforcing Qi, and (5) nourishing Yin (Liang et al., 2003) by their ethnopharmacological efficacies.

In the current review, to support updated systemic information on the use of herbal medicines and their constituents for lung cancer treatment and prevention to cancer researchers, we discussed their ethnopharmacological effects focusing on angiogenesis, metastasis, apoptosis and clinical trial efficacy and finally suggested perspectives for future herbal medicine research with summarized table on family name, effective doses, constituents and molecular targets. We selected peer-reviewed papers on herbal medicines and their phytochemicals for lung cancer treatment *in vitro* and *in vivo* shown through Scientific Database Medline, Scopus and Google scholar. The following keywords were used to search for the literature inside the databases: herb, phytochemical, plant extract, natural product and lung cancer. However, we excluded the papers on the antitumor effects of derivatives from herbal compounds.

2. Anti-lung cancer effects and molecular regulation of herbal medicines *in vitro*

It is important to understand their unique mechanisms of action to be developed as therapeutically useful agents for cancer. Investigation of the molecular mechanisms whereby herbal medicines exert anti-cancer activity has resulted in the development of many targeted therapeutic drugs for cancer treatment (Kukunoor et al., 2003). Molecular approaches provide new viewpoints for early diagnosis and screening of high-risk individuals, determination of prognosis, and identification of innovative treatments (Huber and Stratakis, 2004). In lung cancer therapy, angiogenesis- and metastasis-related factors such as VEGF and MMPs, along with cell proliferation- and survival-related factors such as AKT, NF-κB, Ras, MAPKs, and EGFR, are importantly considered as target molecules for lung cancer therapy (Table 1).

2.1. Apoptosis and herbal medicines

Apoptosis is characterized by a series of morphological alterations, including plasma and nuclear membrane blebbing, cell shrinkage, dissolution of nuclear lamina, and the biochemical process responsible for activation of apoptosis (Jacobson et al., 1994). More than 5000 research papers have been published on apoptosis in lung cancer. Among them, it is of interest that various herbal medicines and phytochemicals can induce apoptotic cell death in lung cancer cells.

The fruit, bark, and roots of *Toona sinensis* (Meliaceae) has been used in Chinese medicine. *Toona sinensis* showed anti-diabetic activity by enhancement of lipolysis and glucose uptake in differentiated 3T3-L1 adipocytes (Yang et al., 2003). *Toona sinensis* leaf extract (TSL-1), a bioactive fraction, has shown anti-cancer effects against lung (Yang et al., 2010) and prostate cancer cells (Chen et al., 2009a). TSL-1 had the inhibitory effect of proliferation 24-h post-treatment (IC_{50} = 1.2 mg/ml) and mediated apoptosis at 0.5 or 1 mg/ml in H441 lung adenocarcinoma cells. TSL-1 induced apoptotic cell morphological changes, sub-G1 accumulation, and poly (ADP)-ribose polymerase (PARP) cleavage. *Ocimum gratissimum* (OG) (Lamiaceae), an aromatic, perennial herb, was traditionally used with its anti-bacterial and anti-diabetic activities and to treat gastrointestinal disorders in Taiwan. OG significantly decreased the cell viability. OG activated apoptosis signaling molecules such as caspase-3 and -9 at the concentrations of 500 or 800 μg/ml in A549 cells, suggesting that OG may be a beneficial candidate for lung carcinoma treatment (Chen et al., 2010a). Likewise, acetone extract of *Bupleurum scorzonerifolium* (Umbelliferae) (BS-AE) (Cheng et al., 2005), and Tianhua (TH-R) from *Trichosanthes kirilowii* Maxim (Cucurbitaceae) (Li et al., 2010a) and its constituent trichosanthin (TCS) (Li et al., 2010b) have been reported to possess anti-cancer activity by inducing apoptosis in A549 lung cancer cells.

Many bioactive compounds from medicinal herbs also have been reported as potent apoptosis inducers in lung cancer cells. The flavonoid polyphenolic compound acacetin (5,7-dihydroxy-4′-methoxyflavone) derived from *Robinia pseudoacacia* (Fabaceae) showed the anti-proliferation effect in A549 cells (IC_{50} = 9.46 μM). Acacetin induced apoptosis and cell cycle arrest via upregulation of p53 and p21/WAF1 proteins at the concentrations of 5 or 10 μM in A549 cells (Hsu et al., 2004). Dihydroartemisinin (DHA) is a artemisinin derivative from *Artemisia annua* (Asteraceae) used for