



Letter to the Editor

Analysis of patents targeting antimetastatic effect using herbal materials



Metastasis is the most critical characteristic and clinically impactful outcome of cancerous disease because metastasis is responsible for approximately 90% of cancer deaths.¹ Despite the remarkable development of surgical and radiation therapies, conventional therapies cannot treat most metastatic tumors.² Recent researcher has proved that metastasis occurs early in the initial phase of cancer growth; accordingly, the detection of metastatic lesions on imaging implies wider spread of cancer cells at the cellular level.³ Furthermore, a novel strategy of antimetastatic therapies is to target both cancer cells themselves and host microenvironments.⁴

On the other hand, antimetastatic potential of herb-derived resources has been frequently investigated. Along with searching the published articles, researchers generally review relevant patents in investigations for drug development. In order to provide practical information for pharmacological researchers and oncologists in the fields of traditional Korean medicine (TKM) or traditional Chinese medicine (TCM), we searched patents related to antimetastatic herbal materials using a patent information search service (www.wipson.com, published until October 2019), and analyzed them according to the year of registration, country (US, Europe, Korea, Japan and China), composition number, preparation, origin of material, cancer cells studied and mechanisms targeted (Supplement 1).

Among 3446 potentially relevant patent applications, 203 (from 511 applications) were registered since the first patent application in 1989. The largest number of patents was registered in Korea (39.9%), followed by China (38.4%), the US (10.8%), Japan (6.4%) and Europe (4.4%), respectively. Seventeen of 203 registered patents (8.4%) were related to herb-derived compounds, while the rest (186 patents, 91.6%) were related to crude herbal materials. Regarding the preparation of the 186 crude materials, 104 were single herbs and 84 were composed of mixture ≥ 2 , as mainly water extraction (87.0%) of medicinal plants (84 patents, 80.8%), respectively (Supplement 2A–C). This might be due to the long traditional use of water-soluble herbal materials.

When we analyzed 186 patents of herbal resources, 350 herbs were shown in 82 patents to be used in combinations with ≥ 2 agents, most frequently *Astragalus membranaceus* (34 patents), *Atractylodes japonica* (25 patents), *Angelica gigas nakai* (24 patents), and *Poria cocos* (21 patents) (Supplement 2D and Supplement 3). While 81 herbs were shown in 104 patents as a single material, and the *Panax ginseng*, *Acanthopanax senticosus*, *Ganoderma atrum* and

Oenanthe javanica were involved in ≥ 4 patents (Table 1). *A. membranaceus*, a typical enhancer of 'Qi' in TKM and TCM, was not listed in the single-material patents; however, its antimetastatic effects have been well reported for combination formulations containing other medicinal herbs.⁵ *P. ginseng* is one of the most well-known herbs used to treat various disorders, such as diabetes mellitus, cancer and neurodegeneration.⁶

Among 203 patents, lung, skin and breast cancer cell lines were the 3 most commonly used (Supplement 4A), which are known to show relatively aggressive metastatic behaviors. The sequential processes of cancer metastasis are well recognized: local infiltration of cancer cells, intravasation, survival in the circulatory system, extravasation and subsequent proliferation in distant organs/tissues.⁷ In accordance with this fact, most patents featured agents with activities on molecules related to proteases, such as MMP9, cell migration, immune modulation and angiogenesis (Supplement 4B). These molecules and phenomena are closely linked to cancer metastasis in the context of tumor cells and the host environment.⁸ For example, polysaccharides from *P. ginseng* and *A. membranaceus* suppressed tumor activity, including metastatic behavior, via modulation of tumor angiogenesis and the Treg cell-related tumor microenvironment.^{9,10}

We have summarized the features of patents related to herb-derived agents targeting metastasis in this study. Our data provide essential information for pharmaceutical studies interested in antimetastasis and cancer management in TKM/TCM clinics.

Acknowledgments

We acknowledge that Bo-Keun Lee, a patent attorney in SYP Patent & Law Firm, helped in searching the patent database.

Data availability

Conceptualization: CGS. Methodology: CGS and SKK. Formal Analysis: CGS and SKK. Investigation: CGS and SKK. Resources: CGS. Data Curation: CGS and SKK. Writing - Original Draft: SKK. Writing - Review & Editing: CGS. Visualization: CGS and SKK. Supervision: CGS. Funding Acquisition: CGS.

The authors declare no conflicts of interest.

This study was supported by the National Research Foundation of Korea (NRF), Republic of Korea (No. 2019R1A2C2088201).

This research did not require an ethical approval as it does not involve any human or animal experiment.

The data supporting the findings of this study are available within the article.

Table 1
Summary for Herbs Having Multiple Patents

<i>Panax ginseng</i> C.A. Meyer (6 in 5 countries)	(1) Inhibit metastasis of melanoma B16-F10 cells to lung (2) Inhibit the adhesion of breast cancer MDA-MB-231 cells to gelatin (3) Inhibit metastasis of colon 26-M3.1 cells to lung
<i>Ganoderma atrum</i> (5 in 4 countries)	(1) Inhibit MMP against gelatinase activity in B16 mouse melanoma cell. (2) Inhibit metastasis of B16-F10 melanoma cells to lung
<i>Acanthopanax senticosus</i> (4 in 1 country)	(1) Inhibit metastasis of colon 26-M3.1 cells to lung
<i>Oenanthe javanica</i> (Blume) DC. (4 in 4 country)	(1) Prevent lung cancer and cancer metastasis to lung (2) Suppress the cyclin D1 oncogene
<i>Agaricus blazei</i> Murill (3 in 3 countries)	(1) Prevent lung cancer and cancer metastasis to lung (2) Suppress the cyclin D1 oncogene (3) Suppress the generation of colon cancer and cancer metastasis to colon
<i>Coriolus versicolor</i> (L.) Qué1 (3 in 2 countries)	(1) Reduce MMP-3 expression
<i>Phaleria macrocarpa</i> (4 in 4 countries)	(1) Inhibit metastasis of human breast cancer MDA-MB-231 cells to lung
<i>Viscum album coloratum</i> (3 in 2 countries)	(1) Inhibit metastasis of melanoma B16-BL6 cells to lung
<i>Antrodia cinnamomea</i> (2 in 2 countries)	(1) Suppress movement, migration and invasion of lung cancer A549 cell (2) Resist to human lung cancer A549 cell metastasis (suppress MMP, plasminogen activator, related proteases)
<i>Oryza sativa</i> (2 in 2 countries)	(1) Inhibit metastasis of colon 26-M3.1 cells to lung (2) Inhibit metastasis of colon DLD1 cells to lung
<i>Araeneus ventricosus</i> (2 in 1 country)	(1) Inhibit metastasis of melanoma B16-F10 cells to lung
<i>Prunella vulgaris</i> L. var. <i>lilacina</i> Nakai (2 in 2 countries)	(1) Inhibit metastasis of B16-F10 melanoma cells to lung
<i>Magnolia officinalis</i> Rehd. Et Wils (2 in 2 countries)	(1) Inhibit MMP-2 and MMP-9 against gelatinase activity by gelatin zymography in bladder cancer T24 and 5637 cell. (2) Decrease infiltration of fibrosarcoma HT-1080 cell into cell membrane
<i>Platycodon grandiflorum</i> A. DC (2 in 1 country)	(1) Decrease infiltration of fibrosarcoma HT-1080 cell into cell membrane (2) Suppress tube formation in angiogenesis in HMEC-1 (2) Inhibit metastasis of melanoma B16-F10 cells to lung
<i>Ginkgo biloba</i> (2 in 2 countries)	(1) Suppress tube formation in human umbilical vein endothelial cell (2) Suppress fibroblast growth factor (FGF) (3) Suppress angiogenesis of egg choriollantoic membrane
<i>Glycine max</i> Merrill (2 in 1 country)	(1) Inhibit metastasis of mouse lung cancer 3LL cell


Supplementary material

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.imr.2020.100427](https://doi.org/10.1016/j.imr.2020.100427).

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11 May 2020

13 May 2020