Letter to the Editor

Analysis of patents targeting antimitastatic 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 antimitastatic therapies is to target both cancer cells themselves and host microenvironments.\(^4\)

On the other hand, antimitastatic 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 antimitastatic 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 Astraogalus membranaceus (34 patents), Atractylodes japonica (25 patents), Angelica gigas nakai (24 patents), and Poria cocos (21 patents) (Supplement 2D and Supplement 3). White 81 herbs were shown in 104 patents as a single material, and the Panax ginseng, Acanthopanax senticosus, Ganoderma atrum and Oenanthe javonica 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 antimitastatic 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 antimitastasis and cancer management in TKM/TCM clinics.

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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.

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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

| Herb                                      | Activity                                                                 |
|-------------------------------------------|--------------------------------------------------------------------------|
| Panax ginseng 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  |
| Ganoderma atrum (5 in 4 countries)        | (1) Inhibit metastasis of colon 26-M:1 cells to lung                     |
|                                           | (2) Inhibit metastasis of B16-F10 melanoma cells to lung                |
| Acanthopanax senticosus (4 in 1 country)   | (1) Inhibit metastasis of colon 26-M:3.1 cells to lung                  |
| Onanthe javanica (Blume) DC. (4 in 4 country) | (1) Prevent lung cancer and cancer metastasis to lung                |
| Agaricus blazei Murill (3 in 3 countries)  | (1) Prevent lung cancer and cancer metastasis to lung                    |
|                                           | (2) Suppress the cyclin D1 oncogene                                      |
|                                           | (3) Prevent the generation of colon cancer and cancer metastasis to colon |
| Coriolus versicolor (L.) Quél (3 in 2 countries) | (1) Reduce MMP-3 expression                                            |
| Phaleria macrocarpa (4 in 4 countries)     | (1) Inhibit metastasis of human breast cancer MDA-MB-231 cells to lung |
| Viscum album coloratum (3 in 2 countries)  | (1) Inhibit metastasis of melanoma B16-B16 cells to lung                |
| Androoa cinnamomea (2 in 2 countries)      | (1) Inhibit metastasis of melanoma B16-F10 cells to lung                |
|                                           | (2) Prevent the generation of colon cancer and cancer metastasis to colon |
| Oryza sativa (2 in 2 countries)            | (1) Inhibit metastasis of colon 26-M:3.1 cells to lung                  |
| Araneus ventricosus (2 in 1 country)       | (1) Inhibit metastasis of melanoma B16-F10 cells to lung                |
| Prunella vulgaris L. var. Inodina Nokai (2 in 2 countries) | (1) Inhibit metastasis of colon DLD1 cells to lung                |
| Magnolia officinalis 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. |
| Platycodon grandiflorum A. DC (2 in 1 country) | (2) Decrease infiltration of fibrosarcoma HT-1080 cell into cell membrane |
|                                           | (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                |
| Ginkgo biloba (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 chorionallantoic membrane              |
| Glycine max 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.

References

1. Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science 2011;331:1559–64.
2. Patricia SS. Tumor metastasis: mechanistic insights and clinical challenges. Nature Med 2006;12:895–984.
3. James ET, Isaiah JF. ACR centennial series: the biology of cancer metastasis: historical perspective. Cancer Res 2010;70:5649–69.
4. Lim B, Woodward WA, Wang X, Reuben JM, Ueno NT. Inflammatory breast cancer biology: the tumour microenvironment is key. Nat Rev Cancer 2018;18:485–99.
5. Tan X, Xu M, Liu F, Xu M, Yao Y, Tang D. Antimetastasis effect of Astragalus membranaceus–Curcuma zedoaria via β-catenin mediated CD105 and EMT signaling pathway in HCT116. Evid Based Complement Alternat Med 2019;2019:e9692350.
6. Xu W, Choi HK, Huang L. State of Panax ginseng research: a global analysis. Molecules 2017;22:e1518.
7. Van Zijl F, Krupitza G, Mukulis W. Initial steps of metastasis: cell invasion and endothelial transmigration. Mutat Res 2011;728:23–34.
8. Oudin MJ, Weaver VM. Physical and chemical gradients in the tumor microenvironment regulate tumor cell invasion, migration, and metastasis. Cold Spring Harb Symp Quant Biol 2016;81:189–205.
9. Sato K, Mochizuki M, Saiki I, Yoo YC, Samukawa K, Azuma I. Inhibition of tumor angiogenesis and metastasis by a saponin of Panax ginseng, ginsenoside-Rb2. Biol Pharm Bull 1994;17:635–9.
10. Li Q, Bao JM, Li XL, Zhang T, Shen XH. Inhibiting effect of Astragalus polysaccharides on the functions of CD4+CD25 highTreg cells in the tumor microenvironment of human hepatocellular carcinoma. Chin Med J 2012;125:786–93.

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