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NEW TNF-α RELEASING INHIBITORS AS CANCER PREVENTIVE AGENTS FROM TRADITIONAL HERBAL MEDICINE, AND HNRNP B1, A NEW EFFECTIVE BIOMARKER FOR CHEMOPREVENTION OF HUMAN LUNG CANCER

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Based on the success of green tea as a cancer preventive, herbal medicines are now also attracting attention as potential sources of cancer preventive agents. Using inhibition of TNF-α release assay, we studied *Acer nikoense* (Megusurino-ki in Japanese): Inhibitory potential was found in the leaf extract, and the main active constituents were identified as geraniin and corilagin. The IC_{50} values for TNF-α release inhibition were 43 μM for geraniin and 76 μM for corilagin, whereas that for (-)-epigallocatechin gallate (EGCG) was 26 μM. Furthermore, treatment with geraniin inhibited okadaic acid tumor promotion in a two-stage carcinogenesis experiment on mouse skin. Geraniin and corilagin are present in another well-known Japanese traditional herb, *Geranium thunbergii* (Genno-shoko). This study reevaluates the significance of geraniin as a new cancer preventive agent.

Clinical trials aiming at human lung cancer prevention have so far proved unsuccessful. Based on results with human epidemiology, we present here heterogeneous nuclear ribonucleoprotein (hnRNP B1) as a lung cancer biomarker and green tea extract as a possible lung cancer preventive. hnRNP B1, with a molecular weight of 37 kDa, is overexpressed in the very early stage of human lung cancer: 58.1% of occult cancer patients and 63.6% of dysplasia patients, for example, showed positive staining of the tissues with anti-hnRNP B1 antibody. We speculated that this overexpression of hnRNP B1 protein might be inhibited by cancer preventive agents, which would mean that hnRNP B1 protein is a reliable indicator of developing lung cancer and therefore a significant biomarker for lung cancer prevention. And treatment with EGCG, (-) epicatechin gallate (ECG) or genistein did indeed inhibit

expression of hnRNP B1 gene and elevated levels of hnRNP B1 protein in human lung cancer cell line A549, associated with inhibition of cell growth. Based on the results of a prospective cohort study on drinking green tea conducted by Dr. Nakachi's group, the preventive effects on lung cancer in both sexes (relative risk of 0.33) were greater than the effects on other cancers, such as those of the colorectum, liver, and stomach. Moreover, we previously reported that the intubation of [^{3}H]EGCG into the stomach of mice resulted in 0.16% of total administered radioactivity in the lungs of female mice 24 h after. Thus, we think, green tea extract, using monitoring with the new biomarker hnRNP B1, may be the key to achieving prevention of human lung cancer.