World of Knowledge

Evidence-based Research and Development of Medicinal Plant Resources in Taiwan for Anti-inflammation and Cancer Chemoprevention

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Introduction:

Plants and plant natural products have been used for treatment or prevention of human diseases throughout history. Due to a high mortality rate for most cancers, in recent years, nutrients and non-nutrient phytocompounds are being extensively explored for their potential preventive effects against cancer. Chemoprevention is now recognized as an essential approach to controlling cancer, and is defined as the use of natural products or synthetic agents to prevent, interrupt or reverse the carcinogenic process, or to reduce the chance that cancer could recur. Phytocompounds with antioxidant, anti-inflammatory, cell cycle modulating, or apoptotic effects are considered to have therapeutic potential for cancer chemoprevention. For instance, tea (*Camellia sinensis*), one of the most popular beverages consumed worldwide, has been demonstrated to have significant bioactivities against tumorigenesis and tumor growth *via* the action of antioxidative catechin derivatives in tea extract. It has been reported that chronic inflammation and the action of proinflammatory mediators, such as NF-κB, iNOS, COX-2, and PGE_2, contribute to neoplastic progression of various cancers. Human clinical studies also show an association of increased iNOS or COX-2 expression with poor prognosis in breast cancer patients. Currently, some phytocompounds or derivatives with anti-inflammatory or antiangiogenic activities (e.g., curcumin, a yellow coloring pigment of *Curcuma longa* L., Zingiberaceae) are being prepared for or are already in clinical trial for the chemoprevention of various cancers. The pressing need for anti-cancer agents has spurred the search for phytocompounds with novel modes of action.

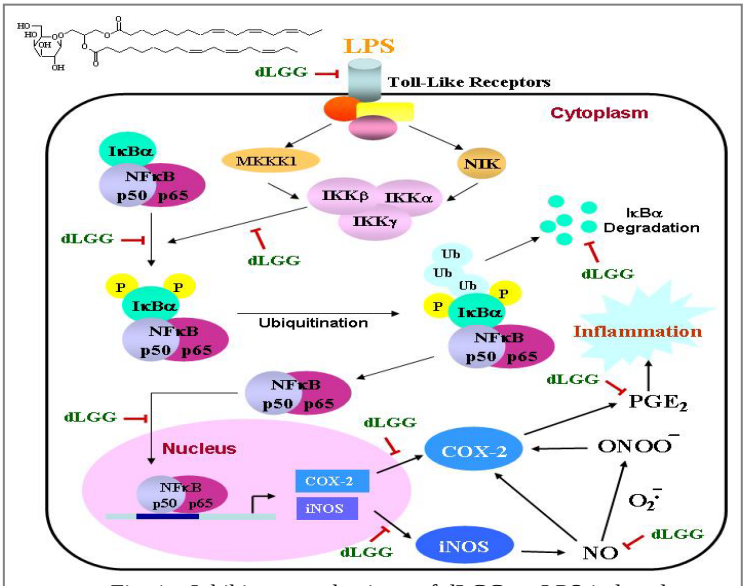

Fig. 1 Inhibitory mechanisms of dLGG on LPS-induced inflammation in macrophages

Discovery of novel phytocompounds from medicinal plants for anti-inflammation and cancer chemoprevention:

We have designed and established various *in vitro* and *in vivo* cell- and gene-based bioassay systems, and mouse inflammatory

and cancer models to investigate and identify novel chemopreventive phytocompounds from indigenous medicinal herbs or woody plants, to assist with the discovery and development of novel natural plant resources in Taiwan for future application as botanical supplements or drugs for cancer prevention. We have screened more than 25 popular medicinal herbal plants and important plantation or indigenous woody plants in Taiwan for their potential antioxidant and anti-inflammatory bioactivities. Some of these plant extracts and phytocompounds have great potential for further development into cancer chemopreventive agents. The study results on three popularly used folk medicines or herbal tea constituents are described as follows.

1. *Crassocephalum rabens* S. MOORE (Asteraceae)

C. rabens (or *C. crepidioides*) is a popular herbal medicine and food supplement in Taiwan for various inflammation-related syndromes. As there was no information regarding the truth of these reputations, we investigated *in vivo* and *in vitro* the anti-inflammatory and cancer chemopreventive properties of extracts and purified phytocompounds from *C. rabens*. We found that a major galactolipid component, 1,2-di-*O*-α-linolenoyl-3-*O*-β-galactopyranosyl-*sn*-glycerol (dLGG), can suppress NF-κB and its downstream inflammatory mediators, NO, iNOS, COX-2 and PGE_2 *in vitro*. We also demonstrated that a dLGG-rich extract from *C. rabens* can significantly suppress B16 melanoma growth in C57BL/6J mice, with activity comparable to the chemotherapeutic drug cisplatin in mice. The results were published in *Cancer Research* 2007, *67*, 6907-6915, and US and ROC patents are pending.

2. *Bidens pilosa* LINN. var. *radiata* (Asteraceae)

B. pilosa has been used as a folk medicine in various medications and as a popular ingredient in herb teas. We were the first group to demonstrate that plant extracts of *B. pilosa* could serve as a good source of caffeoylquinic acid derivatives and flavonoid glycosides which possess potent antioxidant activities (*J. Ethnopharmacology* 2004, *95*, 409-419). A caffeic acid derivative, ethyl caffeate, was further purified and observed to posses anti-inflammatory and therapeutic properties via inhibiting *in vitro* or *in vivo* COX-2 activity at transcriptional, translational, and enzymatic levels. Structure-activity analyses suggested that the catechol moiety and α,β-unsaturated ester group in ethyl caffeate are important and essential structural features for preventing NF-κB DNA complex formation. The detailed mechanisms underlying the anti-inflammatory properties of ethyl caffeate were elucidated (*British J. Pharmacology* 2005, *146*, 352-363).

During the past few years, researchers and clinical scientists have spent considerable efforts in the search for novel agents for use as anti-angiogenic therapeutics against cancer using *in vitro* or *ex vivo* endothelial cell bioassay systems. Through collaborative research efforts, we have identified new and

novel polyacetylene compounds which possess anti-angiogenic activity, as manifested by inhibition of human umbilical vein endothelial cells (HUVECs) proliferation, migration, and the formation of tube-like structures in collagen gel. Polyacetylenes also deregulated the expression of some specific cell-cycle mediators in HUVECs. These are the first reports to demonstrate that polyacetylenes can function as anti-angiogenic agents (*Planta Medica,* 2007, *73*, 655-661 & *Pharmaceutical Research,* 2004, *21*, 2112-2119)

3. *Anoectochilus formosanus* HAYATA (Orchidaceae)

A. formosanus is commonly used in herbal therapies and drink supplements administrated to patients with cancer in Asian countries. However, the pharmacological activities of this empirically used medicinal herb had not been scientifically elucidated. We were the first group to report that plant extracts of *A. formosanus* had strong antioxidant activities, suggesting some potential for its development into a chemopreventive agent (*J. Agri. Food Chem.*, 2002, *50*, 1859-1865). We also observed that an enriched ethyl acetate fraction from the hot water extract of *A. formosanus* had significant anti-proliferative and apoptotic effects on cancer cells, including human MCF-7 breast and B16 melanoma cancer cell lines (*J. Biomedical Science*, 2004, *11*, 928-939 & 2004, *11*, 418-422; US patent issued No. 7033617, 2006; Singapore patent issued No. 120937, 2006; PRC patent pending).

Future prospect:

Due to its unique geography and diverse topography, Taiwan contains a wide range of flora and fauna belonging to three major climatic zones. Taiwan island is famous for the richness and diversity of its plant life, with over 6200 vascular plant species classified to date, which include 4339 indigenous plants with 1067 endemic Taiwanese species (Flora of Taiwan, 2003). The Compositae (Asteraceae) is the third largest family of flowering plants in Taiwan containing 244 species, with approximately of 50% endemic species, and about one third of Compositae species have been anecdotally claimed to have medical potential. Only very few of these medical and pharmacological effects, however, have been scientifically proven. Systematic investigation and identification novel chemopreventive phytocompounds from the rich local plant resources in Taiwan may provide great opportunity in future development into dietary supplement or phytotherapeutics for preventing the life-threatening disease cancer.

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