行政院國家科學委員會補助專題研究計畫成果報告
期末報告

肉桂醛及肉桂樹葉片萃取液對免疫調節及乳癌患者化學抗癌藥物導致的口手足症候群之功效(第 3 年)

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中 華 民 國 103 年 02 月 18 日

中文摘要：桂香是屬於肉桂種的樟屬樹木，也是傳統中藥中，一種著名且常見的處方之一。肉桂醛是桂香樹皮提煉油中主要的成份，並且已被證實具抗發炎的功效。我們認為桂香葉片萃取液亦應具有醫療功效之潛能，但是，其功效至今仍未被確定。本研究目的為探討肉桂醛及桂香葉片萃取液對免疫調節之功效，並提供臨床應用之實證資料，以做為治療乳癌患者因化療藥物所導致之手口足症候群之參考。本研究預定利用三年的時間分別召募一百位接受化療及一百位不接受化療的乳癌患者，以及一百位健康對照組。分別採集這些個案的血液以分析其血液中前發炎細胞素、第一型協助型 T 淋巴球細胞素、第二型協助型 T 淋巴球細胞素，以及各種白血球數目。另一方面，為探討此兩種藥物對免疫調節之功效，本研究預定在第一年的時間，以高壓液相層析儀萃取並分析桂香葉片萃取液之成份，同時，利用動物實驗，給予健康的 BALB/c 小鼠分別餵食不同濃度及不同持續時間的肉桂醛或桂香葉片萃取液，以探討此二種藥物對健康小鼠血液中各種細胞素濃度及各種白血球數目之影響。此外，為瞭解此二藥物對化療藥物所導致之手口足症候群之療效，本研究預定利用第二年的時間，利用動物實驗，隨機分組，以移植腫瘤細胞引導健康的 BALB/cAnN.Cg-Foxn1nu/CrlNarl 裸鼠產生腫瘤，再予注射 doxorubicin（9mg/kg）化療藥物，使裸鼠產生因化療藥物所導致之手口足症候群，分別在不同配對分組的裸鼠中餵食不同濃度及不同持續時間的肉桂醛或桂香葉片萃取液，以探討此二種藥物對化療藥物所導致之手口足症候群之療效及免疫調節之功效。為了進一步探討此二種藥物對各種免疫細胞之增生、附著、及移行功能之影響。本研究預定利用第三年的時間，培養各種不同的免疫細胞株，例如嗜中性白血球、單核球、巨嗜細胞、B 淋巴球、T 淋巴球、以及血管內皮細胞，並予加入不同濃度及不同持續時間的肉桂醛或桂香葉片萃取液後，以實驗方法檢測此二藥物對各種細胞株細胞素之分泌、細胞之增生、附著、及移行功能之影響。我們預期三年內至少可完成以下五大項工作: 1. 瞭解正常人、乳癌患者中有接受化學治療、及無接受化學治療者，血液中前發炎細胞素、第一型協助型 T 淋巴球細胞素、第二型協助型 T 淋巴球細胞素，以及各種白血球數目之差異，藉此瞭解癌細胞及化學治療藥物對人體免疫功能之影響，以作為臨床病徵原因之探討及臨床處置的參考依據。2. 以高壓液相層析儀萃取並分析桂香葉片萃取液之成份，並瞭解其對免疫調節之功效。3. 藉由建立動物實驗模式，瞭解肉桂醛及桂香葉片萃取液對健康的小鼠、長腫瘤之小鼠、患口手足症候群的小鼠、以及長腫瘤並同時患口手足症候群的小鼠，血液

中前發炎細胞素、第一型協助型 T 淋巴球細胞素、第二型協助型 T 淋巴球細胞素、各種白血球數目、白血球細胞膜之血管附著蛋白，例如 Sialy-Lewis X、lymphocyte function-associated antigen-1 (LFA-1)、及 macrophage antigen-1 (Mac-1)，表現量之影響 4. 可瞭解肉桂醛及桂香葉片萃取液對減緩小鼠口手足症候群之療效，以做為日後臨床應用之參考。5. 藉由建立活體外實驗模式，分別培養各種不同的細胞株，例如嗜中性白血球、單核球、巨嗜細胞、B 淋巴球、T 淋巴球、以及血管內皮細胞，以瞭解肉桂醛及桂香葉片萃取液，對各種細胞株細胞素之分泌、細胞之增生、附著、及移行功能之影響。藉此，可更具體且具各別性的瞭解肉桂醛及桂香葉片萃取液對各種細胞所具有的各別性功能。

中文關鍵詞： 肉桂醛、肉桂樹葉片萃取液、免疫調節、口手足症候群、乳癌

英文摘要： Cinnamomum zeylanicum belongs to the cinnamon spice and is one of the most famous traditional Chinese medical prescriptions. Cinnamaldehyde, a major component of cinnamon essential oil extracted from the stem bark of Cinnamomum zeylanicum and Cinnamomum cassia, has been demonstrated having potently anti-inflammatory effect. We suggest that the active components derived from the leaves of Cinnamomum zeylanicum could be also play an inexhaustible potentiality in the application of medicine. In order to clarify the roles of cinnamaldehyde and the extract derived from the cinnamon leaf of Cinnamomum zeylanicum on immunomodulation and their clinical application for chemotherapy-induced hand-foot-mouth disease (HFMD) among patients with breast cancer, we will totally recruit 100 breast cancer patients who will receive chemotherapy and 100 breast cancer patients who will not receive chemotherapy, as well as 100 healthy controls, respectively, to estimate the serum profiles of proinflammatory-, Th1-, and Th2 cytokines, and the cell counts of polymorphonuclear neutrophils (PMNs), monocytes, natural killer (NK) cells, and lymphocytes from blood of patients

acceptance or non acceptance of chemotherapy, and of healthy controls, respectively. On the other hand, to clarify the roles of cinnamaldehyde and the extract derived from the cinnamon leaf of Cinnamomum zeylanicum on immunomodulation, we will obtain aqueous extract derived from cinnamon leaf of Cinnamomum zeylanicum using reversed phase high performance liquid chromatography (HPLC) method and establish an animal study to investigate the effects of these two drugs on the expression and regulation of serum cytokines including proinflammatory-, Th1-, and Th2 cytokines among pathogen-free BALB/c mice acceptance and non acceptance of these two drugs and establish an animal model to induce hand-foot-mouth disease using doxorubicin (9mg/kg) among pathogen-free BALB/cAnN.Cg-Foxn1nu/CrlNarl nude mice acceptance or non acceptance of xenograft of tumor cells to estimate the effects of these two prescriptions on prevention and alleviation of HFMD and regulation of immune response. Moreover, for clarifying the roles of these two drugs on the regulation of proliferation, adhesion, and migration of immune cells.

英文關鍵詞： cinnamaldehyde, the extract of cinnamon leaf from Cinnamomum zeylanicum, immunomodulation, hand-foot-mouth disease, breast cancer

行政院國家科學委員會補助專題研究計畫期末報告

（計畫名稱）

中文：肉桂醛及肉桂樹葉片萃取液對免疫調節及乳癌患者化學抗癌藥物導致的口手足症候群之功效

英文：The immunomodulation by *cinnamaldehyde* and the extract of *cinnamon leaf* from *Cinnamomum zeylanicum* and their therapeutic application for chemotherapy-induced hand-foot-mouth disease among patients with breast cancer

計畫類別：■ 個別型計畫　□ 整合型計畫

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共同主持人：陳達人、楊繼江

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執行單位：中山醫學大學 護理系

中　華　民　國　103 年　01 月　18 日

目　　錄

（一） 計畫中文摘要

桂香是屬於肉桂種的樟屬樹木，也是傳統中藥中，一種著名且常見的處方之一。肉桂醛是桂香樹皮提煉油中主要的成份，並且已被證實具抗發炎的功效。我們認為桂香葉片萃取液亦應具有醫療功效之潛能，但是，其功效至今仍未被確定。本研究目的為探討肉桂醛及桂香葉片萃取液對免疫調節之功效，並提供臨床應用之實證資料，以做為治療乳癌患者因化療藥物所導致之手口足症候群之參考。本研究預定利用三年的時間分別召募一百位接受化療及一百位不接受化療的乳癌患者，以及一百位健康對照組。分別採集這些個案的血液以分析其血液中前發炎細胞素、第一型協助型 T 淋巴球細胞素、第二型協助型 T 淋巴球細胞素，以及各種白血球數目。另一方面，為探討此兩種藥物對免疫調節之功效，本研究預定在第一年的時間，以高壓液相層析儀萃取並分析桂香葉片萃取液之成份，同時，利用動物實驗，給予健康的 BALB/c 小鼠分別餵食不同濃度及不同持續時間的肉桂醛或桂香葉片萃取液，以探討此二種藥物對健康小鼠血液中各種細胞素濃度及各種白血球數目之影響。此外，為瞭解此二藥物對化療藥物所導致之手口足症候群之療效，本研究預定利用第二年的時間，利用動物實驗，隨機分組，以移植腫瘤細胞引導健康的 BALB/cAnN.Cg-Foxn1nu/CrlNarl 裸鼠產生腫瘤，再予注射 doxorubicin (9mg/kg) 化療藥物，使裸鼠產生因化療藥物所導致之手口足症候群，分別在不同配對分組的裸鼠中餵食不同濃度及不同持續時間的肉桂醛或桂香葉片萃取液，以探討此二種藥物對化療藥物所導致之手口足症候群之療效及免疫調節之功效。為了進一步探討此二種藥物對各種免疫細胞之增生、附著、及移行功能之影響。本研究預定利用第三年的時間，培養各種不同的免疫細胞株，例如嗜中性白血球、單核球、巨嗜細胞、B 淋巴球、T 淋巴球、以及血管內皮細胞，並予加入不同濃度及不同持續時間的肉桂醛或桂香葉片萃取液後，以實驗方法檢測此二藥物對各種細胞株細胞素之分泌、細胞之增生、附著、及移行功能之影響。我們預期三年內至少可完成以下五大項工作: **1.** 瞭解正常人、乳癌患者中有接受化學治療、及無接受化學治療者，血液中前發炎細胞素、第一型協助型 T 淋巴球細胞素、第二型協助型 T 淋巴球細胞素，以及各種白血球數目之差異，藉此瞭解癌細胞及化學治療藥物對人體免疫功能之影響，以作為臨床病徵原因之探討及臨床處置的參考依據。**2.** 以高壓液相層析儀萃取並分析桂香葉片萃取液之成份，並瞭解其對免疫調節之功效。**3.** 藉由建立動物實驗模式，瞭解肉桂醛及桂香葉片萃取液對健康的小鼠、長腫瘤之小鼠、患口手足症候群的小鼠、

以及長腫瘤並同時患口手足症候群的小鼠，血液中前發炎細胞素、第一型協助型 T 淋巴球細胞素、第二型協助型 T 淋巴球細胞素、各種白血球數目、白血球細胞膜之血管附著蛋白，例如 Sialy-Lewis X、lymphocyte function-associated antigen-1 (LFA-1)、及 macrophage antigen-1 (Mac-1)，表現量之影響 **4.** 可瞭解肉桂醛及桂香葉片萃取液對減緩小鼠口手足症候群之療效，以做為日後臨床應用之參考。**5.** 藉由建立活體外實驗模式，分別培養各種不同的細胞株，例如嗜中性白血球、單核球、巨嗜細胞、B 淋巴球、T 淋巴球、以及血管內皮細胞，以瞭解肉桂醛及桂香葉片萃取液，對各種細胞株細胞素之分泌、細胞之增生、附著、及移行功能之影響。藉此，可更具體且具各別性的瞭解肉桂醛及桂香葉片萃取液對各種細胞所具有的各別性功能。

關鍵詞: 肉桂醛、肉桂樹葉片萃取液、免疫調節、口手足症候群、乳癌

（二） 計畫英文摘要

Cinnamomum zeylanicum belongs to the *cinnamon spice* and is one of the most famous traditional Chinese medical prescriptions. *Cinnamaldehyde*, a major component of cinnamon essential oil extracted from the stem bark of *Cinnamomum zeylanicum* and *Cinnamomum cassia,* has been demonstrated having potently anti-inflammatory effect. We suggest that the active components derived from the leaves of *Cinnamomum zeylanicum* could be also play an inexhaustible potentiality in the application of medicine. In order to clarify the roles of *cinnamaldehyde* and the extract derived from the *cinnamon* leaf of *Cinnamomum zeylanicum* on immunomodulation and their clinical application for chemotherapy-induced hand-foot-mouth disease (HFMD) among patients with breast cancer, we will totally recruit 100 breast cancer patients who will receive chemotherapy and 100 breast cancer patients who will not receive chemotherapy, as well as 100 healthy controls, respectively, to estimate the serum profiles of proinflammatory-, Th1-, and Th2 cytokines, and the cell counts of polymorphonuclear neutrophils (PMNs), monocytes, natural killer (NK) cells, and lymphocytes from blood of patients acceptance or non acceptance of chemotherapy, and of healthy controls, respectively. On the other hand, to clarify the roles of *cinnamaldehyde* and the extract derived from the *cinnamon* leaf of *Cinnamomum zeylanicum* on immunomodulation, we will obtain aqueous extract derived from *cinnamon* leaf of *Cinnamomum zeylanicum* using reversed phase high performance liquid chromatography (HPLC) method and establish an animal study to investigate the effects of these two drugs on the expression and regulation of serum cytokines including proinflammatory-, Th1-, and Th2 cytokines among pathogen-free BALB/c mice acceptance and non acceptance of these two drugs and establish an animal model to induce hand-foot-mouth disease using doxorubicin (9mg/kg) among pathogen-free BALB/cAnN.Cg-Foxn1nu/CrlNarl nude mice acceptance or non acceptance of xenograft of tumor cells to estimate the effects of these two prescriptions on prevention and alleviation of HFMD and regulation of immune response. Moreover, for clarifying the roles of these two drugs on the regulation of proliferation, adhesion, and migration of immune cells.

Key words: *cinnamaldehyde,* the extract of *cinnamon leaf* from *Cinnamomum zeylanicum,* immunomodulation, hand-foot-mouth disease, breast cancer

研究背景及目的

Background

(A) *Cinnamaldehyde* and the extract of *cinnamon leaf* from *Cinnamomum zeylanicum*

Cinnamomum zeylanicum, a beautiful ornamental tree with golden red bark, is the *cinnamon spice* and is an important food additive as well as one of the most famous traditional Chinese medical prescriptions (1). *Cinnamaldehyde*, a major component of cinnamon essential oil extracted from the stem bark of *Cinnamomum zeylanicum* and *Cinnamomum cassia,*has been demonstrated having potently antimicrobial (2), anti-inflammatory (3), anti-pyretic (4), and anti-tumor cell growth effects (5, 6), and is widely applied to treat influenza, common cold and other inflammatory conditions (3). We suggest that the active components derived from the leaves of *Cinnamomum zeylanicum* could be also play an inexhaustible potentiality in the application of medicine, but its role has not been adequately elucidated.

(B) The roles of proinflammatory-, Th1-, and Th2-cytokines on the regulation of immunomodulation.

Human immune system plays a vital role to protect individual from microbial (7-10) or carcinogenesis (10, 11). Cytokines modulate immunological control through mediating a wide variety of immune response to infectious or inflammatory agents, which may be of importance in the incidence of disease (7-11). Proinflammatory cytokines are responsible to modulate the physiological functions of neutrophils (12-17), and work as part of a cascade that recruit and activate inflammatory cells and induce effectors (18). Some of the proinflammatory cytokines, such as interleukin 1 alpha (IL-α), IL-1 β, IL-6, IL-8, tumor necrosis factor α (TNF-α), and macrophage inflammatory protein-2 (MIP-2) were demonstrated to be associated with the involvement of inflammatory diseases such as mastitis, atherosclerotic plaques, arthrosis, pulmonary inflammation and pelvic inflammatory disease (8, 19-29). IL-1 α and β are produced by cells of the innate immune system and are important mediators for defense against infection (30). IL-1β was also reported to increase the autocrine action of IL-6 through an increase in IL-6 receptor expression in chondrocytes (24) as well as to enhance the production of IL-8 (31, 32). IL-6 plays a vital role on the control of some viral, bacterial, and fungal infection (33) and is a major effector of the acute phase reaction (34). In IL-6-deficient mice, the neutrophils and macrophages were failure to response infection (33). IL-8 was demonstrated to stimulate bovine neutrophil migration in a dose-dependent fashion (32), and the gene expression level

of IL-8 was considered as a predictor for the responsiveness of inflammatory stimulation (35). Moreover, TNF-α was recognized to induce the expression of cellular adhesion molecules, which mediate adhesion of leucocytes to the vascular endothelium (26, 27). In addition, MIP-2, a chemokine induced by TNF-α (36), was reported to recruit neutrophils and T cells from the spleen or bone marrow and enhance the T cell priming in vivo for modulating tissue inflammation (37).

Except for proinflammatory cytokines, type 1 T helper cell (Th1) cytokines including interferon gamma (IFN-r) and interleukin-2 (IL-2) are responsible for cell-mediated immunity and enhance the differentiation of fully cytotoxic T_C cells from their precursors (38-40). Type 2 T helper cell (Th2) cytokines such as IL-4, IL-5, IL-13, and IL-10 stimulate the activation and differentiation of B cells to increase the production of neutralizing antibodies including IgG and IgA and IgE (39, 40). The cross-regulation and ratio balance between Th1 and Th2 cytokines were demonstrated to be associated with the development of inflammatory disease (7, 41-46). These two types of cytokines, promote the growth of the subset that produces them firstly; then, inhibit the development and activity of the opposite subset. For example, IFN-r enhances the expression of an important regulatory molecule that favors the differentiation and activity of Th1 cells and inhibits proliferation and differentiation of the Th2 cells. In contrast with Th1 cytokine IFN-r, Th2 cytokine IL-4 enhances Th2 cell development through decreasing the susceptibility of T helper cells to the cytokine signals that cause the leading of Th1 development, thus, resulting in the promotion of Th2 cells differentiation but inhibiting the differentiation of Th1-cells (47, 48). Recently, our published (7-9, 49), and ongoing studies have been demonstrated that the profiles and ratios of serum proinflammatory-, Th1-, and Th2-cytokines represent a significant information to predict the development of immune responses. We hypothesize that individuals who lack of proper control or homeostasis of immune regulation could be susceptibility to induce inappropriate immune responses, and the prescription which is responsible for the regulation of immunomodulation could be the candidate for the control of inflammatory stimulation and immune responses.

(C) The association between immunomodulation and chemotherapy-induced hand-foot-mouth disease among patients with breast cancer

Breast cancer, an epithelial tumor with highly invasive and metastatic potential, is one of the most frequently occurring malignant neoplasms worldwide (50, 51), and is the fourth leading cause of cancer death among Taiwanese in Taiwan (52). Chemotherapy is an important therapeutic strategic for controlling breast cancer (53, 54). Unfortunately, chemotherapy-induced hand-foot-mouth disease (Figure 1) was

found for a recent period in patients with breast cancer after they received chemotherapy, including liposomal doxorubicin, capecitabine, docetaxel, paclitaxel, vinorelbine, 5-fluorouracil (5-FU), and cisplatin in Taiwan (42, 55-60). However, the mechanism of hand-foot-mouth disease among breast cancer patients who accept chemotherapy is not fully clarified.

Hand-foot-mouth disease (HFMD) is characterized by vesicular eruption, alopecic lesion, erythemic lesion, exudative lesion, eschar lesion, and ulcerative lesion on the palms, soles, and combined with a maculopapular rash and erosive stomatitis (61-67). This syndrome has been reported to be involved in the invasion of a variety strains of the Coxsackie virus (61-63, 66) particular to A16, and the infection of enterovirus 71 (EV71) (64-67). Surprisingly, chemotherapy-induced HFMD seems to be unrelated to the infection of coxsackie viruses or enterovirus 71 (68).

The association between HFMD and immunomodulation is still unclear, however, the productions of Th1 and Th2 cytokines were suppressed in Coxsackie virus B3 infected mice (69). The cytokine secretions of IL-6, IL-12, and TNF-α as well as the stimulation of T cell proliferation were significantly increased by dendritic cells in EV71 infected mice (70), moreover, significantly increased serum IFN-alpha was found when EV71 infected mice treatment with type I interferons (71), and these responses were suggested to reduce the mortality of EV71 infection (67, 70, 71). On the other hand, the applications of chemotherapeutic agents for cancer therapy are limited by their side effect of immunosupression because of its myelosuppressive effect and the toxicity to the dividing immune cells in the bone marrow and peripheral lymphoid tissues (56, 58, 72). Chemotherapy-induced myelosuppression may induce the production of cytokines intend to ablate immunosuppression (72). Moreover, an increased cell count of monocytes but decreased polymorphonuclear cells (PMNs) were found in patients acceptance of chemotherapy. Also, the percentages of cytotoxic T cells and nature killer (NK) cells were increased, however the percentage of B-lymphocytes was dramatically decreased, as well, the ability of phagocytic and intracellular killing effects of PMNs were suppressed during chemotherapy (73). In addition, the decreased cell counts and decreased proliferating ability of leukocytes as well as dysregulation of cytokine secretion were found in cancer patients compared to healthy controls (74, 75). We hypothesize that the incidence of HFMD among breast cancer patients acceptance of chemotherapy may be associated with the dysfunctions of immune system which are resulted from altered or deficient immunomodulation induced by tumor cells or chemotherapy. In order to provide some evidences for clinical application, in this three-year research project, we will totally recruit 100 breast cancer patients who will receive chemotherapy as well as 100 breast cancer patients who will not receive chemotherapy to estimate the serum profiles of

proinflammatory cytokines, including interleukin 1 alpha (IL-α), IL-1 β, IL-6, IL-8, tumor necrosis factor α (TNF-α), and macrophage inflammatory protein-2 (MIP-2), Th1 cytokines such as interferon gamma (IFN-r), interleukin-2 (IL-2), and Th2 cytokines such as IL-4, IL-5, IL-13, and IL-10, as well as the cell counts of PMNs, monocytes, NK cells, and lymphocytes from blood of patients non acceptance and acceptance of chemotherapy every three-week, respectively, as well as to follow up the incidence and record the severity of chemotherapy-induced hand-foot-mouth disease every week during chemotherapy course. Meanwhile, we will recruit 100 healthy controls for detection of serum profiles of cytokines and cell counts from blood for once. The drugs of chemotherapy, data of infections of Coxsackie virus A16 and enterovirus 71, demographic characteristics, and clinical statuses also obtain for controlling other covariates.

(D) The association between immunomodulation and *cinnamaldehyde* and the extract of *cinnamon leaf* from *Cinnamomum zeylanicum*, as well as the application of theses two prescriptions in chemotherapy-induced hand-foot-mouth disease

Cinnamaldehyde was demonstrated to reduce cyclooxygenase (COX)-2 activity and prostaglandin E_2 (PGE_2) production, the lipid inflammatory mediators, in a dose-dependent manner (4) and to decrease IL1-β induced PGE_2 production in mouse cerebral microvascular endothelial cells (76), as well as to inhibit NF-kappa B activation and suppress NF-kappa B-induced inflammatory signaling in human macrophages (77) and endothelial cells (52), respectively. Moreover, it was demonstrated that treatment of *cinnamaldehyde* derivatives, 2'-hydroxycinnamaldehyde (HCA) and 2'-benzoxycinnamaldehyde (BCA), to thymocytes accelerated T-cell differentiation through the blockade of growth signal transduction (78). T-cell effectors have been suggested as a direct target for PGE_2 to modulate Th1 and Th2 cytokine expressions as well as to exert their anti-inflammatory effects (79, 80). IL-2 cytokine was a growth signal for lymphocytes DNA replication (78) and played an important role to protect host from infection through mediating macrophage activation and enhancing the development of Th1 cells (38, 81, 82), and IFN-r was induced by IL-2 in the mitogen-activated T cells (83, 84). As well, IL-2 and IL-10 were demonstrated to protect T cells from apoptosis and improve it viability in infectious mononucleosis (85). When added together with IL-2, IL-4, and B cell-derived T cell growth factor can stimulate mature and immature T cell growth (39). Recently, it was demonstrated that NF-kappa B activation was positively correlated to the polarizing Th2 cytokines profile (86) and the increased CD4+ cells survival (87), also, up-regulation of Th1 cytokine IFN-gamma was based

on the requirement of NF-kappa B (88). We hypothesize that *cinnamaldehyde* and the extract derived from the *cinnamon* leaf of *Cinnamomum zeylanicum* could play an immunomodulator acting as either immunosuppressant or immunostimulator through the control of proinflammatory-, Th1-, and Th2 cytokine expressions, particularly to the regulation of the ratio of Th1 to Th2 cytokines, in cyclooxygenase- and/or NF-kappa B-dependant pathways (4, 52, 76, 77). However, their immunomodulatory effects on proinflammatory-, Th1-, and Th2 cytokines remain unclear. Therefore, in the first year, we also establish an animal study to investigate the effects of *cinnamaldehyde* and the extract derived from the *cinnamon* leaf of *Cinnamomum zeylanicum* on the expression and regulation of serum cytokines including proinflammatory cytokines, such as interleukin 1 alpha (IL-α), IL-1 β, IL-6, IL-8, tumor necrosis factor α (TNF-α), and macrophage inflammatory protein-2 (MIP-2), Th1 cytokines such as interferon gamma (IFN-r) and interleukin-2 (IL-2), as well as Th2 cytokines such as IL-4, IL-5, IL-13, and IL-10 to provide some pharmacological evidences for clinical application. In addition, we suggest that chemotherapy-induced immunosupression can be prevented and alleviated by these two drugs through elicitation and regulation of specific immune response. To clarify the roles of their clinical application, in the second year, we will establish an animal model to induce hand-foot-mouth disease using doxorubicin (9mg/kg) among pathogen-free BALB/cAnN.Cg-Foxn1nu/CrlNarl nude mice acceptance or non acceptance of xenograft of tumor cells to estimate the effects of these two prescriptions on prevention and alleviation of HFMD and regulation of immune response.

(E) The association between the effects of proliferation, adhesion, and migration of immune cells and *cinnamaldehyde* and the extract of *cinnamon leaf* from *Cinnamomum zeylanicum*.

During early innate immune response to exogenous antigens, phagocytes, including neutrophils, macrophages, and dendritic cells, migrate to invaded site and ingest exogenous antigens and secrete cytokines for stimulating inflammation and initiating the response of antigen-specific T and B lymphocytes (9, 89). When naïve T lymphocytes are activated, they proliferate and differentiate into effector cells, such as helper T cells and cytotoxic T cells. These effector cells then migrate to any site where the antigen is present for executing and expanding their specific functions (9, 89). Subsequently, type 1 T helper cells enhance the differentiation of fully cytotoxic T_C cells for inducing cell-mediated immunity through secreting Th1 cytokines (38-40) and Type 2 T helper cells contribute to activate B cells differentiate into plasma cells for production of humoral immunity (39, 40). Therefore, the ability of adhesion, migration, proliferation, and/or differentiation of immune cells, including neutrophils,

monocytes/macrophages, B lymphocytes, and T lymphocytes, play a crucial role in inflammatory response (90-92).

The leukocytes, initially predominantly neutrophils, adhere to vascular endothelium by adhesion molecules, then leave the vessel and migrate to injured site under the attraction of chemotactic agents (90-92). Sialy-Lewis X, the oligosaccharide on leukocytes that binds to selectins, P-selectin and E-selectin, on activated endothelium, as well as, the synthesis of CD18 β subunit of leukocyte integrins, lymphocyte function-associated antigen-1 (LFA-1) and macrophage antigen-1 (Mac-1), conjugate to intercellular adhesion molecule 1 (ICAM-1) distributed on activated endothelium, contribute to the rolling, adhesion, and migration of leukocytes through endothelium to infected tissues, and induce phagocytosis (93-99). Moreover, LFA-1 plays a curial role in the cognate interaction between helper T lymphocytes and B lymphocytes (96) as well as in the promotion of proliferation and cytotoxicity of T lymphocytes (93). On the other hand, leukotriene B4 (LTB4), derive from 5-lipoxygenase pathway, one of two major AA metabolism pathways during AA metabolism proceeding, is produced by neutrophils and some macrophage and is a potent chemotactic agent for neutrophils (100-102). In contrast, lipoxins work as inhibitor of inflammation, once leukocytes migrate to tissue, they gradually change their major lipoxygenase-derived AA products to lipoxins, which inhibit neutrophil chemotaxis and adhesion to vascular endothelium (100, 103, 104). We hypothesize that the balance between up- and down-regulation of the capability of proliferation, adhesion, and migration of immune cells dominate the homeostasis of immunomodulation. Therefore, in the third year, we will establish an in vitro study to investigate the roles of theses two drugs on the effects of proliferation, adhesion, and migration of immune cells, including neutrophils, monocytes, macrophages, B lymphocytes, and T lymphocytes.

Up to now, we have successfully identified and determined an aqueous extract of *cinnamon leaf* from *Cinnamomum zeylanicum* using a reversed phase HPLC method (Figure 2) (105). As shown in Fig. 2, one major peak with retention time at 14.73 min was *cinnamaldehyde* at 285 nm. The results revealed that the quantitative analysis of *cinnamaldehyde* from an aqueous extract of *cinnamon leaf* from *Cinnamomum zeylanicum* was 1.7 mg/ml. Meanwhile, our preliminary data shown that a significantly increased serum concentration of IFN-r was found when pathogen-free BALB/c mice treated with 1mg/mL/kg/day of *cinnamaldehyde* for one week (Fig 3A). Also, significantly increased serum concentrations of IL-2 were found when pathogen-free BALB/c mice treated with 1, 2, and 4mg/mL/kg/day of *cinnamaldehyde* for one, two, and three weeks, although non-significance was found at the second week when treated with 1mg/mL/kg/day of *cinnamaldehyde* (Fig 3B).

According to our preliminary data, we have confidence in our hypothesis that *cinnamaldehyde* may play an important role on the regulation of cytokine expression. On the other hand, our laboratory has successfully established an animal study for inducing chemotherapy-induced hand-foot-mouth disease in Wistar female rat and the xenograft of tumor cells in pathogen-free BALB/cAnN.Cg-Foxn1nu/CrlNarl nude mice (Figure 4) in our other ongoing study. In this study, we will modify these animal models and apply to this proposed project.

研究方法、進行步驟及執行進度

Chemicals and reagents

Trans-cinnamaldehyde with purity ≥99% is purchased from Sigma-Aldrich Co. Ltd. and all other reagents are of HPLC grade commercially available.

Quantitative analysis of Cinnamaldehyde from An Aqueous Extract derived from cinnamon leaf of Cinnamomum zeylanicum (89)

An aqueous extract derived from cinnamon leaf of *Cinnamomum zeylanicum* is dissolved in methanol and further analyzed and injected 20 μl into a reverse phase C18 analytical column (250× 46 mm i.d., 5 μm, Inertsil ODS-2, GL Sciences Inc., Japan) equipped with a guard column. The mobile phase is acetonitrile-0.1% phosphoric acid solution (48:52) at a flow rate of 0.8 ml/min. Detection wavelength is set at 285 nm and column temperature is 35℃. Retention time is collected at 14.76 min. The HPLC system consist of a Shimadzu LC-10AT HPLC pump, a SIL-10AD auto-injector, a SPD-M10A diode array detector and a CTO-10A column oven. Data handling is performed by a Sigma-Plot software program.

Subjects and specimen collection

About one hundred breast cancer patients who will receive chemotherapy and 100 breast cancer patients who will not receive chemotherapy, derived from patients with breast infiltrating ductal carcinoma diagnosed by pathology, according to a system based on a modification of the WHO classification and the TNM system, at Chung Shan University Hospital, Taichung, or Changhua Christian Hospital, Changhua, Taiwan, and 100 healthy controls selected from those who visit the Department of Family Medicine, at either of theses two hospitals, for health examination, based on not having a risk related to breast cancer and match on age, demographic data of race, ethnic group, gender, and residential area, will be recruited for our study, between August 2010 and July 2013. The whole blood specimens will

be obtained from patients with breast cancer before and after they receive chemotherapy every three-week during the course of chemotherapy and from healthy controls for once, respectively. These blood specimens are placed in tubes containing EDTA and immediately centrifuged and stored at $-80^{O}C$. The incidence and the severity of hand-foot-mouth disease will be record, as well as, the association between the severity of hand-foot-mouth disease and the levels of serum cytokines, the number of cell counts, and the dose of chemotherapy among recruited breast cancer patients will be estimate every week during the course of chemotherapy. Associated clinicopathological characteristics, such as clinical stage of breast cancer, breast cancer cell differentiation status, lymph node metastasis, and distant metastasis, as well as the drugs of chemotherapy, data of cell counts are verified by chart review. The study is performed with the approval of the Chung Shan University Hospital Institutional Review Board (IRB) and informed written consent will obtain from each individual.

Detection of Coxsackie virus A 16 and enterovirus 71 infection (66, 106)

Coxsackie virus A 16 and EV71 infections are detected by an immunodot blotting (IDB). Briefly, 50ul of plasma is siphoned through the well of a Bio-Dot apparatus (Bio-Rad, Hercules, CA) that has been layered with a nitrocellulose membrane (MSI, Westboro, MA). The membrane is incubated with antibodies specific to Coxsackie virus A 16 or EV71 (Chemicon, Temecula, CA), respectively, and then with biotinylated rabbit anti-mouse anti-bodies, together with alkaline phosphatase-conjugated streptavidin (Dako, Kyoto, Japan). A positive reaction is identified by development in chromogen-containing NBT/BCIP (nitro blue tetrazolium/5-bromo-4-chloro-3-indolyl phosphate) (Boehringer Mannheim, Germany). Each individual plasma sample is performed in duplicate. 50ul of distill water is used as negative control, and serial dilutions of Coxsackie virus A 16 or EV71 strain (stock at 10^6 $TCID_{50}$/uL) are used as positive controls.

Animal study (107)

All experiments are carried out in accordance with Animals associated guidelines. Pathogen-free BALB/c mice, female, 6-7 weeks of age, and 20-22g of weight, are purchased from the Experimental Animal Research Unit in Taipei, Taiwan. On arrival for one week, the mice are randomly assigned to control and experimental groups, and every matched group with five mice. The experimental groups are treated with varied doses of *cinnamaldehyde*, including 0.25, 0.5, 1, 2, 4 mg/mL/Kg/day, and of the extract derived from *cinnamon* leaf of *Cinnamomum zeylanicum* including 0.106, 0.212, 0.425, 0.85, 1.7mg/mL/Kg/day, for one, two, three, and four weeks. The

control groups are only treated with equal amount of water. All mice are given access to food and water. A total of 240 animals are used in this present study. The animal model in this study has been reviewed and approved by the Institutional Animal Care and Use Committee (IACUC), Chung Shan University, Taiwan.

Measurements of cytokines by enzyme-linked immunosorbent assay (ELISA) (7, 8)

Cytokine concentrations of proinflammatory cytokines, including interleukin 1 alpha (IL-α), IL-1 β, IL-6, IL-8, tumor necrosis factor α (TNF-α), and macrophage inflammatory protein-2 (MIP-2), Th1 cytokines such as interferon gamma (IFN-r), interleukin-2 (IL-2), and Th2 cytokines such as IL-4, IL-5, IL-13, and IL-10, are measured in the plasma using the human or mouse cytokine BD OptEIA ™ ELISA Sets (BD Bioscience, San Diego, U.S.A), for detection of the expression of cytokines derive from human blood and mouse blood, respectively. In brief, the assay is based on conventional sandwich assay technology. The antibody specific to each cytokine is covalently coupled to Luminex microspheres, with each antibody coupled to a different microsphere uniquely labeled with a fluorescent dye. The microspheres are incubated with standards, controls, and samples (100 ul) in a 96-well microtiter filter plate for 2 h at room temperature. After washing with an assay wash buffer (200 ul/well), 100 ul of Working Detector (Detection antibody + SAv-HRP reagent) is added to each well for 1 h at room temperature. After washing, 100 ul of Substrate Solution is added to each well and incubated for 30 minutes at room temperature in the dark. Finally, 50 ul of Stop Solution is added to each well and the plate is analyzed using the read absorbance at 450 nm within 30 minutes of stopping reaction to determine the concentration of the cytokines.

Statistical analysis

Experimental results are presented as the mean±SE. A Mann-Whitney U test is used between two groups for continuous variables. The one-way ANOVA test is used to detect the difference of serum cytokine among three or over three groups, and Scheffe correction is performed to check statistically significant difference between groups. The multiple linear regression is performed to determine the effect of the potential explanatory continuous variables. The distributions of demographic characteristics and clinicopathological features between each compared group is analyzed by Fisher's exact test, and adjusted odds ratios (AORs) with their 95% confidence intervals (CIs) for estimating the associations are estimated by multiple logistic regression models, after controlling for other covariates. *P* value of less than 0.05 is considered significant. The data are analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) statistical software and SAS version 9.0 (SAS Institute, Cary, NC,

USA).

結果： Serum concentrations of IL-2 and IL-4 cytokines were significantly elevated by *cinnamaldehyde*, although IFN-r showed only a slight increase. However, the extract of *Cinnamomum zeylanicum* leaf significantly decreased the serum levels of IFN-r, IL-2, IL-4, and IL-10 cytokine, when compared to untreated groups. However, the Th1 dominant profile of Th1 to Th2 ratio was induced by both drugs.

結論: *Cinnamaldehyde* and the extract of *Cinnamomum zeylanicum* leaf revealed different effects on the expressions of Th1 and Th2 cytokines, but a consistent profile of the Th1/Th2 balance toward the Th1-dominated immune responses in vivo. *Cinnamaldehyde* contributed to the regulation of Th1, Th2 cytokines might be partly dominate to its anti-inflammatory effect. The extract of *Cinnamomum zeylanicum* leaf could be a novel approach for clinical application.

Table 1. Serum concentrations of cytokines response to treatment with different doses of *cinnamaldehyde* for different weeks.

Dose/day	**One week** (mean±SE)	**Two weeks** (mean±SE)	**Three weeks** (mean±SE)	**Four weeks** (mean±SE)
	IFN-r (pg/mL)			
0mg/mL/Kg	26.88±0.80	29.77±2.54	19.84±0.77	27.90±0.89
1mg/mL/Kg	38.57±2.38	37.60±9.20	33.53±3.95	34.35±5.41
2mg/mL/Kg	35.21±1.79	41.98±3.06	33.08±2.61	33.08±3.0
4mg/mL/Kg	33.74±2.69	38.72±3.09	32.01±1.90	35.62±3.55
	IL-2 (pg/mL)			
0mg/mL/Kg	17.48±0.32	21.73±2.44	17.57±0.45	18.02±0.73
1mg/mL/Kg	46.19±1.35	36.90±1.74	32.93±1.68	46.46±9.22

2mg/mL/Kg	54.82±3.46	59.29±5.64	31.68±1.22	41.95±7.94
4mg/mL/Kg	52.92±1.88	56.24±6.0	37.77±3.91	39.12±3.37
	IL-4 (pg/mL)			
0mg/mL/Kg	139.71±8.82	160.11±16.49	143.62±6.14	164.54±12.97
1mg/mL/Kg	192.34±9.94	179.14±2.78	174.04±6.98	169.14±15.36
2mg/mL/Kg	187.87±9.42	231.27±10.54	166.59±5.62	148.51±7.66
4mg/mL/Kg	179.57±9.45	217.66±11.78	173.61±8.74	158.51±11.39
	IL-10 (pg/mL)			
0mg/mL/Kg	1200.0±122.85	1314.77±110.63	1208.33±72.8	1536.11±302.81
1mg/mL/Kg	1256.66±39.73	1221.66±50.93	1361.66±166.05	1530.0±153.62
2mg/mL/Kg	1512.5±136.95	1720.0±210.38	1471.66±156.2	1333.33±108.01
4mg/mL/Kg	1315.0±93.7	1603.33±238.28	1436.67±154.39	1500.0±146.62

Table 2. Serum concentrations of cytokines response to treatment with different doses of the aqueous extract of *Cinnamomum zeylanicum* for different weeks.

Dose/day	**One week** (mean±SE)	**Two weeks** (mean±SE)	**Three weeks** (mean±SE)	**Four weeks** (mean±SE)
	IFN-r (pg/mL)			
0mg/mL/Kg	26.88±0.80	29.77±2.54	19.84±0.77	27.90±0.89
0.425mg/mL/Kg	19.72±2.54	49.24±26.76	15.10±1.29	15.10±1.03
0.85mg/mL/Kg	21.56±2.64	29.15±3.77	14.80±0.81	20.84±1.80
1.7mg/mL/Kg	43.32±10.22	22.73±3.80	16.31±1.32	15.10±1.90
	IL-2 (pg/mL)			
0mg/mL/Kg	17.48±0.32	21.73±2.44	17.57±0.45	18.02±0.73
0.425mg/mL/Kg	10.59±1.05	10.69±0.60	9.73±0.24	10.56±0.72
0.85mg/mL/Kg	13.65±2.21	11.96±2.24	9.40±0.08	12.02±1.51
1.7mg/mL/Kg	14.61±2.64	14.55±1.12	10.16±0.40	10.63±0.81
	IL-4 (pg/mL)			
0mg/mL/Kg	139.71±8.82	160.11±16.49	143.62±6.14	164.54±12.97
0.425mg/mL/Kg	96.88±14.03	96.45±7.53	86.88±3.26	87.99±2.14

0.85mg/mL/Kg	129.16±13.80	102.66±14.20	95.11±8.45	112.45±20.7
1.7mg/mL/Kg	124.45±17.10	119.33±6.69	97.11±2.49	88.0±11.39
	IL-10 (pg/mL)			
0mg/mL/Kg	1200.0±122.85	1314.77±110.63	1208.33±72.8	1536.11±302.81
0.425mg/mL/Kg	475.55±47.90	470.0±6.23	427.77±19.32	577.77±24.02
0.85mg/mL/Kg	519.45±75.64	544.45±129.39	463.33±65.74	510.0±54.05
1.7mg/mL/Kg	546.66±103.72	544.45±50.82	455.55±28.81	441.11±37.25

(1). Chemotherapy-induced hand-foot-mouth disease among patients with breast cancer

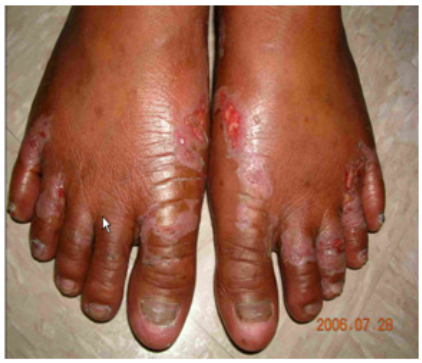


Figure 1A: Painful erythema, moist desquamation and ulceration over feet, especially on 4th, 5th toes

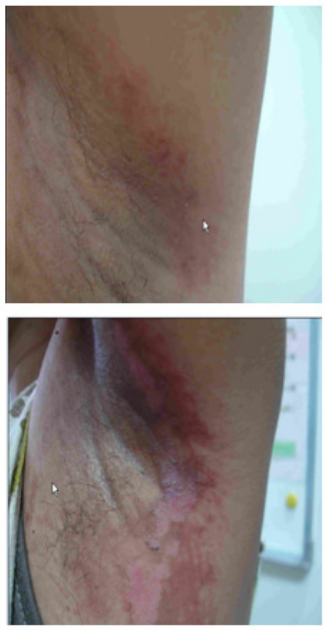


Figure 1B. Painful erythema and ulceration in left axilla

(2). HPLC

Chromatography

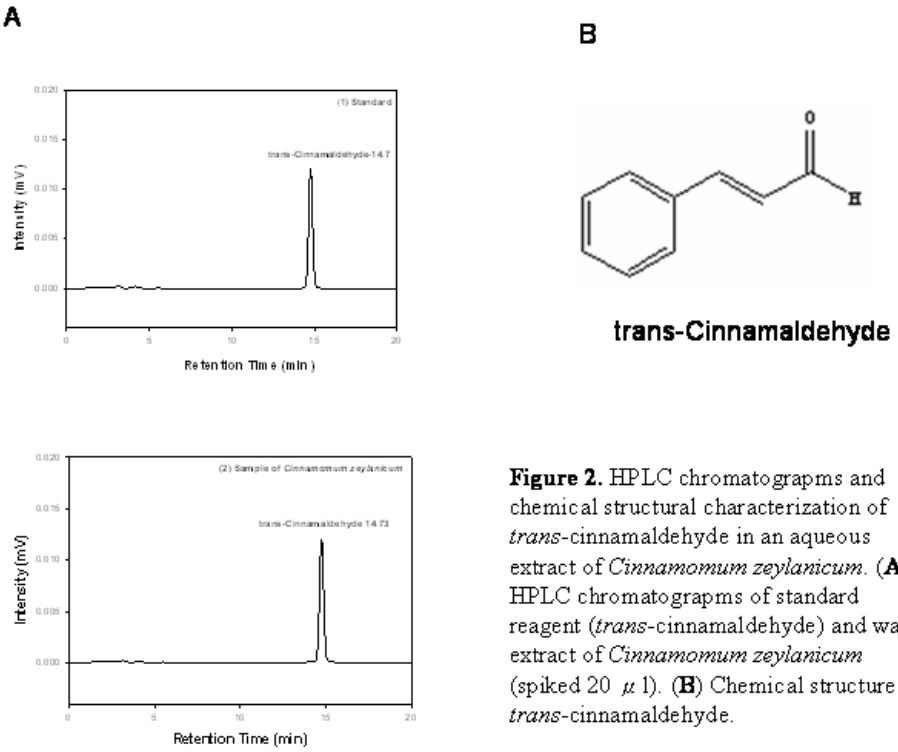


Figure 2. HPLC chromatograpms and chemical structural characterization of *trans*-cinnamaldehyde in an aqueous extract of *Cinnamomum zeylanicum*. (**A**) HPLC chromatograpms of standard reagent (*trans*-cinnamaldehyde) and water extract of *Cinnamomum zeylanicum* (spiked 20 μ l). (**B**) Chemical structure of *trans*-cinnamaldehyde.

(3). Serum concentrations of IFN-r and IL-2 cytokines response to cinnamaldehyde

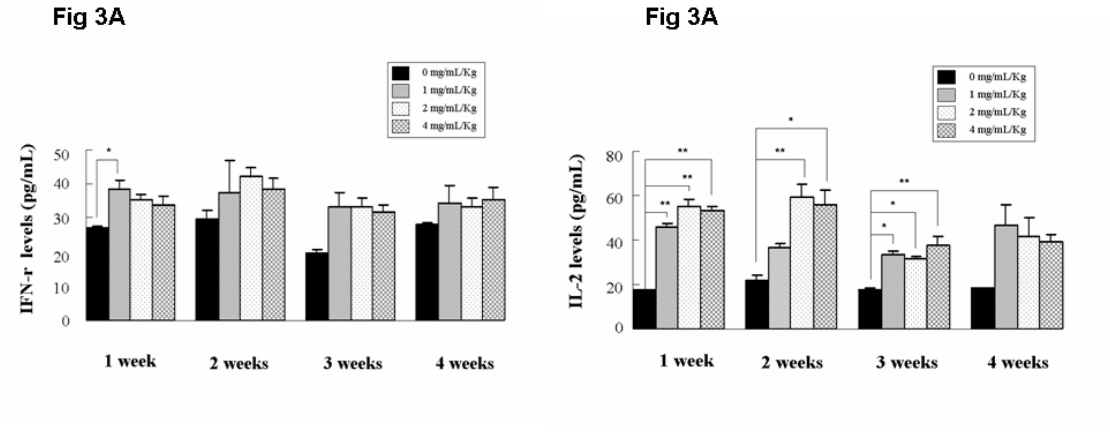


Figure 3. The levels serum cytokines response to different doses of *cinnamaldehyde*. **(A)** A significantly increased serum concentration of IFN-r when treated with 1mg/mL/kg/day of *cinnamaldehyde* for one week **(B)** Significantly increased serum concentrations of IL-2 when treated with 1, 2, and 4mg/mL/kg/day of *cinnamaldehyde* for one, two, and three weeks, but non-significance was found at the second week when treated with 1mg/mL/kg/day of *cinnamaldehyde*. (*: p value <0.05; **: p value <0.001).

(4). Chemotherapy-induced hand-foot-mouth disease in Wistar female rat

Figure 4

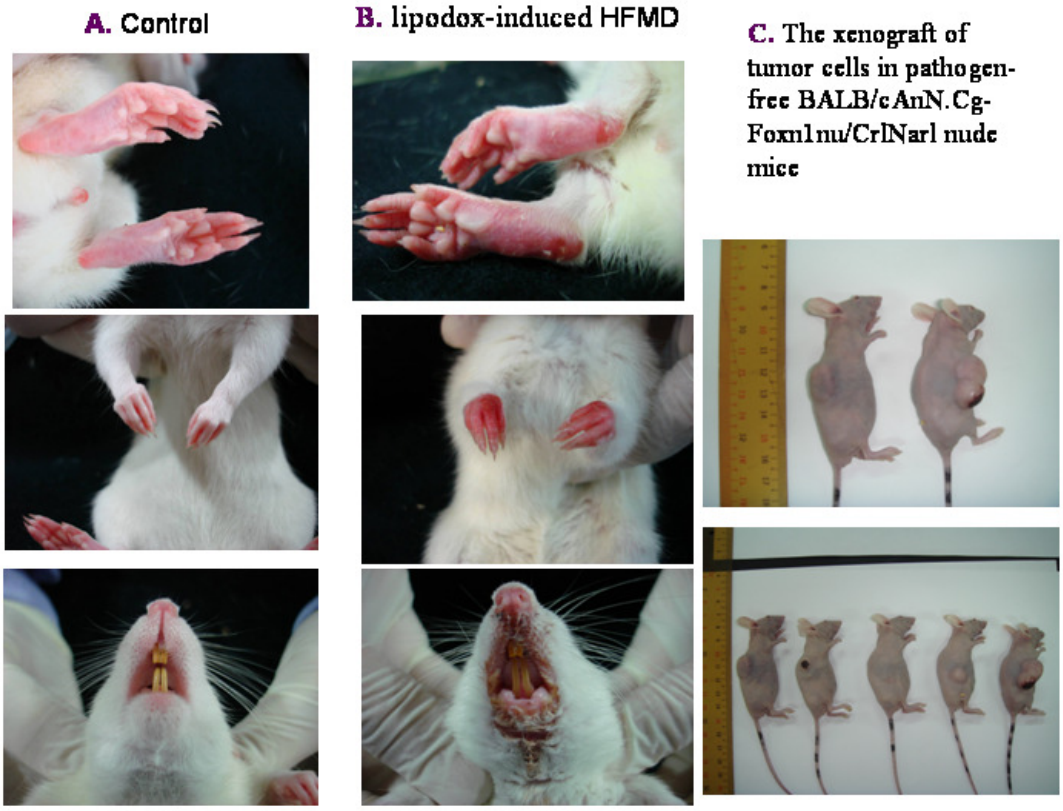
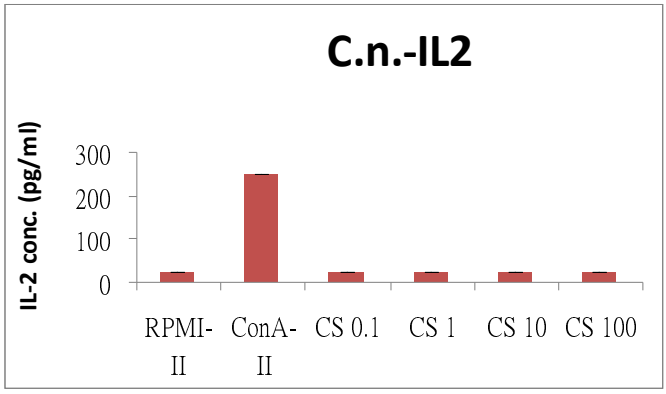
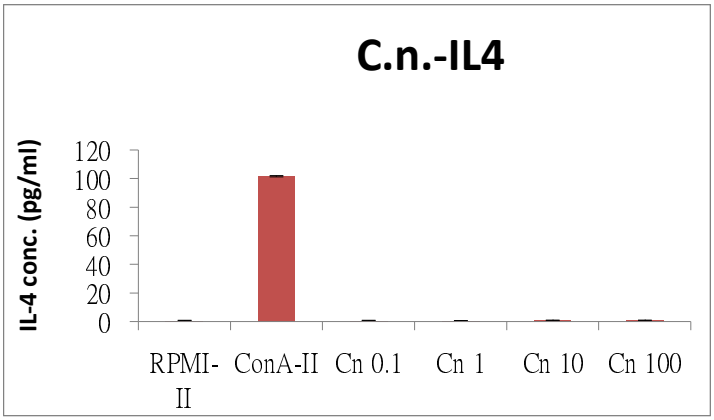


Figure 4. Our laboratory has successfully established an animal study for inducing chemotherapy-induced hand-foot-mouth disease in Wistar female rat and the xenograft of tumor cells in pathogen-free BALB/cAnN.Cg-Foxn1nu/CrlNarl nude mice (Figure 4) in our other ongoing study. In this study, we will modify this animal model and apply to this present study.

(5) Cytokine production by splenocytes response to treatment with different doses of *Clinacanthus nutans* extracts

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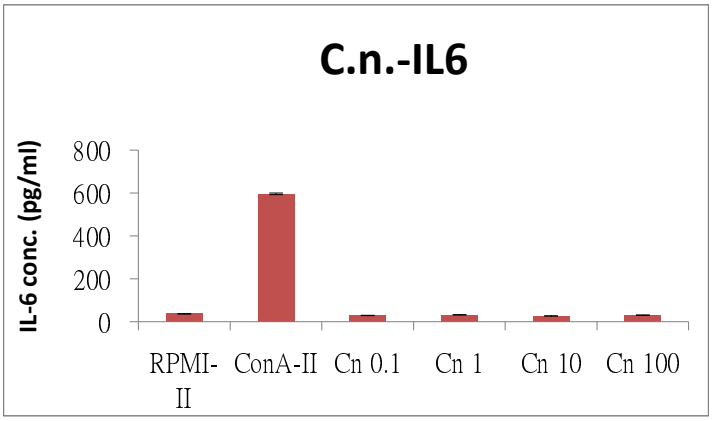
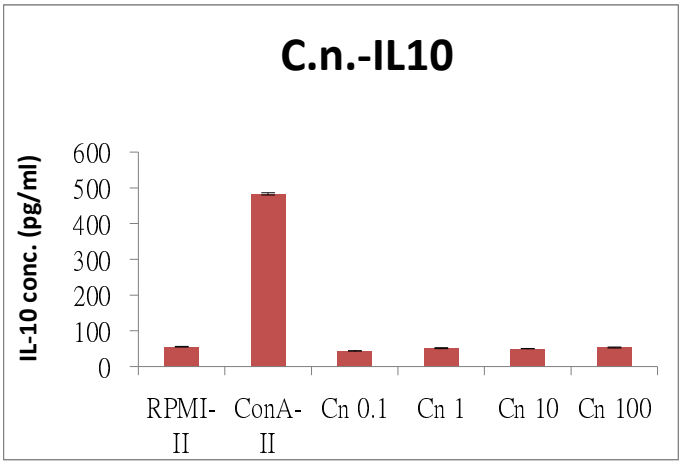
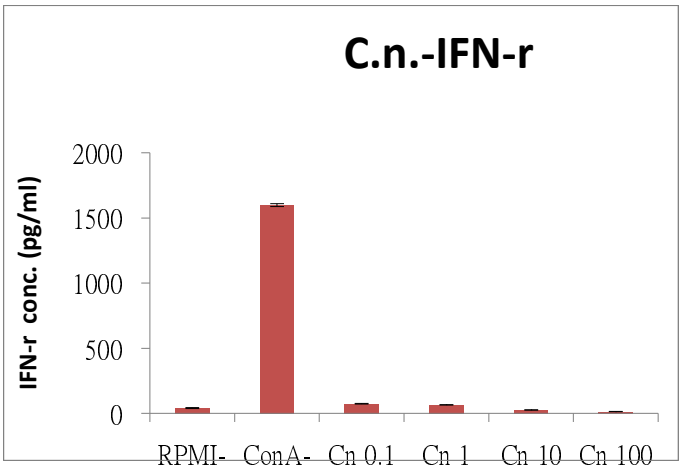
IL-4 conc. (pg/ml)
120
100
80
60
40
20
0
RPMI-II
ConA-II
Cn 0.1
Cn 1
Cn 10
Cn 100


C.n.-IL6
IL-6 conc. (pg/ml)
800
600
400
200
0
RPMI-II
ConA-II
Cn 0.1
Cn 1
Cn 10
Cn 100


C.n.-IL10
IL-10 conc. (pg/ml)
600
500
400
300
200
100
0
RPMI-II
ConA-II
Cn 0.1
Cn 1
Cn 10
Cn 100



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評值： 如期完成研究計畫並將相關研究成果發表於國際期刊共 11 篇 ，其中與乳癌相關之研究論文期刊發表有 7 篇，由此研究計畫延伸之研究論文期刊發表有 4 篇，目前正與彰化基督教醫院癌症醫學研究室合作，探討乳癌的相關機制，並期望藉由血液、體液、或組織切片中各種基因之蛋白質表現量，以及超音波檢查中各種脂質密度之不同來預測疾病之發展與預後。期望研究成果能實際應用於臨床疾病之診斷與治療之參考及疾病之預防。

國科會補助計畫衍生研發成果推廣資料表

日期:2014/02/17

國科會補助計畫	計畫名稱: 肉桂醛及肉桂樹葉片萃取液對免疫調節及乳癌患者化學抗癌藥物導致的口手足症候群之功效
	計畫主持人: 蔡秀婷
	計畫編號: 99-2314-B-040-008-MY3　　學門領域: 一般外科

無研發成果推廣資料

99 年度專題研究計畫研究成果彙整表

計畫主持人：蔡秀婷	計畫編號：99-2314-B-040-008-MY3
計畫名稱：肉桂醛及肉桂樹葉片萃取液對免疫調節及乳癌患者化學抗癌藥物導致的口手足症候群之功效	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	1	1	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	論文著作	期刊論文	11	11	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	1	1	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		

其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)	目前正與彰化基督教醫院癌症醫學研究室合作，探討乳癌的相關機制，並期望藉由血液、體液、或組織切片中各種基因之蛋白質表現量，以及超音波檢查中各種脂質密度之不同來預測疾病之發展與預後。期望研究成果能實際應用於臨床疾病之診斷與治療之參考及疾病之預防。

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：■已發表 □未發表之文稿 □撰寫中 □無

專利：□已獲得 □申請中 ■無

技轉：□已技轉 □洽談中 ■無

其他：(以 100 字為限)

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)

我們發現天然植物肉桂醛萃取物可透過調節細胞素濃度來增強免疫力，其研究結果可做為日後研發天然植物調節人體免疫功能之參考(Phytother Res, IF: 2.068, Rank: 145/261=0.555)。天然植物萃取物唐辛子能藉由降低粒線體之功能，以引導細胞凋亡因子之生成，導致乳房組織癌細胞死亡，其研究結果可做為日後發展乳癌輔助治療之參考(Hum Exp Toxicol, IF: 1.453, Rank: 63/85=0.764) 。另外，我們也發現，SLC34A2 基因(Anticancer Res, IF: 1.713, Rank: 146/197=0.741)、CLDN16 基因、及 HAPLN3 基因(Oncol Rep, IF: 2.297, Rank: 111/197=0.563)在乳癌患者的乳房組織皆有異常的表現量，這些研究結果可做為日後協助乳癌診斷及基因標靶治療之參考。為檢試基因多型性與罹患乳癌的相關性，我們針對新發現的基因多型性 RRM1 -756T>C 及 RRM1 -269 C>A 與罹患乳癌的相關性進行研究探討，我們發現二者沒有顯著的相關(Journal of Clinical Laboratory Analysis, IF:1.356, rank:18/32=0.562)以上研究結果亦已發表於國際期刊。