challenge, alone or with LPS exposure. The anti-inflammatory effects of the flavonoid are partly related to reduction of oxidative stress and partly mediated through activation of cAMP/PKA pathway.

Project Number: 11123011

P68-0093

A Study on Synergistic Bone Anabolic Effects of a Combination Use of Alendronate and Herba Epimedii in Treating Osteoporosis of Ovariactomized Rats

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Introduction and Project Objectives: Osteoporosis, a silent disease, is characterized by compromised bone strength predisposing to an increased risk of fractures. A study conducted in Hong Kong Chinese (Hong Kong Osteoporosis Study) reported that the overall incidence of hip fractures for women older than 65 years was 379 per 100,000 person-years. Nowadays, over 200 million people worldwide are affected by this crippling disease. With increasing life expectancy, the number of post-menopause-associated bone loss will escalate exponentially. Current therapeutic strategies using bisphosphonates e.g. Alendronate (the most potent FDA-approved bisphosphonate) are very effective at lowering the risk of spine and hip fractures. Unfortunately, FDA (2011) announced the incidents of a rare but serious problem (fracture of the thigh bone) after long-term uses of bisphosphonates. Herba Epimedii (Yinyanghuo) has been used for thousands of years in China. Oral consumption of Herba Epimedii extract enhances bone healing and reduces the incident of osteoporosis in animals and in human clinical trials without any side effects. In contrast to monotherapy, combination drug therapy utilizes more than one medications with which individual agent is given at the lowest possible therapeutic dosage with synergistic therapeutic outcomes resulted. In this study, we evaluated the synergistic bone anabolic properties of Alendronate plus Herba Epimedii combination to tackle post-menopausal osteoporosis.

Methods: Osteoblasts were harvested from sham and OVX rats, incubated with Alendronate (1 μM) and Herba Epimedii water extract (1 μg/ml), alone or in combination. OVX rats were administered (daily, 3 months) with Alendronate (0.03 μg/100g, s.c.), alone or in combination with Herba Epimedii water extract (oral gavage, 2 mg/100g).

Results: A generalized reduction of the expression of bone anabolic / transcription factors was detected in osteoblasts of OVX rats compared with sham, and Alendronate plus Herba Epimedii water extract elicited a concentration- and time-dependent increase of all bone anabolic biomarkers measured, with a greater magnitude of increase in OVX rats. Consumption of Alendronate plus Herba Epimedii water extract resulted in the restoration of reduced serum Ca2+ levels of OVX rats. Combined drugs consumption increased the failure load / stress and stiffness of femurs, and improved the micro-structure of the L-5 lumbar vertebra of OVX rats. An atrophic structure with a lower insulin expression was detected in sections of the pancreas of OVX rats which were reversed by combined drugs consumption.

Conclusions: Our results illustrate the bone anabolic effects of Alendronate plus Herba Epimedii water extract in treating oestrogen deficiency-associated osteoporosis.

Project Number: 10110371

P69-0112

Evaluation of the Chronic Toxicity of a Commonly Used Chinese Medicinal Herb Siegesbeckiae Herba

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Introduction and Project Objectives: Siegesbeckiae Herba (SH) is traditionally used for treating chronic diseases such as arthritis. It was first recorded as a low-toxicity herb in "Xin Xiu Ben Cao". To reduce its toxicity, SH is traditionally steamed with rice wine. Acute and sub-chronic toxicity studies showed that SH could induce lung toxicity in mice. However, up to now, the chronic toxicity data of this herb are not available. In this study, we aim to evaluate the chronic toxicities of SH and processed-SH (PSH) in rats, and to explore the underlying mechanisms of SH-induced toxicities and the toxicity-reducing effect of processing.

Methods: Rats were randomly divided into seven groups (n=20), and daily intragastrically administered with distilled water (control), SH [5.0 g/kg/day (group-1), 2.5 g/kg/day (group-2), 1.3 g/kg/day (group-3)] or PSH extracts [5.0 g/kg/day (group-4), 2.5 g/kg/day (group-5), 1.3 g/kg/day (group-6)] for 6 months, respectively. Body weights, clinical signs, urinalysis, hematological and biochemical parameters, histopathological observations and organ indices were compared among all groups. Metabolomics analysis of the most severely damaged organ was performed to identify the mechanisms of SH's toxicities and the toxicity-reducing effect of processing.

Results: Intragastric administration of SH resulted in significant body weight loss in rats. The mean leukocyte counts, neutrophil percentage, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotrasferase (ALT), lactate dehydrogenase (LDH), and the lung and liver indices were significantly increased in SH group. Histopathological damages were observed in the lung and liver tissues of SH-treated rats, and the lung damages were more obvious. While, in PSH group these symptoms were alleviated. Metabolomics analyses showed that fourteen metabolites were significantly altered by the treatment of this herb.

Conclusions: We found that processing with rice wine significantly reduced the chronic toxicities of SH, which supported the traditional Chinese Medicine (TCM) theory "processing can reduce the toxicity of SH". Inhibition of β-catenin signaling might be one of the mechanisms for SH-induced lung toxicity, and free radical scavenging might be responsible for the toxicity-reducing effect of processing. This study provides a scientific justification for the traditional processing theory, and should guide rational and safe clinical applications of SH by helping in optimizing its processing procedure and clinical compatibility.

Project Number: 11122521

P70-0131

Electroacupuncture and Splinting versus Splinting Alone to Treat Carpal Tunnel Syndrome: a Randomized Controlled Trial

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Introduction and Project Objectives: The effectiveness of acupuncture for managing carpal tunnel syndrome is uncertain, particularly in patients already receiving conventional treatments (e.g., splinting). We aimed to assess the effects of electroacupuncture combined with splinting.

Methods: We conducted a randomized parallel-group assessor-blinded 2-arm trial on patients with clinically diagnosed primary carpal tunnel syndrome. The treatment group was offered 13 sessions of electroacupuncture over 17 weeks. The treatment and control groups both received continuous nocturnal wrist splinting.

Results: Of 181 participants randomly assigned to electroacupuncture combined with splinting (n = 90) or splinting alone (n = 91), 174 (96.1%) completed all follow-up. The electroacupuncture group showed greater improvements at 17 weeks in symptoms (primary outcome of Symptom Severity Scale score mean difference [MD] -0.20, 95% confidence interval [CI] -0.36 to -0.03), disability (Disability of Arm, Shoulder and Hand Questionnaire score MD -6.72, 95% CI -10.9 to -2.57), function (Functional Status Scale score MD -0.22, 95% CI -0.38 to -0.05), dexterity (time to complete blinded pick-up test MD -6.13 seconds, 95% CI -10.6 to -1.63) and maximal tip pinch strength (MD 1.17 lb, 95% CI 0.48 to 1.86). Differences between groups were small and clinically unimportant for reduction in pain (numerical rating scale -0.70, 95% CI -1.34 to -0.06), and not significant for sensation (first finger monofilament test -0.08 mm, 95% CI -0.22 to 0.06).

Conclusions: For patients with primary carpal tunnel syndrome, chronic mild to moderate symptoms and no indication for surgery, electroacupuncture produces small changes in symptoms, disability, function, dexterity and pinch strength when added to nocturnal splinting.

Project Number: 09100681

P71-0153
Investigation of the Inhibitory Effects of Metronomic Zoledronate in Combination with Coriolus Versicolor in Cancer Propagation and Bone Metastasis in Breast Tumour Rodent Model

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Breast cancer metastases frequently produce osteolytic bone lesions by activating local osteoclasts to break down existing bone. We previously showed that repeated metronomic dose of zoledronate (anti-resorptive treatment for bone metastases) could reduce tumour burden and exert anti-osteolysis effects in breast cancer-induced osteolysis mouse model. *Coriolus versicolor (CV)*, a medicinal mushroom widely used as adjuvant in cancer patients, was also shown to exhibit anti-tumour and anti-metastatic effects in breast tumour-bearing mice. Hence, the aims of this study were to determine the interaction of metronomic zoledronate (ZOL) and CV aqueous extract in cancer propagation, metastasis and bone destruction using mouse models. The molecular mechanisms of ZOL combined with CV in anti-metastasis and immunomodulation were also delineated using breast cancer cells *in vitro*.

Mice inoculated with human breast cancer cells tagged with a luciferase reporter construct (MDA-MB-231-TXSA) in tibia or mouse breast tumour 4T1 cells in mammary fat pads were treated with CV aqueous extract, metronomic dose of ZOL, or the combination of both. Various parameters in tumour growth, metastasis and immunomodulation were determined after treatments. MDA-MB-231-TXSA and 4T1 cells were subjected to CV and/or ZOL treatments in vitro, and the proliferation, migration as well as protein and mRNA expressions related to these processes were evaluated.

Results showed that combination of CV and ZOL diminished tumour growth without altering the incidence of lung and liver metastasis in intratibial breast cancer model. The combination (CV and ZOL) exhibited significant inhibition in tumour size against ZOL alone and reduced the bone loss in both tumour and non-tumour bearing legs. In the mouse breast tumour metastasis model, the tumour sizes of mice after combined treatment were significantly decreased and were smaller than those after ZOL treatment alone. The proliferative tumour cells and endothelial cells in tumour sections were also reduced in the combined treatment group. Furthermore, mild immunostimulatory effects were observed in mice treated with CV alone. Results from *in vitro* study demonstrated that the anti-tumour and anti-migrating effects of CV and the combined CV and ZOL were likely via PI3K pathway in human breast cancer cells.

In conclusion, our findings suggested that combination of CV and ZOL attenuated breast cancer propagation, protected against breast cancer-induced bone destruction in metastatic breast tumour models. Scientific evidences on the pre-clinical outcome of using CV in combination with metronomic zoledronate in the management of breast cancer and bone metastasis were gained from this study.

Project Number: 10110891

P72-0158
Interactions of Herbs with Statin Drugs and Potential Mediation by Drug Transporters

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Introduction and Project Objectives: Green tea and soy are extensively consumed in daily life. Recent research has shown that green tea catechins and soy isoflavones may influence the activity of drug metabolizing enzymes and drug transporters. We examined whether green tea extract and soy isoflavones might affect the pharmacokinetics of simvastatin and rosuvastatin in healthy subjects and whether these interactions are influenced by polymorphisms in relevant drug transporters, solute carrier organic anion transporter family member 1B1 (SLCO1B1) and ATP-binding cassette sub-family G member 2 (ABCG2).

Methods: The project included two open-label, single-dose, three-phase clinical pharmacokinetic studies. Healthy Chinese male subjects were given a single dose of rosuvatatin 10 mg (Study A) or simvastatin 20 mg (Study B) on 3 occasions: 1. without herbs; 2. with green tea extract; 3. with soy isoflavone extract. The green tea and soy isoflavone extract were given at a dose containing epigallocatechin gallate (EGCG) 800 mg once daily or soy isoflavones ~ 80 mg once daily for 14 days before statin dosing with at least 4-weeks washout period between phases.

Results: In study A (n= 20), intake of green tea extract significantly reduced the systemic exposure to rosuvastatin by nearly one third [geometric mean (% coefficient of variation) area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24h}) from 108.7 (28.9) h•g/L to 74.1 (35.3) h•g/L; geometric mean maximum plasma concentration (C_{max}) from 13.1 (32.2) µg/L to 7.9 (38.3) µg/L, $P<0.001$ for all] without affecting the elimination half-life. The ABCG2 421C>A polymorphism had no effect on this interaction. In study B (n= 18), intake of soy isoflavones was associated with reduced systemic exposure to simvastatin acid [geometric mean (% coefficient of variation) AUC_{0-24h} from 16.1 (44.2) h•g/L to 12.1 (54.6) h•g/L, $P<0.05$] but not the lactone. Further analysis showed that the interaction between simvastatin and the soy isoflavones only occurred in subjects with the SLCO1B1 521TT genotype but not in those with the 521C variant allele.

Conclusions: This study showed repeated green tea catechin or soy isoflavonones administration reduced the bioavailability of statins in