Asian Journal of Chemistry Vol. 19, No. 2 (2007), 867-882

Synergistic Effect of Traditional Chinese Medicine

LIU YINGHONG, KONG JIN MING, CHIA LIAN SAI* and GOH NGOH KHANG
Natural Sciences & Science Education Academic Group, National Institute of Education
Nanyang Technological University of Singapore, Singapore
Fax: (65)68969432; Tel: (65)67903885
E-mail: liuyh00@yahoo.com, lschia@nie.edu.sg

Traditional Chinese medicine is an experience-based medicine, which has existed for millennia. However, some, particularly in the West, doubt the effect and synergy of traditional Chinese medicine as its mechanisms are less definitive than western-style scientific medicine. The traditional Chinese medicine treatment of patients is quite different from Western medicine as a whole as its synergism is based on the concept of balance. So, only those formulae under its synergistic principle and some herbs under the same rule, can work effectively on the whole body. Efficient scientific techniques are required to validate this principle. Global interest in traditional Chinese medicine has increased significantly in recent years, driven by global trends in health care. Recognition of its clinical, pharmaceutical and economic values is growing. Some studies on traditional Chinese medicine have proven its efficiency compared to established medical methods. In this article, the current knowledge and research about traditional Chinese medicine synergy has been reviewed. This provides scientific validation that traditional Chinese medicine makes good use of herbal synergistic effects to act through different molecular channels and sites to achieve the intended function. The synergy between Chinese medicine and Western medicine is also widely concerned. This should lead to greater use of the combination of traditional Chinese medicine and Western medicine for healing.

Key Words: Synergistic effect, Traditional Chinese medicines.

INTRODUCTION

Traditional Chinese medicine (TCM) has a long history of over 5,000 years. In traditional Chinese medicine, the human body and environment are classified according to Yin, Yang and the five elements. In the theory of Yin-Yang, all things in the universe exist in corresponding opposite states of Yin and Yang and there are different aspects of Yin and Yang existing within everything. The healthy state is characterized by a dynamic balance between the Yin and Yang aspects of the body.

Maintaining and restoring the balance of Yin and Yang is an important aspect of Chinese medical philosophy. This concept originated from the most ancient TCM works, Huang Ti Nei Ching (The Yellow Emperor's Medicine Classic, 200 BC), which said: If Yin and Yang are not in harmony, it will be like four seasons without autumn and summer. Therefore, maintenance of Yin-Yang harmony is the best principle for maintaining good health.

In traditional Chinese medicine, health and disease are conditions of the whole organism, a whole entity involving a complex interaction of physical, spiritual, mental, emotional, genetic and environmental factors. This is quite different from Western medicine. Traditional Chinese medicine's specific diagnostic techniques "wang wen wen qie" and therapeutic principles are unique in treating the whole body. Acupuncture, moxibustion, cupping, massage and herbs are all techniques utilized in traditional Chinese medicine to achieve the balance of Yin and Yang, Qi and the vital substances. By using several methods together, traditional Chinese medicine targets patients in different physiological functions and any pathological changes in the body.

Synergistic effects of traditional Chinese medicine

The synergy of herbal medicine is determined by the synergy of organs in the body. Traditional Chinese herbal medicine can correct an imbalance in the body through the interaction of various components of the herbs targeting many organs and elements. Each herb acts on specific organs and "Qi". Qi is the energy that underlies everything in the universe. It is the source of body activity and movement, protects us from illness and keeps our bodies warm.

Formulary approach is the characteristics of traditional Chinese medicine. From the period of Shen Nong, which is recorded in Shen Nong Ben Cao Jing, the earliest Chinese pharmacopoeia, it was believed that single herb might address only one aspect of a person's imbalance. The individual herbs would be less potent. A combination of herbs is considered more effective than individual herb because they have more balancing effects on the body. There are different methods of combining herbs. Herbal combinations can increase or promote the therapeutic effectiveness of traditional Chinese medicine.

In traditional Chinese medicine formulae, the core rule of herb formulae is "Jun Chen Zuo Shi". The first principal ingredient is "Jun", a substance providing the main therapeutic thrust, the second principle ingredient "Chen" enhances or assists the therapeutic actions of the first. It is really a synergistic agent of the primary medicine. The rest serve one or more of the following functions: treat the accompanying symptoms, moderate the harshness or toxicity of the primary ingredient, guide the medicine to the proper organs or exert a harmonizing effect. A traditional Chinese medicine formula commonly contains from 2 to 16 ingredients chosen for their synergistic effect. A classical formula is usually used as a base and herbs are added or subtracted to prepare a custom-made combination that addresses a patient's unique physiological imbalance.

As the side effects of Western medicine are more recognized, many researchers turned to the study of traditional Chinese medicine. Generally speaking, Chinese herbs are usually safer than western pharmaceuticals and have less unpleasant side effects. A synergistic effect is defined in Western medicine as when the effects of two chemicals on an organism are greater than the effect of each chemical individually or the sum of the individual effects. The presence of one chemical enhances the effects of the others. A single herb contains hundreds to thousands of chemicals, few of which have been identified in most cases. They exist in the herb and work together, each playing a different role. It is difficult to validate the effectiveness of individual herb as they are not used alone.

Many Asians take traditional medicine for granted, but in Western countries, many people trust only those fields based on scientific experimentation, such as Western medicine. The Food and Drug Administration of United States asserted that data based on the traditional use of herbs has no validity in 1994. Only in 2001, they first announced that herb nostrum can be used as a medicine but not food. They made strict regulatory rules for the pure components in formulae. The European Parliament and of the Council in 2003 stated that when considering traditional Chinese medicine in case of combinations, the information data relating to the combination of herbs showed that the product proves not to be harmful in the specified conditions of use and the pharmacological effects (or efficacy) of the medicinal product are plausible on the basis of long standing use and experience.

Albert Leung reported that the class of botanicals, consisting mostly of tonics, contains more than one, or one class of active chemical compounds (flavonoids, lignans, sterols, triterpenes, saponins and alkaloids). Hence, their pharmacological actions are not due to a single compound or even a group of compounds, but rather to a synergistic effect of all the compounds present. Once an active compound is isolated and used in its natural or synthesized form, the synergistic nature of the original herb is absent. If this compound is used like a modern drug for a specific indication, it diverges from traditional herbal medicine. This cannot be considered as modernizing traditional Chinese medicine; it is merely a drug discovery using traditional herbs as a raw-material source.

Current knowledge of the validation of synergistic effects

Contemporary science and technology is just only the beginning to assess traditional medicine, especially herbal medicine. The knowledge to validate the synergistic effects of herbal medicine scientifically is lacked. It is tough work to isolate and purify compounds from herbs and test the pharmacological interactions. However, the synergistic effect of traditional Chinese medicine is a theory supported by thousands of years of clinical evidence.

The therapeutic effects of many herbal medicines have been well established. However, the definitive mechanisms of action still need elucidation for many psychoactive herbal medications. Although several mechanisms have been identified, they are often insufficient to account for the observed effects of the plant or its extracts. Synergy may occur through pharmacokinetic and/or pharmacodynamic interactions. There are two types of synergy: pharmacodynamic synergy resulting from two drugs directed at a similar receptor target or physiological system, or pharmacokinetic synergy resulting from the processes of drug absorption, distribution, biotransformation, or elimination. Spinella[1] illustrated synergistic actions in St. John's wort (Hypericum perforatum), kava kava (Piper methysticum) and valerian (Valeriana officinalis) through both pharmacokinetic and pharmacodynamic interactions.

There are three ways to validate the synergistic effects: i) Test the phytopharmacological effects/changes; ii) Monitor the difference in the phytopharmacological effectiveness; iii) Observe the dose response with mixtures of bioactive compounds after using both a single herb or medicine and herbal formulae or extracts, which means a lower dose is used when synergy is generated. All these three methods can be classified by pharmacodynamic and pharmacokinetic synergy. Wagner[2] announced that it would be possible to find a rationale for the synergistic effects of plant extract preparations, by using new target-directed pharmacological screening methods in combination with clinical trials. New approaches have been found in phytopharmacological research of some herbal medicines.

Recently, researchers in many countries have carried out studies on the synergistic effects of some herbs. Medical research has accelerated with advances in genomic, molecular, and chemical analysis, laboratory automation and information technology leading to better drug discovery. In this paper, the synergistic effects of traditional Chinese herbal medicine validated by research and clinical trials is reviewed.

Pharmacodynamic synergy research

In a study testing the effect of Chinese medicine on tumors, Nagasawa *et al.*[3] evaluated the chemopreventive role of motherwort (*Leonurus sibiricus*

L; MW) in lesions of the mammary gland and uterus of GR/A mice. The effects on these lesions of the adsorbed (MW1) and unadsorbed (MW2) fractions of MW separated by ion-exchange resins were studied. The incidence of palpable mammary tumors was suppressed and their growth was retarded by both MW1 and MW2, with no apparent difference between their effects. However, neither of them showed effects on pregnancy-dependent mammary tumors (PDMT), mammary hyperplastic alveolar nodules (HAN) or uterine adenomyosis, whereas MW promoted PDMT and inhibited HAN and adenomyosis. These findings indicate that the synergistic action of MW provides the full effect of this herb.

Extracts of the plant *Sinomenium acutum* have been used safely since ancient times in Chinese medicine for the treatment of rheumatic diseases. It contains the purified alkaloid, sinomenine, which was recently shown to have antiinflammatory and antirheumatic effects. Candinas *et al.*[4] found that the effects of sinomenine in the high responder ACl-to Lewis cardiac transplant model in which allograft rejection occurred 5 d after transplantation. Treatment with sinomenine (15-30 mg/kg/d i.p.) or a subtherapeutic dose of cyclosporine (CsA, 1.5 mg/kg/d, i.m.) prolonged allograft survival only marginally (mean survival of 5.4 and 7.8 d, respectively). In contract, the combination of sinomenine and CsA had a statistically significant synergistic effect with a mean survival of 42.2 d ($P < 0.001$). This indicates the synergistic effects of the extracts of *Sinomenium acutum*.

The aqueous extract of *Chromolaena odorata* and the decoction from the leaves of this plant have been used throughout Vietnam for the treatment of soft tissue wounds, burn wounds and skin infections. The effect of Eupolin extract on hydrated collagen lattice contraction by human dermal fibroblasts, an *in vitro* model of wound contraction is described by Phan *et al.*[5] The significant inhibition of collagen gel contraction by Eupolin extract at 50 to 200 μg/mL is demonstrated in various concentrations by collagen. When the extract at 50 to 150 μg/mL was washed out of the lattices and replaced by fresh medium without Eupolin, the contraction of collagen by the cells was resumed. The visualization of cells in the lattices by incubation in a tetrazolium salt for 2 h showed live cells at 50 to 150 μg/mL of extract. In contract, all cells were killed in the higher extract doses of 300 or 400 μg/mL. These preliminary results showed the inhibitory effect of Eupolin extract on collagen contraction which suggests that a clinical evaluation of its effect on wound contraction and scar quality should be made. This work illustrates that traditional remedies that are used by folk practitioners to improve healing can be examined in a scientific manner using *in vitro* wound-healing models. It also suggests that the synergistic properties of components of the natural extract contribute to the positive effects demonstrated on various wound-healing mechanisms.

In some cases, when some pure compounds isolated from the herbal extracts are used together, the pharmacological interactions disappeared, indicating that there was a synergism in the herbal extracts. Verma *et al.*[6] studied curcumin and genistein, two natural plant products obtained from *Curcuma longa* Linn (turmeric) and soybeans. Both compounds when present at micro molar concentrations are able to inhibit the growth of estrogen-positive human breast MCF-7 cells induced individually or by mixture of the pesticides endosulfan, DDT (dichlorodiphenyltrichloroethane) and chlordane or 17-β estradiol. When curcumin and genistein were added together to MCF-7 cells, a synergistic effect was noted, resulting in a total inhibition of the induction of MCF-7 cells by the highly estrogenic activity of endosulfan/chlordane/DDT mixtures. Bu-Zhong-Yi-Qi-Tang (BZYQT), a Chinese herbal medicine, inhibited the proliferation of human hepatoma cell lines (Hep3B, HepG2 and HA22T) dose-dependently. Major compounds of BZYQT, including astragaloside IV, ginsenoside Rb1, Rg1, saikosaponin and glycyrrhizin, have been identified.

Shung *et al.*[7] investigated the key inhibitors of BZYQT. In this study, Hep3B cells were treated with BZYQT, individual major compounds of BZYQT, and a mixture of the major compounds in the same ratio as present in BZYQT. Significant inhibition of proliferation was detected in BZYQT and its major compounds mixture at a comparable level. No individual major compound examined could suppress the proliferation of Hep3B cells. This data indicated there could be synergistic or additive effects from the ingredients in BZYQT.

Liu[8] found that the vitamin C in apples with skin accounts for only 0.4 % of the total antioxidant activity, suggesting that most of the antioxidant activity of fruit and vegetables may come from phenolics and flavonoids in apples. The results proposed that the additive and synergistic effects of phytochemicals in fruit and vegetables are probably responsible for their potent antioxidant and anticancer activities. These results answered the key question a purified phytochemical did not have the same health benefits as the whole plant or a mixture of herbs in which the phytochemical is present.

Azas *et al.*[9] evaluated a potent *in vitro* synergistic antimalarial interaction using standard isobologram analysis between *Mitragyna inermis* (Willd.) *O. kuntze, Nauclea latifolia* (Sm.), *Guiera senegalensis* (Gmel.) and *Feretia apodanthera* (Del.) extracts. The cytotoxicity of human monocytes and the mutagenic activity of the plant extracts on an *in vitro* system of two β-carboline alkaloids were isolated from *Guiera senegalensis* (harman and tetrahydroharman). The results indicated that these combinations demonstrate a strong, synergistic, inhibitory effect on *in vitro* plasmodial development and are devoid of cytotoxicity towards human cells. Lei *et al.*[10] reported the effects of *Astragalus membranaceus* (AM), *Angelica sinensis* (AS) and their combinations on human umbilical vein endothelial cell (HUVEC) proliferation and cell cycles. This study showed that AM and AS promoted vascular endothelial cell proliferation and DNA synthesis and demonstrated a synergistic effect when they were used in combination, suggesting that these two Chinese herbs could have certain effects on the genesis and development of neogenetic vascularization in ischemic myocardium.

Recently, researchers isolated the pure biodirected compounds or fractions for a synergy study. The results showed a synergistic effect in the mixture of different fractions. Anaya *et al.*[11] investigated the allelochemical potential of *Callicarpa acuminata* (Verbenaceae) by using a biodirected fractionation study as part of a long-term project to search for bioactive compounds among the rich biodiversity of plant communities in the Ecological Reserve E1 Eden, Quintana Roo, Mexico. *Aqueous leachate,* chloroform-methanol extract and chromatographic fractions of the leaves of *C. acuminata* inhibited the root growth of test plants (23-70%). The phytotoxicity exhibited by several fractions and the full extract almost disappeared when pure compounds were evaluated on the test plants, suggesting a synergistic or additive effect.

Fernandes and Varges[12] studied the aqueous extracts of medicinal plants (*Mikania laevigata* and *Campomanesia xanthocarpa*). These were screened for the presence of mutagenic activity in the Salmonella/microsome assay. The extracts of *Campomanesia xanthocarpa* showed frameshift (TA97a strain) signs of mutagenic activity without exogenous metabolism (S9 fraction). The infusions of *Mikania laevigata*, whilst negative for mutagenic activity, showed high percentages of inhibition of mutagenesis induced by mutagens 2AF (2-amino fluorene), in the presence of exogenous metabolism (S9 fraction), for frameshift (TA98) and base pair substitution (TA100) lesions. In addition, these inhibitions were observed against mutagen sodium azide (SAZ) in assays with the TA100 strain, without exogenous metabolism (S9 fraction). A synergistic effect was also observed in frameshift mutagenic events, with direct action in the presence of 1-nitroquinoline-4-oxide (4NQO) and a tendency to a low percentage of action enhancement, in the presence of the 2AF mutagen. The variable responses observed in the extract assays show the potential for interaction of the different active principles in genetic material.

From the study of different extracts, the most effective pure compounds are separated; then the synergistic effects between these compounds are reported. Carpinella *et al.*[13] studied extracts from different parts of *Melia azedarach* L. as potential antifungal agents for selected phytopathogenic fungi. Using a serial agar dilution method, hexane and ethanolic extracts from fruits, seed kernels and senescent leaves exhibited fungistatic activity against *Aspergillus flavus*, *Diaporthe phaseolorum var. meridionales*, *Fusarium oxysporum*, *Fusarium solani*, *Fusarium verticillioides* and *Sclerotinia sclerotiorum*. Both the hexane extract from senescent leaves and the ethanolic extract from the seed kernels were highly effective on all tested fungi, with minimum inhibitory concentration (MIC) values ranging from 0.5 to 25 mg/mL and 0.5 to 5 mg/mL, respectively. In addition, all of the extracts above showed fungicidal activity, with ethanolic seed kernel extract being the most active. Three compounds displaying activity against *F. verticillioides* were isolated from the ethanolic seed kernel extract and were characterized as vanillin (1), 4-hydroxy-3-methoxycinnamaldehyde (2), and (±)-pinoresinol (3), with MICs of 0.6, 0.4, and 1.0 mg/mL, respectively. These compounds also showed a synergistic effect when combined in different concentrations and required four times less concentration to reach complete inhibition in the growth of *F. verticillioides*. Paiva-Martins *et al.*[14] studied the antioxidant activity of some olive oil phenols. Synergistic effects (an 11-20% increase in lag phase) were observed in the antioxidant activity of combinations of α-tocopherol with olive oil phenols both with and without ascorbic acid. These results suggest that changes in the concentration of the effective components can induce some synergism in the mixture of compounds. Such studies may help researchers to discover new drugs from herbal medicine.

Pharmacokinetic synergy

Berenbaum[15] proposed that dose ± response investigations with mixtures of bioactive compounds can be carried out using the isobol method. Hall and Duncan[16] applied this method to the rationalization of the synergistic effects of mixtures of anti-viral compounds. Vorbach *et al.*[17] investigated St. John's Wort (*Hypericum perforatum*) extracts by performing with standardized Hypericum extracts against the synthetic psychopharmacon Imipramin with the indication moderate depression. This resulted in the same reduction of the depression score values on the HAMDA depression scale after a 6-weeks treatment. It appears that 300 mg/day of Hypericum extract containing about 8 ± 10 mg of bioactive compounds (hypericines, hyperforins, avonoids and procyanidins) can be regarded as bioequivalent to 75 mg synthetic Imipramin. Steinke[18] carried out an experiment using the thrombocyte aggregation assay with a mixture of Ginkgolide A and B, two major constituents of Ginkgo biloba and found a typical synergistic effect evidenced by a 'concave up' isobol curve. The successful results were obtained with phytopreparations in controlled clinical trials. However, for these synergistic and dosage phenomena, a scientific mechanism explanation is still lacking.

Animal models and clinical trials have revealed that some traditional Chinese medicines formulae or combined herbal medicines have special pharmacokinetic synergies. Zee-Cheng and Tang[19] reported that Shi-Quan-Da-Bu-Tang (Ten Significant Tonic Decoction) or SQT (Juzentaihoto, TJ 48) demonstrates the synergistic actions of its components in immuno-modulatory and immunopoten-tiating effects (by stimulating hemopoietic factors and interleukin production in association with NK cells, etc.). Hsieh *et al.*[20] compared the anticonvulsive and free radical scavenging activities of UR alone and UR in combination with GE in rats. The results indicated that UR has anticonvulsive and free radical scavenging activities and UR combined with GE exhibits greater inhibition of the onset time of WDS than UR alone. These findings suggest that the anticonvulsive effects of UR and GE may be synergistic.

A synergy index can be tested through animal models or clinical trials. Liu *et al.*[21] studied the synergistic action of a combination of guanghuoxiang volatile oil (B) and sodium artesunate (SA) against *Plasmodium berghei* (P.b) and the resistance-reversal activity against SA-resistant P.b (P.b SA-R). Mice infected with P.b N or P.b R were treated with a combination of B and SA, respectively using a 4-d suppresive test method and linear regression to calculate the SD50 of B and SA for each drug alone and in combination (equally effective dose compatibility). The results were B alone, N:SD50 = 87.64 ± 19.58 (GKD), R:SD50 = 43.24 ± 7.71 (GKD); SA alone, N:SD50 = 0.88 ± 0.01 (MGKD), R:SD50 = 27.69 ± 0.93 (MGKD). B and SA combined, N:B SD50 = 36.89 ± 4.57 (GKD), SA SD50 = 0.39 ± 0.05 (MGKD); R:B SD50 = 7.40 ± 1.30 (GKD), SA SD50 = 4.21 ± 0.74 (MGKD). The synergistic indexes of B and SA in combination were 2.2 for N and 6.6 for R, respectively. The multiple of resistance reversal of B *vs* SA was 6.6. The relative reversal rate was 87.6 %. A combination of B and SA may enhance the antimalarial effect against P.b, reverse the SA-resistance of P. b and delay the occurrence of resistance to SA in N. Giordani *et al.*[22] proposed that *Cryptococcus neoformans* (MIC 80 % = 56.078 µg protein/mL, K_{aff} = 0.059/µg protein mL) was synergized with all *H. brasiliensis* latex concentrations tested. The rates of synergy were about 50, 44 and 55 % with 15, 30 and 60 µg, protein/mL latex, respectively.

Beddows *et al.*[23] observed synergism in the effects for AP combined with sage, turmeric, oregano and marjoram compared with using AP alone to delay sunflower oil becoming rancid. Clove and thyme gave a smaller synergistic effect than basil totally inhibited rancidity. This suggests that synergistic effects happen in plants to different degrees and some plants are even antagonistic to other herbs.

When the components are isolated from the herbal extracts and used together, some tests suggest the presence of a synergistic effect among these plant components. The component alone has no such effects; when some components were combined, a much weaker effect than that of the extracts alone was obtained. The antioxidant activities and components of *Salvia plebeian R.Br*, a Chinese herb was investigated by Liwei and Xinchu[24]. Three antioxidant components were isolated and identified from the herb extracts. The antioxidant properties of the extracts and the two combined antioxidant components were tested in lard at 110°C using the Oxidant Stability Instrument. Their antioxidant activities were much weaker than the crude extracts. Zhu *et al.*[25] evaluated a plant formula and its five components independently for their gastric protective effect against ethanol-induced stomach lesions in rats. Aqueous extracts of the plant formula (0.25-2 g crude drug/kg orally) and its individual components (at the same dose) all showed significant stomach protective effects independently. However, when these extracts were given to rats at a dose of 0.25 g/kg, the five single-herb preparations did not show any activity, but the formula-extract still exhibited a strong protective effect. Chemical examination of the extracts indicated that the major ingredients of the five plants were essential oils, terpenoids, flavonoids, glycosides and saccharides and these may contribute to the stomach protective activity observed. Edris and Farrag[26] investigated the vapors of peppermint oil and two of its major constituents (menthol and menthone) and sweet basil oil and two of its major constituents (linalool and eugenol). They were tested against *Sclerotinia sclerotiorum* (Lib.), *Rhizopus stolonifer* (Ehrenb. exFr.) *Vuill* and *Mucor sp.* (Fisher) in a closed system. The essential oils, their major individual aroma constituents and blends of the major individual constituents at different ratios inhibited the growth of the fungi in a dose-dependent manner. Menthol was found to be the individual aroma constituent responsible for the antifungal properties of peppermint essential oil, while menthone alone did not show any effect at all doses. In the case of basil oil, linalool alone showed a moderate antifungal activity, while eugenol showed no activity at all. Mixing the two components in a ratio similar to their concentrations in the original oil was found to enhance the antifungal properties of basil oil indicating a synergistic effect.

Traditional Chinese medicine and Western medicine synergy

The modernization movement in China in the late 1950's brought traditional Chinese medicine into every medical school in China, to be taught along with Western medicine. The same doctors with the same patients in the same medical setting have practiced it side by side with Western medicine. For most clinical conditions, these two medical approaches are used together and the results are usually better than either would have achieved if used alone. As part of this movement, many western-trained doctors have devoted tremendous amounts of time and energy to scientific studies of traditional Chinese medicine, resulting in a new type of medicine: Integrative Chinese and Western medicine (ICWM). It has been validated through many real clinical cases.

The new European legislation regarding herbal medicine was released on as more herbs are being used in Europe, in particular (in order of importance) as anti-varicose and cough remedies, cold remedies to aid circulation, fight muscular pain, improve digestion, etc. It has been suggested that in the past 30 years, the data on the traditional use of the medicinal products is sufficient, to validate their use if the products prove not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal products are plausible on the basis of long standing use and experience.

Scientists are interested in the case of serious diseases world wide. In recent years, many studies have been carried out on the combined effects of herbal medicine and Western medicine. In the United States, it is very rare for a person with cancer to be treated solely by Chinese medicine, even though many practitioners say that traditional Chinese medicine can often handle cancer on its own, with success in cases that proved untreatable by Western medicine. Many practitioners in China say that the best results against cancer are obtained by means of a joint attack combining traditional Chinese medicine and Western medicine, with the patient pursuing a suitable diet, Chinese Qigong and therapeutic exercise.

In cancer studies, many researchers have reported the synergy of traditional Chinese medicine and Western medicine. Some anticancer drugs can easily penetrate the cancer cells when used in combination with some herbal medicine. Ye *et al.*[27] studied *in vitro* the anticancer interaction between Ys-96, a bisbenzylisoquinoline compound derived from *Stephania tetrandra* and *adriamycin* or *vincristine* against human cancer cell lines. Using human breast cancer cell MCF-7 and its adriamycin-resistant cell line KBv200 in an *in vitro* system, the anticancer interaction between Ys-96 and adriam ycin or vincristine was evaluated with a method reported by Berenbaum[15]. The sum of the fractional inhibitory concentration values (SFIC values) of the combinations with 3 different ratios between Ys-96 and adriamycin or vincristine were markedly less than 1.0 and the shapes of all the isobologram curves were concave. The synergistic interaction between Ys-96 and adriamycin or vincristine against the above human cancer cell lines was positively observed *in vitro*. Fujiki *et al.*[28] suggested the synergistic effects of EGCG, a green tea polyphenol with sulindac or tamoxifen on cancer preventive activity in PC-9 cells. Cal *et al.*[29] reported that resveratrol, a natural compound from grape, has been shown to exert sensitization effects on cancer cells that resulted in synergistic cytotoxic activity when used in combination with cytotoxic drugs in drug-resistant tumor cells.

Schwarz *et al.*[30] examined the Chinese herbal extracts used to treat cancer in conjunction with Western medicine. Eight human pancreatic cancer cell lines (MIA, Panc-1, BxPC, ASPC, HS-766T, CaPan-2, CFPAC and HTB-147) were studied for *in vitro* susceptibility to ethanol extracts of SPES and PC-SPES, two quality-controlled, dried, encapsulated supplements of 15 and 8 Chinese herbs, respectively. Resulting toxicities, alone and in combination with doxorubicin or gemcitabine, were analyzed by [3H] thymidine incorporation or sulforhodamine B staining, colony formation and TUNEL flow cytometry assays. After treatment with PC-SPES, the cell lines consistently displayed a G2 cell cycle block; SPES induced an increase in S phase, with a smaller impact on G2. When added at concentration of 0.2 mM/mL (IC20), both extracts enhanced Panc-1 cell killing mediated by doxorubicin, with an average decrease in the corresponding IC50 of 33 % (range 11-62 %). The combined effects of either extract appeared to be antagonistic in the case of gemcitabine, and additive to mildly synergistic in the case of doxorubicin. These results support the combining of traditional and Western medicine. To date, in many countries, more individual cancer patients who are being treated with Western medicine seek traditional Chinese medicine. The most highly praised blood tonic in the East, dang gui (*Angelica sinensis*), has been used clinically in China to treat cancer of the esophagus and liver with good results. The Chinese people have claimed dramatic success using this herb both alone and in combination with other medicinal agents, in treating cervical cancer and, to a lesser extend, breast cancer in women. It can be administered in infusion or douche form. Many other Chinese herbs could be cited for their documented anti-tumor effects.

In animal studies, when some Western drugs were fed to rats with a herbal medicine, or the effective components extracted from a traditional Chinese medicine tonic, a significantly improved pharmacokinetic effect was observed. Chiou *et al.*[31] observed that mice pretreated with atropine and obidoxime and then administered β-eudesmol, a sesquiterpenol present in Chinese herbs, showed a greater synergistic effect. He *et al.*[32] observed the synergistic effect of *Tripterygium wilfordii* Hook F (TWHF) and cyclospo-rine A in rat liver transplants. Hu and Hang[33] examined the antioxidative effect of extracts from Chinese rose which was measured with $Na_2S_2O_3$-I_2 titrimetric method by using lard as the substrate. Citric acid and amino acid showed synergistic effects in antioxidative activities with extracts of Chinese rose. Ascorbic acid and α-tocopherol also showed strong synergistic antioxidative effects when combined extracts of Chinese rose. The combined antioxidative activities were higher than the activity of tea polyphenols and almost as good as that of *tert*-butyl *p*-dihydroxy benzene (TBHQ). Kangen-Karyu (KGK), containing six herbs, is a traditional Chinese medicine formula created under the theory of traditional Chinese medicine used to invigorate the blood and dispel blood stasis, which arises from poor blood circulation. Toshiak *et al.*[34] attempted to evaluate the interactions between KGK and warfarin. Warfarin was administered orally or intravenously to KGK-treated rats and plasma warfarin concentration and prothrombin time were measured. Although KGK did not influence the absorption or serum protein binding of warfarin, it significantly suppressed the metabolism and elimination of warfarin. Warfarin alone significantly prolonged mice tail-bleeding time, which was further prolonged significantly by KGK at a dose that did not exhibit pharmacokinetic interactions with warfarin. This suggests that this combination might synergistically prevent thrombosis.

The regulatory mechanisms responsible for Western medicine are now influenced by traditional Chinese medicine. In the following reports, traditional Chinese medicine is used as an accelerant to Western medicine. Wang *et al.*[35] proposed that the preventive activity of 1:8 mixture of cymoxanil and mancozeb against Phytophthora infestans was higher than that of either the two single ingredients or the nine other mixtures. The synergistic interaction existed (synergy ratio 2.01) between the two at the mixing ratio of 1:8, whereas additive interaction (synergy ratios ranged from 0.73 to 1.34) existed at mixing ratios ranging from 1:1 to 1:7 and from 1:9 to 1:10, 1:8 was the optimal ratio. The preventive activity of the 1:8 mixture was higher than the curative and the eradicative effects. In addition, the eradicative of synergism of inhibiting sporangia production on lesions was stronger than the eradicative synergism of inhibiting lesion extension and suppressing infection of sporangia. It was stronger than the curative synergism of inhibiting lesion sporulation on detached potato leaflets.

Saada *et al.*[36] found that treatment with aloe vera was also effective in minimizing the radiation-induced increase in plasma glucose levels throughout the experimental period, while it did not ameliorate the increase in plasma insulin levels. It could be concluded that the synergistic relationship between the elements found in the leaf of aloe vera could be a useful adjunct for maintaining the integrity of the antioxidant status. Shin and Kang[37] evaluated the fungitoxic activity of the essential oil of *Agastache rugosa* alone and to determine its combined effect with ketoconazole against *Blastoschizomyces capituatus*. The antifungal activities of the essential oil of *A. rugosa* and its main constituent estragole were investigated using the broth microdilution and disk diffusion methods as well as a checkerboard microtitre assay. Both estragole and the essential oil exhibited strong activity against the tested fungi and showed synergism with ketoconazole against *B. Capitatus*. Both estragole and the essential oil of *A. rugosa* have significant growth-inhibiting activities against *B. capitatus* in addition to a strong synergistic with ketoconazole.

In fact, both Western medicine and traditional Chinese medicine have advantages and weaknesses. Most Chinese people prefer herbal medicines to Western allopathic drugs. Herbal preparations are thought to be more natural, much less dangerous and slower and gentler in action, yet equally or more effective compared to synthetic chemical drugs. If these two types of medicines can be more fully integrated, it would provide a more effective health approach than the present one medicine system, which uses Western medicine as the primary treatment and other alternative medicine, including traditional Chinese medicine as supplements.

Conclusion

Traditional Chinese medicine was developed through thousands of years of "trial and error" and is result-based black box model. Traditional Chinese medicine analyzes multiple variables of output from the body (the black box) to define the status of the system (diagnosis). Then, using corrective inputs (*e.g.* herbs) as intervention, the system is brought back into balance based on trial and error. The lack of understanding of the detailed internal mechanisms of the human black box means that it is difficult to study the detailed mechanisms of treatments that are effective. The numerous components in various herbal medicines target different organs and elements of the human body to act as an intricate synergistic phytopharmaceutical mechanism. In the classical Chinese pharmacopoeia, a variety of herbal formulae were described for use in disease treatment. The therapeutic effects of plant extracts or the constituents of herbal drugs have a thousand years of experience-based validation. Therefore it was postulated that in traditional Chinese medicine many active ingredients work together, rather than one single ingredient. However, as it had never been assessed in detail pharmacological or clinical studies, the complementary, synergistic effects were doubted. In the scientific approach, scientific proof is required.

In the last three decades, traditional Chinese medicine has increased its prevalence in many countries. Germany and France dominate the European herbal market with 39 and 29% of market share, based on value of sales. In America, raw herbal medicine imports have increased year by year. These increases have led scientists to further study the pharmacological synergy of traditional Chinese medicine.

The scientific proof and clinical validation of these herbal formulations include chemical standardization, biological assays, animal models and clinical trials. Recent studies have used a three method approach to scientific phytopharmaceutical study of pharmacokinetic or pharmacodynamic interactions.

Through animal models, biological assays and clinical trials, much stronger phytopharmaceutical effects were observed when using traditional

Chinese medicine formulae or combined herbs as compared to using one herb alone. This indicates that synergistic effects exist within the herbs.

Sometimes, a change in the phytopharmaceutical effects happened because of a change from a single herb or bioactive compound to combined herbs or compounds. The multi herbs can present a different synthesis treatment targets. Synergism was operating between the different herbs and compounds. Through isobol experiments a much lower dose of combined bioactive compounds may be used compared to the amount of bioequivalent drugs used to achieve the same effect.

In addition, more and more scientific evidence has been presented to explain the synergistic mechanism in traditional Chinese medicine. Besides pharmacokinetic or pharmacodynamic interactions, Shi *et al.*[38] established the combined pharmacokinetic-pharmacodynamic (PK-PD) model that forges a link between these two classical disciplines of Eastern and Western medicine to test herbs. It may be used to explain the synergistic mechanism of herbal medicine. Even the new European legislation in year 2003, supports the presence of vitamins or minerals in the herbal medicine products for which there is well-documented evidence of their safety. This does not prevent the product from being eligible for registration as a traditional herbal medicinal product, provided that the action of the vitamins or minerals is ancillary to that of the active herbal ingredients. This reflects the fact that most of the traditional combined products between an herbal and non herbal ingredient are indeed combinations of herbs with vitamins and minerals.

In the last four decades, traditional Chinese medicine has been widely studies in combination with Western medicine. Synergism between Western medicine and traditional Chinese medicine has been scientifically validated. Now, ICWM is the trend in China and it has proven to provide more efficient curative effects than either system alone. In many other countries, traditional Chinese medicine is integrated with Western medicine in the treatment of special disease. In the future, new approaches and methods may be established to provide a clearer explanation of phytopharmaceutical phenomenon. Clinically based traditional Chinese medicine may finally become a modern medicine in its pharmaceutical approach.

REFERENCES

1. M. Spinella, *Altern. Med. Rev.*, **7**, 130 (2002).
2. H. Wagner, *Pure Appl. Chem.*, **71**, 1649 (1999).
3. H. Nagasawa, H Inatomi, M. Suzuki and T. Mori, *Anticancer Res.*, **12**, 141 (1992).
4. D. Candinas, W. Mark, V. Kaever, T. Miyatake, N. Koyamada, P. Hechenleitner and W.W. Hancock, *Transplantation*, **62**, 1855 (1996).
5. T.T. Phan, M.A. Hughes, G.W. Cherry, T.T. Le and H.M. Pham, *J Altern. Complement Med.*, **2**, 335 (1996).
6. S.P. Verma, E. Salamone and B. Goldin, *Biochem. Biophys. Res. Commun.*, **233**, 692 (1997).

7. T.K. Shung, Y. Shih-Liang, H. Chang-Chi, Y. Mei-Do, W. Ting-Fu and L. Jaung-Geng, *Immunopharm. Immuinot.*, **22**, 711 (2000).
8. R.H. Liu, *Am. J. Clin. Nutr.*, **78**, 517S (2003).
9. N. Azas, N. Laurencin, F. Delmas, G.C. Di, M. Gasquet, M. Laget and P. Timon-David, *Parasitol Res.*, **88**, 165 (2002).
10. Y. Lei, Q. Gao and Y.S. Li, *Zhongguo Zhong Xi Yi Jie He Za Zhi*, **23**, 753 (2003)
11. A.L. Anaya, R. Mata, J.J. Sims, A. Gonzalez-Coloma, R. Cruz-Ortega, A. Guadano, B.E. Hernandez-Bautista, S.L. Midland, R. Rios and A. Gomez-Pompa, *J. Chem. Ecol.*, **29**, 2761 (2003).
12. J.B. Fernandes and V.M. Vargas, *Phytother. Res.*, **17**, 269 (2003).
13. M.C. Carpinella, L.M. Giorda, C.G. Ferrayoli and S.M. Palacios, *Agric. Food Chem.*, **51**, 2506 (2003).
14. F. Paiva-Martins, M.H. Gordon and P. Gameiro, *Chem. Phys. Lipids*, **124**, 23 (2003).
15. M.C. Berenbaum, *Pharmacol. Rev.*, **41**, 93 (1989).
16. M.J. Hall and I.B. Duncan, in ed: H.J. Field, Antiviral Agents: the Development and Assessment of Antiviral Chemotherapy, Vol. 2, pp. 29-84, CRC Press, Boca Raton, FL (1988).
17. E.U. Vorbach, W.D. Hubner and K.H. Arnoldt, *J. Geriatr. Psychiatry Neurol.*, **7**, S19 (1994).
18. B. Steinke, Chemisch-analytische und pharmakologische Untersuchungen von p-anzlichen PAF-Antagonistenund Inhibitoren der Thrombozytenaggregation (Allium-Arten, Ginkgo biloba, Pinellia ternata), Thesis, Munich (1993).
19. R.K. Zee-Cheng and Shi-Quan-Da-Bu-Tang, *Methods Find Exp. Clin. Pharmacol.*, **14**, 725 (1992).
20. C.L. Hsieh, N.Y. Tang, S.Y. Chiang, C.T. Hsieh and J.G. Lin, *Life Sci.*, **65**, 2071 (1992).
21. A.R. Liu, Z.Y. Yu, L.L. Lu, Z.Y. Sui, *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi*, **18**, 76 (2000).
22. R. Giordani, P. Regli and J. Buc, *Mycoses*, **45**, 476 (2002).
23. G. Clifford, Beddows, J. Charanjit and J.K. Michael, *Food Chem.*, **73**, 255 (2001).
24. G. Liwei and W. Xinchu, *Food Chem.*, **73**, 299 (2001).
25. M. Zhu, K.T. Lew and P.L. Leung, *Phytother. Res.*, **16**, 276 (2002).
26. A.E. Edris and E.S. Farrag, *Nahrung.*, **47**, 117 (2003).
27. Z. Ye, A. Sun, C. Li, B. Xue, A. Liang, J. Wang, Z. Wang, Y. Tong and H. Feng, *Zhongguo Zhong Yao Za Zhi*, **24**, 556, 576 (1999).
28. H. Fujiki, M. Suganuma, M. Kurusu, S. Okabe, Y. Imayoshi, S. Taniguchi and T. Yoshida, *Mutat. Res.*, **523-524**, 119 (2003).
29. C. Cal, H. Garban, A. Jazirehi, C. Yeh, Y. Mizutani and B. Bonavida, *Curr. Med. Chem. Anti-Canc. Agents*, **3**, 77 (2003).
30. R.E. Schwarz, C.A. Donohue, D. Sadava, S.E. Kane, *Cancer Lett.*, **189**, 59 (2003).
31. L.C. Chiou, J.Y. Ling and C.C. Chang, *Eur. J. Pharmacol.*, **292**, 151 (1995).
32. X. He, D. Verran, C. Hu, C. Wang, L. Li, L. Wang, J. Huang, J. Sun and A.G. Sheil, *Transplant Proc.*, **32**, 2054 (2000).
33. Y. Hu and H. Hang, *Wei Sheng Yan Jiu*, **30**, 336 (2001).
34. M. Toshiaki, W. Hannosuke, O. Takuya, O. Yasuhiro, D. Yoshiharu and K. Yoshihiro, *J. Ethnopharm.*, **82**, 35 (2002).
35. W.Q. Wang, X.Y. Han, X.F. Zhang, L.J. Kang and S.L. Chen, *Meded. Rijksuniv. Gent. Fak. Landbouwkd. Toegep. Biol. Wet.*, **67**, 299 (2002).
36. H.N. Saada, Z.S. Ussama and A.M. Mahdy, *Pharmazie*, **58**, 929 (2003).
37. S. Shin and C.A. Kang, *Lett. Appl. Microbiol.*, **36**, 111 (2003).
38. S.-J. Shi, H. Chen, S.-F. Gu and F.-D. Zeng, *Acta Pharmacol. Sin.*, **24**, 1011 (2003).

(*Received*: 2 February 2005; *Accepted*: 30 June 2006) AJC-5028