ORIGINAL ARTICLE

A Herbal Formula for Prevention of Influenza-Like Syndrome: A Double-Blind Randomized Clinical Trial*

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ABSTRACT **Objective:** To investigate the efficacy of a herbal formula in the prevention of influenza or influenza-like syndrome among elderies residing in old-people's home in Hong Kong. The secondary objectives are to investigate the quality of life (QOL) and symptomology changes among the herbal users and to evaluate the safety of this formula. **Methods:** In ten old people's home or community centres in New Territories, Hong Kong, 740 eligible subjects agreed to join the study and were randomized to receive a herbal formula or a placebo on alternate days over 8 weeks. Among those 740 participants, 113 had provided blood samples for immunological assessments before and after the study drug. Assessments were done at 0, 4, 8 and 12 weeks. Participants were instructed to keep a daily record of body temperature and any symptoms as sore throat, myalgia, running nose or cough, and to report to assessor accordingly. Those reporting body temperature of 37.8 ℃ and above would be visited and a proper nasopharyngeal swab be taken for viral study. **Results:** Seventy-two participants developed influenza-like-symptoms but none of them was proven influenza in their nasopharyngeal swabs, 40 of these patients belonged to the herbal group and 32 to the placebo group, without significant differences between groups. The difference on the changes in QOL between the two groups was not statistically significant. However, in the immunological study, the natural killer cell absolute count was significantly increased in the herbal group compared with the placebo group (463±253 *vs* 413±198, $P<0.05$). **Conclusions:** The herbal preparation was not effective compared with placebo in the prevention of influenza-like syndrome. It was however safe and possibly supporting immunological responses.

KEYWORDS complementary medicine, influenza, herbal treatment

Influenza presents with a syndrome of fever, naso-respiratory disturbances, malaise, and musculo-skeletal aches. In Chinese medicine (CM), "Wen Bing" (温病) meaning feverish diseases, gives close resemblance to influenza. Such respiratory ailments and diseases were so prevalent in ancient China that Wen Bing developed into a highly specialized branch of CM which could be traced back 500 years. According to the traditional Wen Bing precepts, influenza-like diseases can be divided into four stages: (1) fever development, (2) nasal symptoms, (3) fever and chills, and (4) hemoptysis.[1] In modern medicines, the first two of the above-mentioned stages may be viewed as symptoms that usually subside without treatment. The later stages represent more unusual conditions, when bronchitis and late pneumonia occur.

Influenza could be associated with high mortality and high morbidity among the vulnerable groups of people, for instance, the elderly with underlying cardiovascular or pulmonary diseases.[2,3] Vaccination plays a central role in the prevention of influenza. However, the efficacy is short of absolute guarantee because of the changing nature of the responsible virus.

During the severe acute respiratory syndrome (SARS) outbreak in Hong Kong in 2003, a herbal formula was developed in the Prince of Wales Hospital and distributed to over 3,000 hospital workers, with the aim of protecting them from contracting the SARS

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infection.[4] The results of evaluation were encouraging: none of those using the herbal preparation contracted SARS while 0.4% of other health workers were infected. Improvement of influenza-like symptoms and quality of life (QOL) measurements were also observed. Only less than 2% reported minor adverse events.[4] The observation did not allow conclusive deductions since the trial was neither randomized nor placebo-controlled; and during the chaotic period of the deadly epidemic, measures to ensure a proper conduction of a trial were simply lacking. Nevertheless, a study of the immunological state of 40% the herbal consumers indicated that there was objective evidence of improvement of body defense system after two weeks of treatment. Interestingly, the boostering effect subsided two weeks later.[5]

We therefore consider that further exploration on the efficacy of the herbal preparation is justified and a plan for a proper randomized controlled trial is thus constructed. Since the annual record of the Department of Health in Hong Kong, indicated that an endemic of influenza is likely to appear from February to April every year, a preventive program could be organized within this period accordingly.

The primary objective of the study was to investigate the efficacy of the herbal preparation previously used for the prevention of SARS against endemic influenza among a group of at risk elderly people. If unpredictabley, the annual endemic did not happen, the primary objective would have to be changed to the control of influenza like syndrome. The secondary objectives included the safety of using the preparation and the changes in the QOL among the users.

METHODS

Design and Participants

The study was designed as a double-blind, placebo-controlled, and randomized trial. The target participants were dwellers of old-age homes or attendance of elderly centre, aged 60 or above. A total of 10 elderly centres and old age homes were randomly selected from New Territories, Hong Kong. The inclusion criteria included those enjoying stable health and had no influenza-like symptoms on enrollment. Written informed consents were obtained from all the participants before entry into the study and the study protocol was approved properly by the Clinical Research Ethics Committee of the Prince of Wales Hospital. Exclusion criteria included history of hypersensitivity to herbs, regular consumers of other herbal preparations, medications that were known to upset the immuno-modulating function, e.g. steroids, and severe cognitive dysfunctions. Only those who did not receive influenza vaccination in the past six months would be asked to join the blood sample group.

The eligible participants were allocated randomly in a double-blind way to one of the two treatment groups according to a computer generated stratification randomized block design. The stratification was made on old-age home/elderly centre and vaccination status. In each old-age home or elderly centre the participants were randomized separately within the vaccinated group or non-vaccinated group to receive either herbal preparation or placebo. Participants received the 4 g sachet of herbal preparation or placebo on alternate days over 8 weeks. After 8 weeks, participants stopped taking either the herbal preparation or placebo but were followed up by research interviewers at the end of another 4 weeks. The placebo was made of starch that was coloured to resemble herbal tea.

In the 8-weeks study period, participants were instructed to keep a daily record of body temperature and any symptoms such as sore throat, myalgia, running nose and cough, which resembled symptoms of influenza. A research interviewer telephoned each participant twice a week to gather the update data, while individual participants was required to report to the interviewers any time when they suspected contraction of influenza-like illness. When the body temperature was more than 37.8 ℃, a naso-pharyngeal swab would be taken from the individual by the research nurse, and sent for viral investigation. Influenza-like symptoms and adverse reactions were observed and QOL was evaluated at the 0, 4th, 8th and 12th week.

A subgroup was recruited for examination of the blood for immunological markers. Total of 133 participants who did not receive influenza vaccination within 6 months before the study were recruited and consent on voluntary basis. They were required to give 12 mL of blood each before and 8 weeks after the administration of either herbal or placebo intervention.

Herbal Preparation

Every herbal component was tested for heavy metals, microbial and pesticide contaminations and

all test results met the safety requirements in Hong Kong. The formula was prepared as granules ready for consumption as a drink in a qualified laboratory licensed for Good Manufacturing Practice in Hong Kong (Chinese Medicine Industry Development Centre, Hong Kong Institute of Vocational Education, Hong Kong, China). The formula contained 12 commonly used herbs: *Morus alba* L. 8.2%, *Chrysanthemum morifolium* Ramat. 3.3%, *Prunus armeniaca* L. 6.6%, *Forsythia suspense* Vahl 5.5%, *Mentha haplocalyx* Briq. 2.7%, *Platycodon grandi florum* (Jacq.) A. DC. 6.6%, *Glycyrrhiza glabra* L. 2.7%, *Phragmites communis* Trin. 6.6%, *Scutellaria baicalensis Georgi* 13.1%, *Isatis indigotica* Fort. 17.5%, *Astragalus membranaceus* (Fisch.) Bge. 16.4%, *Saposhnikovia divaricata* (Turcz.) Schischk. 10.9%. The placebo was manufactured in the same laboratory and the preparation matched the herbal drink satisfactorily in both colour and taste.

Outcome Measurements

The primary outcome was the number of episodes of influenza and influenza-like illnesses detected in the two different groups (incidence). Influenza-like illness was defined by a fever over 37.8 ℃, plus presence of at least one of the influenza symptoms, e.g. sore throat, cough, running nose, or myalgia. For cases with fever, a nasopharyngeal swab was collected for the laboratory detection of influenza pathogens. The QOL was evaluated using SF-36 questionnaire (Vitality and Mental Health Sub-scales)[6,7] and the immunological state was read from blood samples. Immunological parameters included B lymphocytes, T lymphocytes, T-helper lymphocytes (CD4), T-suppressor lymphocytes (CD8) and natural killer (NK) cells. Basic hematology (complete blood count and white blood cell), and biochemistry for renal and liver functions were included for safety studies.

Statistical Analysis

All data was managed using SPSS 11.0 software. The participants' demographics were first presented descriptively in overall and subgroups aspects. Then parametric and non-parametric statistical analysis methods were used to test the change of health status, flu-like syndrome, immunological status, and safety profile before and after taking study drinks. Intention-to-treat analysis was applied.

RESULTS

Demographic Data

From Dec 2003 to July 2004, a total of 1,483 subjects were screened in 10 elderly homes and elderly centres, and 872 subjects met the inclusion and 740 subjects agreed to join the study with the response rate of 85%. Among the 740 subjects, 133 subjects agreed to provide blood samples for immunology assessments. Before randomization, 740 participants were randomly allocated into either the herbal or placebo group after recruitment and written consent signing. Sixty-six participants drop out shortly after commencement, another 58 participants drop out in the following visit and a total of 124 participants (16.8%) declined participation with 16.5% and 17% respectively belonging to the herbal and placebo groups. Reasons for withdrawals were related to personal preference and mild adverse events which are listed in the flow chart (Figure 1).

At baseline, there were no significant differences between the herbal and the placebo groups. Material including age, gender, habits of herb/dietary supplement intake and medical conditions are shown in Table 1. Also, the renal and liver functions of all 133 participants who volunteered to provide blood sample for immunological assessment were within normal ranges.

During the study period, for the first time in five years in the record of the Department of Health in Hong Kong, there was no outbreak of influenza endemic, either in the general family clinics of the Department of Health, or in the Private Sector.

Our protocol that was designed to meet the endemic therefore the study had to be modified to target on control of influenza-like syndrome, 72 of 740 participants (9.7%) reported to us about fever and symptoms resembling influenza, however, their naso-pharyngeal swabs showed negative results in the viral cultures.

There was no statistical difference in fever occurrence between the herbal and placebo groups [40 (10.6%) *vs* 32 (8.8%), Table 2]. And the symptoms such as running nose was less in the herbal group than in the placebo group (P=0.03, Table 2).

QOL

The QOL on mental health and vitality health were improved in both herbal and placebo groups during the treatment period and washout period (P<0.01, Table 3), with no significant difference between the two groups.

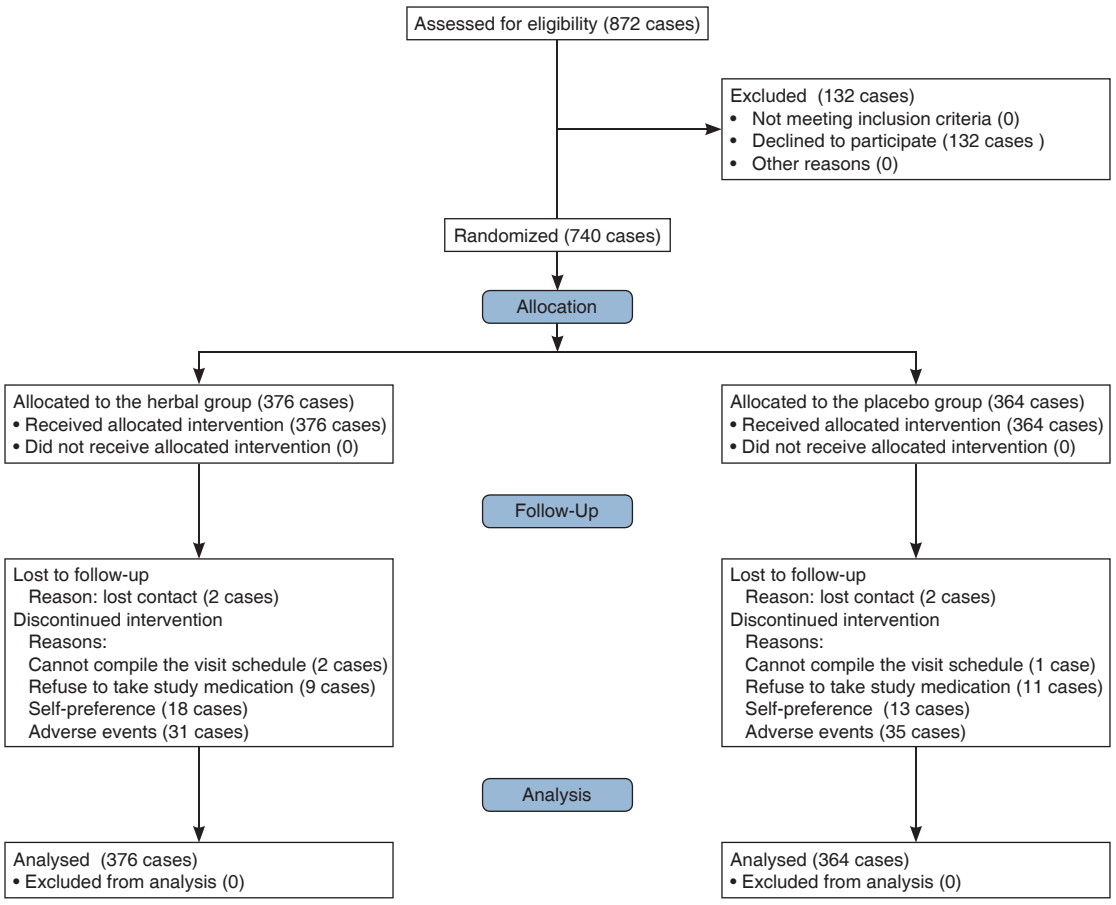

Figure 1. The Flow Chart of the Study

Table 1. Characteristics of the Participants at the Beginning of Intervention before Herbal Treatment (%, $\bar{x} \pm s$)

Variable	Centre (518 cases)			Home (222 cases)			Non-vaccinated (189 cases)			Vaccinated (551 cases)			All (740 cases)		
	Herbal (50.8)	Placebo (49.2)	*P*	Herbal (50.9)	Placebo (49.1)	*P*	Herbal (50.8)	Placebo (49.2)	*P*	Herbal (50.8)	Placebo (49.2)	*P*	Herbal (50.8)	Placebo (49.2)	*P*
Demographics															
Age (years)	72.7±6.9	73.9±6.5	0.04	81.9±7.4	81.7±6.5	0.82	72.1±6.4	74.2±6.6	0.03	76.6±8.5	77.0±7.5	0.59	75.5±8.2	76.3±7.4	0.17
Sex (Male)	19.4	20.0	0.86	9.7	9.2	0.89	33.3	31.2	0.75	10.7	11.8	0.75	16.5	16.8	0.92
Habit															
Drink Chinese tea everyday	44.5	44.7	0.96	21.2	17.4	0.47	41.7	48.4	0.35	36.1	32.5	0.37	37.5	36.5	0.79
Dietary supplements	29.3	33.3	0.32	20.4	15.6	0.36	22.9	26.9	0.53	27.9	28.4	0.89	26.6	28.0	0.66
Medical History															
Hypertension	47.1	49.0	0.67	54.0	48.6	0.43	40.6	40.9	0.97	52.1	51.7	0.91	49.2	48.9	0.94
Diabetic	17.9	18.8	0.78	11.5	15.6	0.37	18.8	9.7	0.08	15.0	20.7	0.08	16.0	17.9	0.49
Heart disease	10.6	9.0	0.53	16.8	16.5	0.95	10.4	11.8	0.76	13.2	11.1	0.44	12.5	11.3	0.60
Stroke	2.7	4.3	0.31	8.0	14.7	0.11	2.1	4.3	0.44	5.0	8.5	0.10	4.3	7.4	0.07
Respiratory disease	6.5	8.6	0.35	8.0	13.8	0.16	4.2	9.7	0.14	7.9	10.3	0.31	6.9	10.2	0.11
High cholesterol	19.0	22.7	0.30	2.7	11.0	0.01	11.5	15.1	0.47	15.0	20.7	0.08	14.1	19.2	0.06
Fever in last 4 weeks*△	1.1	0.0	0.25		0.0	0.0	—	0.0	0.0	—	1.1	0.0	0.25	0.8	0.0

Notes: Student's *t*-test was used on continuous variable, χ^2 test or Fisher's exact test was used on categorical variable, two-tailed, α=0.05; *: any fever in last 4 weeks of treatment start; △: 4 missing cases

Table 2. Influenza-like Symptoms Recorded during Eight-Week-Study [Case (%)]

Group	Case	Fever	Sore throat	Muscle pain	Cough	Running nose
Herbal	376	40 (10.6)	49 (13.0)	34 (9.0)	110 (29.3)	79 (21.0)
Placebo	364	32 (8.8)	58 (15.9)	39 (10.7)	117 (32.1)	101 (27.7)
P value		0.40	0.26	0.45	0.39	0.03

Table 3. QOL in All Participants (Score, $\bar{x} \pm s$)

Group	Time	Case	Mental health	Vitality
Herbal	0 wk	376	79.5 ± 19.5	70.2 ± 21.9
	4 wk	343	85.7 ± 17.7*	75.5 ± 19.3*
	8 wk	322	86.9 ± 16.5*	74.9 ± 21.7*
	12 wk	323	88.2 ± 16.5*	77.0 ± 20.9*
Placebo	0 wk	364	79.6 ± 18.9	67.9 ± 21.7
	4 wk	331	85.9 ± 18.2*	74.5 ± 21.2*
	8 wk	307	86.7 ± 19.1*	73.1 ± 23.5*
	12 wk	308	85.9 ± 19.7*	75.9 ± 22.8*

Note: *P<0.01, compared with the baseline (0wk) within group

Immunological Test

In 133 participants who volunteered to have their blood checked before and after treatment, 20 participants were lost to follow-up due to their personal reasons. Thus, there were 113 subjects providing baseline and post-study blood sample. In the immunological state, there were no different between groups at baseline. After 8-week-treatment, the NK absolute count was significantly enhanced in the herbal group (P<0.05, Table 4). Other immunological parameters had no significant difference.

Vaccination

The majority of subjects had received influenza vaccination within 3 months before the study (vaccinated 551/non-vaccinated 189 cases). The vaccinated and non-vaccinated groups were compared for symptoms and improvement of symptoms after herbal drink. No significant difference was found between the two groups.

Adverse Events

There were 287 participants in the herbal group and 253 in the placebo group who were reported mild adverse effect. Dizziness, headache, sputum, and diarrhea were the most common mild adverse effects. Thirty-one (8.2%) and 35 (9.6%) participants withdrew from the herbal and the placebo group respectively due to the mild adverse events. All mild adverse events subsided 2–3 days either in the dropout group and study groups probably because the reported symptoms were not directly related to the herbal preparation (Table 5).

DISCUSSION

The anti-viral formula was created from the combination of two popular classic formulae, Sangju Decoction (桑菊饮) and Yupingfeng Powder (玉屏风散) modified and supplemented with two other herbal items known to be anti-viral. This trial was designed according to the annual expectation of an influenza endemic which happened for 5 consecutive years from 1999–2003. For some uncertain reasons, the

Table 4. Immunological Changes at Baseline and Post Treatment ($\bar{x} \pm s$)

Group	Case	T lymphs		T suppressor		T helper		NK lymph		B lymph		T helper/ Suppressor ratio
		%	Count	%	Count	%	Count	%	Count	%	Count	(%)
Herbal												
Baseline	70	62.5 ± 10.5	1336 ± 460	22.0 ± 8.8	469 ± 230	38.4 ± 9.5	820 ± 337	21.8 ± 9.8	453 ± 238	14.3 ± 6.8	302 ± 106	2.08 ± 1.06
Post-treatment	57	63.4 ± 10.2	1392 ± 472	22.6 ± 8.9	489 ± 252	38.8 ± 8.7	851 ± 321	21.4 ± 9.9	463 ± 253	13.9 ± 6.9	299 ± 161	2.02 ± 0.98
Change (Post-baseline)		0.40 ± 3.95	38 ± 330	0.21 ± 1.92	16 ± 142	0.05 ± 4.67	16 ± 210	0.35 ± 4.22	24 ± 144	–0.68 ± 2.55	–7 ± 63	–0.04 ± 0.37
Placebo												
Baseline	63	62.3 ± 11.2	1301 ± 447	21.7 ± 9.1	459 ± 262	39.1 ± 9.8	797 ± 286	21.8 ± 11.4	450 ± 247	14.4 ± 5.7	304 ± 147	2.17 ± 1.09
Post-treatment	56	62.6 ± 11.2	1280 ± 483	21.8 ± 8.8	450 ± 265	39.6 ± 9.3	797 ± 311	21.4 ± 10.9	413 ± 198	14.6 ± 5.9	301 ± 162	2.16 ± 1.03
Change (Post-baseline)		0.57 ± 3.31	–5 ± 182	0.48 ± 1.82	5 ± 92	0.41 ± 3.27	4 ± 106	–0.45 ± 3.94	–32 ± 140*	–0.16 ± 2.16	–10 ± 67	–0.04 ± 0.36

Note: *P<0.05, compared with the herbal group

expected endemic did not occur during the trial. Instead, the clinical trial had to shift the target from influenza prevention to the investigation on preventing influenza-like syndrome with herbal preparation.

Table 5. Adverse Reactions

No.	Adverse reaction	Frequency [Case (%)]	
		Herbal	Placebo
1	Dizziness	36 (12.5)	35 (13.8)
2	Cough	4 (1.4)	7 (2.8)
3	Sputum	19 (6.6)	14 (5.5)
4	Abdominal pain	7 (2.4)	14 (5.5)
5	Diarrhea	9 (3.1)	15 (5.9)
6	Vomiting	8 (2.8)	3 (1.2)
7	Nausea	5 (1.7)	2 (0.8)
8	Headache and heavy feeling	34 (11.8)	25 (9.9)
9	Sleepless/insomnia	11 (3.8)	9 (3.6)
10	Dry mouth	7 (2.4)	1 (0.4)
11	Low appetite but not thirsty	1 (0.3)	4 (1.6)
12	Bitter taste	4 (1.4)	1 (0.4)
13	Allergy	2 (0.7)	1 (1.4)
14	Dry/itchy skin	6 (2.1)	4 (1.6)
15	Flatulence	7 (2.4)	9 (3.6)
16	Stomach ache	9 (3.1)	4 (1.6)
17	Tachycardia	4 (1.4)	1 (0.4)
18	Chest pain	0	4 (1.6)
19	Shortness of breath	3 (1)	1 (0.4)
20	Cramp	4 (1.4)	7 (2.8)
21	Hypertension clients increase blood pressure	8 (2.8)	2 (0.8)
22	Chill	5 (1.7)	2 (0.8)
23	Flushing	5 (1.7)	2 (0.8)
24	Tired	8 (2.8)	13 (5.1)
25	Ear discomfort	2 (0.7)	2 (0.8)
26	Hoarse	2 (0.7)	2 (0.8)
27	Eye discomfort	4 (1.4)	8 (3.2)
28	Upper or lower limps numbness	3 (1)	0
29	Facial/feet swelling	1 (0.3)	9 (3.6)
30	Leg pain/foot pain	7 (2.4)	8 (3.2)
31	Generalized bone pain	12 (4.2)	11 (4.3)
32	Dysphagia	0	1 (0.4)
33	Spinal disease	3 (1)	6 (2.4)
34	Gastroenteritis	1 (0.3)	2 (0.8)
35	Discomfort of chest	6 (2.1)	3 (1.2)
36	Dysuria	4 (1.4)	3 (1.2)
37	Gynaecological problem	2 (0.7)	0
38	Frequent bowel movement	1 (0.3)	3 (1.2)
39	Black stool	1 (0.3)	1 (0.4)
40	Constipation	4 (1.4)	1 (0.4)
41	Discomfort of bridge	1 (0.3)	0
42	Frequent urination	3 (1)	2 (0.8)
43	Gum discomfort	4 (1.4)	4 (1.6)
44	Stroke	3 (1)	0
45	Toothache	5 (1.7)	1 (0.4)
46	Stuffy nose	2 (0.7)	3
47	Epistaxis	1 (0.3)	0
48	Dull	1 (0.3)	0
49	Stress	1 (0.3)	0
50	Palpitation	2 (0.7)	0
51	Pleural effusion	1 (0.3)	0
52	Pearl ganglia	1 (0.3)	0
53	Resolving food stagnancy	1 (0.3)	0
54	Vaginitis	1 (0.3)	0
55	Fell and slipped	1 (0.3)	0
56	Feeling hungry	0	1 (0.4)
57	Hyperglycaemia	0	1 (0.4)
58	URTI	0	1 (0.4)
Total		287	253

There is no apparent efficacy of the herbal preparation on the prevention of influenza like symptoms, the preparation showed only better effect than the placebo on nasal discharge. Similar to the results from our previous study using the same herbal preparation during the SARS crisis, objective data on immunological modulation showed clear superiority of the herbal preparation over placebo. In another trial on healthy volunteers aiming at the behavior of immuno-modulating indicators, i.e., T cells and B cells in the lymphocyte series, the results were also positive.[5]

The series of objective data supporting the immuno-modulating efficacy of the herbal preparation threw optimism on the further research of using herbal preparations for the prevention or treatment of influenza or influenza-like upper respiratory viral infection. The direction would include the optimization of the herbal formula, by varying the components of the formula, or better still, by identifying the effective fraction from the gross extraction of the formula. The concept of disease prevention in herbal medicine is not one that follows the logic of immunization, which initiates a prolonged state of positive immuno-

defense. Instead, the mechanism of action could be very much of a short term boostering of the immunological sensitivity which would be beneficial for the early control of an invading viral infection at its early stage.

While seasonal Influenza vaccination was highly recommended to prevent influenza and its complications, especially to high risk groups, such as healthcare workers, chronic illness, pregnant women, children less than 6 years, elderly persons aged above 65 years.[8] The cost-effectiveness analysis and reports pronounced the vaccination program could reduce both health-care costs and productivity losses associated with influenza illness.[9,10] While most developed country and area like United States, United Kingdom, Canadian, Australia, including Hong Kong had implemented national vaccination programs against influenza annually in the form of free or subsidized offer to the high risk groups, the community acceptance of pre-pandemic influenza vaccination was rather low.[11-14] In the 2009/2010 swine Influenza vaccination program among developed countries, due to the low take-up rate, the over abundance of unused vaccine ended up with inevitable destruction.[15,16] With the rising popularity of herbal medicine, some of the known antiviral activities, immuno-supportive and symptom relieving effects, our herbal formula could be offered as a viable option by itself or as an adjuvant to the vaccination program.

Disclosures

All authors disclose no conflicts of interest in this work.

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