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Phytochemical Extracts Do Not Exhibit the Characteristic Pharmacological Properties of Chinese Tonifying Herbs

Kam Ming Ko*, Hoi Yan Leung

Division of Life Science, Hong Kong University of Science & Technology, Hong Kong SAR, China
Email: *bcrko@ust.hk

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Abstract

This study investigated the tonifying properties of phytochemical extracts marketed as nutraceuticals, specifically their potential to enhance Yang, Qi, Yin, and Blood functions according to Chinese medicine theory. We assessed four extracts enriched with quercetin, resveratrol, catechins, and curcumin through established pharmacological assays for each functional category of Chinese tonifying herbs. Results indicate that none of the extracts demonstrated Yang or Qi-invigorating effects, suggesting that they do not enhance cellular energy metabolism similar to Yang and Qi tonifying herbs. The resveratrol-enriched extract exhibited some Yin-nourishing properties, albeit less effective than the Yin herb *Ligustri Lucidum Fructus*. Additionally, catechin- and curcumin-enriched extracts increased nitric oxide production but did not stimulate erythropoietin levels, raising questions about their Blood-enrichment capabilities. Overall, the findings suggest that while these nutraceuticals offer various health benefits, they may not significantly influence the Zang Xiang physiological system in Chinese medicine, highlighting the importance of using Chinese tonifying herbs for a holistic approach to safeguarding health.

Keywords

Phytochemicals, Yang, Qi, Yin, Blood, Zang Xiang

1. Introduction

Preventive health is a major trend in the 21st century. In Western countries, nutraceutical products are commonly used to promote health and prevent diseases, often enriched with phytochemicals such as polyphenols and flavonoids [1]-[3]. A well-known example is resveratrol, a natural polyphenolic compound found

in grapes, red wine, berries, and peanuts [4]. Another important polyphenol is curcumin, the active ingredient in turmeric [5]. Catechins, primarily found in green tea, are flavonoids recognized for their complex structure with multiple hydroxyl groups [6]. Quercetin, a flavonol, can be found in various foods, including apples, berries, grapes, onions, and tea [7]. Research from both *in vivo* and *in vitro* pharmacological studies indicates that these phytochemicals provide potential health benefits, such as antioxidant, anti-inflammatory, cholesterol-lowering, cardiovascular protective, and anticancer actions in humans [8]-[11].

In Chinese medicine, tonifying herbs are used to enhance bodily functions. The Zang Xiang System, which outlines the physiological framework of Chinese medicine, emphasizes the importance of balancing Yin and Yang, as well as Qi and Blood, for optimal health [12]-[14]. The purpose of using these tonifying herbs is to restore imbalances and holistically promote overall wellness in humans. Previous studies in our laboratory have established *in vitro* pharmacological assays for these herbs across four functional categories: Yang invigoration, Qi invigoration, Yin nourishment, and Blood enrichment [15]-[20]. Comparisons of the pharmacological properties using cell-based assays among these categories revealed that Yang-invigorating and Qi-invigorating herbs enhance mitochondrial ATP production [17], while Yin-nourishing herbs stimulate antigen-induced splenocyte proliferation [18], and Blood-enriching herbs promote the production of nitric oxide (NO) and/or erythropoietin (EPO) [19]. Notably, Yang and Qi herbs enhance mitochondrial ATP production through different mechanisms [17]. By assessing Chinese tonifying herbs (9 - 10 in number) in each functional category using the above-listed assays, specific pharmacological assays have been identified to create a pharmacological index that characterizes the unique effects of Chinese tonifying herbs within the framework of Chinese medicine theory.

Given that the pharmacological actions of phytochemicals occur within the anatomical and physiological system described in Western medicine, we aimed to investigate whether phytochemical-based health products exhibit tonifying effects (Yang, Qi, Yin, Blood) in comparison to Chinese tonifying herbs.

2. Materials and Methods

2.1. Reagents

Fetal bovine serum (FBS), minimum essential medium (MEM) and Dulbecco's modified Eagle's medium (DMEM) were obtained from Life Technologies was obtained from Life Technologies Corporation (Carlsbad, CA). DMEM (without glucose and phenol red), adenosine triphosphate (ATP), adenosine diphosphate (ADP), RPMI-1640 medium (without phenol red), penicillin, streptomycin, dimethyl sulfoxide (DMSO), MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide), and lipopolysaccharide (LPS) were purchased from Sigma Chemical Co. (St. Louis, MO). The luciferase kit was obtained from Perkin Elmer (Boston, MA). Concanavalin A (Con A) and sodium pyruvate were obtained from Santa Cruz Biotechnology Inc. (Santa Cruz, CA). Bio-Rad protein assay dye rea-

gent concentrate was obtained from Bio-Rad (Hercules, CA, USA). Human erythropoietin (EPO) ELISA kits were purchased from Wuhan Fine Biotech Co., Ltd. (FineTest) (Wuhan, HB, P.R. China). Phytochemical extracts were purchased from iHerb: Quercetin (Natural Factors, 500 mg quercetin per 700 mg powder); Curcumin (NOW Foods, containing turmeric root extract (Curcuma longa) with minimum 95% curcuminoids); Resveratrol (Natural Factors, containing 500 mg wine grape (Vitis vinifera) concentrate (fruit) plus resveratrol from Japanese knotweed and 250 mg natural trans-resveratrol per 750 mg powder); Catechins (DaVinci Laboratories, containing green tea (Camellia sinensis L.) leaf extract yielding 70% Epigallo-catechin-3-gallate (a polyphenol)). Chinese herbal extracts were purchased from PuraPharm International (H.K.) Ltd (Hong Kong SAR, China); the percentage yield from the crude herb of *Cynomorii Songaricum Herba* (Purapharm 1235), *Panax Ginseng Radix* (Purapharm 1304), and *Ligustri Lucidum Fructus* (Purapharm 1074) were 20%, and that of *Angelica Sinensis Radix* (Purapharm 1017) was 33%.

2.2. Cell Culture

H9c2 cells, which are a subclone of rat heart myoblast cells, were purchased from the American Tissue Culture Centre (ATCC) (Rockville, MD, USA). Cells were cultured as monolayers in DMEM, supplemented with 10% (v/v) heat-inactivated FBS (HIFBS), 100 IU/mL of penicillin, 100 μg/mL of streptomycin, 1 mM sodium pyruvate, and 3.7 g/L $NaHCO_3$. All cells were grown under an atmosphere of 5% (v/v) CO_2 in air at 37˚C in a 90 mm culture plate.

HepG2 cell line originated from the human liver and was purchased from ATCC. Cells were cultured in MEM supplemented with 10% (v/v) FBS, 100 IU/mL of penicillin, 100 μg/mL of streptomycin, 1 mM sodium pyruvate and 1.5 g/L $NaHCO_3$. All cells were cultured in an atmosphere of 5% CO_2 at 37˚C in a 90 mm culture plate.

2.3. ATP Generation Capacity (ATP-GC) Assay

1) Drug pre-incubation and ATP Generation

H9c2 cells were seeded in four 24-well plates (25,000 cells/0.5 mL). After stable attachment, the cells were pre-incubated for 4 h (for testing yang-invigorating effect) or 24 h (for testing Qi-invigorating effect) with a medium containing different concentrations (concentration ranges were listed in the result table) of phytochemical or herbal extracts dissolved in DMSO, 0.2% (v/v). Following the incubation, the cells were washed with phosphate-buffered saline (PBS-A, 200 μL/well; 136 mM NaCl, 2.7 mM KCl, 8.1 mM Na_2HPO_4, 1.5 mM KH_2PO_4, pH 7.2) and treated with 50 μg/mL digitonin at 37˚C for 3 min, except for the protein measurement plate, which was stored at 4˚C until protein determination. For the plate used for measuring basal ATP level, cells were incubated at 4˚C with ATP incubation buffer (120 mM KCl, 5 mM KH_2PO_4, 2 mM EGTA, 10 mM HEPES, 0.1 mM $MgCl_2$, 0.5% BSA, pH 7.4, 150 μL/well) and 30% (w/v) perchloric acid (PCA,

30 μL/well). For the plates used for ATP generation, cells were supplemented with 0.18 mM ADP, 5 mM pyruvate, and 15 mM L-malic acid (all dissolved in ATP incubation buffer, 100 μL for each reagent/well) and incubated at 37˚C for 7.5 and 15 min, respectively, followed by the addition of 30% PCA (60 μL/well). The plates (for measuring basal ATP and ATP generation) were then centrifuged at 540 ×*g* for 20 min at 4˚C. After centrifugation, aliquots (80 μL) of supernatants were neutralized with 60 μL 1.4 M $KHCO_3$ in 1.5 mL micro-centrifuge tubes, followed by vortex mixing and centrifugation at 2150 ×*g* for 10 min [17].

2) ATP assay

To account for ATP contamination in the ADP preparation, an ADP blank was prepared by aliquoting ADP, pyruvate, L-malic acid, and 30% PCA, as described earlier, to 1.5 mL in a micro-centrifuge tube, followed by vortex mixing and centrifugation at 20,000 ×*g* for 5 min. ATP standards (ranging from 0.0005 - 1.0 mM) were prepared by 10-fold serial dilutions. Aliquots (300 μL) of standard solutions were added to 60 μL 30% PCA, followed by vortex mixing, and 80 μL of the standard solutions, as well as the ADP blank, were neutralized with 60 μL 1.4 M $KHCO_3$, followed by vortex mixing and centrifugation at 20,000 ×*g* for 5 min. Fifty microliters of ATP standards (0.0005 - 1 mM) or tested samples were applied to 96-well white plates with 50 μL 10-fold diluted luciferase enzyme prepared in luciferase dilution buffer (250 mM Tricine, 5 mM EDTA (free acid), 5 mM dithiothreitol, 50 mM $MgSO_4$, pH 7.8 adjusted by 1 M KOH). The luminescence was read using a microplate reader. ATP content was estimated from an ATP standard calibration curve. ATP-GC was expressed in nmol/mg protein, and the area under the curve (AUC1) of the graph plotting ATP generation against incubation time was then computed. These AUC1 values were used to calculate the percentage of control (% Control-1), and then the AUC2 of the graph plotting % Control-1 against incubation time was computed. These AUC2 values were used to calculate the percentage of control (% Control-2) for comparison [17].

2.4. Protein Measurement

Proteins were extracted from the cultured cells using 0.1% Triton X in PBS-A, followed by 10-min of shaking at room temperature. Aliquots (10 μL) of samples, as well as BSA standards, were mixed with working protein-dye solution (200 μL/well), and the reaction mixtures were allowed to stand at room temperature for 5 min. The absorbance of the samples was then read at 595 nm [17].

2.5. NO Release Assay

HepG2 cells were seeded in 6-well plates at a cell concentration of 600,000 cells/2 mL. After stable attachment, the cells were rinsed with PBS-A and then pre-incubated for 5 h (HepG2 cells) with a DMEM (without glucose and phenol red) supplemented with 1mM sodium pyruvate, 25 mM glucose, 10% (v/v) FBS, 3.7 g/L $NaHCO_3$ containing different concentrations of phytochemical or herbal extracts (concentration ranges being listed in the result table) [dissolved in DMSO, 0.2%

(v/v)]. After the incubation, supernatants of the culture medium were collected for the measurement of NO release, and the attached cells were rinsed with PBS-A and lysed with 0.1% (w/v) Triton-X in PBS-A. The lysates were used to measure protein concentrations by the Bradford method using BSA as the standard. The amount of NO released into the medium from phytochemical/herbal extract-incubated cells was measured using the Griess assay. The Griess assay is a spectrophotometric method based on a diazotization reaction for the detection of nitrite (NO_2^-) formed as a result of the oxidation of NO. Griess reagent solutions were prepared as follows, and sodium nitrite was dissolved in distilled deionized water (double-distilled (dd)H_2O) and used as a standard:

1) VCl_3 reduction solution: 80 mg VCl_3 was partly dissolved in a small amount of ddH_2O (around 2 mL), 0.84 mL hydrochloric acid (HCl, 37%) was added, and the solution was diluted to 10 mL with ddH_2O;

2) NED solution (0.1%): 1 mg NED was dissolved in 1 mL ddH_2O;

3) Sulfanilamide solution (2%): 0.02 g sulfanilamide was dissolved in 1 mL 10% (v/v) HCl;

4) Working Griess solution: 5 parts A + 1 part B + 1 part C.

One hundred and twenty microliters of supernatant/standard/medium blank were pipetted into a 96-well plate. Working Griess solution (100 μL) was applied to the corresponding wells. The sample mixtures were incubated at 45˚C for 60 min. The absorbance of sample mixtures was measured at 550 nm following incubation. The amount of NO released from the cells was expressed in nmol/mg protein, and this value was used to calculate the percentage of control (% control) for comparison [19].

2.6. EPO Assay

HepG2 cells were seeded 24-well plates at a cell concentration of 150,000 cells/0.5 mL, and following stable attachment, cells were incubated for 48 h with a medium containing different concentrations (concentration ranges being listed in the result table) of phytochemical/herbal extracts [dissolved in DMSO, 0.2% (v/v)]. After incubation, cells were rinsed with PBS-A and lysed with lysis buffer (0.3 mL per well; 50 mM Tris, 0.9% NaCl, 0.1% SDS, pH 7.3). The lysates were used to measure protein concentration and EPO levels with the Bradford protein dye and ELISA kit, respectively. The EPO level was expressed in mIU/mg protein, and this value was used to estimate the percentage of control for comparison [19].

2.7. Mitogen-Induced Splenocyte Proliferation

1) Animal care

Adult female ICR mice were maintained under a 12-hour dark/light cycle at an ambient temperature of approximately 22˚C with ad libitum access to food and water. Experimental protocols were approved by the Research Practice Committee at the Hong Kong University of Science and Technology (AEP-2023-0062).

2) Splenocyte isolation

Splenic tissue from mice was processed by pressing through a stainless-steel mesh sieve with a glass pestle in 25 mL RPMI-1640 medium to achieve a single-cell suspension. This suspension was centrifuged at 400 ×*g* for 5 min, and the resulting pellet was washed once with RPMI medium. Red blood cells in the pellet were lysed using 4.5 mL of water, and the lysis was halted by adding 0.5 mL of 10X Hank's Balanced Salt Solution (HBSS: 1.4 M NaCl, 53 mM KCl, 4.4 mM KH_2PO_4, 55.6 mM glucose and 3.36 mM Na_2HPO_4) and 5 mL RPMI-medium supplemented with 5% (v/v) HIFBS. After another round of centrifugation, the pellet was resuspended in RPMI-1640 medium supplemented with 10% HIFBS for cell counting, using 0.4% trypan blue. The cells were then adjusted to 5×10^6 cells/mL, and aliquots (80 μL) of the cell suspension were seeded in each well of a 96-well plate [18].

3) Drug incubation and Con A/LPS stimulation *in vitro*

Phytochemical/herbal extracts (dissolved in DMSO) were added at a range of concentrations in μg/mL (being listed in the result tables). Con A/LPS was added at final concentrations of 0.5, 1, 2, and 4 μg/mL. Splenocytes were then cultured for 72 h at 37˚C in a humidified atmosphere of 5% CO_2 in air. Thereafter, the extent of cell proliferation was assessed.

4) MTT-based cell proliferation assay

An aliquot (10 μL) of MTT (5 mg/mL in PBS-A) was added to each well. After 4 h of incubation, 100 μL of solubilization buffer (10% sodium dodecyl sulfate, 45% dimethylformamide, pH 4.7 adjusted by glacial acetic acid) was added, and the mixtures were incubated in 5% CO_2 at 37˚C overnight to dissolve the colored crystals. The extent of splenocyte proliferation was determined by measuring the absorbance at 600 nm using a microplate reader. The extent of Con A/LPS-stimulated proliferation of isolated splenocytes was estimated by computing the AUC (by GraphPad Prism) of a graph plotting the percentage of initial absorbance (mean absorbance of cells stimulated with mitogen/mean absorbance of cells not stimulated with mitogen × 100%) against mitogen concentrations. The extent of mitogen-stimulated proliferation of isolated splenocytes was estimated by comparison with the control [18].

2.8. Data Analysis

Data from various pharmacological assays were analyzed by computing the area under the curve (AUC, estimated by GraphPad Prism) for graphs plotting percent control values against concentrations, expressed as 1-, 2-, or 4-fold of the lowest effective concentration (determined by response value significantly higher than the control). The activity index was determined by the ratio of AUCsample to AUCcontrol. The Yin index (*i.e.* composite index) was calculated by summing the T cell (Con-A stimulated) and B cell (LPS-stimulated) indices, while the Blood index (*i.e.* composite index) was a summation of the EPO and NO indices.

2.9. Statistical Analysis

Data, which were expressed as mean ± SD, were analyzed by Student's t-test to detect significant differences between groups when $p < 0.05$.

3. Results

Table 1 shows that the extract of *Cynomorii Herba* significantly increased ATP-GC values after 4 h of pre-incubation, indicating its Yang-invigorating property. In contrast, none of the other phytochemical extracts tested showed any measurable enhancement.

Table 1. Effect on ATP-GC (Yang). H9c2 cells were pre-incubated with phytochemicals/*Cynomorii Herba* extract at increasing concentrations for 4 h to test their Yang-invigorating effect. All tested concentrations exhibited no detectable cytotoxicity as reflected by protein content. Values given were mean ± SD (n = 4) and expressed as percent control when compared with the untreated control. The control value (AUC2) was 750 ± 19.4. *Significantly different from control with p-value < 0.05 (using Student's t-test).

Phytochemical/Herbal extract	Concentration (μg/mL)	% Control (mean ± SD)
Cynomorii Herba	0	100 ± 0.59
	31.3	114 ± 2.46*
	62.5	115 ± 1.45*
	125	126 ± 0.96*
Quercetin	0	100 ± 3.86
	15.6	83.6 ± 5.14*
	31.3	76.0 ± 9.55*
	62.5	72.7 ± 6.49*
Curcumin	0	100 ± 2.59
	3.9	92.7 ± 8.43
	7.8	91.3 ± 3.35*
	15.6	95.6 ± 3.12
Resveratrol	0	100 ± 2.51
	7.8	96.7 ± 1.33
	15.6	95.1 ± 5.55
	31.3	101 ± 4.53
Catechins	0	100 ± 1.78
	7.8	88.6 ± 3.94*
	15.6	90.8 ± 1.71*

Table 2 shows that the *Ginseng Radix* extract significantly raised ATP-GC values following 24 h of pre-incubation, suggesting its Qi-invigorating property. The other phytochemical extracts did not exhibit any noticeable stimulating effects.

Table 2. Effect on ATP-GC (Qi). H9c2 cells were pre-incubated with phytochemicals/*Ginseng Radix* extract at increasing concentrations for 24 h to test their Qi-invigorating effect. All tested concentrations exhibited no detectable cytotoxicity as reflected by protein content. Values given were mean ± SD (n = 4) and expressed as percent control when compared with the untreated control. The control value (AUC2) was 750 ± 29.4. *Significantly different from control with p-value < 0.05 (using Student's t-test).

Phytochemical/Herbal extract	Concentration (μg/mL)	% Control (mean ± SD)
Ginseng Radix	0	100 ± 3.14
	31.3	117 ± 3.64*
	62.5	116 ± 1.68*
	125	120 ± 4.61*
Quercetin	0	100 ± 3.33
	0.98	97.1 ± 5.48
	1.95	91.6 ± 1.98
	3.9	97.3 ± 7.87
Curcumin	0	100 ± 3.61
	0.49	92.1 ± 10.6
	0.98	93.8 ± 5.31
	1.95	82.8 ± 7.89*
Resveratrol	0	100 ± 5.47
	1.95	93.7 ± 6.00
	3.9	97.5 ± 3.33
	7.8	90.9 ± 8.78
Catechins	0	100 ± 4.82
	3.9	99.8 ± 6.87
	7.8	100 ± 8.42

Table 3. Effect on mitogen-induced splenocyte proliferation (Yin). Mouse splenocytes were isolated as described in Materials and methods. Isolated splenocytes were co-incubated with phytochemicals/*Ligustri Fructus* extract at increasing concentrations and different concentrations of ConA or LPS for 72 h to test their Yin-nourishing effect. All tested concentrations exhibited no detectable cytotoxicity as reflected by protein content. Values given were percent control when compared with untreated control and expressed as mean ± SD (n = 4). The ConA-induced blastogenesis control value was 2608 ± 943 (AUC), and LPS-induced blastogenesis control value (AUC) was 2107 ± 704. *Significantly different from control with p-value < 0.05 (using Student's t-test).

Phytochemical/Herbal extract	Concentration (μg/mL)	ConA-induced blastogenesis % Control (mean ± SD)	LPS-induced blastogenesis % Control (mean ± SD)
Ligustri Fructus	0	100 ± 0.00	100 ± 0.00
	31.3	122 ± 6.34*	124 ± 4.63*
	62.5	121 ± 7.13*	126 ± 4.63*
Quercetin	0	100 ± 0.00	100 ± 0.00
	0.12	95.8 ± 5.28	101 ± 6.34

Continued

	0.25	90.8	±	2.82*	97.1	±	4.13
	0.49	84.5	±	4.50*	92.4	±	3.95
Curcumin	0	100	±	0.00	100	±	0.00
	0.24	88.3	±	5.04	102	±	3.80
	0.49	86.8	±	5.37*	97.9	±	4.09
	0.98	83.7	±	6.65*	89.2	±	9.34
Resveratrol	0	100	±	0.00	100	±	0.00
	0.49	125	±	8.16*	104	±	3.94
Catechins	0	100	±	0.00	100	±	0.00
	0.98	98.3	±	3.20	99.6	±	3.61
	1.95	103	±	2.96	99.4	±	4.94

Table 3 indicates that the *Ligustri* Fructus extract enhanced ConA/LPS-induced splenocyte proliferation, serving as an indirect measure of its Yin-nourishing property. Among the four extracts tested, only the resveratrol-enriched extract significantly stimulated ConA-induced splenocyte proliferation.

Table 4 reveals that the *Angelica Radix* extract significantly increased EPO and NO production, which together serve as indirect measures of Blood-enrichment property. The catechin-enriched and curcumin-enriched extracts only increased NO production.

Table 4. Effect on EPO and NO release (Blood). HepG2 were incubated with phytochemicals/*Angelicae Radix* extract at increasing concentrations for 48 h (EPO assay) or 5 h (NO release assay) to test their Blood-nourishing effect. All tested concentrations exhibited no detectable cytotoxicity as reflected by protein content. Values given were percent control when compared with untreated control and expressed as mean ± SD (n = 4). The EPO level control value was 956 ± 62 (mIU/mg protein) and the control value of NO released was 1.62 ± 0.71 (nmol/mg protein).

Phytochemical/Herbal extract	EPO level		NO release	
	Concentration (μg/mL)	% Control (mean ± SD)	Concentration (μg/mL)	% Control (mean ± SD)
Angelica Radix	0	100 ± 3.17	0	100 ± 6.97
	250	119 ± 6.26*	500	150 ± 12.1*
	500	135 ± 1.08*		
Quercetin	0	100 ± 2.79	0	100 ± 7.66
	0.98	96.7 ± 3.52	31.3	98.4 ± 9.82
	1.95	90.3 ± 11.2	62.5	76.2 ± 6.41*
	3.9	88.7 ± 11.1	125	84.1 ± 9.40
Curcumin	0	100 ± 2.79	0	100 ± 7.66
	1.95	65.0 ± 1.45*	62.5	127 ± 10.2*
	3.9	71.7 ± 3.82*		
	7.8	76.1 ± 3.29*		

Continued

Resveratrol	0	100 ± 2.79	0	100 ± 7.66
	15.6	90.4 ± 7.86*	125	103 ± 6.57
	31.3	101.6 ± 5.93	250	105 ± 6.86
Catechins	0	100.0 ± 2.79	0	100 ± 7.66
	15.6	80.6 ± 6.33*	125	171 ± 8.67*
	31.3	94.8 ± 11.8	250	266 ± 15.5*

According to the data analysis described in the Materials and Methods section, none of the tested phytochemical extracts demonstrated detectable Yang or Qi-invigorating properties. The positive control had Yang and Qi indices of 1.18 and 1.15, respectively (Table 5). Among the four tested phytochemical extracts, only the resveratrol-enriched extract exhibited moderate Yin-nourishing property, with a Yin index of 1.12, compared to *Ligustri Fructus* extract's index of 2.34. Additionally, the stimulation of NO production by the curcumin- and catechin-enriched extracts indicated mild and moderate Blood-enriching property, with Blood indices of 1.12 and 1.77, respectively. In contrast, the *Angelicae Radix* extract, which stimulated both EPO and NO production, had a Blood index of 2.43.

Table 5. A summary of Yang, Qi, Yin and Blood indices of tested phytochemical and herbal extracts. ND = undetable.

Phyto-chemical	Yang Index	Qi Index	Yin Index			Blood Index		
			IndexT	IndexB	Composite index	InedxNO	IndexEPO	Composite index
Quercetin	ND	ND	ND	ND	ND	ND	ND	ND
Curcumin	ND	ND	ND	ND	ND	1.14	ND	1.14
Resveratrol	ND	ND	1.12	ND	1.12	ND	ND	ND
Catechins	ND	ND	ND	ND	ND	1.77	ND	1.77
Cynomorii Herba	1.18							
Ginseng Radix		1.15						
Ligustri Fructus			1.16	1.18	2.34			
Angelica Radix						1.25	1.18	2.43

4. Discussion

The present study aimed to investigate whether phytochemical extracts marketed as nutraceutical health products have tonifying properties, specifically Yang-invigoration, Qi-invigoration, Yin-nourishment, and Blood-enrichment, according to Chinese medicine theory. We examined four popular nutraceutical products enriched with quercetin, resveratrol, catechins, and curcumin.

Our results indicated that none of the tested nutraceutical products demonstrated Yang- or Qi-invigorating properties, as assessed by validated pharmacological indices (Table 1 and Table 2). This suggests that their active components

may not enhance cellular energy metabolism, unlike Yang and Qi tonifying herbs which contain active component(s) such as β-sitosterol, ursolic acid and ginsenosides that can enhance mitochondrial ATP generation [20]-[22].

However, the resveratrol-enriched product showed Yin-nourishing property, but much less effective than that of *Ligustri Fructus*, a well-known Yin tonifying herb in Chinese medicine, which contains oleanolic acid that might stimulate antigen-induced T/B cell proliferation by acting on toll-like receptor [18] [22]-[23]. In this regard, resveratrol may enhance the proliferation of splenocytes under ConA stimulation via toll-like receptors. Further confirmation of the Yin-nourishing action of the resveratrol extract is needed through *ex vivo* studies, as indicated in our previous research [24].

In contrast, both catechin- and curcumin-enriched extracts increased NO production but did not affect EPO levels. This raises questions about their Blood-enrichment capabilities, which are typically associated with *Angelica Radix* which contains ferulic acid that can stimulate both NO and EPO production [25] [26].

Overall, the tested nutraceuticals enriched with phytochemicals may not significantly influence the Zang Xiang physiological system in Chinese medicine due to the absence of tonifying properties. Instead, their active components—quercetin, resveratrol, catechins, and curcumin—have been found to offer various pharmacological benefits within the anatomical physiological system [8]-[11]. While Chinese tonifying herbs contain a range of active compounds such as terpenoids, flavonoids, and phenylpropanoids that produce diverse pharmacological effects, the full spectrum of chemical components in these herbs might be essential for their actions within the Zang Xiang physiological system and hence produce tonifying action. Thus, we hypothesize that utilizing Chinese tonifying herbs may provide a holistic approach to addressing sub-healthy conditions in humans.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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