Review Article

Journal of Intercultural Ethnopharmacology
www.jicep.com
DOI: 10.5455/jice.20140917122310

# Pharmacological effectiveness of the active phytochemicals contained in foods and herbs

**Hiroyasu Satoh**

Health Life Science, Shitennoji University, Habikino, Osaka, Japan

**Address for correspondence:**
Dr. Hiroyasu Satoh, Health Life Science, Shitennoji University, 3-2-1 Gakuenmae, Habikino, Osaka 583-8501, Japan. Tel.: 81-72-956-3181, Fax: 81-72-956-6011, E-mail: hysat@shitennoji.ac.jp

**Received:** September 03, 2014
**Accepted:** September 17, 2014
**Published:** September 27, 2014

## ABSTRACT

Food ingestions generally regulate many physiological functions to maintain a healthy life. Furthermore, herbal medicine is prescribed for the prevention and the treatment of various diseases. There are not a few herbal medicine-derived drugs (phytochemicals) clinically using now. The phytochemicals such as digitalis, curare, morphine, quinidine, atropine, and so on are so much important drugs for clinical treatments. Herbal medicine and foods are composed of many constituents. The pharmacological actions that contain phytochemicals are exerted each by each mediated through different receptors, ionic channels, and cellular signal transductions. Thus, they produce multiple pharmacological and pathophysiological functions mediated by the complex interactions with lots of the ingredients.

KEY WORDS: Anti-ageing effects, foods, herbal medicine, mixture, profitable effects, phytochemicals

## INTRODUCTION

In plants, there are a lot of phytochemicals which contain many minerals and plenty nonsoluble dietary fibers to produce various physiological functions. Phytochemicals are in general classified by alkaloids, flavonoids, terpenoids, carotenoids polyketides, and phenylpropanoids. They exert anti-oxidative stress action [1], radical scavenging activity [2,3], antibacterial actions [4], and cardio-and neuro-vascular actions [5,6]. Moreover, the anti-ageing effects [7] and the improvement of poor blood circulation [8,9] have also been reported.

Herbal medicine is also composed of many herbs (from several to more than 10 constituents) and possesses plenty phytochemicals in each herb of the formulations for various clinical treatments [10]. In the phytochemicals of foods, as well as herbs, there are well-known numerous bioactive substances; i.e., lycopene in tomato, anthocyanin in blueberry and red wine, caffeine, theophylline and catechins in coffee and tea, capsaicin in paprika and red pepper, and quercetin in onion and many herbs. The pharmacological actions of some phytochemicals investigated so far in my laboratory and their important roles for cardiovascular and intestinal functions are discussed.

## METHYLXANTHINES

Caffeine contained in coffee or tea is popularly in widespread use for a long time. Caffeine and theophylline are the well-known phytochemicals, as well using as a clinical drug. In cardiac Purkinje fibers, caffeine at 0.5-10 mM caused an initial transient increase and a subsequent decrease in the contractile force [11-13]. Caffeine's effects are modulated by the changes in the concentration of intracellular calcium $[Ca^{2+}]_i$. Under the conditions to elevate $[Ca^{2+}]_i$, the positive inotropic effect was reduced (or abolished), but the negative inotropic effect was further enhanced. Once $[Ca^{2+}]_i$ was declined, the positive inotropic effect was potentiated, and the negative inotropic effect was reduced or abolished. Therefore, the negative inotropic effect of caffeine is mostly related to the development of cellular calcium overload but not to $Ca^{2+}$ depletion in sarcoplasmic reticulum (SR). The same responses had been shown in cardiac electrophysiological actions [14]. Although the mechanisms by which calcium overload decreases the force are not fully known, caffeine modifies a key factor to regulate $Ca^{2+}$ homeostasis such as $Ca^{2+}$ channel, ryanodine receptor on SR, and $Ca^{2+}$ sensitivity to cardiac muscle.

Moreover, the arithmetic skill was enhanced by the intake of coffee (with 180 mg caffeine) at 40-60 min later under double-blind experiments [15], presumably resulting from the blockade of brain adenosine receptor [16,17]. Simultaneously, the systemic blood pressures (SBP) diastolic blood pressures (DBP) increased, but the heart rate (HR) decreased. In other methylxanthines, tea (mainly caffeine) decreased SBP and did not affect DBP. HR was markedly reduced. Cocoa (mainly

about 200 mg theobromine) reduced both SBP and DBP and also slightly decreased HR. Simultaneously, as indices of wave reflection; an augmentation index (AI), the ratio of ejection and reflection pressures from the radial artery was also measured [6]. The AI and the central systemic arterial blood pressure (CBP) significantly increased by 11.6% and 6.8% with coffee, and by 13.1% and 2.8% with tea, but decreased by 4.3% and 3.8% with cocoa, respectively. Cocoa contains theobromine, caffeine, cacao polyphenols, and theophylline (much lower content). In the cocoa, however, the content of theobromine or caffeine is not enough to elicit the significant effects by itself. Theobromine also antagonizes adenosine receptor-like caffeine. The methylxanthine derivatives cause the accumulation of Cyclic adenosine monophosphate (cAMP) by phosphodiesterase (PDE) inhibition, resulting in the productions of many physiological and pharmacological effects via protein kinase A (PK-A) activity. We, daily take some drinks containing several methylxanthines (and other phytochemicals). The resultant responses are exhibited as a net of the effects of the constituents and ingredients contained in a drink. A cup of coffee or tea increases human vascular wall tone, but a cup of cocoa decreases it, presumably due to the cardiovascular and central nervous modulation as a mixture.

## Anthocyanins

Anthocyanins at 0.03-3 mg/ml from cassis and bilberry caused the potent vasorelaxation in rat aorta in a concentration-dependent manner [18]. Moreover, in 38 healthy paramedical students (averaged 26 years old), after an oral administration (100 mg/a tablet), the SBP and DBP had less or no effect; by −1.4% and −0.9% in cassis, and by −0.6% and −0.6% in bilberry anthocyanins, respectively. The HR decreased by 4.6% and 7.8%. Simultaneously, cassis and bilberry anthocyanins elevated AI by 5.0 ± 2.7% and 9.4 ± 2.4% ($P < 0.05$), and CBP by −1.1% and 1.3%, respectively. Thus, bilberry anthocyanin exhibited the stronger effects. The responses were lasted for approximately 1 h. Both anthocyanins increased human vascular wall tone and then, elevated the AI (in spite of the potent vasodilatation in isolated rat aorta), but had no or less effect on the HR, blood pressure, and CBP.

## Capsaicin

The hemodynamic functions of 34 healthy students (approximately 24.3 years old) were also measured in comparison between a fiery noodle with so much hot flavor and non-hot noodle [19]. The indicator of hot taste is not clear yet, although Scoville heat unit is present. The Scoville scale of the hot and fiery noodle used in this study was never indicated anywhere. But it was not so easy for usual persons take all hot noodles. Both increased the blood pressure and the CBP. Hot noodle elevated especially the SBP by 9.2 ± 3.2% and the DBP by 29.5 ± 3.3% ($P < 0.05$), but non-hot noodle had less or no effect. The HR was reduced by 6-9% in both noodles. The AI increased and reached to maximal (by 12.7 ± 2.3%, $P < 0.05$) at 20 min later in hot noodle, whereas it had just a weak enhancement in non-hot noodle. These responses were lasted for 40-60 min. Capsaicin contained in the hot and fiery foods causes the acute hemodynamic effects, and may exert the multiple profitable actions as a hot medicine; the stimulation of energy metabolism, the enhancements of endothelial (NO)- and immune (immunoglobulin M)-activities, and potentiation of anti-oxidative stress action, as well as the elevation of body temperature.

## Bilobalide

Most healthful foods are also derived from the bioactive substances in plants or animals. Bilobalide contained in *Ginkgo biloba* extract (GBE) at 1 $\mu$M enhanced the L-type $Ca^{2+}$ current ($I_{CaL}$) by 40.0 ± 2.3% ($n = 6$, $P < 0.05$), and the delayed rectifier $K^+$ outward current ($I_{Krec}$) by 14.0 ± 2.3% ($n = 6$, $P < 0.05$), concentration-dependently. The inwardly rectifying $K^+$ current ($I_{K1}$) was unaffected. These responses were reversible (approximately 70-80% of control) after 10-20 min washout [5,20].

In general, the vasodilating actions decreased in accordance with ageing. The comparison between the vasodilating actions induced by GBE (as a health food in Japan) and the phytochemical, bilobalide, was examined [21-23]. The vasorelaxation induced by bilobalide at 30 $\mu$M significantly decreased from 11.8 ± 1.4% ($n = 4$) in 5-week-old rats to 2.3 ± 1.5% ($n = 5$, $P < 0.01$) in 25-week-old rats, and at 100 $\mu$M from 20.2 ± 3.4% ($n = 4$) to 5.6 ± 2.5% ($n = 5$, $P < 0.01$), respectively. On the other hand, GBE at 1 mg/ml decreased it from 28.4 ± 3.8% ($n = 5$) in 5-week-old rats to 23.7 ± 7.1 ($n = 7$) in 25-week-old rats, but not significantly. The maximum vasodilatation induced by GBE (3 mg/ml) was 73.7 ± 2.1% ($n = 4$, $P < 0.001$) in 10-week-old rats. Bilobalide (a phytochemical) elicited the age-dependent attenuation, but GBE (a mixer-maxter) maintained more vasodilatation even at elder ages.

Although the mechanisms are still unclear, there are several possibilities. The effect on the L-type $Ca^{2+}$ channel in the fetal bovine is more marked than that in the adult, indicating an alteration of $Ca^{2+}$ channel density. And the age-related modulation of $Ca^{2+}$ channel inhibitor is not due to changes in affinity to drugs but is due to alterations in the population of the $Ca^{2+}$ channel. Moreover, the vasodilatations induced by the bilobalide and GBE are produced mediated through the endothelium-dependent mechanisms (endothelium-derived relaxing factor [EDRF]) [21]. The endothelium-dependent vasorelaxation (via NO release) is slowly attenuated along with ageing. The vasodilations by both drugs would be also modulated by the other mechanisms, as well as the alterations of $Ca^{2+}$ channel, cAMP, $PGI_2$, and PK-C. Besides bilobalide, GBE contains numerous constituents such as terpenoids (ginkgolides A, B, and C) and flavonoids (quercetin and rutin), which by themselves also produce vasodilating actions. Each contributes to the GBE-induced vasodilatation, and GBE as a whole produces the mixed responses [24]. The phenomena resemble the characteristics of Japanese herbal (Kampo) medicine as a mixture of herbal drugs; more effective for elder persons [10].

## Quercetin

Quercetin, a kind of flavonoids, contains in many herbal medicines as well as onion. Quercetin causes lots of profitable physiological actions. In guinea pig ventricular cardiomyocytes, quercetin at 0.3-300 $\mu$M decreased the action potential duration and inhibited the underlying ionic currents ($I_{CaL}$, $I_{Krec}$ and $I_{K1}$) [24]. In rat aorta, quercetin (0.1-100 $\mu$M) relaxed the contraction induced by 5 $\mu$M NE concentration-dependently [20,22]. NG-monomethyl-L-arginine acetate (L-NMMA) at 100 $\mu$M decreased the quercetin (100 $\mu$M)-induced vasorelaxation from 97.0 ± 3.7% ($n$ = 10, $P$ < 0.05) to 78.0 ± 11.6% ($n$ = 5, $P$ < 0.05). Endothelium removal as well attenuated the vasodilatation. In the presence of both L-NMMA (100 $\mu$M) and indomethacin (10 $\mu$M), the quercetin-induced vasorelaxation was further reduced by high K (30 mM) or 10 $\mu$M tetraethyl ammonium (TEA). Among $K_{Ca}$ channel inhibitors, the quercetin-induced vasodilatation decreased at 0.3 $\mu$M apamin (sensitive to SK), but not at 30 nM charybdotoxin (sensitive to BK and IK) [25]. Under KCl-induced vasoconstriction, the quercetin-induced vasorelaxation was inhibited by PK-C inhibitors; Gö6983 (α-, β-, γ-, δ, and ζ-sensitive) dilated stronger than Ro-31-8425 (α-, β-, γ-, and ε-sensitive) [26].

Furthermore, the involvement with an endothelium-derived hyperpolarizing factor (EDHF) was investigated using rat mesenteric artery because EDHF is considered not contributed to the vasodilatation of aorta. The quercetin-induced vasodilatation was almost resistant to both L-NG-nitro arginine methyl ester (L-NAME, an NO-synthesis inhibitor) (100 $\mu$M) and indomethacin (100 $\mu$M), presumably related with EDHF. The candidates of EDHF are considered as $K^+$, epoxyeicosatrienoic acid and $H_2O_2$ from endothelium. The L-NAME/indomethacin-resistant quercetin-induced vasodilatation was inhibited by TEA (1 mM), and also by gap junction inhibitors of 18α- (100 $\mu$M) and 18β- (50 $\mu$M) glychrrhetinic acids [27,28]. Therefore, quercetin dilates the vascular smooth muscle mediated by endothelium-dependent (EDRF, EDHF, and gap junction) and-independent (the inhibitions of $I_{CaL}$, SK channel, and PK-Cδ, and $PGI_2$ production) mechanisms.

## Sinomenin and Tetrandrine

Mokuboito (Mu-Fang-Yi-Tang) is composed of four herbal drugs; *Sinomenium acutum*, *Cinnamomi* cortex, *Ginseng* radix, and gypsum. S. *acutum* (a vine plant), the main constituent, possesses the phytochemicals such as sinomenine, tetrandrine, and magnoflorine. They are alkaloid. Sinomenine (1 mM) and tetrandrine (100 $\mu$M) inhibited the ionic currents to the same extent [29]. At 1 mM sinomenine inhibited the $I_{CaL}$ at 0 mV by 18.2 ± 2.1% (n = 6, P < 0.05). The $I_{Krec}$ at 60 mV was inhibited by 16.2 ± 2.6% (n = 6, P < 0.05), and the $I_{K1}$ at −120 mV by 47.2 ± 3.8% (n = 6, P < 0.01). As a result, these phytochemicals simultaneously affected the action potential configurations. Sinomenine (300 $\mu$M) and tetrandrine (30 $\mu$M) had almost the similar effects, but magnoflorine (1 mM) had less or no effect. Interestingly, sinomenine abolished the dysrhythmias elicited by the cellular $Ca^{2+}$ overload. Thus, these phytochemicals have the profitable electropharmacological and cardioprotective actions.

In the analyses of the age-related effects, sinomenine (100 $\mu$M) alone dilated NE-induced vasoconstriction by 68.8 ± 5.2% ($n$ = 6, $P$ < 0.01) in 10-weeks old rats, but only by 18.6 ± 1.5% ($n$ = 6, $P$ < 0.01) in 65-weeks old rats [30,31]. *S. acutum* caused the vasodilatations at 3 mg/ml by 96.7 ± 4.8% ($n$ = 7, $P$ < 0.01) in 10-weeks old rats, and by 46.0 ± 5.7% ($n$ = 6, $P$ < 0.01) in 65-weeks old rats. Mokuboito at 3 mg/ml dilated aorta by 98.9 ± 2.8% ($n$ = 7, $P$ < 0.01) in 10-weeks and by 97.5 ± 13.5% ($n$ = 6, $P$ < 0.01) in 65-weeks old rats. Thus, Mokuboito, *S. acutum* (multiple compounds) and sinomenine (single phytochemical) by themselves had the potent vasodilating actions. However, the pharmacological effects of just single phytochemical are strongly influenced in advance with ageing. In contrast, *S. acutum* (multiple compounds) suppresses the age-dependent attenuation of vasodilating action, and Mokuboito (as a mixture) maintains the marked action. In short, *S. acutum*- and sinomenine-induced vasodilatations decreased along with ageing, but Mokuboito has less or no effect on the age-dependent attenuation in any aged rats. The mixture is so much important against the age-dependent alterations of the effectiveness. Thus, herbal medicine produces more effective pharmacological stability [32]. Mokuboito exhibits as a net mediated by the complicated interactions among the contained ingredients.

## Paeoniflorin and Glychrrhetic Acid

Shakuyakukanzoto (Shao-yao-Gan-chao-Tang), a traditional formulation of Kampo medicine, is composed of paeoniae radix and glycyrrhizae radix. Shakuyakukanzoto relaxed 0.3 $\mu$M carbachol (CCh)-induced contraction of rat ileum in a concentration-dependent manner [33]. Both components (paeoniae radix and glycyrrhizae radix) each dilated the CCh-induced contraction. Main ingredient is paeoniflorin in paeoniae radix and glycyrrhetic acid in glycyrrhizae radix. Both phytochemicals and the metabolic products (18-α- and 18-β-glycyrrhetinic acids) had almost the same actions. Under the conditions with spontaneous contractions, an application of Shakuyakukanzoto completely abolished the abnormal contractions. Thus, Shakuyakukanzoto caused the potent relaxant actions not only by the anti-cholinergic effect but also by $Ca^{2+}$ channel and PDE inhibitory effects [34]. Furthermore, Shakuyakukanzoto produces an anti-spasmodic action. However, the whole effects induced by Shakuyakukanzoto are never equal with a sum of each effect of the phytochemicals in paeoniae radix and glycyrrhizae radix. The responses are exhibited as a net among the contained ingredients.

## Phytochemicals in a Mixture

Phytochemicals by themselves generally produce anti-arteriosclerosis (or protection of ischemia and stroke) and improve poor blood circulation, resulting from the great vasodilating actions due to such multiple mechanisms as endothelium-dependent actions (EDRF and EDHF), and endothelium-independent actions ($PGI_2$ production, PDE inhibition, $Ca^{2+}$

channel inhibition, and PK-C inhibition) [35,36]. Moreover, phytochemicals have anti-oxidative stress action [1] and radical scavenging activity [37], produce anti-inflammation and immuno-modulation [38], and induce the mRNA leading to the production of some functional proteins.

There is a quite difference between single phytochemical and mixture drugs with a lot of ingredients (including phytochemicals). The effects of herbal medicine (a mixter-maxter) are never just a sum of each effect induced by all ingredients. The contained phytochemicals exhibit the pharmacological effects via the interaction with other contained ingredients, but never by themselves alone [39]. On the complex interactions, the effect of a phytochemical may be potentiated or attenuated (or blocked).

Mixture of plenty phytochemicals plays an important role for the anti-ageing effects and the potentiation of effective pharmacological and physiological responses. Advance in ages produces various pathophysiological deleterious changes such as plaque formation in vascular systems. Simultaneously, the age-dependent functional depressions of receptors, ion channels and cellular signal transduction pathways must be caused in the endothelium, and cardiac and smooth muscle cells. As a result, the age-related alterations would be responsible for physiological and anatomical reductions. Furthermore, ageing declines the sensitivity to drugs. However, herbal medicine generally modulates the age-dependent changes and can maintain the pharmacological effects (but not fully). In Kampo medicine, Rokumigan (Liu-Wei-Wan) possesses six herbs as a base, Hachimijiogan (Ba-Wei-Di-Huang-Wan), eight herbs (Rokumigan plus two herbs), and Goshajinkigan (Niu-Che-Shen-Qi-Wan), ten herbs (more two herbs are added to Hachimijiogan). These formulations increase in order to the number of contained ingredients in increment of two herbs. The larger the number of the contained ingredients of herbs become, the more potent vasodilatation is produced [39]. Furthermore, the addition of Gypsum (mainly calcium sulfate) produced stronger vasodilatation in Kampo medicine (Japanese herbal medicine) such as Mokuboito and Chotosan (Diao-Teng-San).

For elder persons, therefore, the mixture (such as health foods and herbal medicine) with lots of ingredients (and phytochemicals) plays a key role for much more effectiveness. The similar effectiveness might be also expected in general foods. Herbal medicine as a mixture keeps the balance and can produce either vasoconstriction or vasodilatation. Increasing the number of phytochemicals can maintain the effectiveness to some extent in elder rats, presumably due to compensation of the age-dependent decline of pharmacological sensitivity to the receptors.

## CONCLUSION

Now, out of a number of residual phytochemicals which are not western drugs exit. From the modern in detail analyses, many phytochemicals have recently been discovered to possess the effective pharmacological activities including the modification of the genes of target; the hormone secretions for long life such as ghrelin, adiponectin and aquaporins, and switch-on of the long-life genes like sirtuins [40,41].

In the future, can some phytochemicals independently become a new drug? The development needs so much more clinical pharmacological tests, accompanied with long-term and huge cost. If so, it is not easy for any pharmaceutical company to start newly to develop a phytochemical as a new drug. Hence, it is doubtful that a phytochemical in herbs will be able to become independently as a clinical drug. Each phytochemical in herbs never plays an important role each by each, but exerts as a mixture of herbal medicine, leading to more effectiveness for the multiple diseases and the age-related disorders [10]. This is the most important role for the phytochemicals.

## REFERENCES


1. Keen CL, Holt RR, Oteiza PI, Fraga CG, Schmitz HH. Cocoa antioxidants and cardiovascular health. Am J Clin Nutr 2005;81:298S-303.
2. Sakagami H, Satoh K, Fukamachi H, Ikarashi T, Shimizu A, Yano K, *et al.* Anti-HIV and vitamin C-synergized radical scavenging activity of cacao husk lignin fractions. *In Vivo* 2008;22:327-32.
3. Motohashi N, Kawase M, Kurihara T, Shirataki Y, Kamata K, Nakashima H, *et al*. Relationship between radical intensity and biological activity of cacao husk extracts. Anticancer Res 1999;19:1125-9.
4. Hirao C, Nishimura E, Kamei M, Ohshima T, Maeda N. Antibacterial effects of cocoaon periodontal pathogenic bacteris. J Oral Biosci 2010;52:283-91.
5. Satoh H. Suppression of pacemaker activity by *Ginkgo biloba* extract and its main constituent, bilobalide in rat sino-atrial nodal cells. Life Sci 2005;78:67-73.
6. Satoh H. Comparative actions of cocoa, tea and coffee intakes on human pressure pulse wave and arterial stiffness. Food Funct 2009;5:31-7.
7. Mato T, Kamei M, Ito R, Sawano M, Inokuchi K, Nakata K, *et al*. Beneficial effects of cocoa in perivascular mato cells of cerebral arterioles in SHR-SP (Izm) rats. J Clin Biochem Nutr 2009;44:142-50.
8. Fisher ND, Hollenberg NK. Aging and vascular responses to flavanol-rich cocoa. J Hypertens 2006;24:1575-80.
9. McCarty MF, Barroso-Aranda J, Contreras F. Potential complementarity of high-flavanol cocoa powder and spirulina for health protection. Med Hypotheses 2010;74:370-3.
10. Satoh H, editor. Basics of Evidences-Based Herbal Medicine. Kerala: Research Signpost; 2010.
11. Satoh H, Vassalle M. Reversal of caffeine-induced calcium overload in cardiac Purkinje fibers. J Pharmacol Exp Ther 1985;234:172-9.
12. Satoh H, Vassalle M. Role of calcium in caffeine-norepinephrine interactions in cardiac Purkinje fibers. Am J Physiol 1989;257:H226-37.
13. Satoh H, Vassalle M. Ca(++)-dependence of caffeine modulation of the rate-force relation in canine cardiac Purkinje fibers. J Pharmacol Exp Ther 1996;278:826-35.
14. Satoh H, Hasegawa J, Vassalle M. On the characteristics of the inward tail current induced by calcium overload. J Mol Cell Cardiol 1989;21:5-20.
15. Satoh H, Tanaka T. Comparative pharmacology between habitual and non-habitual coffee-drinkers: A practical class exercise in pharmacology. Eur J Clin Pharmacol 1997;52:239-40.
16. Kuribara H, Asahi T, Tadokoro S. Behavioral evaluation of psycho-pharmacological and psychotoxic actions of methylxanthines by ambulatory activity and discrete avoidance in mice. J Toxicol Sci 1992;17:81-90.
17. De Sarro A, Grasso S, Zappala M, Nava F, De Sarro G. Convulsant effects of some xanthine derivatives in genetically epilepsy-prone rats. Naunyn Schmiedebergs Arch Pharmacol 1997;356:48-55.
18. Satoh H. Comparative effects of anthocyanins (cassis and bilberry) onarteriosclerotic parameters: Analysis from human pressure pulsewave and arterial stiffness. Food Funct 2013;11:2-8.
19. Satoh H. Effects of capsaicin (by taking a fiery noodle) on

hemodynamic parameters and arterial stiffness. Food Funct 2013;12:7-12.
20. Satoh H. Effects of *Ginkgo biloba* extract and bilobalide, a main constituent, on the ionic currents in guinea pig ventricular cardiomyocytes. Arzneimittelforschung 2003;53:407-13.
21. Nishida S, Satoh H. Mechanisms for the vasodilations induced by *Ginkgo biloba* extract and its main constituent, bilobalide, in rat aorta. Life Sci 2003;72:2659-67.
22. Nishida S, Satoh H. Comparative vasodilating actions among terpenoids and flavonoids contained in *Ginkgo biloba* extract. Clin Chim Acta 2004;339:129-33.
23. Nishida S, Satoh H. Age-related changes in the vasodilating actions of *Ginkgo biloba* extract and its main constituent, bilobalide, in rat aorta. Clin Chim Acta 2005;354:141-6.
24. Satoh H. Comparative electropharmacological actions of some constituents from *Ginkgo biloba* extract in guinea-pig ventricular cardiomyocytes. Evid Based Complement Alternat Med 2004;1:277-84.
25. Nishida S, Satoh H. Possible involvement of Ca activated K channels, SK channel, in the quercetin-induced vasodilatation. Korean J Physiol Pharmacol 2009;13:361-5.
26. Nishida S, Satoh H. Vasorelaxation mechanisms of quercetin in rat arteries. J US China Med Sci 2009;6:54-62.
27. Takeda Y, Ward SM, Sanders KM, Koh SD. Effects of the gap junction blocker glycyrrhetinic acid on gastrointestinal smooth muscle cells. Am J Physiol Gastrointest Liver Physiol 2005;288:G832-41.
28. Nishida S, Satoh H. Role of gap junction involved with endothelium-derived hyperpolarizing factor for the quercetin-induced vasodilatation in rat mesenteric artery. Life Sci 2013;92:752-6.
29. Satoh H. Electropharmacological actions of the constituents of sinomeni caulis et rhizome and mokuboi-to in guinea pig heart. Am J Chin Med 2005;33:967-79.
30. Nishida S, Satoh H. *In vitro* pharmacological actions of sinomenine on the smooth muscle and the endothelial cell activity in rat aorta. Life Sci 2006;79:1203-6.
31. Nishida S, Satoh H. Vascular pharmacology of mokuboito (mu-fang-yi-tang) and its constituents on the smooth muscle and the endothelium in rat aorta. Evid Based Complement Alternat Med 2007;4:335-41.
32. Satoh H, Nishida S. Lack of the age-dependent alteration by mokuboito (Mu-Fang-Yo-Tang). J US China Med Sci 2012;9:1-8.
33. Satoh H, Tsuro K. Pharmacological modulation by Shakuyakukanzoto (Shao-Yao-Gan-Cao-Tang) and the ingredients in rat intestinal smooth muscle. Chin Med 2011;2:62-70.
34. Saegusa Y, Sugiyama A, Takahara A, Nagasawa Y, Hashimoto K. Relationship between phosphodiesterase inhibition induced by several Kampo medicines and smooth muscle relaxation of gastrointestinal tract tissues of rats. J Pharmacol Sci 2003;93:62-8.
35. Duarte J, Pérez-Vizcaíno F, Zarzuelo A, Jiménez J, Tamargo J. Vasodilator effects of quercetin in isolated rat vascular smooth muscle. Eur J Pharmacol 1993;239:1-7.
36. Liu L, Riese J, Resch K, Kaever V. Impairment of macrophage eicosanoid and nitric oxide production by an alkaloid from *Sinomenium acutum*. Arzneimittelforschung 1994;44:1223-6.
37. Murota K, Terao J. Antioxidative flavonoid quercetin: Implication of its intestinal absorption and metabolism. Arch Biochem Biophys 2003;417:12-7.
38. Yamasaki H. Pharmacology of sinomenine, an anti-rheumatic alkaloid from *Sinomenium acutum*. Acta Med Okayama 1976;30:1-20.
39. Satoh H. Pharmacological characteristics of Kampo medicine as a mixture of constituents and ingredients. J Integr Med 2013;11:11-6.
40. Mattson MP. Dietary factors, hormesis and health. Ageing Res Rev 2008;7:43-8.
41. Elekofehinti OO, Omotuyi IO, Kamdem JP, Ejelonu OC, Alves GV, Adanlawo IG, *et al.* Saponin as regulator of biofuel: Implication for ethnobotanical management of diabetes. J Physiol Biochem 2014;70:555-67.



**Source of Support: Nil, Conflict of Interest: None declared.**