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# The Pharmacological Effects of Herbs on Catecholamine Signaling

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## Abstract

Herbs have many biologically and pharmacologically active compounds such as flavonoids and stilbenes. They have been used in remedies for various disorders. Here we review the effects of herbs on catecholamine synthesis and secretion in cultured bovine adrenal medullary cells. Ikarisoside A (1.0–100  $\mu\text{M}$ ), a flavonol glycoside, inhibited the catecholamine secretion induced by acetylcholine (0.3 mM). This inhibition was associated with the suppression of  $^{22}\text{Na}^+$  and  $^{45}\text{Ca}^{2+}$  influx induced by acetylcholine. The ethanol extract (0.0003–0.005%) of matsufushi (extract of pine nodules) inhibited the catecholamine secretion induced by acetylcholine. SJ-2, one of the stilbene compounds isolated from matsufushi, inhibited acetylcholine-induced catecholamine secretion. Matsufushi extract and SJ-2 reversibly inhibited acetylcholine-induced  $\text{Na}^+$  currents in *Xenopus* oocytes expressed with  $\alpha 3\beta 4$  nicotinic acetylcholine receptors. Sweet tea is the processed leaves of *Hydrangea macrophylla*. The extract of sweet tea (0.3–1.0 mg/ml) suppressed catecholamine secretion induced by acetylcholine (0.3 mM). Moreover, sweet tea (0.1–1.0 mg/ml), ikarisoside A (1.0–100  $\mu\text{M}$ ), and matsufushi (0.001–0.003%) or SJ-2 (10–30  $\mu\text{M}$ ) inhibited acetylcholine-induced  $^{14}\text{C}$ -catecholamine synthesis from  $^{14}\text{C}$ -tyrosine. These findings indicate that ikarisoside A, matsufushi (or SJ-2), and sweet tea inhibit the catecholamine secretion and synthesis induced by acetylcholine in cultured bovine adrenal medullary cells and probably in sympathetic neurons.

**Keywords:** adrenal medullary cells, catecholamine secretion, ikarisoside A, matsufushi, sweet tea

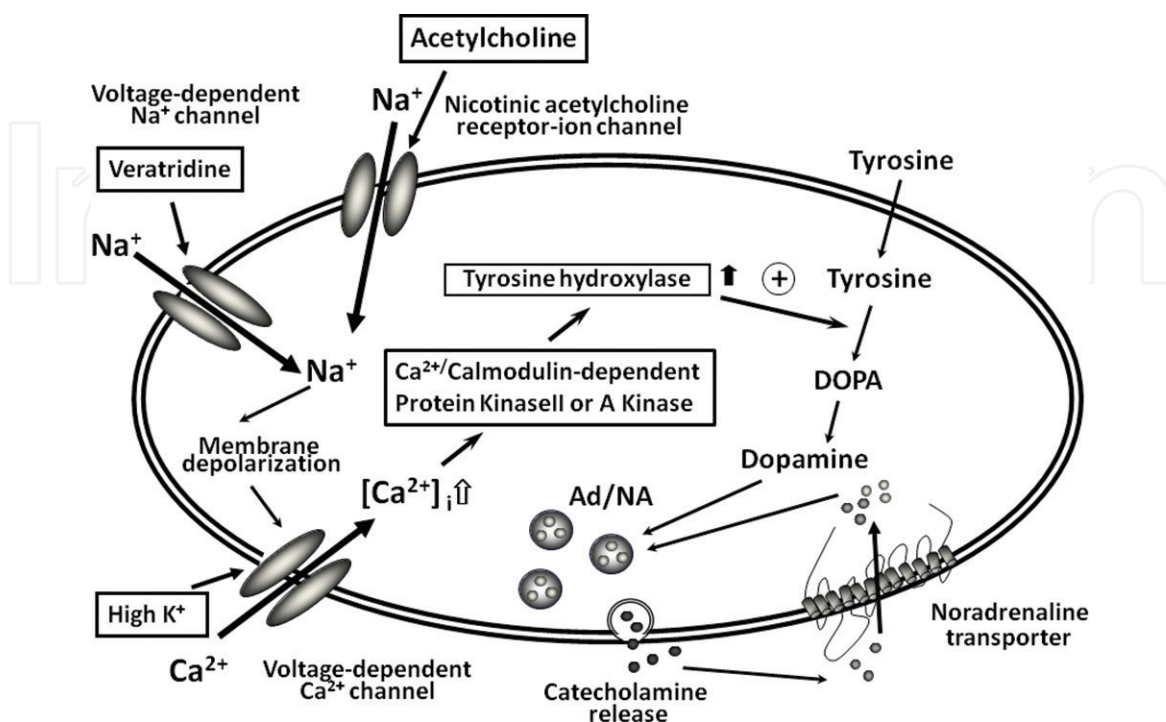
## 1. Introduction

Since herbs have many biologically and pharmacologically active compounds such as flavonoids and stilbenes, they have been used in remedies for various disorders. A high dietary intake of herbs has become a focus of research because of herbs' potential to reduce the risks of diseases such as hypertension, coronary heart disease, diabetes, and cancers [1, 2]. Flavonoids are a group of plant secondary metabolites with variable phenolic structures, and they are found in plants, fruits, vegetables, roots, stems, flowers, wine, and tea [3, 4]. Over 5000 individual flavonoids have been reported [5], and 6 principal groups of flavonoids

(flavones, flavonols, flavanones, flavanols, isoflavones, and anthocyanidins) are relatively common in human diets [1]. Polyphenol stilbenes have attracted scientific attention. For example, resveratrol (*trans*-3,4',5-trihydroxy- stilbene) is a natural phytoestrogen found in grapes, berries, and red wine [6, 7] that was reported to be implicated in the beneficial effect of red wine, i.e., the lower incidence of coronary artery disease in certain populations such as the French and the Greeks, despite diets rich in saturated fat and a rate of high smoking, which has been dubbed the “French paradox” [8].

In the human body, the most abundant catecholamines are adrenaline, noradrenaline, and dopamine, all of which are produced from phenylalanine and/or tyrosine. Catecholamines are biosynthesized mainly in the adrenal medulla, the postganglionic fibers of the sympathetic nervous system, and the central nervous system [2, 9, 10]. Catecholamines play very important roles in aspects of the cardiovascular system such as heart rate and blood pressure, blood glucose levels, and the general functions of the central and peripheral sympathetic nervous system [9].

Adrenal medullary cells derived from embryonic neural crests are functionally homologous to sympathetic postganglionic neurons [2, 10]. Our research demonstrated that in cultured bovine adrenal medullary cells, at least three distinct types of ionic channels participate in catecholamine secretion, including nicotinic acetylcholine receptor (nAChR)-ion channels, voltage-dependent  $\text{Na}^+$  channels, and voltage-dependent  $\text{Ca}^{2+}$  channels [2, 11]. In these cells, the  $\text{Na}^+$  influx induced by acetylcholine (ACh) via nAChR-ion channels or by veratridine via voltage-dependent  $\text{Na}^+$  channels is a prerequisite for  $\text{Ca}^{2+}$  influx via the activation of voltage-dependent  $\text{Ca}^{2+}$  channels and subsequent catecholamine secretion; in contrast, high  $\text{K}^+$  directly gates voltage-dependent  $\text{Ca}^{2+}$  channels to increase the  $\text{Ca}^{2+}$  influx without increasing the  $\text{Na}^+$  influx [10, 11] (**Figure 1**). ACh-induced  $\text{Ca}^{2+}$  influx is also a prerequisite for the stimulation of catecholamine synthesis associated with the activation of tyrosine hydroxylase [2, 12–15]. The mechanisms underlying the stimulation of catecholamine synthesis and secretion mediated by these ion channels in adrenal medullary cells are thought to be similar to those of



**Figure 1.** The mechanism underlying the regulation of catecholamine synthesis, secretion, and reuptake in bovine adrenal medullary cells.

noradrenaline in the sympathetic neurons and brain noradrenergic neurons [2]. Thus, adrenal medullary cells have provided a good model for the detailed analysis of antipsychotic [16], cardiovascular [17], and analgesic [18] drugs that act on catecholamine synthesis, secretion, and reuptake [2].

We have demonstrated the effects of several flavonoids and polyphenol stilbenes on catecholamine synthesis and secretion. For example, the treatment of bovine adrenal medullary cells with daidzein (an isoflavone derived from soy beans) stimulated basal catecholamine synthesis but inhibited the catecholamine synthesis and secretion induced by ACh [2, 19]. Genistein (another isoflavone in soy beans) but not daidzein stimulated the function of noradrenaline transporter in a human neuroblastoma cell line, SK-N-SH cells [2, 20]. Nobiletin (a compound of polymethoxy flavone in citrus fruits) stimulated the basal synthesis and secretion of catecholamines, but it suppressed both the ACh-induced synthesis of catecholamines and ACh-induced secretion of catecholamines [2, 21]. Resveratrol also inhibited the catecholamine synthesis and secretion induced by ACh [2, 22].

The present review summarizes our recent and current studies of the pharmacological effects of herbs and their components, i.e., ikarisoside A (a flavonol glycoside); matsufushi (extract of pine nodules), one of matsufushi's stilbene components (SJ-2); and sweet tea on the catecholamine signaling induced by ACh in cultured bovine adrenal medullary cells and on ACh-induced  $\text{Na}^+$  current in *Xenopus* oocytes expressing  $\alpha 3\beta 4$  nAChRs.

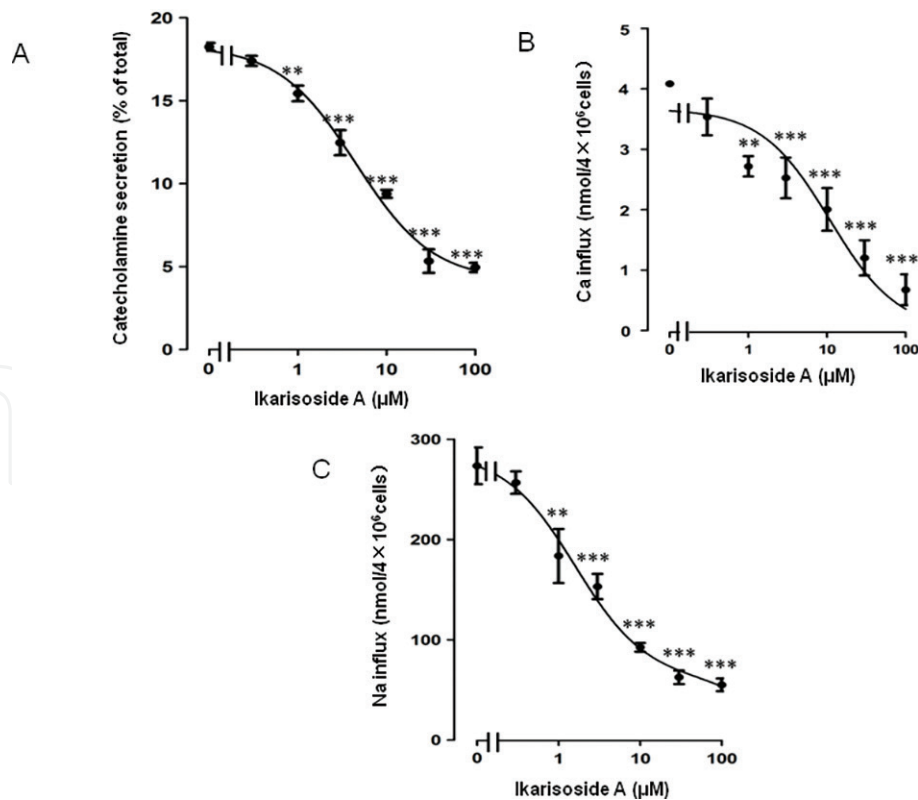
## 2. Inhibitory effects of ikarisoside A, but not its aglycon, on the catecholamine secretion and synthesis induced by ACh

Ikariside A is a natural flavonol glycoside derived from plants of the genus *Epimedium*, which have been used in traditional Chinese medicine as tonics, antirheumatics, and aphrodisiacs [10, 23, 24], and is used as a tonic supplement in Japan. Ikariside A has antioxidant and anti-inflammatory effects [23] and anti-osteoporosis effects [10, 25]. Icariin, another flavonoid in the genus *Epimedium*, has an anti-stress effect in the forced swimming test in mice [26].

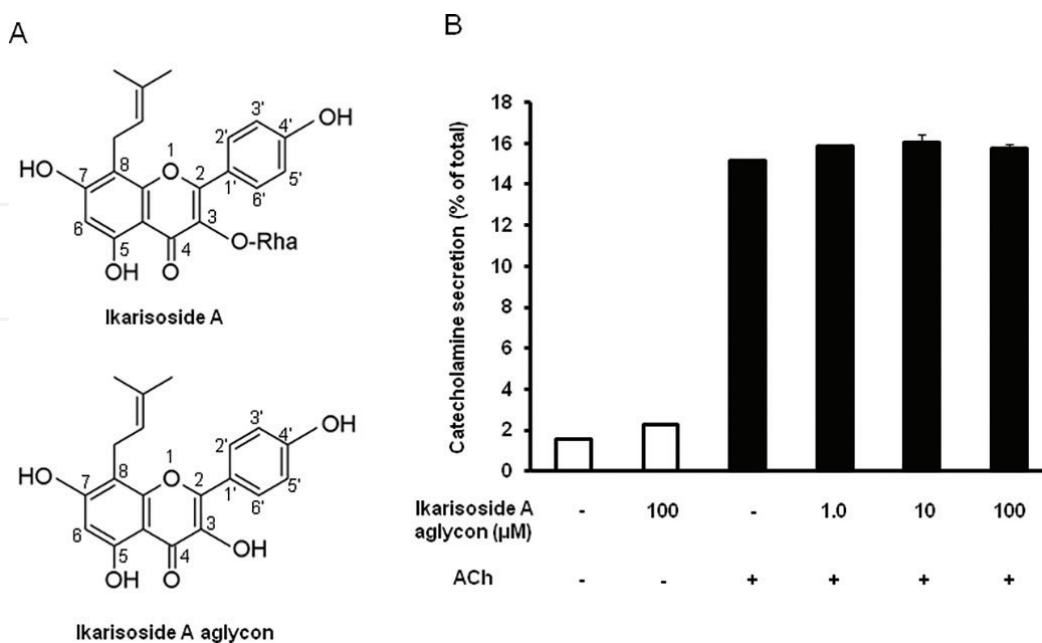
We observed that ikarisoside A (1–100  $\mu\text{M}$ ) concentration dependently inhibited the secretion of catecholamines induced by ACh (0.3  $\mu\text{M}$ ) (**Figure 2A**), but not the secretion of catecholamines induced by veratridine and 56  $\text{mK}^+$  [10]. Ikariside A also suppressed the  $^{22}\text{Na}^+$  influx and  $^{45}\text{Ca}^{2+}$  influx induced by ACh in a concentration-dependent manner similar to that of catecholamine secretion (**Figure 2B, C**) [10]. Ikariside A is a flavonol glycoside with one rhamnose at the 3 position in the chemical structure. The aglycon of ikarisoside A is 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)-4H-chromen-4-one (**Figure 3A**). It is interesting to note that the aglycon of ikarisoside A had little effect on catecholamine secretion induced by ACh (0.3  $\mu\text{M}$ ) (**Figure 3B**), suggesting that the rhamnose moiety at the 3 position of ikarisoside A is essential to inhibit the function of nAChR-ion channels [10]. Ikariside A (1.0–100 or 10–100  $\mu\text{M}$ ) inhibited ACh (0.3  $\text{mM}$ )-induced  $^{14}\text{C}$ -catecholamine synthesis from  $^{14}\text{C}$ -tyrosine and tyrosine hydroxylase activity [10].

## 3. Inhibitory effects of matsufushi and its stilbene component, SJ-2, on the catecholamine synthesis and secretion induced by ACh

Pine nodules of *Pinus tabulaeformis* or *Pinus massoniana* are formed by pine bark proliferation at places on the trunk or limbs that have undergone damage, either

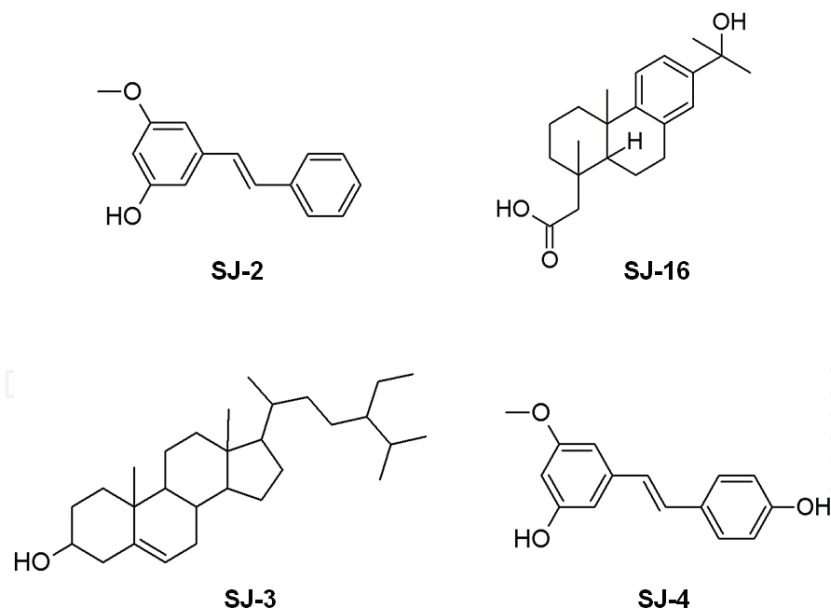


**Figure 2.** Effects of ikarisoside A on ACh-induced catecholamine secretion (A),  $^{45}\text{Ca}^{2+}$  influx (B), and  $^{22}\text{Na}^{+}$  influx (C). (A) Cultured bovine adrenal medullary cells ( $10^6$ /well) were stimulated with ACh (300  $\mu\text{M}$ ) in the presence or absence of ikarisoside A (0.3–100  $\mu\text{M}$ ) for 10 min at 37°C. Catecholamine secretion is expressed as a percentage of the total catecholamines in the cells. (B and C) Cells ( $4 \times 10^6$ /well) are stimulated with ACh (300  $\mu\text{M}$ ) and 1.5  $\mu\text{Ci}$  of  $^{45}\text{CaCl}_2$  (B) or  $^{22}\text{NaCl}$  (C) in the presence or absence of ikarisoside A (0.3–100  $\mu\text{M}$ ) for 5 min at 37°C.  $^{45}\text{Ca}^{2+}$  influx and  $^{22}\text{Na}^{+}$  influx were expressed as  $\text{nmol}/4 \times 10^6$  cells. Data are means  $\pm$  SEM from three separate experiments carried out in triplicate. \* $P < 0.01$  and \*\* $P < 0.001$  vs. ACh alone (by one-way ANOVA with Dunnett's multiple comparison post hoc test) (cited from [25]).



**Figure 3.** Structures of ikarisoside A and its aglycon (A) and the effect of aglycon of ikarisoside A on the catecholamine secretion induced by ACh (0.3 mM) (B). (A) Chemical structures of ikarisoside A and its aglycon (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)-4H-chromen-4-one). (B) Cells ( $10^6$ /well) were incubated with or without aglycon of ikarisoside A (1–100  $\mu\text{M}$ ) and ACh (300  $\mu\text{M}$ ) for 10 min at 37°C. Catecholamine secretion is expressed as a percentage of the total. Data are means  $\pm$  SEM from three separate experiments carried out in triplicate (cited from [25]).

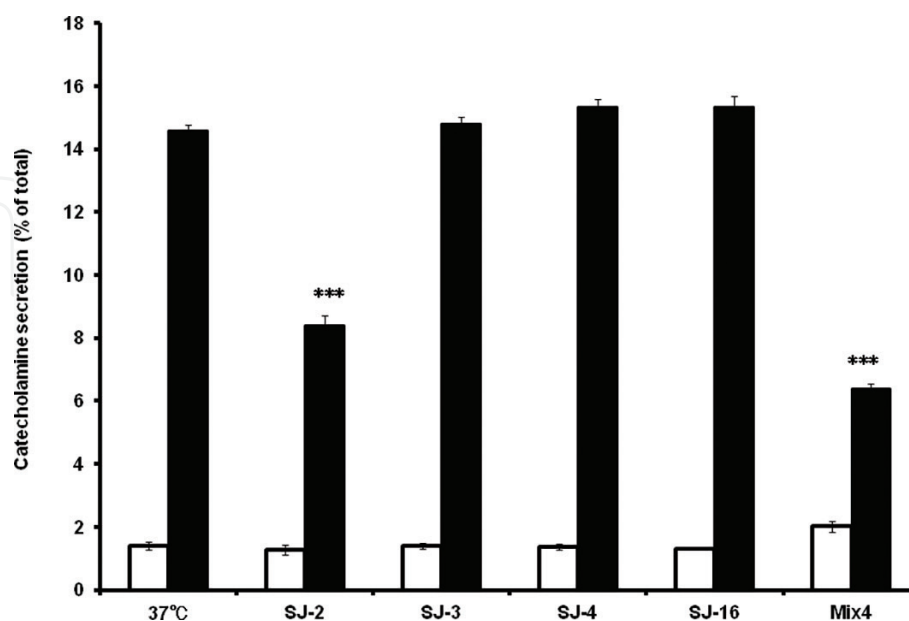




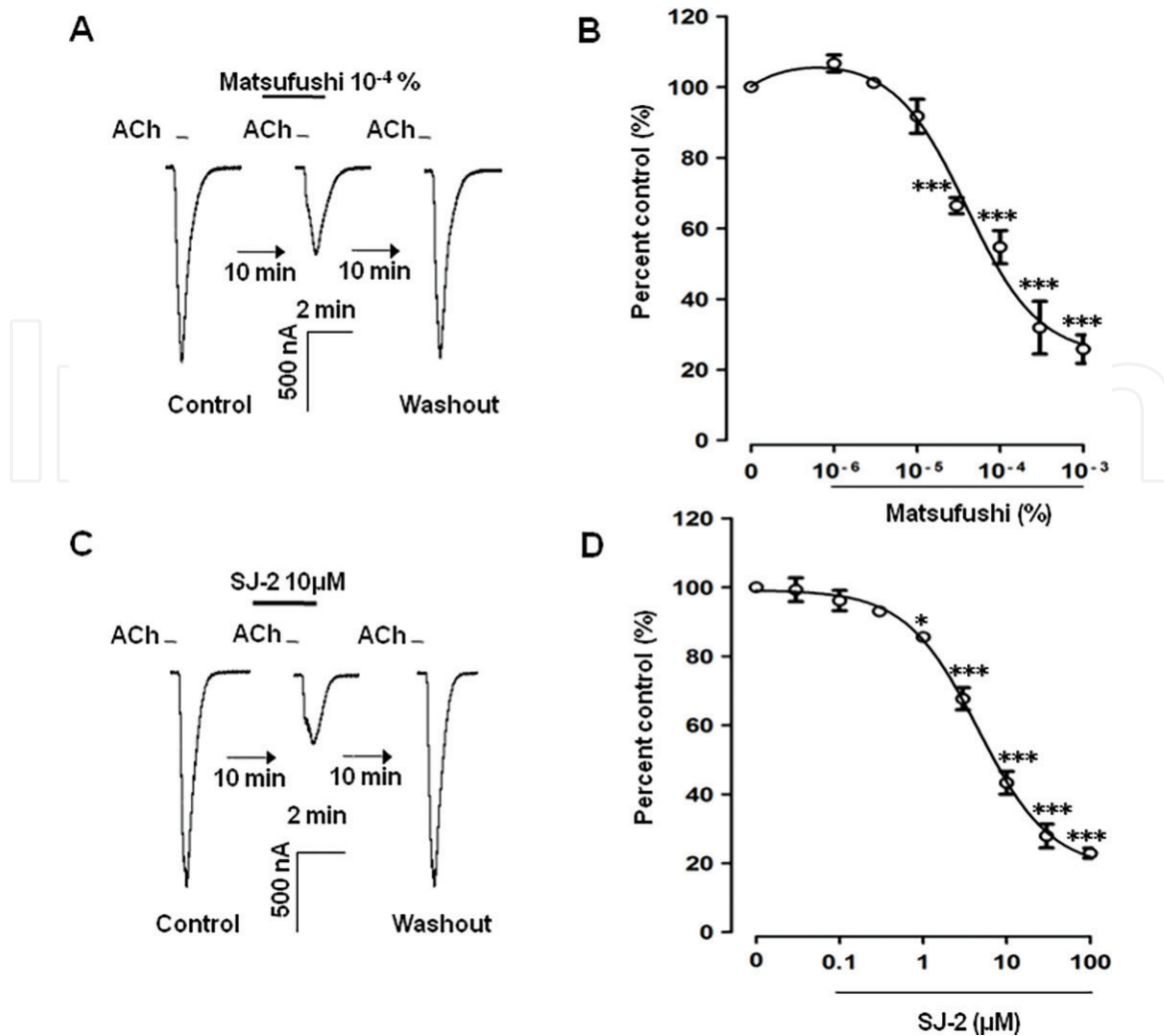
**Figure 4.**  
 Chemical structures of SJ-2, SJ-3, SJ-4, and SJ-16 (cited from [28]).

by pests or physical injury [27]. The effective curative components in pine nodule extract (matsufushi) have been used as an analgesic for joint pain, rheumatism, neuralgia, dysmenorrhea, and other complaints in traditional Chinese medicine [27–29]. Matsufushi is used as a healthy supplement in Japan.

Matsufushi ethanol extract (0.0003–0.005%) concentration dependently inhibited the catecholamine secretion and  $^{45}\text{Ca}^{2+}$  influx induced by ACh (0.3 mM) and veratridine (0.1 mM), but not 56 mM  $\text{K}^+$  in cultured bovine adrenal medullary cells [27]. Four compounds (SJ-2, SJ-3, SJ-4, and SJ-16) were isolated from matsufushi extract (Figure 4). SJ-2, a phenol stilbene, and the mixture of four compounds (Mix4; SJ-2, SJ-3, SJ-4, and SJ-16), but not each of the other separate compounds, inhibited the catecholamine secretion (Figure 5) and  $^{45}\text{Ca}^{2+}$  influx [27] induced by ACh (0.3 mM). In *Xenopus* oocytes



**Figure 5.**  
 Effects of SJ-2, SJ-3, SJ-4, SJ-16, and their mixture (Mix4) on catecholamine secretion induced by ACh in cultured bovine adrenal medullary cells. The cells ( $10^6$ /well) were incubated with or without SJ-2 (10  $\mu\text{M}$ ), SJ-3 (10  $\mu\text{M}$ ), SJ-4 (10  $\mu\text{M}$ ), SJ-16 (10  $\mu\text{M}$ ), and their mixture (Mix4) (10  $\mu\text{M}$ ) for 10 min at 37°C. Catecholamine secretion is expressed as a percentage of the total catecholamines in the cells. Data are means  $\pm$  SEM from three separate experiments carried out in triplicate. \*\*\*  $P < 0.001$  vs. ACh alone. Rha: rhamnose (cited from [28]).



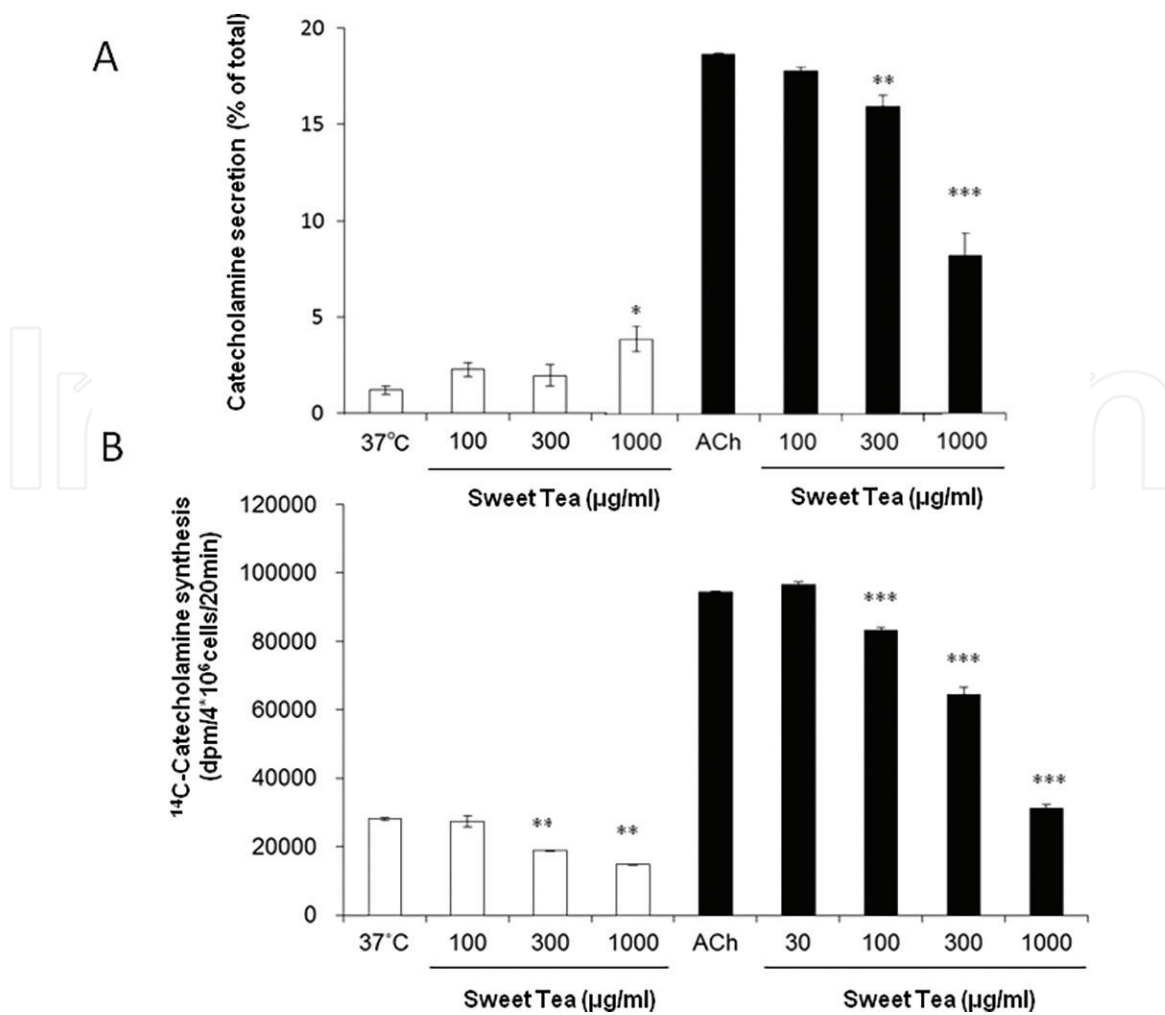
**Figure 6.**

Effects of ethanol extract of matsufushi and SJ-2 on inward currents induced by ACh in *Xenopus* oocytes expressing rat  $\alpha 3\beta 4$  nAChRs. Representative traces from a single *Xenopus* oocyte are shown. The currents of matsufushi-treated (A) and SJ-2-treated (C) oocytes were recorded for 10 min after recording of the control currents, and the washout currents were obtained for 10 min after matsufushi extract and SJ-2 treatment. Matsufushi extract (0.0001%) and SJ-2 (10  $\mu$ M) suppressed the currents induced by the EC<sub>50</sub> (0.2 mM) of ACh, and the inhibitory effects were reversible. Concentration-response curves for the inhibitory effects of matsufushi extract (B) and SJ-2 (D) on ACh-induced currents. The peak current amplitude in the presence of matsufushi extract and SJ-2 was normalized to that of the control, and the effects are expressed as percentages of the control. Data are presented as means  $\pm$  SEM from four separate experiments carried out in triplicate.  $P < 0.05$  and  $***P < 0.001$  vs. the control (cited from [28]).

expressed with  $\alpha 3\beta 4$  nAChRs, matsufushi extract and SJ-2 reversibly inhibited ACh (0.2 mM)-induced Na<sup>+</sup> currents (Figure 6A, C). Matsufushi extract (0.00003–0.001%) (Figure 6B) and SJ-2 (1–100  $\mu$ M) (Figure 6D) significantly suppressed the Na<sup>+</sup> current in a concentration-dependent manner [27]. In addition, matsufushi and SJ-2 suppressed the ACh (0.3 mM)-induced <sup>14</sup>C-catecholamine synthesis from <sup>14</sup>C-tyrosine and tyrosine hydroxylase activity [27]. These results suggest that matsufushi extract inhibits ACh-induced catecholamine synthesis and secretion mainly due to SJ-2 via the suppression of Na<sup>+</sup> influx mediated through nAChR-ion channels [27].

#### 4. Effects of the extract of sweet tea on catecholamine secretion and synthesis in adrenal medullary cells

Sweet tea is the processed leaves of *Hydrangea macrophylla* var. *thunbergii* Makino (*hydrangeae dulcis folium*), which is listed in the Japanese Pharmacopeia XV and used as a sweetening agent for diabetic patients. It also has antimicrobial and anti-allergic



**Figure 7.** Effects of sweet tea on <sup>14</sup>C-catecholamine synthesis from [<sup>14</sup>C]tyrosine (A) and tyrosine hydroxylase activity (B) in the cells. (A) Cells ( $4 \times 10^6$ /dish) were incubated with L-[U-<sup>14</sup>C] tyrosine (20  $\mu$ M, 1  $\mu$ Ci) in the presence or absence of sweet tea (100–1000  $\mu$ g/ml) and with or without 300- $\mu$ M ACh at 37°C for 20 min. The <sup>14</sup>C-catecholamines formed were measured. (B) Cells ( $10^6$ /well) were incubated with L-[1-<sup>14</sup>C] tyrosine (18  $\mu$ M, 0.2  $\mu$ Ci) in the presence or absence of sweet tea (100–1000  $\mu$ g/ml) and with or without 300  $\mu$ M ACh at 37°C for 10 min, and tyrosine hydroxylase activity was measured. Data are means  $\pm$  SEM from three separate experiments carried out in triplicate.  $P < 0.05$ , compared with 37°C (control), and \*\*  $P < 0.01$  and \*\*\*  $P < 0.001$  vs. ACh alone in (A), and \*\*  $P < 0.01$  vs. 37°C (control) and \*\*\*  $P < 0.001$  vs. ACh alone in (B).

effects [30, 31]. Sweet tea is used as a healthy tea in Japan. There is, however, little evidence regarding sweet tea's effects on the sympathetic nervous system activity.

We investigated the effects of the extract of sweet tea on adrenal medullary cell function. A dry powder of sweet tea prepared from fermented leaves of *hydrangeae dulcis folium* was solubilized at 5.0 mg/ml and extracted at 90°C for 60 min. The extracted solution of sweet tea was used after centrifugation and filtration. The extract of sweet tea (1.0 mg/ml) slightly increased the basal secretion of catecholamines (Figure 7A), whereas it suppressed the catecholamine secretion induced by ACh (0.3 mM) in a concentration-dependent manner (300–1000  $\mu$ g/ml) (Figure 7A). In addition, the extract of sweet tea (300- or 100–1000  $\mu$ g/ml) inhibited basal and ACh (0.3 mM)-induced <sup>14</sup>C-catecholamine synthesis from <sup>14</sup>C-tyrosine, respectively (Figure 7B). Sweet tea at concentrations of 3 mg/ml is usually used for drinking.

## 5. The insight of pharmacological potential of herbs in the catecholamine signaling induced by ACh in adrenal medulla

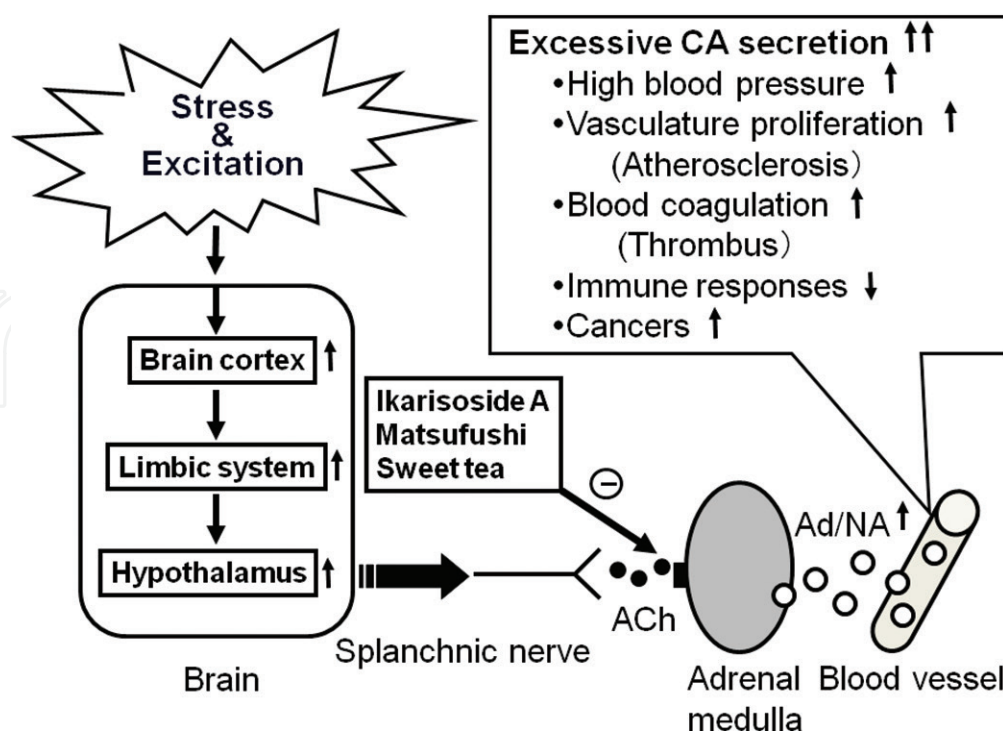
Adrenal medullary cells are derived from the embryonic neural crest and share many physiological and pharmacological properties with postganglionic sympathetic



neurons [2]. The stimulation of AChRs in these cells increases the synthesis of catecholamines and causes the secretion of catecholamines into the systemic circulation [2, 11, 14]. In adrenal medullary cells, the  $\text{Na}^+$  influx induced by ACh via nAChR-ion channels is a prerequisite for  $\text{Ca}^{2+}$  influx via the activation of voltage-dependent  $\text{Ca}^{2+}$  channels and the subsequent catecholamine secretion and synthesis; in contrast, high  $\text{K}^+$  directly gates voltage-dependent  $\text{Ca}^{2+}$  channels to increase  $^{45}\text{Ca}^{2+}$  influx [2, 11] (**Figure 1**).

As we noted, ikarisoside A and matsufushi (or SJ-2) inhibited the catecholamine secretion induced by ACh, but not the secretion induced by 56 mM  $\text{K}^+$  [10, 27]. In addition, ikarisoside A [10] and matsufushi [27] or SJ-2 [27] suppressed the  $\text{Na}^+$  current induced by ACh in *Xenopus* oocytes expressing  $\alpha\beta 4$  nAChRs. These results suggest that the herbs and their components used as described herein inhibit the ACh-induced secretion and synthesis of catecholamines via a suppression of  $\text{Na}^+$  influx mediated through nAChRs in adrenal medullary cells [10, 27].

It is well known that catecholamines have important roles in the regulation of normal function in the central and peripheral sympathetic nervous systems as a neurotransmitter but also in the adrenal medulla as an endocrine hormone [10]. Strong and prolonged stress causes massive amounts of catecholamine release, which can lead to cardiovascular diseases (such as hypertension, coronary heart disease, heart failure, and atherosclerosis), and such stress also suppresses the immune system to induce some cancers [2, 9, 10]. Indeed, chronic heart failure is associated with the activation of the sympathetic nervous system as manifested by an increased circulating level of noradrenaline and increased regional activity of the sympathetic nervous system [2, 32]. It was reported that the stress hormone adrenaline stimulates  $\beta 2$ -adrenoceptors to activate the Gs-protein-dependent protein kinase A and the  $\beta$ -arrestin-1-mediated signaling pathway, which, in turn, suppresses p53 levels and triggers DNA damage [2, 33]. On the basis of these previous and present results, it appears that the herbs and their components such as ikarisoside A, matsufushi



**Figure 8.**

*Inhibitory mechanism of plant herbs (ikarisoside A, matsufushi, and sweet tea) on stress or excitation-induced excessive catecholamine secretion. Prolonged and strong stress or excitation stimulates the brain cortex, limbic system, and hypothalamus which evoke acetylcholine release from the splanchnic sympathetic nerves. Released acetylcholine induces a massive secretion of catecholamines from the adrenal medulla which may cause various deleterious symptoms or diseases such as high blood pressure (hypertension), vasculature proliferation (atherosclerosis), blood coagulation (thrombus), immune suppression, and cancers ([2] modified).*

(or SJ-2), and sweet tea suppress the induction of a hyperactive catecholamine system induced by strong stress or emotional excitation (**Figure 8**).

## 6. Future perspective

Although the in vitro effects of the herbs and herb components described herein have been well clarified using cultured bovine adrenal medullary cells and *Xenopus* oocytes, the in vivo results are not yet clear. To confirm the pharmacological effects of these herbs on the catecholamine system, further in vivo studies of the effects of the administration of herbs to animals or humans are needed [2, 27]. We observed a disturbance of the autonomic nervous balance in women with climacteric symptoms measured by a power spectral analysis of heart rate variability [34]. Using this assay method, we will examine the effect of herbs on the autonomic nervous activity under some stress conditions.

## 7. Concluding remarks

We have reviewed the evidence that herbs and their components such as ikariso-side A, matsufushi (or SJ-2), and sweet tea inhibit the catecholamine synthesis and secretion induced by ACh in cultured bovine adrenal medullary cells and summarized them in **Table 1**. These findings may provide new insights into the pharmacological potentials of herbs on the hyperactive catecholamine system induced by stress.

Herb	Epimedium	Pine nodule	Sweet tea
Supplement	+	+	+
Compound	Ikarisoside A	SJ-2	ND
ACh-induced Na <sup>+</sup> current	↓	↓	ND
ACh-induced Ca <sup>2+</sup> influx	↓	↓	ND
Catecholamine secretion			
Basal	→	→	↑
ACh-induced	↓	↓	↓
Catecholamine synthesis			
Basal	→	→	↓
ACh-induced	↓	↓	↓

*Supplement +, available in Japan; ND, not determined.*

**Table 1.**  
 Summary of the effects of herbs and their components on catecholamine secretion and synthesis.

## Conflict of interest

The authors have no conflict of interest to declare.

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## Abbreviations

ACh	acetylcholine
nAChR	nicotinic acetylcholine receptor

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