# Novel inhibitors for histidine decarboxylase from plant components

**Author:**

Yoko Nitta[1*]

Hiroe Kikuzaki[2]

Hiroshi Ueno[3]

**Affiliation:**

[1] Department of Nutritional Science, Faculty of Health and Welfare Science, Okayama Prefectural University, 111 Kuboki, Soja, Okayama, 719-1197 Japan
E-mail:
nitta@fhw.oka-pu.ac.jp
* Correspondence author

[2] Department of Food Science and Nutrition, Nara Women's University, Kitauoyanishi-machi, Nara, 630-8506 Japan
E-mail:
kikuzaki@cc.nara-wu.ac.jp

[3] Laboratory of Applied Microbiology and Biochemistry, School of Agriculture, Ryukoku University, Shiga 520-2194, Japan
E-mail:
ueno@agr.ryukoku.ac.jp

**Abstract**

Histamine is a bioactive amine that affects a wide range of biological activities in the human body. In this review, we discuss the active components of spices and herbs that can inhibit histidine decarboxylase (HDC), an enzyme that catalyzes synthesis of histamine. We screened 21 spices and 122 medicinal plants by carrying out inhibition assays with recombinant human HDC. Among spices, flavonoid glycosides of allspice, quercetin 3-*O*-β-D-glucuronide 6''-methyl ester and quercetin 3-*O*-(2-*O*-galloyl) glucoside, at 1 mM inhibited HDC by 64 and 55%, respectively. Among medicinal plants, ellagitannins of meadowsweet, rugosin D, rugosin A, rugosin A methyl ester, and tellimagrandin II inhibited HDC significantly with $K_i$ values of approximately 0.35-1 μM. These results indicate that plant components are promising sources for novel inhibitors of HDC.

**Keywords:** histamine, inhibitors, flavonoid glycoside, ellagitannin, medicinal plant

## 1. Introduction

Histidine decarboxylase (HDC) catalyzes the synthesis of histamine, a bioactive amine that affects various biological activities including gastric acid secretion, capillary dilatation, smooth muscle contraction, neurotransmission, inflammation, and allergic reactions. HDC inhibition would lead to control of some of these activities, so it is desirable to develop suitable HDC inhibitors for pharmacological purposes; however, no such inhibitors are available for clinical use. Highly purified native HDC from mammalian sources is available (1-6); for example, HDC from livers of fetal rats and from mouse mastocytoma P-815 cells (7, 8). However, the amounts of these highly purified native HDC is limited, making them unsuitable for pharmacological studies. Recently, expression of the active form of human recombinant HDC was carried out and its crystal structure was determined (9). Hence, it is now possible to perform inhibition studies to seek active components from plant sources with the use of recombinant human HDC. In this review, we summarize the recent findings.

## 2. Spices

### 2.1. Some spices show HDC inhibitory activity (10).

Twenty-one species of spices, including clove, allspice, cinnamon, Japanese pepper, rosemary, bay leaf, sage, peppermint, mustard, anise, tarragon, marjoram, fenugreek, cumin, paprika, garlic, saffron, ginger, black pepper, red pepper and nutmeg, were tested for their inhibitory activity on HDC. While both ethanol and water extracts were examined, significant inhibition was observed for allspice, cinnamon, clove, and Japanese pepper (10). Essential oils can be extracted from these spices; thus, the inhibitory activities of essential oil components, i.e. eugenol, α-pinene, β-pinene, limonene, cineole, phellandrene, terpineol, and anethole, were also examined (10). Eugenol inhibited most potently among these compounds; however, the tested concentration was much higher than that estimated from the spice extracts (10). The results suggest that there are other more potent inhibitors existing in these spices.

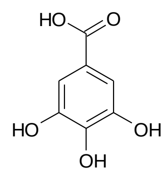
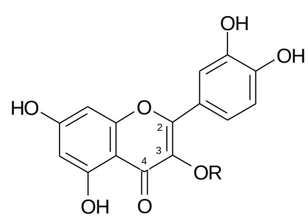
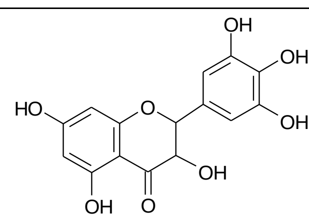
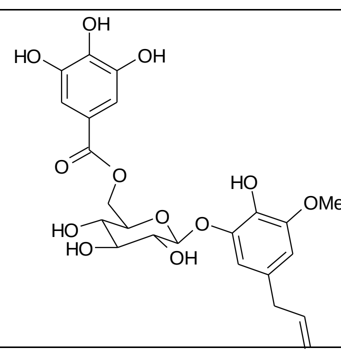
### 2.2 Flavonoid glycosides of allspice inhibit HDC activity (11)

We investigated the inhibitory activities of compounds obtained from *Pimenta dioica*, called allspice. Two quercetin glycosides from *P. dioica*, quercetin 3-*O*-β-D-glucuronide 6''-methyl ester and quercetin 3-*O*-(2-*O*-galloyl) glucoside, inhibited most potently, with 64 and 55% inhibition at 1 mM, respectively. Other compounds tested were 14 *P. dioica* compounds including gallic acid, quercetin, quercetin 3-*O*-β-D-glucopyranoside, hyperoside (quercetin 3-*O*-β-D-galactopyranoside), quercetin 3-*O*-arabinoside, quercetin 3-*O*-(2-*O*-galloyl) glucoside, quercetin 3-*O*-β-D-glucuronide 6''-methyl ester, quercetin 3-*O*-β-D-glucuronide, ampelopsin, pimentol, eugenol 4-*O*-β-D-(6-*O*-galloyl) glucopyranoside, (4*S*)-α-terpineol 8-*O*-β-D-(6-*O*-galloyl) glucopyranoside, (4*R*)-α-terpineol 8-*O*-β-D-

(6-*O*-galloyl)glucopyranoside, and eugenol as summarized in Table 1. Gallic acid, quercetin, quercetin 3-*O*-β-D-glucuronide, (4*S*)-α-terpineol 8-*O*-β-D-(6-*O*-galloyl) glucopyranoside, and eugenol did not show inhibitory activity in the examined conditions. Epigallocatechin gallate, a green tea polyphenol, has been previously reported to inhibit HDC activity (12, 13) with an inhibitory rate of 75% at 1 mM, higher than those of quercetin 3-*O*-β-D-glucuronide 6''-methyl ester and quercetin 3-*O*-(2-*O*-galloyl) glucoside.

**Table 1.** Compounds used for HDC inhibition

| Compound | Structure | | Inhibitory rate % at 1 mM |
|---|---|---|---|
| Gallic acid |  | | < 1 |
| Quercetin |  | R = H | < 1 |
| Quercetin 3-O-β-D-glucopyranoside | | R = β-D-Glc | 15 ± 3 |
| Hyperoside | | R = -β-D-Gal | 28 ± 1 |
| Quercetin 3-*O*-arabinoside | | R = -Ara | 30 ± 2 |
| Quercetin 3-*O*-(2-*O*-galloyl)-β-D-glucoside | | R = -(2-*O*-galloyl)Glc | 55 ± 6 |
| Quercetin 3-*O*-β-D-glucuronide 6''-methyl ester | | R = -methyl glucuronide | 64 ± 7 |
| Quercetin 3-*O*-β-D-glucuronide | | R = -glucronide | < 1 |
| Ampelopsin |  | | 20 ± 6 |
| Pimentol |  | | 7 ± 1 |

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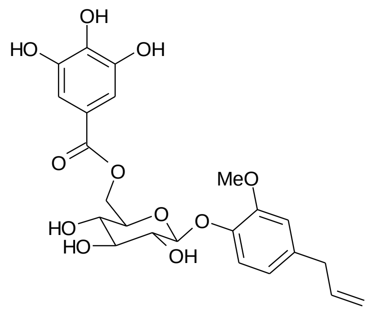
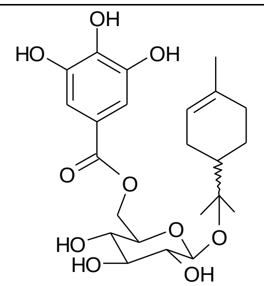
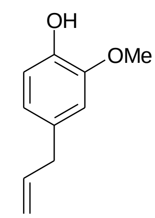
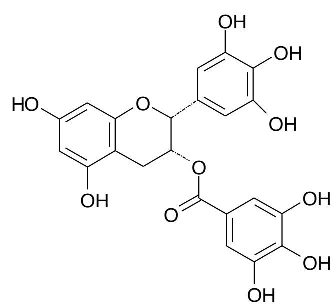
|---|---|---|
| Eugenol 4-*O*-β-D-(6-*O*-galloyl)glucopyranoside |  | < 1 |
| (4*S*)-α-terpineol 8-*O*-β-D-(6-*O*-galloyl)glucopyranoside<br>(4*R*)-α-terpineol 8-*O*-β-D-(6-*O*-galloyl)glucopyranoside |  | 19 ± 2<br>21 ± 6 |
| Eugenol |  | < 1 |
| Epigallocatechin gallate |  | 75 ± 3 |

### 3. Medicinal plants

#### 3.1. Plants of rose family can inhibit HDC activity (14)

Exploration of possible candidates for inhibition of HDC activity was carried out with 122 species of medicinal plants (Table 2). Plant samples were prepared by 50% ethanol extraction. Of these, 21 samples inhibited HDC activity significantly, with a >30% inhibitory rate. In particular, *Artocarpus lakoocha*, amla, and meadowsweet showed more than 90% inhibitory activity. Table 3 summarizes the results of 21 extract samples as listed by their taxonomic family category. Over 30% of these samples belong to the rose family (Fig. 1).

**Table 2.** Medicinal plants tested for HDC inhibition.

| *Taxonomic family* | *Binomial name* (common name) |
|---|---|
| *Acoraceae* | *Acorus calamus* |
| *Adoxaceae* | *Sambucus nigra* (Elder) |
| *Amaranthaceae* | *Bassia scoparia* |
| *Amaryllidaceae* | *Allium fistulosum* (Welsh onion seed)<br>*Allium tuberosum* (Chinese chives seed) |
| *Apiaceae* | *Angelica keiskei* (Ashitaba)<br>*Angelica pubescens* (Angelica pubescens rhizome)<br>*Centella asiatica*<br>*Daucus carota* (Carrot)<br>*Foeniculum vulgare* (Fennel)<br>*Peucedanum praeruptorum* (Peucedanum Root) |
| *Apocynaceae* | *Gymnema sylvestre* |
| *Aquifoliaceae* | *Ilex kaushue* (Kuding) |
| *Araceae* | *Pinellia ternate* |
| *Araliaceae* | *Aralia elata* (Aralia elata root bark)<br>*Eleutherococcus senticosus* (Siberian ginseng)<br>*Panax notoginseng* |
| *Asparagaceae* | *Polygonatum falcatum* (Polygonatum rhizome)<br>*Polygonatum odoratum*<br>*Ruscus aculeatus* (Butcher's broom) |
| *Asteraceae* | *Arnica montana*<br>*Artemisia capillaris* (Capillary wormwood)<br>*Aster tataricus*<br>*Atractylodes lancea*<br>*Echinacea purpurea* (Purple coneflower)<br>*Helianthus annuus* (Sunflower)<br>*Solidago virgaurea* (Goldenrod)<br>*Tanacetum vulgare* (Tansy)<br>*Xanthium strumarium* (Xanthium fruit) |
| *Berberidaceae* | *Epimedium grandiflorum* (Horny goat weed) |
| *Bignoniaceae* | *Handroanthus impetiginosus* (Lapacho) |
| *Brassicaceae* | *Brassica juncea* (Mustards) |
| *Brassicaceae* | *Draba nemorosa* (Woodland draba seed) |
| *Burseraceae* | *Boswellia serrata* |
| *Campanulaceae* | *Codonopsis pilosula* (Codonopsis Root) |
| *Caprifoliaceae* | *Lonicera japonica* (Lonicera leaf and stem) |
| *Caryophyllaceae* | *Stellaria media* (Chickweed) |
| *Combretaceae* | *Terminalia chebula* (Chebulic myrobalan) |
| *Convolvulaceae* | *Cuscuta japonica* (Japanese dodder seed) |
| *Cucurbitaceae* | *Cucurbita moschata* (Pumpkin seed)<br>*Gynostemma pentaphyllum* (Jiaogulan, Amachazuru)<br>*Trichosanthes kirilowii* (Trichosanthes seed) |

| | |
|---|---|
| *Cupressaceae* | *Juniperus communis* (Common juniper) |
| *Dioscoreaceae* | *Dioscorea mexicana* (Mexican yam) |
| *Euphorbiaceae* | *Euphorbia kansui*<br>*Euphorbia lathyris* (Caper spurge) |
| *Fabaceae* | *Astragalus sinicus* (Astragalus sinicus seed)<br>*Cassia mimosoides*<br>*Dolichos lablab* (Dolichos seed)<br>*Melilotus officinalis* (Yellow sweet clover)<br>*Senna alexandrina* (Alexandrian senna)<br>*Trifolium pretense* (Red clover)<br>*Vicia faba* (Broad bean)<br>*Vigna angularis* (Adzuki bean)<br>*Vigna radiate* (Mung bean) |
| *Gnetaceae* | *Gnetum gnemon* (Gnetum leaf) |
| *Icmadophilaceae* | *Thamnolia vermicularis* (Snow tea) |
| *Iridaceae* | *Iris domestica* (Leopard lily root) |
| *Juglandaceae* | *Juglans ailantifolia* (Japanese walnut)<br>*Juglans regia* (Walnut) |
| *Lamiaceae* | *Nepeta cataria* (Catnip)<br>*Perilla frutescens var. crispa* (Shiso fruit)<br>*Perilla frutescens var. crispa* (Shiso leaf) |
| *Lauraceae* | *Lindera aggregata* (Evergreen lindera)<br>*Lindera umbellate* (Kuromoji) |
| *Malvaceae* | *Abutilon avicennae* (Abutilon avicennae seed)<br>*Hibiscus syriacus* (Hibiscus syriacus bark)<br>*Theobroma cacao* (Cocoa beans) |
| *Moraceae* | *Artocarpus lakoocha*<br>*Morus bombycis* (Mulberry leaf) |
| *Myrtaceae* | *Eucalyptus* (Eucalyptus leaf) |
| *Nelumbonaceae* | *Nelumbo nucifera* (Nelumbo seed) |
| *Oleaceae* | *Fraxinus lanuginose* (Fraxinus lanuginose bark)<br>*Ligustrum lucidum* (Chinese privet fruit) |
| *Orchidaceae* | *Dendrobium nobile* (Dendrobium stem)<br>*Gastrodia elata* |
| *Papaveraceae* | *Corydalis yanhusuo* (Corydalis tuber) |
| *Parmeliaceae* | *Dolichousnea longissima* |
| *Pedaliaceae* | *Harpagophytum procumbens* (Devil's claw)<br>*Sesamum radiatum* (Black sesame) |
| *Phyllanthaceae* | *Phyllanthus emblica* (Amla) |
| *Pinaceae* | *Pinus sylvestris* (Scots pine) |
| *Plantaginaceae* | *Plantago asiatica* (Plantago seed) |
| *Poaceae* | *Sorghum bicolor* (Sorghum) |
| *Polygonaceae* | *Rumex crispus* (Yellow dock) |
| *Primulaceae* | *Primula vulgaris* (Primrose) |
| *Ranunculaceae* | *Cimicifuga simplex* (Cimicifuga rhizome)<br>*Clematis terniflora* |

| | |
|---|---|
| *Rhamnaceae* | *Hovenia dulcis* (Japanese rasin tree fruit)<br>*Ziziphus jujube* (Chinese date) |
| *Rosaceae* | *Alchemilla vulgaris* (Lady's mantle)<br>*Cydonia oblonga* (Quince)<br>*Filipendula ulmaria* (Meadowsweet)<br>*Prunus armeniaca* (Apricot kernel)<br>*Prunus japonica* (Japanese bush cherry seed)<br>*Prunus persica* (Peach leaf)<br>*Rosa multiflora* (Rosa multiflora fruit)<br>*Rosa roxburghii* (Roxburgh rose)<br>*Rubus chingii* (Raspberry)<br>*Sanguisorba officinalis* (Great burnet root) |
| *Rubiaceae* | *Cinchona pubescens* (cinchona bark)<br>*Galium aparine* (Cleavers)<br>*Galium spurium* (False cleavers) |
| *Rutaceae* | *Citrus junos* (Yuzu)<br>*Evodia rutaecarpa* (Evodia fruit) |
| *Santalaceae* | *Viscum album* (Mistletoe) |
| *Schisandraceae* | *Schisandra chinensis* (Schisandra fruit) |
| *Smilacaceae* | *Smilax regelii* (Sarsaparilla root) |
| *Solanaceae* | *Lycium chinense* (Lycium leaf) |
| *Styracaceae* | *Styrax benzoin* (Gum benzoin) |
| *Taxaceae* | *Taxus cuspidata* (Japanese yew) |
| *Tiliaceae* | *Tilia cordata* (Small-leaved lime) |
| *Typhaceae* | *Typha latifolia* (Bulrush pollen) |
| *Valerianaceae* | *Valeriana officinalis* (Valerian) |
| *Violaceae* | *Viola tricolor* (Heartsease) |
| *Vitaceae* | *Vitis coignetiae* (Mountain grape bark) |
| *Zingiberaceae* | *Alpinia katsumadai* (Alpinia katsumadai seed)<br>*Alpinia officinarum* (Lesser galangal rhizome)<br>*Amomum xanthioides* (Amomum seed)<br>*Curcuma longa* (Tumeric)<br>*Zingiber officinale* (Ginger) |
| *Zygophyllaceae* | *Tribulus terrestris* (Tribulus fruit) |

**Table 3.** Medicinal plants that inhibit HDC

| *Taxonomic family* | Tested sample number | *Binomial name* (common name) | Part of plant |
|---|---|---|---|
| *Rosaceae* | 10 | *Alchemilla vulgaris* (Lady's mantle) | Grass |
| | | *Cydonia oblonga* (Quince) | Fruit |
| | | *Filipendula ulmaria* (Meadowsweet) | Flower |
| | | *Prunus armeniaca* (Apricot kernel) | Seed |
| | | *Prunus japonica* (Japanese bush cherry seed) | Seed |
| | | *Rosa roxburghii* (Roxburgh rose) | Fruit |
| | | *Rubus chingii* (Raspberry) | Fruit |
| *Asteraceae* | 9 | *Solidago virgaurea* (Goldenrod) | Grass |
| | | *Artemisia capillaris* (Capillary wormwood) | Flower |
| *Fabaceae* | 9 | *Cassia mimosoides* | Grass |
| | | *Senna alexandrina* (Alexandrian senna) | Leaf |
| *Zingiberaceae* | 5 | *Alpinia officinarum* (Lesser galangal rhizome) | Root |
| *Asparagaceae* | 3 | *Polygonatum falcatum* (Polygonatum rhizome) | Root |
| *Labiatae* | 3 | *Nepeta cataria* (Catnip) | Grass |
| *Juglandaceae* | 2 | *Juglans regia* (Walnut) | Seed |
| *Moraceae* | 2 | *Artocarpus lakoocha* | Wood |
| *Amaranthaceae* | 1 | *Bassia scoparia* | Fruit |
| *Combretaceae* | 1 | *Terminalia chebula* (Chebulic myrobalan) | Fruit |
| *Myrtaceae* | 1 | *Eucalyptus* (Eucalyptus leaf) | Leaf |
| *Phyllanthaceae* | 1 | *Phyllanthus emblica* (Amla) | Fruit |
| *Polygonaceae* | 1 | *Rumex crispus* (Yellow dock) | Root |

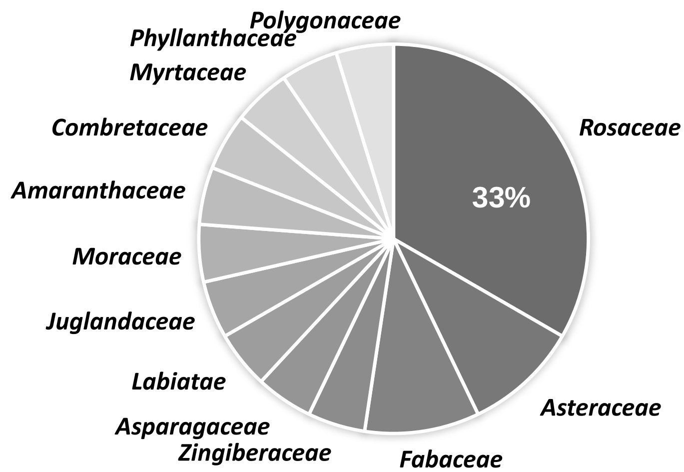
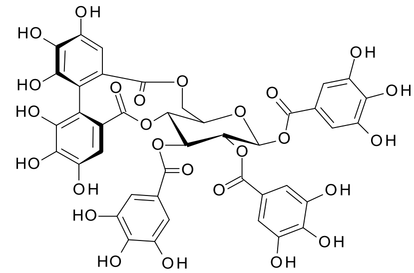
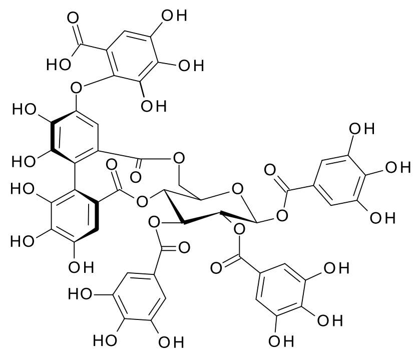
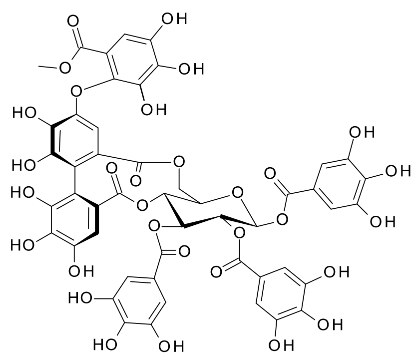
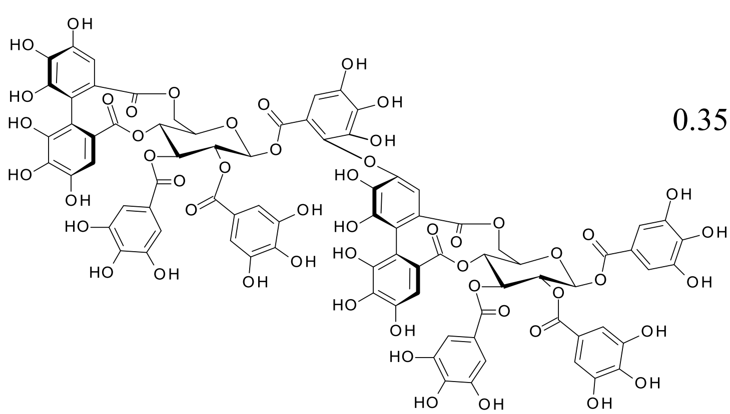



**Figure 1.** Proportion of taxonomic families exhibiting HDC inhibition.

### 3.2. Ellagitannins of meadowsweet are potent HDC inhibitors (15)

*Filipendula ulmaria*, also called meadowsweet, is a member of the rose family. Ethyl acetate extracts of the petals of meadowsweet give fractions containing ellagitannins, including rugosin D, rugosin A, rugosin A methyl ester (a novel compound), and tellimagrandin II. When the inhibitory activity against HDC was examined for each fraction, 4 ellagitannins exhibited a noncompetitive type of inhibition with $K_i$ values of approximately 0.35-1 μM (Table 4). Ellagitannins appear to be potent HDC inhibitors since their $K_i$ values are nearly equal to that of an existing inhibitor, histidine methyl ester, with $K_i$ = 0.46 μM. Also, ellagitannins are more than 10-times as potent as previously found inhibitors, catechins, including epigallocatechin gallate and epicatechin gallate, with $K_i$ of values 38 and 10 μM, respectively (13).

**Table 4.** Compounds identified from meadowsweet as HDC inhibitors.

| Compound | Structure | $K_i$ (μM) |
|---|---|---|
| Tellimagrandin II |  | 0.94 ± 0.08 |
| Rugosin A |  | 1.00 ± 0.00 |
| Rugosin A methyl ester |  | 0.41 ± 0.14 |
| Rugosin D |  | 0.35 ± 0.10 |

## 4. Applications for preventing food poisoning (16)

Practical use of potent ellagitannin inhibitors was explored for bacterial HDC. Some bacterial HDCs, such as that of *Morganella morganii*, a gram-negative bacterium, require pyridoxal-5'-phosphate as a cofactor, similar to mammalian HDC. *M. morganii* is typically found in fish and is known to generate histamine by HDC activity at > 100 ppm, in excess of the Codex standard (CODEX STAN 190-1995). Fish meat contaminated with histamine causes various unfavorable reaction such as tingling or burning sensation in or around the mouth or throat (17). Whether the fish and/or *M. morganii* are alive or not, once histamine has accumulated, there is a risk of food poisoning. Hence, there is practical use for bacterial HDC inhibition.

Potent inhibitors found for human HDC, rugosin D, rugosin A methyl ester, tellimagrandin II, and rugosin A, were examined for *M. morganii* HDC *in vitro*. All of these inhibitors inhibited *M. morganii* HDC with $IC_{50}$ values in the micromolar range (Table 5). Effective concentrations of rugosin A, tellimagrandin II, and rugosin D in 2 wt% extracts were 200~400 μM (Table 5).

Mackerel meat was obtained from a nearby supermarket and examined for histamine accumulation. One sample of mackerel meat was treated with 2% extract of meadowsweet flowers and another treated with a phosphate buffered saline (PBS) buffer. Histamine levels were measured for up to 2 days, and the control samples showed significant increases in histamine levels, exceeding 100 ppm (Table 6). Meadowsweet treatment prevented histamine accumulation in mackerel.

**Table 5.** $IC_{50}$ of ellagitannins for *M. morganii* HDC and concentration in 2.0 wt% meadowsweet extract.

| Compound | $IC_{50}$ (μM) | Concentration (μM) |
|---|---|---|
| Tellimagrandin II | 6.1 | 344 |
| Rugosin A | 6.8 | 421 |
| Rugosin A methyl ester | 4.4 | <10 |
| Rugosin D | 1.5 | 207 |

**Table 6.** Histamine content in mackerel meat (individual samples numbered 1-11) treated by PBS or 2.0 wt% meadowsweet extract for 0-48 h at 22±3 °C. -, less than 100 ppm; +, more than 100 ppm.

| | PBS Histamine content | | | Meadowsweet extract Histamine content | | |
|---|---|---|---|---|---|---|
| | 0 h | 24 h | 48 h | 0 h | 24 h | 48 h |
| No. 1 | - | + | + | - | - | - |
| No. 2 | - | - | - | - | - | - |
| No. 3 | - | - | + | - | - | - |
| No. 4 | - | - | + | - | - | - |
| No. 5 | - | - | + | - | - | - |
| No. 6 | - | + | + | - | - | - |
| No. 7 | - | + | + | - | - | + |
| No. 8 | - | + | + | - | - | + |
| No. 9 | - | + | + | - | - | + |
| No. 10 | - | + | + | - | - | + |
| No. 11 | - | + | + | - | - | + |

## 5. Conclusions

As our study and others show, novel and potent inhibitors of HDC are found in plants. This fact proofs that plants are a promising source for novel inhibitors of HDC. Among spices, flavonoid glucosides were identified as novel inhibitors of HDC. Among medicinal plants, ellagitannins were identified as novel and potent inhibitors of HDC. Numerous flavonoid glucosides and ellagitannins have been identified in plants. More potent and specific inhibitors of HDC likely exist in plants, and further investigations are now in progress.

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