Antioxidant compounds of *Petasites japonicus* and their preventive effects in chronic diseases: a review

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*Petasites japonicus* (**P. japonicus**) is a plant of the Asteraceae family that is native to Japan. Sesquiterpenoids, lignans, and flavonoids are components of **P. japonicus**. Regarding the biological activity of **P. japonicus**, its anti-allergic effect has been researched extensively using IgE antigen-stimulated degranulation of RBL-2H3 cells or passive cutaneous anaphylaxis reaction in experimental animal models. The study of the antioxidant activity of **P. japonicus** was initiated approximately 15 years ago using *in vitro* assays. In addition, its *in vivo* effect has also been examined in animal models with induced oxidative injury. Moreover, recently, many types of antioxidant compounds have been rapidly and simultaneously identified using the liquid chromatography–mass spectrometry technique. The number of reports on the other functions of this plant, such as its neuroprotective and anti-inflammatory effects, has been increasing. In this review, I summarized the studies of functional foods derived from **P. japonicus**, which may provide a basis for the development of potential functional foods. Finally, I discuss the future research avenues in this field.

**Key Words:** *Petasites japonicus*, antioxidant activity, anti-allergy, neuroprotection, metabolic improvement

**P. japonicus** is a plant of the Asteraceae family that is native to Japan. Sesquiterpenoids such as petasin and bakkenolides, fukinolic acid, lignans, and flavonoids (e.g., the aglycones of quercetin and kaempferol), are components of **P. japonicus**. The flower bud of **P. japonicus** is a fukinoto and one of the wild plants that are harvested in spring. The flower buds and stems are used as foods in Japan and Korea. Moreover, the roots and stems of **P. japonicus** have long been used as a traditional Chinese medicine for the treatment and prophylaxis of migraine, tension headache, and spasms of the urogenital tract. The flower buds of **P. japonicus** are used in the northern area of the Kanto region; its leaves are very large and extend upward. Rawan-buki grows naturally in Hokkaido and is a kind of **P. japonicus** subsp. giganteus Kitam. Among them, Awaharuka has been cultivated for its high-quality flower buds, which has a suitable shape and tightly closed petals.

Furthermore, **P. japonicus** subsp. giganteus Kitam, a subspecies of **P. japonicus**, is cultivated in the northern area of the Kanto region; its leaves are very large and extend upward. Rawan-buki grows naturally in Hokkaido and is a kind of **P. japonicus** subsp. giganteus Kitam.

**Antioxidant Compounds and *in vitro* Antioxidant Activity of **P. japonicus**

The antioxidant activity of the extracts from different tissues of **P. japonicus** was examined in various *in vitro* systems, such as the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay and ferrie-reducing ability of plasma (FRAP) assays. Moreover, its antioxidant compounds were identified using a combination of an antioxidant assay with high-performance liquid chromatography (HPLC), liquid chromatography–tandem mass spectrometry (LC–MS/MS), and NMR techniques (Table 1). Matsuura et al. screened for antioxidative compounds in the flower buds of **P. japonicus** subsp. gigantea Kitam using the HPLC–DPPH method, and identified caffeic acid and several quercetin glucosides by HPLC coupled to a diode array detector, as well as 7H-NMR and flash desorption mass spectrometry analyses. In **P. formosanus**, petasiformin A was identified as a phenylpropanoyl sulfonic acid with DPPH radical scavenging activity. In **P. japonicus**, petasignolide A is purified and isolated kaempferol as the active compounds of the stems of **P. japonicus**. The antioxidant activity of the active compound was examined by DPPH radical scavenging assay, thioarbituric acid-reactive substance (TBARS) assay in the linoleic acid model system, and lipoxygenase inhibition assay. Moreover, several

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compounds such as caffeoylquinic acids and its isomer, quercetin, kaempferol glycosides, and fukinolic acid in the leaves and roots were identified. Among them, 3,5-di-O caffeoylquinic acid exhibited the greatest radical scavenging capacity, as assessed using an HPLC system with post-column online antioxidant detection based on ABTS* radical scavenging activity. Lee et al. (27) identified four flavonoids in P. japonicus leaves and reported that quercetin-3-O-β-D-galactoside, which was extracted among these flavonoids, showed the highest aldose reductase inhibitory activity on rat lens and was a potent agent against diabetic complications.

With the advancement of analyses and compound identification based on LC–MS/MS, antioxidant compounds have been identified rapidly using on-line HPLC–DPPH or on-line ABTS*. Choi et al. (26) analyzed 10 components, including catechin, di-caf- feoylquinic acid isomers, and naringin, luteolin, liquiritin, kaempferol, and chrysoeriol derivatives and examined the anti-oxidant activity of extracts from the roots, stems, and leaves of Korean P. japonicus (Meowi) using DPPH, ABTS*, superoxide radical scavenging activities, and FRAP assays. Moreover, those authors also reported the anti-inflammatory effects of these compounds. We evaluated the antioxidant activity of an 80% ethanol extract of the flower buds of P. japonicus using oxygen radical absorbance capacity (ORAC) and DPPH radical scavenging activity. The ORAC values were attributed to H-ORAC; therefore, the trends in the results of the DPPH radical scavenging assay were consistent with those of the ORAC assay. Moreover, the antioxidative compounds that were determined using HPLC–DPPH methods and identified and quantified using LC–MS/MS included six antioxidative active compounds: caffeic acid, 3-O-cafeoylquinic acid [3-O-cafeoylquinic acid (chlorogenic acid)], fukinolic acid, and three di-cafeoylquinic acids (3,4-di-O-cafeoylquinic acid, 3,5-di-O-cafeoylquinic acid, and 4,5-di-O-cafeoylquinic acid). Fukinolic acid and 3,4-di-O-cafeoylquinic acid are major active compounds based on their activity and abundance. (26) Conversely, Watanabe et al. (25) reported that DPPH was epigallocatechin-3-O-gallate>fukinolic acid>chlorogenic acid and that the order of potency of the scavenging hydroxyl radical was epigallocatechin-3-O-gallate>fukinolic acid>gallic acid based on a mouse macrophage Raw 264.7 cell assay.

As mentioned above, the representative antioxidant components are caffeic acid, di-cafeoylquinic acid, fukinolic acid, and quercetin glycosides. The difference in their composition seems to depend on the tissue, the method of extraction, and the assay. Caffeic acid, caffeoylquinic acid, and quercetin glycosides are widely distributed in the plant kingdom, while fukinolic acid is specific to P. japonicus. The structures of fukinolic acid and fukiic acid in P. japonicus were reported by Sakamura et al. (31) in 1973, which yield enzymatic browning substances by oxidation. Black cohosh (Actaea racemosa) is used as an herb in America and Europe and is a member of the Ranunculaceae family that contains caffeic acid and fukinolic acid, which is a derivative of caffeic acid. (31) Cimicifuga heracleifolia is also closely related to the genus Actaea. These plants contain fukinolic acid and cimicifugic acids, (32,33) which are caffeic acid derivatives with documented antioxidant activities. (31)

Furthermore, the antioxidant activities of P. japonicus were examined using an in vitro assay with the cell lines Raw264.7 and HCT-116, a human colorectal carcinoma cell line. Nitric oxide (NO) production was inhibited by fukinolic acid, as a main

Table 1. Analysis and identification of antioxidant compounds in P. japonicus

<table>
<thead>
<tr>
<th>Assay</th>
<th>Compound (Source, part, and fraction)</th>
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<tr>
<td>HPLC-DPPH</td>
<td>Quercetin 3-O-β-D-glucoside, quercetin 3-O-β-D-6′′-O-acetylglucoside, rutin, caffeic acid (70% ethanol extraction of P. japonicus subsp. gigantea Kitam. flower bud)</td>
<td>Matsuura et al. (2002)</td>
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<td>Scavenging superoxide anion, NO, DPPH, radical scavenging, Raw 264.7</td>
<td>Chlorogenic acid, fukinolic acid, 3,5-dicaffeoyl quinic acid, and 3,4,5-tricaffeoyl quinic acid (leaves of P. japonicus Fr. Schmidt)</td>
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<td>DPPH radical scavenging assay, TBARS in the linoelic acid model system, lipoxygenase inhibition assay</td>
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<td>HPLC system with post-column online antioxidant detection based on ABTS* radical scavenging activity</td>
<td>5-Caffeoylquinic acid, fukinolic acid, 3,5-di-O-cafeoylquinic acid, quercetin-3-O-(6′′-acetyl)-β-D-glucopyranoside, 4,5-di-O-cafeoylquinic acid, and kaempferol-3-O-(6′′-acetyl)-β-D-glucopyranoside (methanol extract of P. japonicus leaves and roots)</td>
<td>Kim et al. (2012)</td>
<td>(6)</td>
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<td>Aldose reductase inhibition on rat lenses</td>
<td>Kaempferol-3-O-(6′′-acetyl)-β-D-glucoside, quercetin-3-O-(6′′-acetyl)-β-D-glucoside, kaempferol-3-O-β-D-glucoside, quercetin-3-O-β-D-glucoside (methanol extract of P. japonicus leaves)</td>
<td>Lee et al. (2015)</td>
<td>(27)</td>
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<td>Scavenging activity against superoxide anion radical, LLC-PK1 cells</td>
<td>Ethyl acetate extract of P. japonicus (high polyphenol and flavonoid content)</td>
<td>Kim et al. (2016)</td>
<td>(28)</td>
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<td>DPPH scavenging activity, ABTS* scavenging activity, superoxide radical scavenging activity, FRAP assays, RAW 264.7</td>
<td>3,5-Dihydroxy-7,3′,4′,5′-tetramethoxy flavanone hydroxy feruloyl glucoside, dicaffeoylquinic acid, naringenin hexoside, luteolin-7-O-(6′′-dihydroxypropyl)-glucosyl-8-C-pentosyl-glucoside, liquiritin, 3,4-di-O-cafeoylquinic acid, 1,3-O-dicafeoylquinic acid hexoside, kaempferol-3-O-acetylglucoside, chrysoeriol-methyl ether (Korean P. japonicus leaves, stems, and roots)</td>
<td>Choi et al. (2017)</td>
<td>(29)</td>
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<td>HPLC-DPPH, ORAC</td>
<td>3-O-Caffeoylquinic acid, fukinolic acid, 3,4-di-O-cafeoylquinic acid, 3,5-di-O-cafeoylquinic acid, and 4,5-di-O-cafeoylquinic acid (80% ethanol extract of P. japonicus (Sieb. et Zucc.) Maxim. flower bud)</td>
<td>Hiemori-Kondo et al. (2020)</td>
<td>(30)</td>
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HPLC-DPPH, high performance liquid chromatography-1,1-diphenyl-2-picyrylhydrazyl; NO, nitric oxide; TBARS, thiobarbituric acid-reactive substance; ABTS*, 2,2′-azino-bis(3-ethylbenothiazoline-6-sulfonic acid); FRAP, ferric-reducing ability of plasma; ORAC, oxygen radical absorbance capacity.
Table 2. In vivo antioxidant activity of P. japonicus and its derived compounds

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<td>Kainic acid-challenged mice</td>
<td>Restore TBARS values and cytosolic GSH levels in the brain</td>
<td><em>P. japonicus</em> butanol extract (400 mg/kg) gavage for 4 days</td>
<td>Oh et al. (2005)</td>
<td>(34)</td>
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<tr>
<td>Kainic acid-challenged mice</td>
<td>Restore TBARS values and cytosolic GSH levels in the brain</td>
<td>Petasagnolide A in <em>P. japonicus</em> (Sieb. et Zucc.) Maxim. leaves (40 mg/kg for 4 days)</td>
<td>Cui et al. (2005)</td>
<td>(35)</td>
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<tr>
<td>Kainic acid-treated mice</td>
<td>Antioxidant and antiseizure activities</td>
<td>Petasagnolide A in <em>P. japonicus</em> (Sieb. et Zucc.) Maxim. leaves (50 mg/kg for 4 days)</td>
<td>Min et al. (2005)</td>
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<td>Alcohol-treated Sprague-Dawley rats</td>
<td>Suppression in the decrease in AST activity, suppression or increase in the hepatic activities of catalase and GSH-Px, and increase in GSH levels</td>
<td>Ethanol extract of <em>P. japonicus</em> (Sieb. et Zucc.) Maxim. leaves and stems (200 mg/kg/day)</td>
<td>Cho et al. (2007)</td>
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<td>CCl&lt;sub&gt;4&lt;/sub&gt;-induced lipid peroxidation, hepatotoxicity in rats</td>
<td>Increase in anti-lipid peroxidative effects and decrease in the levels of GGT, GPT, ALP, BUN, and cholesterol</td>
<td>Methanol extract of <em>P. japonicus</em> (1.0 g/kg)</td>
<td>Park (2007)</td>
<td>(37)</td>
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<td>Monosodium L-glutamate-treated ICR mice</td>
<td>Improvement in plasma lipid profiles and decrease in oxidative stress by the upregulation of hepatic antioxidant enzymes</td>
<td>The butanol fraction from the methanol extract of butterbur (<em>P. japonicus</em> Max.) leaves (0.1% or 0.3% for 1 week and on day 7)</td>
<td>Park et al. (2010)</td>
<td>(38)</td>
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<td>F344/Ducr/J rats</td>
<td>Increased liver weight, increased TBARS and glutathione levels in the serum and liver, and hepatic GR and GST activities</td>
<td><em>P. japonicus</em> leaves and its acetone extract (5% leaf powder for 4 weeks)</td>
<td>Han et al. (2012)</td>
<td>(39)</td>
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<tr>
<td>Iron-induced oxidative ICR mice, plasma TBARS of C57BL/6 mice fed with a high-fat diet</td>
<td>Suppression in plasma TBARS production in ICR mice, plasma TBARS, and decrease in triglyceride concentrations in C57BL/6 mice</td>
<td><em>P. japonicus</em> (Sieb. et Zucc.) Maxim. flower bud (80% ethanol extract) (8 g of powder base/kg or 1% for 16 weeks)</td>
<td>Hiemori-Kondo et al. (2020)</td>
<td>(30)</td>
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</tbody>
</table>

TBARS, thiobarbituric acid-reactive substance; GSH, glutathione; AST, aspartate aminotransferase; GSH-Px, glutathione peroxidase; CCl<sub>4</sub>, carbon tetrachlore; GGT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; GR, glutathione reductase; GST, glutathione S-transferase.

phenolic constituent in *P. japonicus*. Moreover, the polyphenolic extracts of leaves and roots exhibited anti-inflammatory effects by inducing the levels of the lipopolysaccharide-activated cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) proteins. Conversely, its higher cytotoxic activity (IC<sub>50</sub> < 25.0 µg/mL) against HCT-116 cells compared with that of *Angelica gigas* (34.75 µg/mL), *Erythronium japonicum* (44.06 µg/mL), and *Aster scaber* (54.87 µg/mL) has been shown. Moreover, based on an assay that used LLC-PK1 cells, an epithelial cell line of renal origin, it was shown that the ethyl acetate fraction of *P. japonicus* exhibited a high antioxidant activity via the upregulation of heme oxygenase 1 and thioredoxin reductases through the activation of the nuclear factor erythroid-2-related factor 2 (Nrf2) signaling pathway.

**In vivo Antioxidant Activity of *P. japonicus***

With regard to oxidative stress in vivo, several examinations are performed (Table 2). Antioxidative effects of petasagnolide A or the butanol extract from the leaves of *P. japonicus* challenged with kainic acid have been reported in mouse brain based on TBARS value. Furthermore, improvement in seizure in kainic acid-treated mice by petasagnolide A has also been reported. In addition, antioxidant activities of the methanol extract of *P. japonicus* Max. have been demonstrated in monosodium L-glutamate-challenged mice. They performed two types of *in vivo* assays to evaluate the antioxidant activity of the flower bud extracts of *P. japonicus*. An animal model of Fe-nitritolipocacetate induced acute oxidative injury and mice fed with normal or high-fat diets were used as models of chronic disorders. The administration of the extracts orally to ICR mice prior to iron injection significantly suppressed the production of plasma TBARS, thus indicating that the flower bud extracts exert antioxidant effects under acute oxidative stress conditions. Moreover, the administration of these extracts at a concentration of 1% to C57BL/6 mice fed with high-fat diets for 16 weeks significantly decreased TBARS and triglyceride concentrations in the plasma of the mice, with no toxic symptoms. The effect of a methanol extract of *P. japonicus* on hepatotoxicity in rats induced by alcohol or carbon tetrachloride was also examined. The extract revealed protective effect and anti-lipid peroxidative effects in liver by decrease in glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and alkaline phosphatase, which is increased in the case of cardiovascular and biliary tract diseases. Cholesterol increased on liver cirrhosis and blood urea nitrogen directed post in liver function also decreased.

In contrast, Han et al. have reported an increase in hepatic TBARS values and glutathione reductase and glutathione S-transferase activities and hepatic cytochrome mRNA expression following diets with 5% acetone extract of *P. japonicus* leaf powder, as revealed by the presence of pyrrolizidine alkaloids. Therefore, considering that a high amount of antioxidants were required to suppress the acute reaction, the amount of the toxic compound present in the *P. japonicus* flower bud extracts should be considered.

**Anti-Allergic Effect of *P. japonicus***

The anti-allergic effect of *P. japonicus* is well known at the research (Table 3). Regarding the former, RBL-2H3 cells from rats with basophilic leukemia with high-affinity IgE receptors are often used. The degranulation of IgE-antigen-stimulated RBL-2H3 cells leads to the release of β-hexosaminidase, similar to that observed for histamine and leukotriene. Therefore, β-hexosaminidase or its cytokine are measured and the inhibitory effect is examined. Yoshikawa et al. reported the degranulation inhibitory effect by fukinoside A from *P. japonicus*. Shimoda et al. examined the inhibitory effects of an aqueous ethanol extract of

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the aerial parts of Japanese *P. japonicus* and screened for active compounds. Several compounds, such as fukinones, caffeic acid, and di-cafeoylquinic acids, were identified as inhibitors. In *vivo*, the inhibitory effect of *P. japonicus* extracts on allergic reactions was examined using a passive cutaneous anaphylaxis (PCA) reaction on experimental guinea pig, rats, or mice.[40,42] An ovalbumin-induced asthma model was also used to examine the anti-allergic effect of this plant. Recently, eremiphane lactone, a novel family of sesquiterpene compound, was isolated from *P. japonicus* leaves and of crude butanol extracts of *P. japonicus* var. *giganteus* Hort. It is suggested that petatewalide B has anti-allergic and anti-inflammatory effects.

**Neuroprotection by *P. japonicus***

Neuroprotective and anti-inflammatory activities are examined using *in vitro* assays with cell lines such as PC12 or B103 (Table 4). The neuroprotective effects of petaslignolide A isolated from *P. japonicus* leaves and of crude butanol extracts of *P. japonicus* leaves treated with kainic acid have been reported in the mouse brain.[35,54] Moreover, the ethanol fraction and quercetin and kaempferol 3-O-(6''-acetyl)-β-glucopyranoside on β-secretase 1 (BACE1) production in B103 cells showed the presence of inhibitory activity and reducing the extracellular secretion of amyloid β (Aβ).[45] Many patients with Alzheimer’s disease (AD) have deposition of Aβ in cortical blood vessels, leading to cerebral amyloid angiopathy. Aβ is directly responsible for the free radical production and lipid peroxidation, leading to apoptosis and cellular death. BACE1 is a key enzyme in the production of Aβ because of the deposition of the Aβ-peptide after proteolytic processing of the amyloid precursor protein by BACE1 and γ-secretase during the progression of AD. Therefore, BACE1 is a prime target for therapeutic intervention in AD. In addition, the

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**Table 3. Anti-allergic effect**

<table>
<thead>
<tr>
<th>Assay</th>
<th>Effect and mechanism</th>
<th>Source and compounds</th>
<th>Author</th>
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<tbody>
<tr>
<td>Guinea pig PCA</td>
<td>Anti-histaminic and anti-allergic activities</td>
<td>6β-Hydroxyeremophilenolide and 6β,8-dihydroxyeremophilenolide from the rhizomes of <em>P. japonicus</em> Maxim. var. giganteus Hort.</td>
<td>Tobinaga et al. (1983)</td>
<td>(40)</td>
</tr>
<tr>
<td>RBL-2H3 mast cells</td>
<td>Inhibition of β-hexosaminidase release; degranulation</td>
<td>Fukinose A from <em>P. japonicus</em> Maxim.</td>
<td>Yoshikawa et al. (2006)</td>
<td>(41)</td>
</tr>
<tr>
<td>IgE-sensitized RBL-2H3 cells, rat PCA reaction, a guinea pig trachea strip</td>
<td>Inhibition of β-hexosaminidase release (leukotriene C4/D4/E4 synthesis and TNF-α production) and PCA reaction and suppression of smooth muscle constriction induced by histamine and leukotriene D4</td>
<td>70% ethanol extract from aerial parts of Japanese butterbur, (-)-fukinone, caffeic acid, 2β-hydroxyfukinone, chlorogenic acid, fukinolic acid, 4,5-dicafeoylquinic acid, 3,5-dicafeoylquinic acid, 4,5-dicafeoylquinic acid methyl ester, and dotorioside II</td>
<td>Shimoda et al. (2009)</td>
<td>(42)</td>
</tr>
<tr>
<td>IgE-sensitized RBL-2H3 cells, mouse PCA reaction</td>
<td>Inhibition of IgE antigen-stimulated degranulation, TNF-α and IL-4 cytokine expression and transcription factor NF-κB, IgE-antigen-induced PCA reactions</td>
<td>Ethyl acetate extract from fermented <em>P. japonicus</em> leaves</td>
<td>Bae et al. (2009)</td>
<td>(43)</td>
</tr>
<tr>
<td>RBL-2H3 mast cells, peritoneal macrophages, ovalebumin-induced asthma model</td>
<td>Inhibition of degranulation, gene inductions of iNOS synthase and COX-2</td>
<td>Bakkenolide B from <em>P. japonicus</em> (Sieb. et Zucc.) Maxim. leaves</td>
<td>Lee et al. (2013)</td>
<td>(44)</td>
</tr>
<tr>
<td>RBL-2H3 mast cells, C6 glioma cells, ovalbumin-induced asthma model</td>
<td>Suppression of β-hexosaminidase and fluorescence change of Ca2+, inhibition of iNOS induction, NO production, and accumulations of eosinophils, macrophages, and lymphocytes</td>
<td>Petatewalide B from <em>P. japonicus</em> (Sieb. et Zucc.) Maxim. leaves</td>
<td>Choi et al. (2016)</td>
<td>(45)</td>
</tr>
<tr>
<td>RBL-2H3 mast cells</td>
<td>Inhibition of degranulation activated via high affinity IgE receptor, FceRI</td>
<td>6β-Angeloyloxy-3β,8-dihydroxyeremophyl-7(11)-ene-12,8β-olide</td>
<td>Qian et al. (2016)</td>
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<td>RAW264.7 macrophages, docking studies</td>
<td>Inhibition of the production of both PGE2 and NO, expressions of iNOS and COX-2, and high affinity with iNOS and COX-2</td>
<td>Boiled water extract of the leaves of <em>P. japonicus</em>, petasitesin A and cimicifugic acid D</td>
<td>Lee et al. (2019)</td>
<td>(47)</td>
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PCA, passive cutaneous anaphylaxis; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NO, nitric oxide; PGE2, prostaglandin E2.
suppression of reactive oxygen species (ROS) and the subsequent recovery of apoptotic cell death by the inhibition of Aβ-induced apoptotic cellular damage, ROS generation, and caspase-3 activity by kaempferol 3-O-(6''-acetyl)-β-glucopyranoside was reported.\(^{(56)}\) Kaempferol also showed neuroprotective effects on HT22 glutamate-induced oxidative stress cells by the regulation of the expression levels of Bcl-2, Bid, AIF, and MAPK.\(^{(57)}\) The treatment with Japanese butterbur decreased Aβ levels in vitro.\(^{(60)}\) Moreover, the attenuate memory impairment and neuronal cell death in Aβ-induced AD model using \(P.~japonicus\) leaves was also demonstrated.\(^{(61)}\) The protective effects of sesquiterpenoids against neuronal cell death and its promoting effects on neurite outgrowth from PC12 cells have been reported.\(^{(57,59)}\) Recently, protein aggregation has been described as the principal component of numerous protein misfolding pathologies termed proteinopathies, such as AD, Parkinson’s disease, prion diseases, and AA amyloidosis with treatment needs. An automated real-time microliter-scale high-throughput screening system for amyloid aggregation inhibitors using quantum-dot nanoprobes that can simultaneously screen throughput screening system for amyloid aggregation inhibitors has been developed and \(P.~japonicus\) was assessed.\(^{(62)}\) However, subsp. giganteus seemed to have low inhibitory effects.

### Metabolic Improvement by \(P.~japonicus\)

There are few reports of anti-obesitic and anti-adipogenic activities (Table 5). Han et al.\(^{(64)}\) reported that high-fat diet containing 3% chikusetsusaponins isolated from \(P.~japonicus\) rhizomes significantly increased the fecal content and triacylglycerol level in rats at day 3. In addition, orally administered chikusetsusaponins also exhibited inhibition in the elevation of the plasma triacylglycerol and the pancreatic lipase activity, delaying the intestinal absorption of dietary fat. Lee et al.\(^{(60)}\) demonstrated the inhibitory activity of pancreatic lipase in leaf and stem in vitro. Watanabe et al.\(^{(65)}\) have reported that the administration of diets comprising \(P.~japonicus\) ethanol extracts resulted in a decrease in weight gain, visceral fat accumulation, plasma cholesterol, and glucose concentrations in mice fed with a high-fat diets. Its energy expenditure is reported to be upregulated by flavonoids, such as quercetin.\(^{(66)}\) The mechanism consists in the suppression of preadipocyte differentiation/three adipogenic transcription factors, the peroxisome proliferator-activated receptor (PPAR) \(γ\), the CCAAT enhancer-binding protein, and the sterol regulatory element-binding protein 1C, with a decrease in body weight, gain and accumulation of visceral fat tissue, and amelioration of the plasma cholesterol concentration. Adachi et al.\(^{(67)}\) reported that petasin modulates glucose metabolism and activates AMPK through the inhibition of mitochondrial respiration. Moreover, S-petasin isolated from \(P.~japonicus\) extracts yielded reduction of glucose uptake and inhibition of triglyceride accumulation by inhibiting the PPAR-\(γ\) signaling pathway in the 3T3-L1 cell line. These results indicate that S-petasin has anti-adipogenic activity.\(^{(68)}\) Based on this information, petasin is thought to be a representative candidate for the regulation of obesity. However, the mechanism underlying the improvement of metabolic syndrome and obesity is limited by the uptake of glucose and the activation of AMPK. Moreover, S-petasin is the only active compound identified as anti-obesitic in \(P.~japonicus\). Nevertheless, it has been reported that caffeic acid and chlorogenic acid increase body weight, lipid metabolism, and obesity-related hormone levels in mice fed with high-fat diets.\(^{(69)}\) Because many compounds occur in \(P.~japonicus\), as shown in Table 1, the identifica-
tion of other mechanisms and active compounds are needed for the management of metabolic syndrome.

**Anti-Cancer Effect of *P. japonicus***

Reports on the anti-cancer effects of this plant are scarce (Table 6). Picrasin B isolated from *Picrasma quassioides* inhibited tumor growth and showed antitumor activity against P-388 lymphocyte leukemia cells. In addition, fukinolide isolated from *P. japonicus* showed antitumor activity; however, it was not as strong as that observed by picrasin B. Petasin from *P. japonicus* shoot inhibited tumor growth and showed antitumor activity against P-388 lymphocyte leukemia cells. For the growth inhibition afforded by the methanol extract occurs via the inhibition of the Akt/mTOR and Wnt signaling pathways in Hep3B hepatocellular carcinoma (HCC) cells, suggesting that the extract inhibition against P-388 lymphocyte leukemia cells. In addition, picrasin B showed antitumor activity against P-388 lymphocyte leukemia cells. Although there are some reports of the apoptotic effect of *P. japonicus* extracts, there is little information on their antitumor activity.

### Possible Adverse Effects of *P. japonicus* and Attention to Pyrrolizidine Alkaloids

As described above, Han et al. reported an increase in hepatic TBARS values after diets including a 5% acetone extract of *P. japonicus* leaf powder, as revealed by the presence of pyrrolizidine alkaloids. Pyrrolizidine alkaloids are toxic and can cause liver damage and cancer. Several types of pyrrolizidine alkaloids have been identified that are mainly found in plant families such as Asteraceae, Aabaceae, and Oraginaceae. Pyrrolizidine alkaloids are toxic and can cause liver damage and cancer.
have been reported, as described above, attention must be paid to the use of large amounts of the extract at once individually, particularly for patients with diseases, pregnant women, or children.15,16 Conversely, the concentrations of pyrrolizidine alkaloids can be decreased by boiling and simmering the plant in tap water.17 Therefore, the reduction of the concentrations of pyrrolizidine alkaloid is recommended before the consumption of the stems or flower buds of *P. japonicus*.

**Conclusion**

In this review, I described the potential pharmacological efficacy of *P. japonicus* extracts or its isolated compounds, such as polyphenols and sesquiterpenes. It can also be a useful bioresource in the production of functional ingredients. However, the bioactive compounds of this plant have not been explored in detail in *vivo*, except for the antioxidative activity of petasignolide A in the brain, usefulness of petawalide B in anti-asthma, and activities of petasin and chikusetsusaponins in improvement of the metabolism of fat and glucose. In *vivo* examinations were primarily performed using plant powder or crude extracts. Therefore, it is important to identify and purify active compounds for its functional utilization. In particular, it would be interesting to elucidate the *in vivo* effects of bioactive compounds that exist only in *P. japonicus*.

Studies focusing on neuroprotective and anti-inflammatory functions have been increasing, indicating increased concern toward anti-aging to prolong healthy life expectancy. Some mechanisms underlying neuroprotection have been elucidated and the AD preventive effect of *P. japonicus* or its derived compounds is expected. However, few *in vivo* examinations on this function have been conducted; hence, further studies are required to elucidate their bioactivities. Moreover, *in vivo* studies for anti-obesity and anti-cancer effects are necessary for health promotion and prevent of disease. This requires comparison with other plants and active compounds to exhibit its predominance. In addition, clinical trials on some functions, including anti-allergic effects, have been conducted for *P. hybridus*, but few have been conducted for *P. japonicus*. We must also consider the concerning adverse effects of pyrrolizidine alkaloids. When using several active compounds in crude extracts, we must ensure that there is no contamination of pyrrolizidine alkaloids. In the future, we must conduct clinical trials for the utilization of these *P. japonicus* effects; if we can obtain beneficial effects without adverse events in the trial, it may be used as a safe food material or pharmacological source.

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**Abbreviations**

Aβ | amyloid β  
---|---  
ABTS+ | 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)  
AD | Alzheimer’s disease  
AMPK | AMP-activated protein kinase  
BACE1 | β-secretase 1  
COX-2 | cycloxygenase-2  
DPPH | 1,1-diphenyl-2-picrylhydrayl  
FRAP | ferric-reducing ability of plasma  
HPLC | high-performance liquid chromatography  
iNOS | inducible nitric oxide synthase  
LC–MS/MS | liquid chromatography–tandem mass spectrometry  
NO | nitric oxide  
Nrf2 | nuclear factor erythroid 2-related factor 2  
ORAC | oxygen radical absorbance capacity  
PCA | passive cutaneous anaphylaxis  
PAPP | peroxisome proliferator-activated receptor  
ROS | reactive oxygen species  
TBARS | thiobarbituric acid-reactive substance

**Conflict of Interest**

No potential conflicts of interest were disclosed.

**References**


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