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Research Article

The effect of hot melt extrusion of *Polygonatum odoratum* on antioxidant activity and extraction efficiency

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Abstract: *Polygonatum odoratum (P. odoratum)* contains many low water solubility active ingredients, but it cannot show high extraction efficiency in the case of *P. odoratum*, which is mainly used as tea. In this study, the physiologically active components and antioxidant activity of *P. odoratum* cultivated in Samcheok were compared after hot melt extrusion (HME) processing with additives. After extraction, total phenolic and flavonoid content and antioxidant activity were measured. The 2,2-diphenyl-1-picrylhydrazide (DPPH) and '2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays were used to evaluate antioxidant activity. Total phenols and flavonoids in hot melted extruded *P. odoratum* were all increased compared to non-extruded *P. odoratum* (Con) and increased in the order of F2>F1>F3. A decrease in IC_{50} value was observed in HME *P. odoratum*, and a correlation between an increase in active ingredients such as phenols and flavonoids and antioxidant activity was confirmed. These results suggest that the application of HME increases the water solubility of *P. odoratum* and that differentiated *P. odoratum* can be manufactured through HME.

Keywords: Hot-melt extrusion, *Polygonatum odoratum*, Solubility, Antioxidant

1. Introduction

Polygonatum species belong to the Asparagus family and are widely distributed throughout the Northern Hemisphere (Gong et al., 2023). There are 71 species of plants, of which more than 37 species have been used as medicine or functional foods in traditional Chinese medicine and other traditional medicine (Mariod et al., 2023). *Polygonatum odoratum* (*P. odoratum*) is a perennial herb native to Europe, China, Korea, and Japan. (Zhou et al., 2015). The dried rhizome of *P. odoratum* has been widely used to treat lung diseases and upset stomachs and to improve insulin resistance (Shu et al., 2009). *P. odoratum* has been used as an herb to relieve dryness and quench thirst by promoting secretion of body fluids (Liu et al., 2015). It is also commonly used as an immune conditioning agent to improve myocardial ischemia (Lee et al., 2021). In addition, various biological activities such as antioxidant activity (Chansiw et al., 2019), anti-inflammatory activity (Okonogi et al., 2016), anti-diabetic activity (Jiang et al., 2018), anticancer activity (Khuayjarernpanishk et al., 2022), and reduction of blood glucose levels have been found (Deng et al., 2012). The main components of *P. odoratum* include steroidal saponins, polysaccharides, flavonoids, and polyphenols (Wang et al., 2013), and polyphenols such as phenolic acid and flavonoids are used for the radical scavenging ability of plants (Chansiw et al., 2018). Polysaccharides are also known to be important bioactive ingredients with anti-tumor, anti-diabetic and antioxidant functions (Chen et al., 2014).

Hot melt extrusion (HME) is a physical method of extruding powdered ingredients with a rotating screw at high temperature and pressure, derived from the Latin word “extrude,” where extrude means to push (Crowley et al., 2007; Kaur & Bhasin, 2022). Particles are produced with uniform density and shape by HME, and coarse particles are produced in nano-size due to high shear force (Azad et al., 2019; Patil et al., 2016). This technology does not use solvents, making it environmentally friendly and time- and cost-efficient (Hwang et al., 2017). Natural products processed through HME can plasticize materials by causing chemical reactions and molecular structure modifications through physical forces, and in the case of poorly soluble components, water solubility can be increased (Go et al., 2022; Lu et al., 2014). Reducing particle size and increasing surface area may also improve the water solubility of the active

ingredient (Ryu et al., 2022). In studies using HME, effects such as increased total phenol and flavonoid content and increased antioxidant activity were reported (Lee et al., 2023). During the HME process, pressure is generated at a set temperature, causing melting of the API and polymer excipients, which can melt the polymer at a lower temperature than the melting point of the drug (Alshetaili et al., 2020). The melt viscosity is reduced and the API is molecularly dispersed within the matrix (Gupta et al., 2023). Producing compounds with desired shapes and properties requires appropriate selection of excipients and optimization of processing conditions. Ascorbyl palmitate, mannitol, and poloxamer 188 are used as excipients in HME manufacturing process. Ascorbyl palmitate is used in the food industry as a natural antioxidant and can also be used as a powerful plasticizer (Kim et al., 2022; M.-O. Park et al., 2022). Mannitol was used to improve the wettability of the formulation (Ogawa et al., 2018). Poloxamer 188 was used as a plasticizer to assist HME to improve the solubility of the formulation (Chokshi et al., 2005; Hu et al., 2018).

In this study, HME processing was performed by adding appropriate excipients to improve the bio accessibility and functionality of compounds present in *P. odoratum*. The purpose of this study was to confirm the increase in phenol and flavonoid content and improved antioxidant effect of *P. odoratum* using HME technology.

2. Materials and Methods

2.1. Materials

P. odoratum rhizomes used in the experiment were obtained from cultivation for 7 years at Mt. Yukbaek (Samcheok, Korea). Folin–Ciocalteu's phenol reagent, gallic acid, and quercetin were purchased from Sigma–Aldrich (St. Louis, MO, USA). Sodium carbonate was purchased from Daejung (Siheung, Korea). Potassium acetate was purchased from TCI (Tokyo, Japan). Aluminum chloride hexahydrate, 2,2-diphenyl-1-picrylhydrazyl (DPPH) (044150), and L-ascorbic acid were purchased from Alfa Aeasar (Ward Hill, MA, USA).

2.2. Preparation of P. odoratum powder using HME

HME conditions for *P. odoratum* are shown in table 1. CON is *P. odoratum* powder without HME processing, and F1 is *P. odoratum* powder with HME processing. F2 and F3 were HME processed by adding the excipients ascorbyl palmitate, mannitol, and poloxamer 188 in different ratios. The extruded sample after HME is dried and ground into powder form. The ground sample is extracted with stirring using distilled water at 100 °C for 2 hours. The extract was filtered through whatman No.6 filter paper and concentrated using a rotary vacuum concentrator at 40°C. The content of *P. odoratum* in the HME formulations was calculated by converting it to 100 percent.

Table 1. The HME formulations condition of *P. odoratum*

	CON	**F1**	**F2**	**F3**
HME	X	O	O	O
P. odoratum	100	100	60	50
Ascorbyl palmitate	-	-	30	40
Mannitol	-	-	5	5
Poloxamer 188	-	-	5	5
Total	100	100	100	100

2.3. Total phenolic content

The Folin-Ciocalteau method was used to measure total phenol content. 0.2 ml of sample diluted to 1 mg/ml and 0.6 ml of distilled water (DW) were added to the test tube. 0.8 ml of sodium carbonate diluted to 7.5% and 1 ml of folin-Ciocalteau reagent were added. The mixture is left at room temperature for 45 minutes to react, and then the absorbance is measured at 760 nm. Caffeic acid was used as the standard, and the content was calculated from the standard curve.

2.4. Total flavonoid content

0.1 ml each of 10 % aluminum chloride hexahydrate and 1 M potassium acetate were added, and 2.8 ml of DW was added. This mixture is left at room temperature for 40 minutes to react, and then the absorbance is measured at 415 nm. The standard used was quercetin, and the content was obtained from the standard curve.

2.5. Antioxidant activity

The antioxidative potential of *P. odoratum* was determined by using DPPH and ABTS free radical scavenging assay. 0.5 ml of each extract was mixed with 0.4 mM concentration of DPPH solution in a test tube. The reaction was left in the dark room at room temperature for 20 minutes. 7mM $ABTS^{+}$ solution is mixed with 2.45 mM potassium persulfate in a 1:1 ratio, reacted in the dark for 16 hours, and then diluted with PBS (0.1 M, pH 7.4) to obtain an absorbance of 0.9 at 730 nm. 0.03 ml of extract solution at each concentration and 0.15 ml of ABTS solution were mixed and reacted for 15 minutes in the dark. The absorbance of the reacted sample was measured at 517 and 730 nm. Radical scavenging activity was calculated using the following formula:

$$Radical\ scavenging\ (\%) = \frac{(Absorbance\ of\ control - Absorbance\ of\ sample)}{Absorbance\ of\ control} x\ 100$$

2.6. Statistical analysis

GraphPad (version 5.0; GraphPad Software, Inc., San Diego, CA, USA) was used for all statistical analyses, and the results of repeated experiments of TPC, TFC, DPPH radical scavenging activity and ABTS radical scavenging activity were expressed as mean and standard deviation (SD) values.

3. Results

3.1. Total phenolic and flavonoid contents

Figure 1 shows the total phenolic content (TPC) and total flavonoid content (TFC) of *P. odoratum* and HME formulations. TPC was calculated after creating a calibration curve using gallic acid as a standard. TPC of CON, F1, F2, and F3 were found to be 7.19 ± 0.54, 30.29 ± 6.95, 36.19 ± 1.45, and 18.81 ± 2.65 mg/g, respectively. CON was a *P. odoratum* to which the HME process was not applied and showed the lowest TPC content. A significant increase in TPC was confirmed in all formulations with HME applied, and among them, the content of F2 was about five times higher than that of CON. TFC was calculated after creating a calibration curve using quercetin as a standard. The TFC of CON, F1, F2, and F3 were 4.53±2.68, 5.04±0.17, 6.62±0.44, and 4.84±0.83 mg/g, respectively, and there was no significant difference.

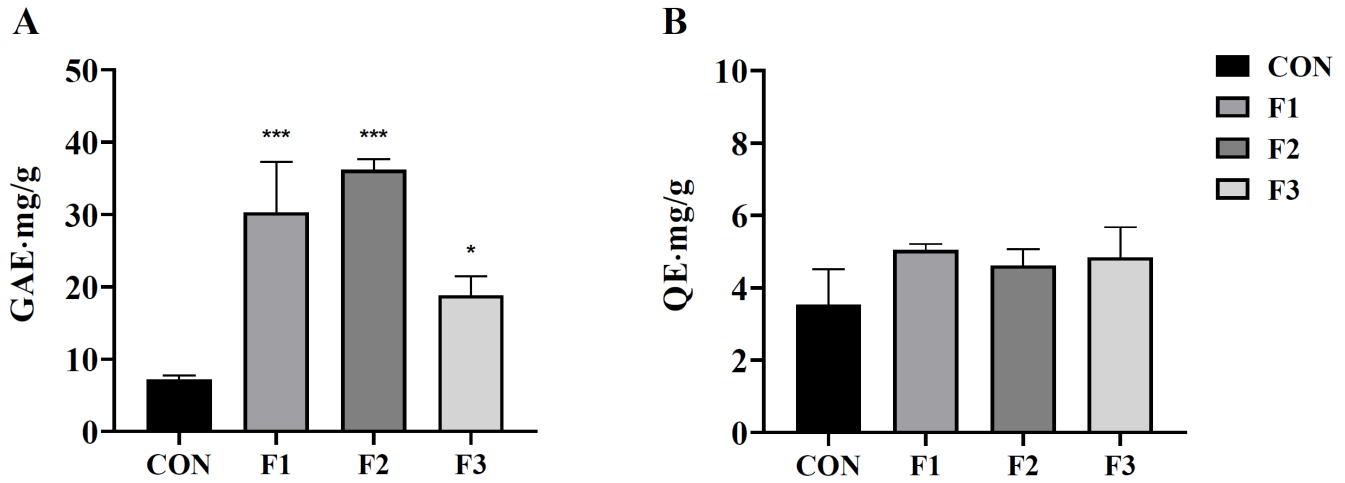

Figure 1. (A) Total phenol and (B) flavonoid contents of *P. odoratum* and HME formulations. Data represented as mean ± SD. *p < 0.05, ***p < 0.001. The test was performed in triplicate.

3.2. Antioxidant

The DPPH and ABTS radical scavenging rates (%) of *P. odoratum* and HME formulations are shown in Figure 2. The DPPH radical scavenging rate (%) values increased in a concentration-dependent manner at all concentrations, and the HME formulation was higher than the control. The DPPH radical scavenging rate was significantly different from the control at all concentrations except 5 mg/mL, and the F2 formulation had the highest DPPH radical scavenging rate. The ABTS radical scavenging rate (%) values also increased at all concentrations and were significantly different from the control at 4 mg/ml. IC_{50} values of *P. odoratum* and HME formulations are presented in Table 2. The IC_{50} value indicates the amount of antioxidant required to reduce DPPH and ABTS free radicals by 50 % (Pumtes et al., 2016). The IC_{50} values of CON, F1, F2, and F3 for DPPH radical were 6.23 ± 0.65, 6.02 ± 0.58, 5.54 ± 0.66, and 5.79 ± 0.23 mg/m. All samples showed lower IC_{50} values than CON samples that were not subjected to HME, with F2 showing the lowest IC_{50} value. In the ABTS assay, the IC_{50} values of CON, F1, F2, and F3 were 5.12 ± 0.28, 4.84 ± 0.47, 4.62 ± 0.65, and 4.68 ± 0.31 mg/ml. In the DPPH and ABTS assay, all samples showed lower IC_{50} values than CON without HME, with F2 showing the lowest IC_{50} value.

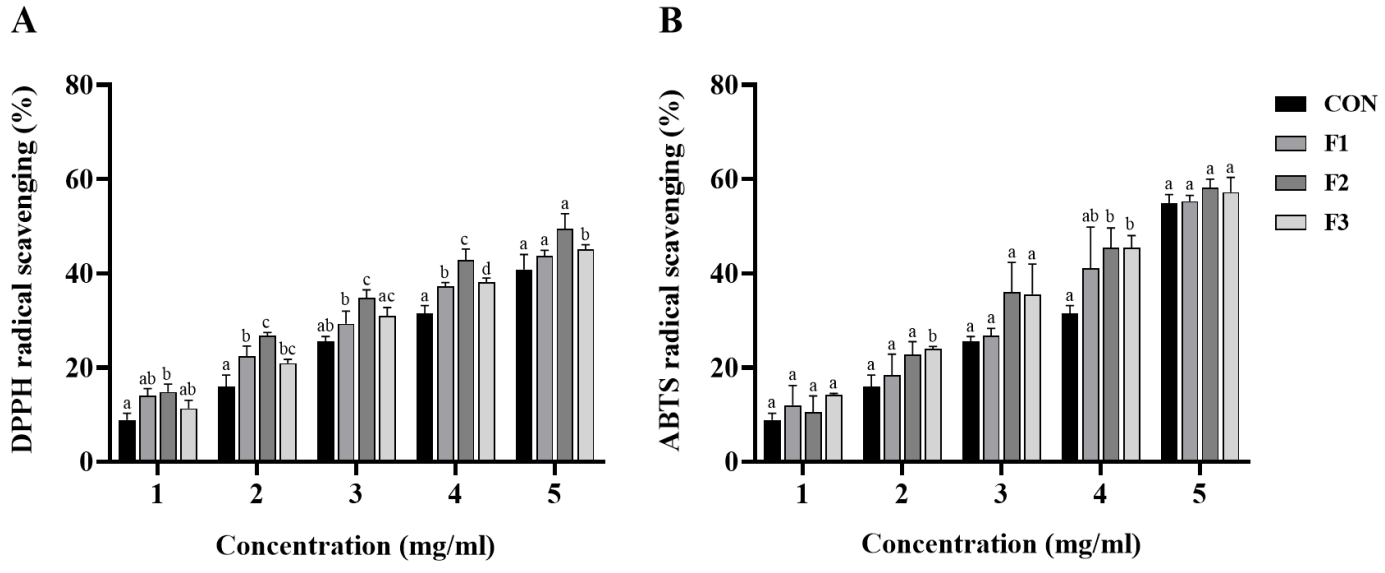

Figure 2. (A) DPPH and (B) ABTS free radical scavenging (%) of *P. odoratum* and HME formulations. Different lowercase letters in each concentration presents statistically significant difference (One-way ANOVA and Tukey's multiple comparisons test, $P < 0.05$). The data were presented as mean ± SD. The test was performed in triplicate.

Table 2. IC_{50} of *P. odoratum* and HME formulations. The data were presented as mean ± SD. The test was performed in triplicate.

	DPPH IC_{50} (mg/ml)	ABTS IC_{50} (mg/ml)
CON	6.23 ± 0.65	5.12 ± 0.28
F1	6.02 ± 0.58	4.84 ± 0.47
F2	5.54 ± 0.66	4.62 ± 0.65
F3	5.79 ± 0.23	4.68 ± 0.31

4. Discussion

In this study, HME process improved the water solubility of *P. odoratum*. Polyphenolic compounds are phytochemicals commonly found in certain plants and form a diverse group of chemically characterized secondary metabolites (Gebicki & Nauser, 2021). It has also been reported to have various physiological effects such as antioxidant and anti-inflammatory (Wojdyło et al., 2007). The total phenol content of hot melt extruded *P. odoratum* was higher in the order of F2>F1>F3. The flavonoid content did not increase significantly, but the phenol content increased up to 5 times more than CON. The insignificant difference in TFC may be due to the low flavonoid content of *P. odoratum*. An increase in the TPC of natural products through the application of HME has been reported in previous studies (M. O. Park et al., 2022). The high temperature and transfer force of HME can increase the extraction efficiency due to the strong shear force that forms an amorphous structure and partially breaks down the ester bond and conjugate portion between the phenolic compound and the cell wall of the complex (Repka et al., 2018; Yu et al., 2002). These results suggest that the water solubility of other active ingredients contained in phenolic compounds increases through HME.

P. odoratum subjected to the HME process showed a decrease in IC_{50} values for DPPH and ABTS radicals. F2, which had the highest total phenol and flavonoid content, showed the highest antioxidant activity. Increased total phenol and total flavonoid content in plants is positively correlated with their ability to scavenge free radicals (Zhou et al., 2020). The high temperature and transfer force of HME can increase solubility by forming amorphous structures and destroying cellular components. F2 was a formulation with added excipients and showed better activity than F1 with no excipients. In fact, bioactive substances and polymers used as excipients can be extruded together to reduce particle size and increase water solubility (Go et al., 2021). Additionally, ascorbyl palmitate, Poloxamer 188, can improve the processability of biopolymers by causing a decrease in glass transition temperature, strain tension, and electrostatic charge (Adnan et al., 2020).

These results demonstrate that HME can be used to improve the extraction efficiency of *P. odoratum* and increase its antioxidant activity. Furthermore, the HME process is not limited to *P. odoratum* and can be applied to other natural products. In a previous paper, it was reported that the HME process improved the water solubility of natural products and increased their antioxidant activity (Azad et al., 2022). This study presents a novel approach to improve the water solubility of *P. odoratum* by applying HME, increase the phenol content, and maximize the antioxidant activity. HME technology can effectively preserve the physiologically active components of *P. odoratum* and contribute to increasing its bioavailability. These research results can expand the industrial utilization potential of *P. odoratum* and enable new applications in various fields. It is expected that further research will optimize HME technology and develop various application methods to maximize the functionality of other natural products including *P. odoratum*.

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Conflicts of Interest: The authors declare no conflict of interest.

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