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Review article

Chemical analysis of *Panax quinquefolius* (North American ginseng): A review

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ABSTRACT

Panax quinquefolius (PQ) is one of the best-selling natural health products due to its proposed beneficial anti-aging, anti-cancer, anti-stress, anti-fatigue, and anxiolytic effects. In recent years, the quality of PQ has received considerable attention. Sensitive and accurate methods for qualitative and quantitative analyses of chemical constituents are necessary for the comprehensive quality control to ensure the safety and efficacy of PQ. This article reviews recent progress in the chemical analysis of PQ and its preparations. Numerous analytical techniques, including spectroscopy, thin-layer chromatography (TLC), gas chromatography (GC), high-performance liquid chromatography (HPLC), liquid chromatography/mass spectrometry (LC/MS), high-speed centrifugal partition chromatography (HSCPC), high-performance counter-current chromatography (HPCCC), nuclear magnetic resonance spectroscopy (NMR), and immunoassay, are described. Among these techniques, HPLC coupled with mass spectrometry (MS) is the most promising method for quality control. The challenges encountered in the chemical analysis of PQ are also briefly discussed, and the remaining questions regarding the quality control of PQ that require further investigation are highlighted.

Contents

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1. Introduction

Ginseng is a perennial herb of the genus *Panax* (Araliaceae family) with fleshy roots [1]. The *Panax* species that are most widely used as medicinal herbs include *Panax quinquefolius* L. (PQ, North American ginseng) [2], *Panax ginseng* C. A. Mayer (PG, Asian or Korean ginseng) [3], *Panax japonicus* (T. Nees) C. A. Mey. (Japanese ginseng) [4], *Panax notoginseng* (Burkill) F.H. Chen (PN, Sanchi ginseng) [5], and *Panax vietnamensis* Ha & Grushv. (Vietnamese ginseng) [6]. PQ is native to both Canada and eastern USA and is recognized as a valuable 'tonic' that is similar to PG [7]. As one of the best-selling medicinal herbs in the world [8,9], PQ is well documented in the China Pharmacopeia (CP) [10] and the US Pharmacopeia (USP) [11]. Both in vitro cell and in vivo animal studies have indicated that PQ exhibits a variety of pharmacological activities, including antioxidative [12,13], antidiabetic [14], anti-inflammatory [15], anti-cancer [16], neuroprotective [17], immunomodulatory [18], and prophylactic [19] effects. Its high value and strong export market have resulted in the overharvesting of wild PQ, causing it to be listed as a threatened species in Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) in 1973. A chemical analysis of PQ is needed to effectively assess the difference between wild and cultivated PQ and to develop long-term sustainability policies for native PQ. The active constituents of PQ roots appear to include polyacetylenes [20–22], polysaccharides [23,24], and triterpene saponins [25–27], called ginsenosides. Ginsenosides are believed to be the main constituents responsible for the bioactivities of PQ. The content of ginsenosides in PQ roots, however, varies greatly depending on the location [28] and affects the therapeutic effects of PQ. In fact, PG was recently misrepresented as PQ in health products and dietary supplements either unintentionally or for economic gain due to the markedly higher price of the latter [9,29–31]. The different *Panax* species have different pharmacological actions due to variations in the types and quantities of saponins and thus have different clinical indications [32,33]. In addition, PQ requires 4–6 years to grow and mature for harvest, which is sufficient time for the PQ roots to accumulate chemical contaminants, such as pesticides. Several reports have found the presence of organohalogens and organophosphorus pesticides and their metabolites in PQ raw materials and products [34–37]. Therefore, comprehensive quality control is vital to guaranteeing the safety and quality of PQ and has become the focus of many studies. Many analytical techniques such as HPLC, NMR, GC, HPTLC and immunoassay have been used to differentiate between wild and cultivated PQ [38,39] and to distinguish among different species of *Panax* [40–43]. Actually, several reviews on the chemistry [44–47], pharmacology [48–50], contaminants [51] and other aspects [52,53] of PQ have been published in the last few years. However, the development of a chemical analysis of PQ, which is critical for quality control, was not summarized.

In this review, we discuss the quality control and chemical analysis of PQ with a focus on the application of hyphenated liquid chromatographic techniques.

2. Chemistry

Ginsenosides, which share a dammarane-type triterpenoid saponin structure [54], are the major characteristic constituents of PQ. Most ginsenosides have a rigid four trans-ring steroid skeleton. The names of many ginsenosides are known by synonyms, which can introduce challenges for quality control. To date, a total of 98 ginsenosides have been identified in PQ, and these include both naturally occurring compounds and those resulting from steaming and biotransformation [44]. As summarized in several reviews [9,55–60], ginsenosides are generally classified into four groups (Fig. 1): protopanaxadiol-type (PPD; Rb1, Rc, Rb2, Rd, Rg3, and Rh2 ginsenosides), protopanaxatriol-type (PPT; Rg1, Re, Rg2, and Rh1 ginsenosides), ocotillol-type (24-(*R*)-pseudoginsenoside F11) and oleanolic acid-type (Ro ginsenoside). The PPD and PPT groups are usually found in their neutral forms [61], although acidic moieties of these ginsenosides also exist (such as malonyl-Rb1, malonyl-Rc, malonyl-Rb2, and malonyl-Rd) [62]. These malonyl ginsenosides have been reported to constitute a significant portion of the total ginsenosides in PQ [63–65]. Among the isolated and identified ginsenosides, Rb1, Rb2, Rc, Rg1, Re and Rd account for 90% of the total content [66] and have been used as marker compounds in the routine chemical analysis of PQ products [27,67–69]. Rb1 [70,71], Rg1 [72,73], Rb2 [74,75], Rg3 [76,77], Rh2 [78,79], Rd [80,81], and Re [76,82] have been cited in several studies as the main compounds responsible for many of the pharmacological actions of PQ. The ginsenoside profiles of PQ and PG differ in their total ginsenoside content, ratio of PPD to PPT, and the presence of other marker ginsenosides, such as 24-(*R*)-pseudoginsenoside F11, which is only found in PQ [83,84], and Rf, which is present in PG and absent in PQ [85,86]. The notoginsenoside R1, in contrast, is a major ingredient of PN roots [87] that has often been used as a marker compound for the identification of PN from PG and PQ [88].

Polyacetylenes [22,50,89] and arginine [90,91], are also pharmacologically active constituents of PQ. The most bioactive and abundant polyacetylenes in PQ are falcarinol (panaxynol) and panaxydol (Fig. 2). Polyacetylenes appears to play an important role in the potential anti-cancer effect of ginseng and other plant species of the Araliaceae and Apiaceae plant families [22,92,93]. Arginine is a major amino acid constituent of PQ. The arginine derivatives, arginyl-fructose and arginyl-fructosyl-glucose are intermediate products of the Maillard reaction. The chemical structures of panaxynol, panaxydol, arginyl-fructose and arginyl-fructosyl-glucose are shown in Fig. 2.

3. Analytical techniques

Several qualitative and quantitative analytical techniques have been developed for the quality evaluation of PQ. These analytical techniques include spectroscopy, thin-layer chromatography (TLC), gas chromatography (GC), high-performance liquid chromatography (HPLC) combined with various detectors, high-speed centrifugal partition chromatography (HSCPC) and high-performance counter-current chromatography (HPCCC), nuclear magnetic resonance (NMR) spectroscopy, and immunoassay. The analytical methods for assessing PQ and PQ-containing preparations are listed in Table 1.

3.1. Spectroscopy

A number of spectroscopic methods, including infrared (IR), near-infrared (NIR) and Raman, have been used for the analysis of PQ. IR reflectance spectroscopy is an attractive technique due to its speed, non-destructiveness, and lack of or low amount of sample preparation required compared with traditional chromatographic methods. Combined with pattern-recognition techniques, IR has been applied for PQ analysis [97] and *Panax* species authentication and quality control [94,95,101]. The moisture content, which is one of the most important quality indexes of processed PQ, can be determined by NIR within several seconds [101]. Yap et al. found a unique IR spectral fingerprint in the 2000–600 cm^{-1} region, named the '2-6PC rule', which can be used for categorizing unknown samples of ginseng, discriminating among commercial ginseng products, and distinguishing PQ and PG from morphological fakes [95,96]. Several studies have applied 2D-IR and 2D-FTIR to authenticate

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