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•Review•

Saposhnikoviae divaricata: a phytochemical, pharmacological, and pharmacokinetic review

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[ABSTRACT] *Saposhnikoviae divaricata* (Turcz.) Schischk (SD) is a traditional Chinese herb commonly used to treat clinical conditions such as rheumatism and allergic rhinitis. This review article evaluates a collection of works on *in vitro* and biochemical studies of SD. The discourse on the diverse class of chromones and coumarins in SD offers an insight to the pharmacological effects of these bioactive constituents as anti-inflammatory, analgesic, immunoregulatory, antioxidative, and anti-proliferative agents. It is highlighted that there is a structural relationship between the constituents and bioactive activities, which in effect provides a valid reasoning and reaffirm the use of SD in the treatment of the pathologies in Chinese medicine.

[KEY WORDS] *Saposhnikoviae divaricata*; Chinese herbal medicine; Anti-inflammatory; Analgesic; Immunomodulatory; Anti-proliferative

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Introduction

Saposhnikoviae divaricata (Turcz.) Schischk (SD), an umbelliferous genus, is widely found in the northern and northeastern territories of China and cultivated in many other areas such as Anhui, Shanxi, and Gansu provinces. It is known as “Fang Feng” in China, “Bou-hu” in Japan and “Bangpung” in Korea. The Chinese terminology of this herb literally translates “to avert wind”, and the dried roots of this plant is generally applied to treat pathogenic conditions of wind-damp-cold in Chinese medicine (CM). SD is an important component in traditional Chinese medicine clinical practice and commonly used for the treatment of rheumatism, arthralgia, general aches, headaches, stroke, fever, cold, and allergic rhinitis. The Chinese Pharmacopoeia Commission [1] ranked SD as a top-grade herb, and it is described to possess pungent, sweet and slight warm properties. SD has a wide spectrum of use in the CM. Its applications are recorded and well established in the CM classical text the Shen Nong’s *Materia Medica* (*Shen Nong Ben Cao Jing*) which is the oldest pharmaceutical monograph in CM, dating back to Qin-Han dynasty. In the Shen Nong’s *Materia Medica*, SD is graded as a premium-grade herb cited for its multiple effects: immunoprotective capability in warding off cold (also otherwise known as dispelling wind-cold and relieving exterior pathogens in CM), relief of edema-induced pain (expelling dampness from the acupuncture meridians) and anti-spasmogenic activity (expelling wind and relieving convulsion). Similarly, in the Collected Works of Materia Medica (*Ben Cao Hui Yan*), authored by NI Zhu-Mo in the Ming dynasty, a herbal monograph outlined the multiple use of SD for the treatment of arthritis instilled with dampness, joints pain, tetanus, atrophy and flaccidity of muscles, headaches, cold, fevers, cough, adiaphoresis, nasal congestion, pharyngeal dryness syndrome, cerebrovascular accident, early onset of small pox, and anxiety in children. CM clinicians today still use SD for the same pathologies cited. In response to the pressing need to align CM for an evidence-based approach, there is an emergence of scientific research on the bioactive constituents and the therapeutic effects of SD. Therefore, the objective of this review article is to provide a systematic review of phytochemical, pharmacological, and pharmacokinetic perspectives of the experimental studies on SD.

Methods

The following databases were searched from their respective receptions up to January 2016: PubMed; EMBASE;

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AMED; CINAHL; Cochrane Library; MEDLINE; ScienceDirect; SCOPUS; Web of Science; China Network Knowledge Infrastructure; CQVIP; and Wanfang Data. The keywords used for the literature search included: Fang Feng and its English, botanical and pharmaceutical names. The papers identified from the search were screened according to the criteria laid out in the Australian Regulatory Guidelines for Complementary Medicines and Therapeutic Goods Orders for quantitative and qualitative analysis of herbal medicine by the Australian Therapeutic Goods Administration (TGA). TGA adopts the British Pharmacopoeia and Therapeutic Goods Orders as the official guidelines for testing and acceptance criteria for herbal substances, herbal preparations, and herbal medicinal products, inclusive of traditional herbal medicinal products [2]. TGA also recognizes other international pharmacopoeias for guidelines on assessing and testing botanicals in complementary medicine.

The selection criteria included process controls of the herbal substances, reporting reference standards such as authentication of reference materials and profile chromatograms, and analytical procedures and validation data. Papers in English or Chinese language are considered for this review. Scientific rigors were called upon to determine the chemical markers of herbs through the use of strict parameters in testing, quantitative and qualitative measures of the bioactive components, such as fingerprint spectrum, correlations differentiation, and stability evaluation, reference standards, and toxicological assessments. According to the TGA, reporting referencing standards includes naming the origin of the plant materials and its authentication [2]. A plant specimen voucher number (PSVN) is an upmost requirement for referencing standards in botanical testing [3]. It enables traceability of the plant material, allows access to the storage of crude plant for researchers who seek to cross verify data, further scientific investigations or commercial purposes, should there be discrepancies in the drug products produced from the plant source. Essentially, a lack of PSVN essentially thwarts scientific research from the onset and may cause legal repercussions if used for commercial purposes. Attempts to compare bioactive yield outcomes of these studies was unfeasible in this review, owing to differences in extraction weights and yield units used in the papers such as relative standard deviation, microliters or milligrams per liters. The scientific process of reporting chemical profiling by spectroscopic and/or chromatographic fingerprint should include calibration curves that depict the peak area ratio and the percentage of relative abundance of the bioactive compounds yielded from the plant material in study.

Results

A total 135 papers were identified through the literature search. Among them, 10 *in vitro* studies, 25 phytochemistry studies, and 9 phytochemistry with *in vitro* studies were considered for screening after 86 non-*Saposhnikoviae divaricata* and 5 non-phytochemistry related papers were excluded. Phytochemistry papers were further screened according to the selection criteria and 21 papers were excluded due to non-PSVN (n = 17), different reporting standards of measure standard (n = 2), standard procedures of reporting chromatographic profile not followed (n = 1) and study on soil element of SD (n = 1). As a result, 4 SD phytochemical studies only [4-7] adhered to the scientific rigors that ensure the integrity in validation and robustness in quantitative outcomes. Among 9 phytochemistry papers with *in vitro* studies [8-16], 5 [11, 13-16] were selected based on their relevance, but the phytochemistry component did not adhere to the selection criteria. A total of 10 *in vitro* studies only were included in this review [17-26]. Fig. 1 illustrates the study selection process.

Bioactive compounds

Crude plant of SD contains chromones, coumarins, polyacetylenes, and acid esters. A summary of these bioactive compounds of SD reported in the included studies are shown in Table 1. The crude dried roots of SD contain chromones and coumarins, which are both heterocyclic compounds, derived from the flavonoids. Chromone is a class of oxygen-containing heterocyclic compound with a benzo annelated γ-pyrone ring, belonging to a subclass of the flavonoids known as flavone [10]; while coumarin, a benzopyrone, structurally consists of a benzene ring fused to a pyrone ring. A total of 9 chromones are identified in the included studies. The 5 main chromones, prim-*O*-glucosylcimifugin (GC), 4′-*O*-*β*-D-glucosyl-5- *O*-methylvisamminol (GV), cimifugin (C), Sec-*O*-glucosylhamaudol (GH), and 5-*O*-methylvisamminol (MV), are abundant in SD, in particular GC and GV. These chromones are discovered to exhibit strong pharmacological activities in attenuating inflammatory [4], scavenging free radical [20], and inhibiting pain [8] in *in vitro* studies.

Aside from the chromones, a total of 22 coumarins are identified in SD from the included studies. New discoveries of coumarins in SD have also emerged over recent years. Three new coumarin compounds are discovered to have effects against porcine epidemic diarrhea virus (PEDV): divaricoumarin A, divaricoumarin B, and divaricoumarin, with molecular formulae being $C_{25}H_{32}O_{12}$, $C_{25}H_{30}O_{12}$, and $C_{25}H_{30}O_{12}$, respectively [10] (Fig. 2). Among the SD coumarins tested, Praeruptorin B is found to have the strongest effect against PEDV in Vero cells. *In vitro* results reveal Praeruptorin B is able to inhibit viral replication at the stage of protein syntheses. Although PEDV is essentially a viral infection in pigs, this coronavirus stems from the same family of the human coronaviruses, such as severe acute respiratory syndrome and Middle East respiratory syndrome [10]. Praeruptorin B, a coumarin from SD, could potentially offer a novel anti-viral drug research for the intractable human coronavirus diseases. In addition, phenylpropanoid fatty acid ester, defined chemically as (±)-2-hydroxy-3-(4-hydroxy-3- methoxyphenyl)-3-methoxypropyl nervonic acid ester and divaricatol are discovered to inhibit nitric oxide (NO) in lipopolysaccharide (LPS)-induced mouse