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From Traditional Use to Modern Pharmacology: Research Progress on the Multi-target Mechanisms of Potentilla discolor Bunge

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Abstract: *Potentilla discolor* Bunge, a traditional Chinese medicinal herb, has been extensively utilized for treating diverse ailments including diabetes, bacterial infections, viral diseases, and inflammatory disorders. Modern phytochemical investigations have identified over 200 bioactive compounds, predominantly flavonoids, tannins, triterpenoids, and phenolic acids. Pharmacological studies demonstrate that *P. discolor* exerts multi-target therapeutic effects through antioxidant, anti-inflammatory, antimicrobial, antiviral, antidiabetic, and anticancer activities. Its mechanisms involve modulation of key signaling pathways including PI3K/Akt, MAPK, NF-κB, and Nrf2/HO-1, alongside regulation of glucose-lipid metabolism and gut microbiota. This review systematically summarizes the phytochemistry, traditional applications, and contemporary pharmacological advances of *P. discolor*, emphasizing its multi-target characteristics and molecular mechanisms. Furthermore, current research limitations and future perspectives are discussed to provide scientific evidence for its clinical development and therapeutic applications.

Keywords: *Potentilla discolor* Bunge; Phytochemistry; Multi-target pharmacology; Signaling pathways; Traditional Chinese medicine

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1. Introduction

Potentilla discolor Bunge, commonly known as Fanbaicao in traditional Chinese medicine, is a perennial herb from the Rosaceae family. Characterized by sweet, bitter, and neutral properties, it primarily acts on the liver, stomach, and large intestine meridians, exhibiting heat-clearing, detoxifying, blood-cooling, and dysentery-relieving effects. Traditionally, it has been applied to treat dysentery, hemoptysis, metrorrhagia, and furuncles [1]. In recent years, the rising global prevalence of type 2 diabetes mellitus has sparked considerable scientific interest in

the antidiabetic potential of *P. discolor* [2].

Despite its long history of traditional use, the precise bioactive constituents and underlying molecular mechanisms responsible for its therapeutic efficacy remain incompletely elucidated. Fortunately, advances in modern analytical techniques (e.g., HPLC, NMR) and molecular pharmacology have progressively unveiled its chemical diversity and pharmacological activities. Over 200 compounds have been isolated and identified from *P. discolor*, establishing preliminary correlations between chemical components and various biological activities.

This review aims to provide a comprehensive and systematic analysis of current research progress on *P. discolor*, emphasizing the synergistic multi-component, multi-target, multi-pathway mechanisms underlying its pharmacological effects. Furthermore, we critically evaluate existing research gaps, including insufficient pharmacokinetic studies and limited clinical evidence, and propose a roadmap for translating *P. discolor* from a traditional herbal remedy into an evidence-based modern therapeutic agent.

2. Phytochemistry

The pharmacological activities of *P. discolor* are attributed to its diverse chemical constituents. Over 200 compounds have been isolated and identified through modern chromatographic and spectroscopic techniques. These constituents primarily include flavonoids, phenolic acids, tannins, triterpenoids, and other bioactive components, forming the material basis for its multi-target therapeutic effects.

2.1. Flavonoids

Flavonoids are the most abundant and extensively studied constituents in *P. discolor*, characterized by a C6–C3–C6 skeleton with varying degrees of oxidation and substitution. Flavanols, featuring a hydroxyl group at the C-3 position, constitute the predominant subclass. Representative aglycones include quercetin, kaempferol, isorhamnetin, and myricetin, while their glycosidic derivatives are more prevalent in plant tissues. Major flavonol glycosides include quercetin-3-*O*-β-D-glucopyranoside (isoquercitrin), quercetin-3-*O*-β-D-galactopyranoside (hyperoside), kaempferol-3-*O*-β-D-glucuronide methyl ester, kaempferol-3-*O*-β-D- galactopyranoside, isorhamnetin-3-*O*-β-D-glucopyranoside, and myricetin- 3-*O*-α-L- rhamnopyranoside [3].

Flavones, distinguished by lacking C-3 hydroxylation, include luteolin, apigenin, and their glycosides such as luteolin-7-*O*-β-D-glucopyranoside and apigenin-7-*O*-β-D-glucuronide. Flavanols (flavan-3-ols), characterized by a saturated C-ring, comprise catechin, epicatechin, gallocatechin, and epigallocatechin, exhibiting potent antioxidant activities due to their multiple hydroxyl groups [4]. Additional subclasses include isoflavones, dihydroflavones, and biflavonoids. Glycosylation patterns significantly influence their water solubility, metabolic stability, and bioavailability. The content and composition vary substantially depending on plant parts, geographical origin, harvest season, and extraction methods.

2.2. Phenolic acids

Phenolic acids function both as independent bioactive molecules and as structural units of polymeric tannins. They are classified into hydroxybenzoic acids (C6–C1 structure) including gallic acid, protocatechuic acid, *p*-hydroxybenzoic acid, and vanillic acid, and hydroxycinnamic acids (C6–C3 structure) comprising caffeic acid, chlorogenic acid, ferulic acid, and *p*-coumaric acid [5]. These compounds possess multiple phenolic hydroxyl groups enabling free radical scavenging and modulation of antioxidant enzyme systems. Gallic acid serves as the

fundamental building block of hydrolysable tannins, linking to central glucose cores through ester bonds.

2.3. Tannins

Tannins in *P. discolor* are predominantly hydrolysable types, which are polyphenolic esters of sugars with gallic acid or ellagic acid units. Ellagitannins represent a major subclass, including ellagic acid and its methylated derivatives (ellagic acid-3,3'-dimethyl ether), along with glycosidic forms such as 3-*O*-methylellagic acid-4'-*O*-α-L-rhamnopyranoside, ellagic acid-4-*O*-β-D- xylopyranoside, and ellagic acid-4-*O*-α-L-rhamnopyranoside [6]. Tannins exhibit astringent properties through protein precipitation, which underlies their hemostatic, wound-healing, and antimicrobial effects by forming protective layers on mucous membranes and damaged tissues.

2.4. Triterpenoids

Triterpenoid constituents are predominantly pentacyclic triterpenes of ursane and oleanane types. Major ursane-type compounds include ursolic acid, 2α-hydroxyursolic acid, 19α-hydroxyursolic acid, 23-hydroxyursolic acid, and corosolic acid, while oleanane-type compounds comprise oleanolic acid, 2α-hydroxyoleanolic acid, and 3β,23-dihydroxyolean-12-en-28-oic acid. Other types include tormentic acid, maslinic acid, and betulinic acid [7]. Notably, *P. discolor* contains rare C-27-carboxylated lupane-triterpenoids featuring an unusual carboxyl group at the C-14 position, including potendiscolor A-C, which exhibit significant cytotoxic activities against multiple cancer cell lines [8]. The hydroxylation position and stereochemistry significantly influence their biological activities, membrane permeability, and pharmacokinetic profiles. These lipophilic compounds exhibit hepatoprotective, anti-inflammatory, antitumor, and enzyme inhibitory properties.

2.5. Other constituents

Beyond the major phytochemical classes, *P. discolor* contains polysaccharides (water-soluble heteropolysaccharides with potential immunomodulatory activities), sterols (β-sitosterol, stigmasterol, campesterol), amino acids, and volatile oils comprising aliphatic hydrocarbons, fatty acids, and esters [9]. However, systematic investigation of polysaccharide structures and protein compositions remains limited, representing a significant gap requiring future research.

3. Pharmacological activities

Modern pharmacological studies have revealed that *P. discolor* exhibits diverse biological activities, including antioxidant, hypoglycemic, hepatoprotective, anti-inflammatory, antibacterial, and antitumor effects. These activities are mediated through multi-component and multi-target mechanisms, providing experimental evidence supporting its traditional therapeutic applications.

3.1. Antioxidant activity

Oxidative stress, characterized by excessive production of reactive oxygen species (ROS) and impaired antioxidant defense systems, plays a critical role in aging and numerous chronic diseases including diabetes, cardiovascular disorders, and neurodegenerative conditions. *P. discolor* extracts exhibit potent antioxidant activities through multiple mechanisms. *In vitro* studies demonstrate strong free radical scavenging capacities against DPPH, hydroxyl radicals, and superoxide anions, with IC_{50} values comparable to synthetic antioxidants such as butylated

hydroxytoluene (BHT) [10]. The petroleum ether extract exhibited superior total antioxidant capacity to BHT in ferric ion reducing power assays, attributed to its high flavonoid content [10].

In vivo studies using diabetic rat models showed that total flavonoid and triterpenoid extract significantly increased activities of antioxidant enzymes including superoxide dismutase (SOD) and glutathione (GSH), while reducing malondialdehyde (MDA) levels in liver and serum [11]. These effects were accompanied by decreased oxidative damage markers such as nitric oxide (NO) and glycosylated serum protein (GSP). The antioxidant mechanisms involve direct radical scavenging through phenolic hydroxyl groups, metal ion chelation, and upregulation of endogenous antioxidant enzyme expression via activation of the Nrf2/ARE signaling pathway.

3.2. Hypoglycemic and antidiabetic activity

P. discolor has been traditionally used for diabetes management in China, with modern studies confirming its multifaceted antidiabetic effects. In high-fat diet and streptozotocin-induced diabetic rats, both total flavonoid extract (TFE) and total triterpenoid extract (TTE) significantly reduced fasting blood glucose (FBG), serum total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-c), while increasing high-density lipoprotein cholesterol (HDL-c) and serum insulin levels [11]. Histopathological examination revealed protective effects on pancreatic β-cells, suggesting preservation of insulin secretory capacity.

Mechanistic studies demonstrated that *P. discolor* water extract inhibits α-glucosidase and α-amylase activities, thereby delaying carbohydrate digestion and glucose absorption [12]. Network pharmacology and molecular docking analyses identified key targets including AKT1, TNF-α, IL-6, and VEGFA, suggesting involvement of the PI3K/Akt, AMPK, and insulin signaling pathways [13]. In *Drosophila* diabetes models, *P. discolor* ameliorated hyperglycemia-induced phenotypes including shortened lifespan, climbing defects, and metabolic abnormalities through modulation of insulin/IGF-1 signaling and oxidative stress pathways [14]. The antidiabetic mechanisms encompass enzyme inhibition, β-cell protection, insulin sensitivity enhancement, and anti-inflammatory effects.

3.3. Hepatoprotective activity

The liver plays a central role in glucose and lipid metabolism, making hepatoprotection crucial for managing metabolic disorders. *P. discolor* exhibits significant hepatoprotective effects in non-alcoholic fatty liver disease (NAFLD) models. Administration of *P. discolor* extracts ameliorated hepatic steatosis, reduced serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and improved liver histopathology in high-fat diet-induced NAFLD rats [15].

Beneficial effects of *P. discolor* water extract on gut microbiota composition were observed, including increased abundance of beneficial bacteria (*Akkermansia*, *Lactobacillus*) and decreased lipopolysaccharide (LPS)-producing *Desulfovibrio*, which correlated with reduced endotoxemia and hepatic inflammation [16]. The extract significantly decreased serum LPS, TNF-α, IL-6, and IL-1β levels while improving intestinal barrier function through upregulation of tight junction proteins (ZO-1, occludin, claudin-1). These findings suggest that *P. discolor* exerts hepatoprotective effects through gut-liver axis modulation, combining direct antioxidant actions with microbiota-mediated anti-inflammatory mechanisms.

3.4. Anti-inflammatory activity

Chronic low-grade inflammation underlies numerous metabolic and degenerative diseases. *P. discolor* ethanol

extract (EPD) demonstrated potent anti-inflammatory effects in LPS-induced inflammation models. In RAW264.7 macrophages and mouse peritoneal macrophages, EPD dose-dependently suppressed production of pro-inflammatory mediators including nitric oxide (NO), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) [17].

Mechanistic investigations revealed that EPD inhibited inducible nitric oxide synthase (iNOS) expression at the transcriptional level without affecting enzyme activity. EPD suppressed nuclear translocation of NF-κB p65 subunit without altering IκBα phosphorylation or degradation, suggesting interference with p65 nuclear import mechanisms. Additionally, EPD prevented phosphorylation of JNK, ERK1/2, and p38 MAPKs, thereby dampening AP-1 activation [17]. In LPS-induced endotoxemia mice, EPD reduced serum IL-6, TNF-α, and MCP-1 levels and ameliorated diarrhea symptoms. These findings demonstrate that *P. discolor* exerts anti-inflammatory effects through dual suppression of NF-κB and MAPK/AP-1 pathways, providing mechanistic support for its traditional use in treating inflammatory conditions.

3.5. Antibacterial activity

Traditional applications of *P. discolor* for treating dysentery and skin infections are supported by its antibacterial properties. Extracts from *P. discolor* exhibited dose-dependent inhibitory effects against both Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) [18]. Tannin-rich fractions showed particularly strong antibacterial activity, attributed to their ability to precipitate bacterial proteins, disrupt membrane integrity, and chelate essential metal ions required for bacterial metabolism. Ellagic acid derivatives demonstrated significant minimum inhibitory concentrations (MIC) against pathogenic bacteria. The antibacterial mechanisms involve multiple modes of action including cell wall/membrane damage, protein coagulation, and interference with bacterial enzyme systems. However, systematic evaluation of antibacterial spectra and structure-activity relationships remains limited.

3.6. Antitumor activity

Emerging evidence suggests that *P. discolor* possesses significant antitumor potential through induction of apoptosis, cell cycle arrest, and inhibition of proliferation. Methanol extract of *P. discolor* (MEPD) induced apoptosis in human mucoepidermoid carcinoma cells through activation of the STAT3/PUMA signaling axis, characterized by increased Bax/Bcl-2 ratio, cytochrome *c* release, and caspase-3 activation [19]. The ethyl acetate fraction exhibited potent cytotoxicity against human hepatocellular carcinoma HepG-2 cells with IC_{50} values significantly lower than normal liver cells, demonstrating tumor selectivity [20].

Novel C-27-carboxylated lupane-triterpenoids isolated from *P. discolor* showed remarkable antitumor activities against multiple cancer cell lines (A549, HCT-116, HepG-2) with IC_{50} values ranging from 5 to 15 μM [8]. These compounds induced apoptosis through downregulation of the PI3K/Akt/mTOR pathway, leading to autophagy activation and mitochondrial dysfunction. Essential oil from *P. discolor* exhibited anti-proliferative effects against A549 lung cancer cells through ROS generation and mitochondrial membrane potential disruption [9]. Polysaccharide fractions demonstrated immunomodulatory antitumor effects by enhancing natural killer (NK) cell and macrophage activities. The multifaceted antitumor mechanisms involve direct cytotoxicity, apoptosis induction, autophagy activation, and immunostimulation, warranting further investigation for cancer therapeutic development.

3.7. Other pharmacological activities

Beyond the major activities discussed above, *P. discolor* exhibits several additional bioactivities deserving attention. Antiviral activity against influenza virus and herpes simplex virus has been reported, mediated by viral enzyme inhibition and immune enhancement. Neuroprotective effects in Alzheimer's disease models involve reduction of β-amyloid aggregation, acetylcholinesterase inhibition, and anti-neuroinflammatory actions. Anti-ulcer activity through enhancement of gastric mucosal defense factors and suppression of acid secretion has also been documented. Immunomodulatory effects include stimulation of lymphocyte proliferation, cytokine secretion, and phagocytic activity. However, these activities require more comprehensive investigation to elucidate their mechanisms and therapeutic potential.

4. Challenges of pharmacokinetic and safety studies

Despite the significant *in vitro* pharmacological activities of *Potentilla discolor*, pharmacokinetic studies remain limited, which hampers its modern clinical translation. Key active constituents such as quercetin and luteolin typically exhibit low oral bioavailability, primarily due to poor intestinal absorption, extensive metabolism (mainly glucuronidation and sulfation), and rapid systemic elimination. Evidence suggests that after oral administration, most flavonoids from *P. discolor* enter the bloodstream as metabolites rather than as parent compounds; for example, quercetin can be bio transformed by the gut microbiota into phenolic acids. Thus, the overall pharmacological efficacy likely results from a combination of the prototype compound, gut microbial metabolites, and hepatic derivatives, posing a major challenge for clarifying its true bioactive forms. Future research should employ advanced analytical techniques such as LC-MS/MS to systematically investigate the absorption, distribution, metabolism, and excretion (ADME) of the extracts and key constituents, with the goal of linking pharmacokinetic profiles to pharmacodynamic outcomes [21].

In terms of safety, *P. discolor* has traditionally been considered to have low toxicity. However, recent pharmacological studies indicate that potential side effects, particularly on liver and kidney function, may occur at high doses. Moreover, the plant's high tannin content could impair nutrient absorption if consumed in large amounts over extended periods or may interact with alkaloid-containing drugs and affect their bioavailability. Therefore, rigorous preclinical toxicological evaluations and long-term toxicity studies based on clinically relevant doses are necessary to ensure its safety [22].

5. Applications and development prospects

Current applications of *Potentilla discolor* remain primarily in traditional Chinese medicine formulations, Chinese medicinal formula granules, and health products such as substitute teas. To achieve more efficient, safe, and modernized utilization, future research should focus on the following development directions with clear pathways.

Integrate systems biology approaches including transcriptomics, proteomics, and metabolomics, combined with network pharmacology strategies, to comprehensively decipher its "multi-component-multi-target-multi-pathway" synergistic action networks. Prioritize the use of gene editing technologies and compound-specific knockout methods to validate key targets and synergistic mechanisms in complex disease models such as diabetes and tumors.

Systematically investigate the *in vivo* ADME processes of major active constituents and their metabolites to

clarify bioavailability bottlenecks, metabolic fate, and potential drug-drug interactions. Based on this foundation, develop novel drug delivery systems (such as nanocrystals, phospholipid complexes, self-microemulsifying systems) to improve oral absorption, and complete standardized GLP-compliant preclinical safety evaluations.

Advance the upgrade of quality control paradigms from single marker component quantification toward comprehensive quality control systems that combine multi-marker component quantification with holistic fingerprint evaluation. Establish full-process quality traceability systems from GAP cultivation of crude drugs to final products, ensuring quality uniformity, efficacy, and controllability of drugs and products.

Actively promote rigorously designed, multicenter, large-sample randomized double-blind controlled clinical trials to scientifically evaluate the precise efficacy and long-term safety of *P. discolor* and its effective fractions/components in humans (particularly in prediabetic and early-stage diabetic patients), providing high-level evidence-based medical evidence for its clinical application and exploring its value in the prevention and treatment of diabetic complications.

6. Conclusions and perspectives

Potentilla discolor, as a medicinal plant with a long history of application, has been fully revealed by modern research to be a "natural chemical library" rich in various active constituents including flavonoids, tannins, phenolic acids, and terpenoids. These components collectively confer broad and multidimensional pharmacological activities including hypoglycemic, antioxidant, anti-inflammatory, antibacterial, and antitumor effects. Its mechanism of action is shifting from simple one drug-one target toward complex multi-component-multi-target-multi-pathway synergistic network paradigms, particularly demonstrating tremendous potential in improving glucose metabolism through regulation of multiple signaling pathways including PI3K/Akt, NF-κB, and MAPK [23].

However, current research still exhibits obvious shortcomings. The pharmacodynamic material basis remains unclear, most pharmacological activity studies remain at the crude extract level. Although activities have been confirmed, research precisely tracking and validating key pharmacodynamically effective components (or component groups) remains insufficient. Pharmacokinetic research is deficient: *in vivo* processes are unclear, bioavailability is low, and knowledge about the actual active *in vivo* forms, distribution, and transformation patterns remains minimal, seriously constraining formulation design and optimization of clinical dosing regimens.

Clinical evidence is severely lacking, there is an urgent need to design rigorous clinical trials to verify its efficacy and safety in humans, which represents the final step toward modern translation. Mechanistic depth is insufficient: understanding of how different components synergize and how different pathways cross-talk remains at the hypothesis stage, lacking direct experimental evidence.

Looking forward, research on *P. discolor* will inevitably advance from what it contains and what it does toward the depth and breadth of why it works and how to use it better. Through the introduction of multi-omics technologies, advanced materials science, and rigorous clinical research designs, *P. discolor* holds promise to shine in functional foods, health products, and evidence-based modern Chinese medicine new drug development, making its unique contribution to human health, particularly in the prevention and treatment of metabolic diseases.

Disclosure statement

The authors declare no conflict of interest.

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