



# *Pueraria tuberosa*: A Review on Traditional Uses, Pharmacology, and Phytochemistry

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*Pueraria tuberosa* (Roxb. ex Willd.) DC. (Fabaceae), also known as Indian Kudzu (vidari kand), is a perennial herb distributed throughout India and other Asian countries. Traditionally, tuber and leaves of this plant have extensively been reported for nutritional and medicinal properties in Ayurveda as well as in Chinese traditional practices. The objective of the present review is to compile and update the published data on traditional uses, pharmacological potential, and phytochemistry of compounds isolated from the plant *Pueraria tuberosa*. *P. tuberosa* extracts and its purified compounds possess multiple activities such as anticancer, anticonvulsant, antidiabetic, antifertility, anti-inflammatory, antioxidant, anti-stress, antiulcerogenic, cardioprotective, hypolipidemic, hepatoprotective, immunomodulatory, nephroprotective, nootropic, neuroprotective, and wound healing. Tuber and leaf extracts of *P. tuberosa* contain several bioactive constituents such as puerarin, daidzein, genistein, quercetin, irisolidone, biochanin A, biochanin B, isoorientin, and mangiferin, which possess an extensive range of pharmacological activities. The extensive range of pharmacological properties of *P. tuberosa* provides opportunities for further investigation and presents a new approach for the treatment of ailments. Many phytochemicals have been identified and characterized from *P. tuberosa*; however, some of them are still unexplored, and there is no supporting data for their activities and exact mechanisms of action. Therefore, further investigations are warranted to unravel the mechanisms of action of individual constituents of this plant.

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## INTRODUCTION

As per the World Health Organization (WHO) estimation, about 65–80% of people all over the world seek herbal therapies to cure primary health conditions (Robinson and Zhang, 2011). Surprisingly, only 15% of the global flora has been assessed for pharmacological potential (De Luca et al., 2012). WHO has published four volumes of the monographs on selected medicinal plants to support the research in the field of herbal medicine (WHO, 2009). In India, Ayurveda, Unani, Siddha, Homeopathy, and Folk medicine are commonly used as traditional alternative medicine practices for treating different ailments. Among the modern civilizations, India has long been known for its rich treasure of medicinal plants, and about more than 7,000 plant remedies have been categorized and documented by the AYUSH system of medicine (National Medicinal Plants Board,

Government of India, 2020). One of the medicinally important plants discussed in this review is *Pueraria tuberosa* (Roxb. ex Willd.) DC. (Fabaceae), also known as Indian Kudzu (vidari kand). It is a rapidly growing large perennial climber with big tuberous roots (**Figures 1–4**) (Indian Medicinal Plant Database) and is distributed throughout India, Pakistan, and Nepal (Keung, 2002). Lianas of *P. tuberosa* has also been found to grow at 4,000 feet in the Himalayan mountain series (*Pueraria tuberosa*—Vikaspedia, 2020). In Ayurveda, it is known as vidari (vidari kand). The tuber of this plant is sweet (Ayurvedic pharmacopoeia of India, 2001) and is widely used in the treatment of fever, menorrhagia, skin diseases, wounds, bronchial asthma, and jaundice. Apart from the traditional uses of this plant as mentioned in ancient literature like Sushruta Samhita (Sanskrit: सुश्रुत संहिता), several studies have been reported on different pharmacological activities of *P. tuberosa* extracts and its purified compounds, viz., anticancer (Adedapo et al., 2017), anticonvulsant (Basavaraj et al., 2011), antidiabetic (Oza and Kulkarni, 2018a), antifertility (Gupta et al., 2005), anti-inflammatory (Tripathi et al., 2013), antioxidant (Shukla et al., 2018a), anti-stress (Verma et al., 2012), antiulcerogenic (Gindi et al., 2010), cardioprotective (Patel et al., 2018), hypolipidemic (Tanwar et al., 2008), hepatoprotective (Xia et al., 2013), immunomodulatory (Patel et al., 2016), nephroprotective (Shukla et al., 2018b), nootropic (Rao et al., 2008), neuroprotective (Xing et al., 2011), and wound healing activities (Kambhoja and Murthy, 2007). Previously, Maji et al. (2014) broadly highlighted the phytochemical and therapeutic potential of *P. tuberosa* in various pharmacological activities. However, the information about the doses of plant extracts used and the models implied for the studies (*in vitro* or *in vivo*) in different pharmacological activities was missing. In addition, chemical structures of only few phytoconstituents isolated from *P. tuberosa* have been given. Therefore, this review is aimed to provide an up-to-date summary of the literature on traditional uses, doses, and types of studies used to confirm pharmacological activities and phytochemical constituents isolated from *P. tuberosa* plant with their chemical structures and IUPAC names.

## METHODOLOGY

Relevant literature for this review on *P. tuberosa* has been sourced from PubMed, ScienceDirect, Web of Science, PubChem, Google Scholar, SciFinder, and Scopus database. The articles published in English before September 2020 on traditional uses, pharmacology of extracts, and various phytoconstituents isolated from different parts of *P. tuberosa* were included in this review. The keywords used for retrieving relevant studies were *Pueraria tuberosa* plant, Indian Kudzu, vidari kand, tuber extract, traditional uses, phytochemical constituents, pharmacological activity, and *in silico*, *in vitro*, and *in vivo* studies.

Data inclusion criteria included (a) published/peer-reviewed scientific manuscripts; (b) ethnopharmacological studies; (c) tuber extracts with different solvents; (d) studies on the mechanism of actions of plant extracts and their phytoconstituents; (e) *in silico*, *in vitro*, and *in vivo* studies.

Exclusion criteria included (a) repetitive studies and information not meeting the inclusion criteria; (b) studies performed with extracts of other *Pueraria* species; (c) opinion to the editors, case studies, abstracts of the conferences, any unpublished data, and reports.

## Synonyms (Ayurvedic pharmacopoeia of India, 2001)

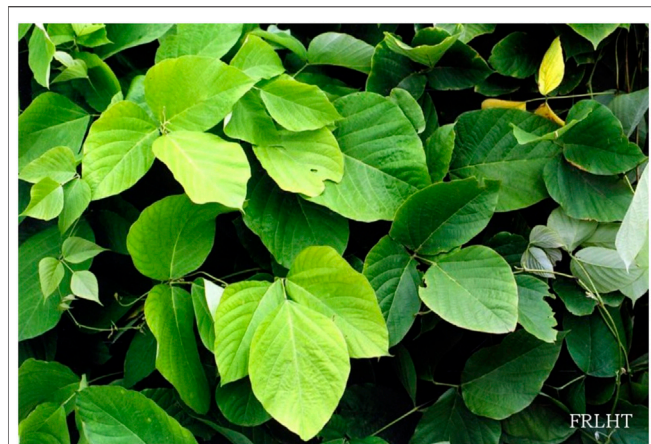
Assamese: Bhedeleon, Bhuikumra  
 Bengali: Bhuikumra, Bhumikusmanda, Vidari  
 English: Indian kudzu  
 Gujrati: Bhoikolu, Bhonykoru, Eagio, Sakharvel, Vidarikanta,  
 Hindi: वदिरीकंद (Vidarikanda), बनकुमड़ा (Bankumara)  
 Kannada: Gumadi belli, Gumadigida, Nelagumbala Gudde,  
 Nelagumbala, Nelagumbula  
 Malayalam: Mudakku  
 Marathi: Bhuikohala, Ghodvel  
 Oriya: Bhuiankakharu  
 Punjabi: Siali, Surala  
 Sanskrit: भूमकुष्माण्ड (Bhumikusmanda), गजवाजपिरिया (Gajavajipriya), कन्दपलाश (Kandapalash), स्वादुकन्दा (Svadukanda), वदिरी (Vidari), इक्षुगन्धा (Iksu-Gandha).  
 Tamil: Nilapooani  
 Telugu: Darigummati, Nelagummuda

## Scientific Classification (Rawtal et al., 2019)

Kingdom: Plantae  
 Subkingdom: Trachebionta  
 Superdivision: Spermatophyta  
 Division: Magnoliophyta  
 Subclass: Rosidae  
 Order: Fabales  
 Family: Fabaceae  
 Genus: *Pueraria* DC.  
 Species: *Pueraria tuberosa*

## Traditional Uses

In Ayurveda, vidari kand (*Pueraria tuberosa*) has been described as a plant having good nutritional value. Besides, the plant also possesses aphrodisiac, diuretic, galactagogue (Kirtikar and Basu, 1935), energizing (Maji et al., 2014), and spermatogenic (Chauhan et al., 2013) properties. It has been prescribed for treatment for all three doshas (i.e., for the complications of three different energies, viz., Vata, Kapha, and Pitta) of human body (Ayurvedic pharmacopoeia of India, 1999; Dalal et al., 2013). The powdered form of tuber is primarily used in combination with cow's milk as a galactagogue agent to abrogate lack of milk production after childbirth and also as an anabolic agent along with *Piper longum* L. (Piperaceae) powder to cure malnutrition in children. For relieving excessive menstruation, the powder is used with honey. A mixture of powdered *P. tuberosa* and wheat or barley fried in ghee (clarified butter) with milk has been advised for sexual enervation and strength. For spermatorrhoea, fresh tuber juice of this plant with cumin seeds and sugar has been used therapeutically (Puri, 2003).



**FIGURE 1** | *Pueraria tuberosa* (Roxb. ex Willd.) DC. (Fabaceae): (1) Leaf. (2–4) Tuber.

Traditionally, *P. tuberosa* has been used along with other medicinal plants in different combinations to prepare therapeutic Ayurvedic formulation. Some of the important Ayurvedic formulations utilizing *P. tuberosa* are “Ashwagandharishta”, a traditional remedy for epilepsy (Tanna et al., 2012), “Maha visagarbha taila”, a traditional remedy for sciatica and joint disorders (Kumawat et al., 2017), and “Nityananda rasa”, “Sarasvatarista”, “Satavaryadi ghrta” (Ayurvedic pharmacopoeia of India, 2001), “Marma gutika” (Kumar, 2016), and “Vidaryadi ghrta” (Sharma et al., 2018).

Traditional uses of *Pueraria* species, namely, *Pueraria montana* var. *thomsonii* (Benth.) (Fabaceae) and *Pueraria montana* var. *lobata* (Willd.) (Fabaceae), have been reported for their medicinal properties such as antiemetic, antitoxic, cold, countering the effect of alcohol abuse, anti-stress agent, neck stiffness, hypohidrosis, migraines, hypoglycemia, and certain cardiovascular diseases in the Chinese Medicinal Herbs, a book written by Li Shih Chen (Li, 2003; Croom, 2004).

## Pharmacology

In phytopharmacological/ethnopharmacological research, scientific community should follow best practices in designing and conducting studies and reporting the results of analyzing pharmacological properties of the plant extracts and compounds of natural origin (Heinrich et al., 2020). Therefore, while reporting biological activities of any plant/herbal product, detailed information about the characterization of the plant extracts, their phytoconstituents, doses, duration of treatment, type of models used in the studies, toxicological data, and so forth should be clearly presented for the benefit of research community (Heinrich et al., 2020). Various pharmacological activities of the tuber extracts of *P. tuberosa* have been explored, and a graphical summary of these activities is shown in **Figure 5** and **Table 1**.

## Nephroprotective Activity

Several studies have shown that *P. tuberosa* plant possesses nephroprotective activities. Oral administration of methanolic tuber extract to cisplatin- (8 mg/kg body weight) induced kidney



**FIGURE 2** | Indian Medicinal Plant database.

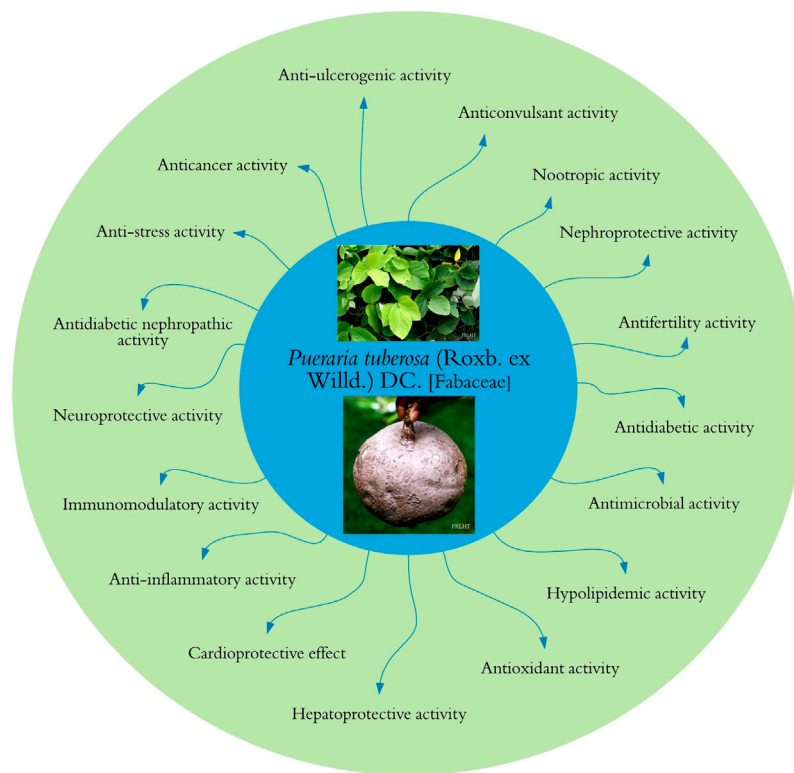


**FIGURE 3** | Pankaj Oudhia/<https://www.discoverlife.org>.

damaged rats showed a dose-dependent protective effect (Nagwani and Tripathi, 2010). Tuber extract significantly reduced blood urea nitrogen, serum creatinine, glutathione, and superoxide dismutase (SOD) levels. The extract could control deoxyribonucleic acid (DNA) damage and catalase activities, cellular necrosis, and tubular swelling and prevent coagulation of proteins, in contrast to the control group. The nephroprotection of tuber extract of the plant has been attributed to its free radical scavenging activity (Nagwani and Tripathi, 2010). Feeding of biscuits made up of powder of *P. tuberosa* tuber



**FIGURE 4** | "*Pueraria tuberosa* (Willd.) DC. Vidari Kand, Patal Kumrha", by Ravi Upadhyay, <https://indiabiodiversity.org/observation/show/269544>, licensed under CC BY 3.0).



**FIGURE 5** | Pharmacological activities of *Pueraria tuberosa*.

for 10 days showed significant recovery in cisplatin-induced nephrotoxicity in Swiss mice. However, at higher dose, aspartate aminotransferase and alanine aminotransferase levels were temporarily elevated, so monitoring of liver functions, periodically, is imperative when continuing this regimen for longer periods such as a food supplement for cancer patients undertaking cisplatin chemotherapy (Tripathi et al., 2012). The methanolic extract of *P. tuberosa* ameliorated glycerol-induced acute kidney injury in rats by affecting the lipid peroxidation,

SOD, and catalase activity with a lesser accumulation of hyaline casts and a lesser degree of tubular necrosis on histology of the kidney (Yadav et al., 2016a). Water decoction of *P. tuberosa* has also been reported to significantly reverse cisplatin-induced nephrotoxicity in rats (Yadav et al., 2016b). Hydroalcoholic tuber extracts of *P. tuberosa* showed nephroprotective activity in sodium arsenate- (1 mg/kg body weight) induced oxidative kidney tissue damage in rats (Rani et al., 2017). The nephroprotective effect through free radical scavenging activity

**TABLE 1** | Pharmacological activities of tuber extract of *Pueraria tuberosa*.

Extract	Dose tested	Pharmacological activity	Model used for study ( <i>in vivo</i> or <i>in vitro</i> )	Reference
Aqueous	50 mg/100 g b/w 50 mg/100 g b/w for 35 days 50 mg/100 g b/w for 10 days	Antidiabetic	<i>In vivo</i>	Srivastava et al. (2015); Srivastava et al. (2017); Srivastava et al. (2018); Srivastava et al. (2019)
Ethanol	100–400 mg/kg b/w for 5 days	Immunomodulatory	<i>In vivo</i>	Patel et al. (2016)
Tuber powder	250 mg/kg b/w	Immunomodulatory	<i>In vivo</i>	Shilpashree et al. (2015)
Aqueous	250 mg/ml given orally to rats for 14 days	Hepatoprotective	<i>In vivo</i>	Pandey et al. (2019)
Ethanol and methanol	125, 250, 500, and 1,000 µg/ml	Antioxidant	<i>In vitro</i>	Likhitkar and Pande (2017)
Aqueous	200, 400, and 700 µg/ml for 24, 48, and 72 h	Anticancer	<i>In vitro</i>	Adedapo et al. (2017)
Hydroalcoholic	64 and 128 µg/ml for 24 h	Anticancer	<i>In vitro</i>	Aruna et al. (2018)
Ethyl acetate	31.5–500 µg/ml for 72 h	Anticancer	<i>In vitro</i>	Satpathy et al. (2020)
Aqueous	50–100 mg/100 g b/w for 20 days	Antidiabetic nephropathy	<i>In vivo</i>	Shukla et al. (2017); (2018a); (2018b)
Hydroalcoholic	20–40 mg/100 g b/w for 14 days	Antidiabetic nephropathy	<i>In vivo</i>	Tripathi et al. (2017)
Methanolic	20 mg/kg b/w for 14 days and 40 mg/kg b/w for 7 days	Antidiabetic nephropathy	<i>In vivo</i>	Yadav et al. (2019)
Methanolic	20 and 40 mg/100 g b/w for 2 days	Nephroprotective	<i>In vivo</i>	Yadav et al. (2016a)
Butanol and ethyl acetate	50 mg/100 g b/w for 5 days	Nephroprotective	<i>In vivo</i>	Yadav et al. (2016b)
Methanolic	200 mg/ml	Antibacterial	<i>In vitro</i>	Pandya et al. (2019)
Hydroalcoholic	50, 100, and 200 mg/kg b/w for 30 days	Neuroprotective	<i>In vivo</i>	Umarani et al. (2016)

b/w: body weight.

was supported in a study, where streptozotocin- (STZ-) induced diabetic nephropathic rats, treated with aqueous tuber extract of *P. tuberosa*, exhibited an upsurge in activity of antioxidant enzymes, lowered oxidative stress, apoptosis, and urinary albumin excretion in a concentration-dependent manner (Shukla et al., 2018a). Methanolic tuber extract of the plant showed substantial protection in diabetic nephropathy induced by the administration of alloxan in rats (120 mg/kg body weight) by decreasing urea and creatinine and improving physiology of the kidney (Yadav et al., 2019). The supplementation of tuber extract of the *P. tuberosa* showed protection of kidney from oxidative stress and cellular injury. It also improved kidney physiology and parameters of kidney function test by reducing cellular apoptosis. These studies indicate that *P. tuberosa* extracts have nephron-protective potential and might lead to promising therapeutic agents for treating kidney diseases.

### Antioxidant Activity

Methanolic and hexane tuber extract of *P. tuberosa* exhibited a strong free radical scavenging activity in a concentration-dependent fashion. These results showed that the methanolic extract of this plant exhibited better activity than the hexane extract in trapping hydroxyl radicals and inhibited lipid peroxidation, which indicated potent antioxidant property (Pandey et al., 2007). Hot water tuber extract of the plant *P. tuberosa*, supplemented with milk in Swiss mice, showed potent antioxidant activities in liver and red blood cells. Besides, a remarkable difference in glutathione levels was also observed in the control (172 µg/ml) and supplemented groups (*P. tuberosa*:

1,212 µg/ml and *P. tuberosa* + milk: 1,308.2 µg/ml). *P. tuberosa* along with milk has antioxidant property as evidenced by higher phagocytic activity, increased immunoglobulin levels, and reduced glutathione and lipid peroxidation (Sawale et al., 2013). *P. tuberosa* extracted with chloroform, acetone, methanol, and hot water was used to determine its antioxidant potential by using ferric reducing antioxidant power (FRAP) assay, metal chelating, phosphomolybdenum, and free radical scavenging using DPPH (2,2'-diphenyl-1-picrylhydrazyl radical) and ABTS (3-ethylbenzothiazoline-6-sulfonic acid) assay. The results showed that acetone extract of *P. tuberosa* has potent antioxidant activity (Viji and Paulsamy, 2015).

### Antidiabetic Activity

Oral gavage of ethyl acetate tuber extract of *P. tuberosa* (250 mg/kg body weight) to alloxan-induced diabetic rats for seven days showed a pronounced decrease in blood glucose levels (Raghuwanshi and Jain, 2011). Studies suggested that chloroform, petroleum ether, ethanol, and aqueous tuber extracts of *P. tuberosa* confer significant antidiabetic activity in STZ- (50 mg/kg body weight) induced diabetic rats by a single intraperitoneal injection (Tripathi and Kohli, 2013). Water extract of root of *P. tuberosa* showed significant inhibition of dipeptidyl peptidase-4 (DPP-IV) that causes an enhanced half-life of active glucagon-like peptide-1 hormone. This hormone regulates glucose-dependent insulin release from β-cells of the pancreas in rats (Srivastava et al., 2015). In Srivastava et al.'s next study, they found that *P. tuberosa* water extract increased the glucose homeostatic potential through DPP-IV inhibitory pathway

and the bioactive components robinin and puerarone, and this inhibitory activity was also confirmed by *in silico* molecular docking (Srivastava et al., 2017). Aqueous extract of tuber of *P. tuberosa* has further been reported to act as incretin receptor agonist and downregulated  $\beta$ -cells apoptosis and protected STZ-induced diabetes in rats (Srivastava et al., 2018). Aqueous tuber extract of the plant showed an elevated expression of nephrin and SOD and a declined expression of cysteinyl aspartate specific proteinase 3 (caspase-3), interleukin 6 (IL-6), nuclear factor kappa B (NF- $\kappa$ B), protein kinase C epsilon type (PKC $\epsilon$ ), tumor necrosis factor alpha (TNF- $\alpha$ ), vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), and hypoxia-inducible factor 1-alpha in STZ-induced diabetic rats (Srivastava et al., 2019). In another experiment, it has been shown that administration of *P. tuberosa* water extract in alloxan-induced rat diabetic model resulted in decrease in SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), and alkaline phosphates level and improved deformed hepatocytes and significant decrease in blood glucose levels as well as apoptosis (Pandey et al., 2019). The tuber extract contains different bioactive compounds that may act as agonists on glucagon-like peptide-1 hormone released from intestine and can also protect  $\beta$ -cells of the pancreas. It also resulted in decreased expression of different inflammatory and apoptotic markers during hypoxic injury to  $\beta$ -cells as evidenced by decreased apoptosis of  $\beta$ -cells. The extract also inhibited DPP-IV enzyme as an incretins receptor agonist, and hence it is emanating from the above studies that *P. tuberosa* has antidiabetic potential.

### Anti-Stress Activity

Adult male Wistar rats subjected to cold immobilization stress, pretreated with 70% hydroethanolic tuber extract of *P. tuberosa* (200 and 400 mg/kg body weight) for 5 days, showed significant protection from gastric mucosal damage, reduced corticosterone level in the blood, and no enlargement of spleen and adrenals as compared to *Withania somnifera* (L.) Dunal (Solanaceae) rhizome extract (100 mg/kg body weight). These studies established the anti-stress effect of *P. tuberosa* (Pramanik et al., 2011). In a human trial, hypertensive patients were divided into two groups: group 1 was given capsules with 0.75 g tuber powder, whereas group 2 was given placebo capsules with lactose powder administered for 12 weeks. Group 1, treated with 1.5 g (twice a day) tuber powder of *P. tuberosa* for 12 weeks, showed a gradual decrease in systolic, diastolic, and mean blood pressure as well as a tolerant decrease in fibrinogen and increased plasma fibrinolytic activity (Verma et al., 2012). In stress-mediated disorders, the hypothalamic-pituitary-adrenal (HPA) axis is dysregulated which changes the levels of corticosteroids in plasma and monoamine in the brain. The extract of this plant might act on mucosal layer of the gastrointestinal, cardiovascular, and nervous (HPA) system, suggestive of anti-stress activity by a reduction in stress hormones.

### Antidiabetic Nephropathic Activity

STZ-induced diabetic rats with nephropathy were given tuber extract of *P. tuberosa* (30 mg/100 g, body weight) for 20 days and

exhibited a significant reduced severity of diabetic nephropathy by enhanced expression and activity of MMP-9 and degrading the accumulation of extracellular matrix in kidney tissue (Tripathi et al., 2017). Levels of nephrin, a biomarker of early glomerular injury, in the kidney of diabetic nephropathic rats were restored after treatment with tuber extract of *P. tuberosa* (Shukla et al., 2017). The diabetic nephropathic inflammatory response is mediated by NF- $\kappa$ B and its activated phosphorylated derivative (pNF- $\kappa$ B). Improved levels of these transcription factors and inflammatory cytokines (IL-6 and TNF- $\alpha$ ) in the kidney of STZ-induced (55 mg/kg body weight) diabetic nephropathic rats were observed, and treatment with extracts from the tuber of *P. tuberosa* significantly negated these changes in a dose-dependent manner (Shukla et al., 2018b). Amelioration of renal damage was evaluated by renal functional tests, histopathology, and oxidative stress in alloxan-induced diabetic nephropathy. *P. tuberosa* methanolic extract showed renal protection by decreasing urea and creatinine and improved kidney physiology and histopathology changes through antioxidant mechanisms (Yadav et al., 2019). These studies are indicative of nephro-protection offered by *P. tuberosa* in diabetic nephropathy; however, this protective effect needs to be further explored, including studies on the protection of renal and glomerular cells mediated by different signaling pathway in the antidiabetic nephropathy.

### Anti-Inflammatory Activity

The ethyl acetate and methanolic tuber extracts of *P. tuberosa* showed considerable anti-inflammatory potential compared to the control and standard drugs, ibuprofen, and nitrofurazone ointment in the rat paw edema method (Kambhoja and Murthy, 2007). The methanolic tuber extract of the plant significantly prevented the carrageenan-induced inflammation by lowering the glutathione content, catalase, SOD activity, and enhancing lipid peroxidase and C-reactive proteins in rats in a sequential manner (Tripathi et al., 2013). Isoorientin, isolated from the tuber of *P. tuberosa* plant, showed significant anti-inflammatory activity in LPS-treated mouse macrophage (RAW 264.7) cell line. It was also effective against carrageenan-induced inflammation on paw edema and air pouch mouse models. These studies revealed the downregulation in the expression of proinflammatory genes such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF- $\alpha$ , and inactivation of NF- $\kappa$ B. Moreover, there was activation of antioxidant enzymes, catalase and glutathione-S-transferase (Anilkumar et al., 2017). The anti-inflammatory property of extracts of *P. tuberosa* in these studies appears to be mediated by lipid peroxidation, inactivation of the NF- $\kappa$ B pathway, and downregulation of proinflammatory cytokines.

### Immunomodulatory Activity

Immunomodulatory activities of plant extract (0.4%) with milk as a carrier given to Swiss mice for 28 days were evaluated. The result showed a significantly higher phagocytic activity and immunoglobulin concentration, reduced glutathione content, and thiobarbituric acid reactive substances level compared to the control (Sawale et al., 2013). Reversed phase high-performance

liquid chromatography (RP-HPLC) analysis of ethanolic tuber extract of the plant revealed that bioactive compounds involved in the immunomodulatory activities are genistein (1.37%), daidzein (1.70%), and puerarin (8.31%). Oral administration of these extracts builds up innate and humoral immune responses against sheep red blood cells challenged rats (Maji et al., 2014). The immunomodulatory activity of petroleum ether extract of *P. tuberosa* was evaluated by carbon clearance assay (Granuloplectic index). The extract and *Withania somnifera* (L.) Dunal (Solanaceae) at 250 mg/kg body weight (Medicinal Plant Names Services, e) exhibited enhanced phagocytic activity of peritoneal macrophages to clear the carbon particles (Shilpashree et al., 2015). The ethanolic extract of tuber increased the phagocytic activity of macrophages in the mice model. The extract also inhibited both the cell mediated and humoral immunity, which supports its potent immunomodulatory activity (Patel et al., 2016).

### Anticancer Activity

There is no significant toxicity of mangiferin isolated from tuber of *P. tuberosa* on normal cell lines (mouse fibroblast NIH-3T3, RAW 264.7, HEK293, and mouse lymphocytes) in cell viability assay *in vitro*; however, it is cytotoxic to various cancer cell lines like K562, MCF7, HEPG2, Jurkat cells, and A549 (Bulugonda et al., 2017). Furthermore, the anticancer and apoptotic potential of the hydroalcoholic tuber extract of *P. tuberosa* was investigated by cell viability assay. The extract showed a 50% inhibition of cell viability against human colon carcinoma (HT-29) cells at a concentration of 63.91 µg/ml. Cells also exhibited DNA fragmentation that is the hallmark of apoptosis, apoptotic cell death, and increased expression of certain proapoptotic genes (Aruna et al., 2018). The silver nanoparticles biosynthesized with aqueous extract of the *P. tuberosa* showed *in vitro* anticancer potential on different cancer cell lines (breast MCF-7 and MDA-MB-231; ovarian SKOV-3; brain U-87 cancer). However, the mechanism behind this activity needs exploration for therapeutic use (Satpathy et al., 2018). Antioxidant-enriched fraction also exhibited *in vitro* cytotoxicity in the breast (MCF-7 and MDA-MB-231) and ovarian (SKOV-3) cancer cells (Satpathy et al., 2020).

### Other Pharmacological Properties

*P. tuberosa* has been attributed as one of the most sought plants that proved to be effective against multiple diseases and ailments. Alcoholic and aqueous extracts of *P. tuberosa* tuber were studied for nootropic effect in mice and rat models of amnesia induced by scopolamine and diazepam. The inflexion ratio observed was considerably high and comparable with piracetam, the standard drug in an elevated plus-maze experiment. Flavonoids present in the *P. tuberosa* tuber extracts have been reported for nootropic effect by interacting with cholinergic, adrenergic, serotonergic, and GABAergic system (Rao et al., 2008). The neuroprotective properties of this plant were also studied in chronic foot-shock stressed rat model showing unpredictable and inescapable nature of physiological malfunctions, increase in anxiety level, decrease in male sexual indices, and behavioral changes. All these symptoms were abolished by this plant's tuber extract

(Pramanik et al., 2010). Neurotoxicity induced by sodium arsenate was ameliorated by hydroalcoholic extract which strengthens its memory and restores muscle strength and locomotor activity. Biochemical and histopathological changes are suggestive of the protective property of the extract in maintaining normal functional status of the brain in arsenate neurotoxicity (Umarani et al., 2016).

Alcoholic tuber extract of *P. tuberosa* was studied for anticonvulsant activity in pentalene tetrazole, strychnine, and maximal electroshock-induced convulsions in animals. Different doses of the extract (50, 100, and 200 mg/kg body weight) were compared with the standard drug, diazepam (5 mg/kg body weight). The medium and high doses exhibited potent anticonvulsant activity as compared to the control group (Basavaraj et al., 2011). The ethanolic and methanolic extract of leaf, stem, and tuber of *P. tuberosa* showed a wide range of antimicrobial activity against bacteria, *Escherichia coli*, *Bacillus cereus*, *Salmonella paratyphi*, and *Staphylococcus aureus*, as well as fungus, *Candida albicans*, *Aspergillus fumigates*, and *Alternaria solani*, on agar diffusion assay (Sadguna et al., 2015). The tuber extracts of *P. tuberosa* with different solvents exhibited a wide range of antimicrobial activity on selected bacterial and fungal pathogens (Aruna et al., 2016). The chloroform and water extracts of tuber of *P. tuberosa* showed significant antibacterial activity against *Klebsiella pneumoniae* and *Staphylococcus aureus* and methanolic extract on *Staphylococcus aureus* and *Streptococcus agalactiae* (Pandya et al., 2019). The metabolites in *P. tuberosa* extracts may be behind the mechanism involved in the antimicrobial action, which may interact with the microbial cell membrane resulting in microbial cell death. The antiulcerogenic activity of aqueous leaf extract of *P. tuberosa* on cold restraint stress, pyloric ligation, and ethanol-induced gastric ulcer rat models was observed. There was significant inhibition in gastric lesions by 76.6% in cold restraint stress, 80.1% in pyloric ligation, and 70.6% in ethanol-induced rat models (Gindi et al., 2010).

In metabolic disorders also, *P. tuberosa* extracts exhibited a hypolipidemic effect. Oral administration of butanol tuber extract of *P. tuberosa* at a dose of 150 mg/kg body weight showed a pronounced protective effect against CCl<sub>4</sub>-induced hepatotoxicity in adult male rats (Shukla et al., 1996). Rats maintained on high cholesterol diet upon the treatment demonstrated a substantial reduction in serum cholesterol, triglycerides (TG), low-density lipoproteins (LDL), and very-low-density lipoproteins (VLDL) levels (Tanwar et al., 2008). These results were corroborated in another study where nonalcoholic fatty liver disease (NAFLD), induced in rats by feeding a high fat diet, was treated with water extract of this plant. Antioxidant activity with reduced lipid peroxidation and enhanced activities of SOD and catalase enzymes were observed. A similar finding was observed by Tripathi et al. in the NAFLD rats model which also showed a reduction in serum TG and cholesterol values (Tripathi and Aditi, 2020). The ethanolic extract of *P. tuberosa* showed a dose-dependent immunosuppressant activity as evident by a decrease in antibody titer and also a reduction in hematological

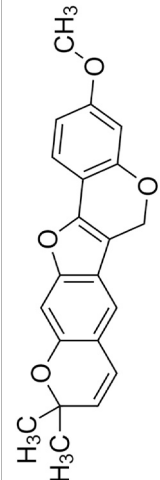
**TABLE 2 |** Pharmacological activities of phytoconstituents of *Pueraria tuberosa*.

Purified compound studied	Chemical structure	Model used for study (in silico/in vitro/in vivo)	Dose tested	Pharmacological activity	Conclusion	References
<b>Puerarin [1]</b> (C <sub>15</sub> H <sub>10</sub> O <sub>4</sub> )		<i>In vivo</i>	100 mg/kg b/w for 7 days	Nephroprotective	Suppression of oxidative stress production and S-nitrosylation of proteins in the diabetic kidneys and MMP-9	Zhong et al. (2014)
<b>IUPAC name:</b> -(7-hydroxy-3-(4-hydroxyphenyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one)		<i>In vivo</i>	20, 40, and 80 mg/kg b/w/day for 8 weeks	Antidiabetic	Hypoglycemic effect which supports its antidiabetic property and renal protective effects via the mechanism of attenuating SIRT1/FOXO1 pathway	Xu et al. (2016)
		<i>In vivo</i>	2.5 mg/kg b/w/day for 2 weeks	Antioxidant	Suppressed macrophage activation by inhibiting iκB, ERK, and p38 activity and reactive oxygen species production	Tanaka et al. (2016)
		<i>In vitro</i>	10 and 50 μM	Anticancer	Suppressed MCF-7 and MDA-MB-231 cell LPS-stimulated migration, invasion and adhesion by inhibition of the NF-κB pathway and phosphorylation of ERK	Lu et al. (2017)
		<i>In vivo</i>	500 mg/kg b/w/day for 6 weeks	Antidiabetic	Improved insulin resistance and reduced diabetic foot ulcers	Yu et al. (2017)
		<i>In vitro</i>	0.01, 0.1, 1, 10, and 100 μmol/L	Anticancer	Puerarin-induced apoptosis in human bladder cancer cells was mediated by activation of the mTOR/p70S6K signaling pathway	Jiang et al. (2018)
		<i>In vivo</i>	25, 50, and 100 mg/kg b/w/day for 12 weeks	Antidiabetic	Hypoglycemic effects, prevented cataract development and progression in diabetic rats by reducing oxidative stress through the Nrf2/HO-1 signaling pathway	Zhang and Li (2019)
		<i>In vivo</i>	50 mg/kg b/w/day for 14 weeks	Anti-inflammatory	Reduced inflammatory regulators (TNF-α, IL-1β, COX2, and MMP-14) and inhibited HDAC1/HDAC3 signaling	Guo et al. (2019)
		<i>In vivo</i>	5, 10, 20, and 40 mg/kg b/w for 12 weeks	Nephroprotective	Protects podocytes from diabetes-induced injury through HMOX1 and SIRT1-mediated upregulation of autophagy	Li et al. (2020)
<b>Daidzein [2]</b> (C <sub>15</sub> H <sub>10</sub> O <sub>4</sub> )		<i>In vitro/in vivo</i>	<i>In vitro</i> : 12.50–50 μM; <i>In vivo</i> : 1 g/kg b/w for 12 weeks	Anti-inflammatory	Reduced adipose tissue inflammation through the upregulation of PPARγ, which might result in alleviating insulin resistance in obesity	Sakamoto et al. (2014)
<b>IUPAC name:</b> -(7-hydroxy-3-(4-hydroxyphenyl)chromen-4-one)		<i>In vitro/in vivo</i>	<i>In vitro</i> : 0.5–100 μM; <i>In vivo</i> : 10 mg/kg and 20 mg/kg b/w for 27 days	Anticancer	Reduced viability of bladder carcinoma RT112 cells by inducing G1/S phase arrest and apoptosis and inhibited tumor growth	He et al. (2016)
		<i>In vitro/in vivo</i>	<i>In vitro</i> : 12.50–400 μM; <i>In vivo</i> : 10 mg/kg and 20 mg/kg b/w for 27 days	Anticancer	Reduced the cell viability and colony formation in concentration-dependent manner and inhibited tumor growth	Zheng et al. (2017)
		<i>In vitro/in vivo</i>	<i>In vitro</i> : 0.75–200 μM; <i>In vivo</i> : 10–40 μg/kg b/w	Anticancer	Induced G2M cell cycle arrest and suppressed the ovarian tumor growth	Hua et al. (2018)
<b>Genistein [3]</b> (C <sub>15</sub> H <sub>10</sub> O <sub>6</sub> )		<i>In vivo</i>	20, 40, and 60 mg/kg b/w	Cardioprotective	Significantly attenuated the release of LDH, CK in a dose-dependent manner	Gu et al. (2016)
<b>IUPAC name:</b> -(5-hydroxy-3-(4-hydroxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one)		<i>In vitro</i>	50 and 100 μM for 48 h	Antidiapogenic and antiipogenic	Activated AMP-activated protein kinase α (AMPKα), and inhibited sterol regulatory element-binding transcription factor-1c (SREBP-1c)	Choi et al. (2020)
<b>Genistein [4]</b> (C <sub>15</sub> H <sub>10</sub> O <sub>6</sub> )		<i>In vivo</i>	10 and 20 mg/kg b/w 3 times a week for 10 weeks	Nephroprotective	Reduced renal inflammation, oxidative stress, and apoptosis in diabetic mice	Emaraby et al. (2011)
		<i>In vitro</i>	10 nmol/L to 5 μmol/L	Antidiabetic	Acted on pancreatic β-cells; activation of the cAMP/PKA signaling cascade	Lu et al. (2006)
		<i>In vitro</i>	0.2, 1, and 5 mg/kg b/w once daily	Wound healing	Suppression of FoxO1, iNOS activity, and oxidative stress	Te et al. (2013)
		<i>In vitro</i>	5, 10, and 25 μM for 24 h	Antioxidant	Activated AMPK and increased PTEN expression	Paik et al. (2010)
		<i>In vivo</i>	2.5–10 mg/kg b/w for 14 days	Neuroprotective	Reduced the infarct volume, improved the neurological deficit, and prevented cell apoptosis after ischemia	Qian et al. (2012)
		<i>In vivo</i>	10 mg/kg b/w 1 h before surgery	Nootropic	Anelkated ag-induced impairment of short-term spatial memory in rats through an estrogenic pathway and reduced oxidative stress	Bagheri et al. (2011)
<b>IUPAC name:</b> -(5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one)		<i>In vivo</i>	1 mg/kg b/w from day 16 until day 60	Anti-stress	Lowered blood pressure, restored ACE, PKC-βII, and eNOS expression, and preserved renal ultrastructural integrity	Palanisamy and Venkataraman (2019)

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**TABLE 2 |** (Continued) Pharmacological activities of phytoconstituents of *Pueraria tuberosa*.

Purified compound studied	Model used for study (in silico/in vitro/in vivo)	Dose tested	Pharmacological activity	Conclusion	References
 <p>Lupinose PA4 [5] (Dey et al., (2007))</p>	<i>In vitro/in vivo</i>	<i>In vitro</i> : 20 ng/ml; <i>in vivo</i> : 1.5 mg/200 g b/w for 12 days	Antidiabetic	Stimulated IR- $\beta$ and akt phosphorylation	Dey et al. (2007)
 <p>Tuberosin [6] (C<sub>27</sub>H<sub>32</sub>O<sub>4</sub>) IUPAC name-[7-dimethyl-8,12,20-troxapentacyclo [11,8,0,0<sup>2,1</sup>,0<sup>4,5</sup>,0<sup>6,14</sup>]heptosa-2 (11),3,5,9,14 (19),15,17-heptiene-1,17-diol]</p>	<i>In vitro</i>	50, 100, 300, and 600 ng/ml	Antioxidant	Inhibited LPS-induced NO production in a concentration-dependent manner, expression of iNOS proteins	Pandey and Tripathi (2010)
 <p>3-O-methylanthrotuberosin [7] (C<sub>27</sub>H<sub>32</sub>O<sub>4</sub>) IUPAC name-[17-methoxy-7,7-dimethyl-8,12,20-troxapentacyclo [11,8,0,0<sup>2,1</sup>,0<sup>4,5</sup>,0<sup>6,14</sup>]heptosa-1(13),2(11),3,5,9,14 (19),15,17-octene]</p>	<i>In vitro</i>			Pharmacological activity not reported	
 <p>Puerarostan [8] (C<sub>27</sub>H<sub>32</sub>O<sub>4</sub>) IUPAC name-[3,9-dihydroxy-4-methoxy-8-(3-methylbut-2-enyl)-1]benzofuro [3,2-c]chromen-6-one]</p>				Pharmacological activity not reported	

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**TABLE 2 |** (Continued) Pharmacological activities of phytoconstituents of *Pueraria tuberosa*.

Purified compound studied	Model used for study (in silico/in vitro/in vivo)	Dose tested	Pharmacological activity	Conclusion	References
<p><b>β-sitosterol [9]</b> (C<sub>27</sub>H<sub>46</sub>O) IUPAC name: [(3S,8S,9S,10R,13R,14S,17R)-6-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta [a]phenanthren-3-ol</p>	<p><i>In vivo</i></p> <p>20 mg/kg b/w</p> <p><i>In vitro</i></p> <p>0.25 μg/ml and 2.5 μg/ml</p> <p><i>In vivo</i></p> <p>20 mg/kg b/w</p>	<p>Anti-collis</p> <p>Anti-proliferative for mast cell</p> <p>Nephroprotective</p>	<p>Ameliorated HFD-induced colitis by inhibiting the binding of LPS to toll-like receptor 4 in the NF-κB pathway</p> <p>Decreased thymic stromal lymphopoietin (TSLP) induced mast cell proliferation</p> <p>β-sitosterol showed significant positive changes to nephrotoxicity-induced rats; altered biochemical parameters were restored to near normal</p>	<p>Kim et al. (2014)</p> <p>Han et al. (2015)</p> <p>Sharmila et al. (2016)</p>	
<p><b>Biochanin a [10]</b> (C<sub>16</sub>H<sub>12</sub>O<sub>4</sub>) IUPAC name: [5,7-dihydroxy-3-(4-methoxyphenyl)chromen-4-one]</p>	<p><i>In vivo</i></p> <p>10, 20, and 40 mg/kg b/w for 28 days</p> <p><i>In vitro</i></p> <p>5–20 μM for 1 h</p> <p><i>In vitro</i></p> <p>2–4 μM</p> <p><i>In vitro</i></p> <p>2.5–100 μM</p>	<p>Antidiabetic</p> <p>Antitoxic against 2,3,7,8-tetrachlorodibenzo-p-dioxin</p> <p>Vasodilatory</p> <p>Anti-inflammatory</p>	<p>Increased NAD-dependent deacetylase sirtuin-1 (SIRT1) expression in pancreatic tissue</p> <p>Inhibited the TCDD-induced loss of triglycerides in 3T3-L1 adipocytes, showing increased differentiation of 3T3-L1 preadipocytes to adipocytes when compared with the cells exposed to TCDD alone</p> <p>Interfered with the cGMP pathway in isolated coronary arteries and vasodilatory effect</p> <p>Suppressing iNOS, COX-2, MyD88, and TLR-4 protein expressions and akt and ERK1/2 pathway activation</p>	<p>Oza and Kulkarni (2018b)</p> <p>Choi et al. (2019)</p> <p>Miglos et al. (2020)</p> <p>Berköz et al. (2020)</p>	
<p><b>Biochanin B [11]</b> (formononetin) (C<sub>14</sub>H<sub>12</sub>O<sub>4</sub>) IUPAC name: [7-hydroxy-3-(4-methoxyphenyl)chromen-4-one]</p>	<p><i>In vitro</i></p> <p>3.45 μmol/L in Vero cells and 3.98 μmol/L in SK-N-SH cells</p> <p><i>In vivo</i></p> <p>1 and 100 μM for 2 weeks</p> <p><i>In vivo</i></p> <p>5, 10, and 20 mg/kg b/w</p> <p><i>In vivo</i></p> <p>15, 50, and 75 mg/kg b/w for 5 days</p> <p><i>In vitro</i></p> <p>0–280 μM for 24 and 48 h</p> <p><i>In vitro</i></p> <p>2.5, 5, and 10 μM for 24 h</p> <p><i>In vivo</i></p> <p>10, 20, and 40 mg/kg b/w for 28 days</p> <p><i>In vitro</i></p> <p>30 μM for 24 h</p> <p><i>In vitro</i></p> <p>5 mM</p> <p><i>In vitro</i></p> <p>25–100 μM for 24 h</p> <p><i>In vivo</i></p> <p>25, 50, and 100 mg/kg b/w for 6 days</p> <p><i>In vitro/in vivo</i></p> <p><i>In vitro</i>: 150 μmol/L for 12, 24, and 48 h</p> <p><i>In vivo</i>: 50 mg/kg b/w for 4 weeks</p> <p><i>In vivo</i></p> <p>10 mg/kg b/w</p> <p><i>In vivo</i></p> <p>100 mg/kg b/w for 14 weeks</p> <p><i>In vivo</i></p> <p>10–50 mg/kg b/w for 10 days</p> <p><i>In vivo</i></p> <p>20 and 40 mg/kg b/w for 10 weeks</p>	<p>Anti-enterovirus 71</p> <p>Hair growth activity</p> <p>Antidiabetic</p> <p>Nephroprotective</p> <p>Anticancer</p> <p>Neuroprotective</p> <p>Antidiabetic</p> <p>Anti-inflammatory</p> <p>Cardioprotective</p> <p>Nephroprotective</p> <p>Anti-collis</p> <p>Anticancer</p> <p>Anticancer</p> <p>Hepatoprotective</p> <p>Hepatoprotective</p> <p>Neuroprotective</p>	<p>Inhibited EV71-induced COX-2 expression and PGE2 production via MAPKs pathway involving ERK, p38, and JNK</p> <p>Topical formononetin treatment induced hair regrowth in the depilated telogenic C57BL/6 mice and restored the length of hair shafts and size of hair follicles</p> <p>Inhibited apoptosis of β-cell of the pancreas and promoted islet β-cell regeneration</p> <p>Promoted proliferation of surviving renal tubular cells and inhibited apoptosis after cisplatin-induced acute kidney injury</p> <p>Significant increase in Bax/Bcl-2 ratio accompanied with elevated level of cleaved-caspase-3 and cleaved-caspase-9 after formononetin treatment</p> <p>Inhibited neuroinflammation in BV2 microglia cells stimulated with LPS and also suppressed production of the proinflammatory cytokines TNF-α, IL-6, and IL-1β from the cells</p> <p>Reduced insulin resistance and attenuated hyperglycemia in type II diabetes, which could be due to increased expression of SIRT1 in pancreatic tissues</p> <p>Inhibited HMGB1 release by decreased HMGB1 acetylation via upregulating SIRT1 in a PPARα-dependent manner</p> <p>Pre-treatment with formononetin reduced myocardial tissue injury, improved cardiac function, and decreased apoptosis in heart tissue</p> <p>Formononetin-treated cells were morphologically normal compared to the cells undergoing cisplatin-induced death and showed potent protective effect against cisplatin-mediated LLC-PK1 cell (renal tubular epithelial cell) death</p> <p>After formononetin administration, there was less infiltration of neutrophils and macrophages in the injured colonic tissue and also a significant decrease in the level of inflammatory cytokines TNF-α and IL-1β in the colon of mice with acute colitis</p> <p>Inhibited MDA-MB-468 cell survival in a dose- and time-dependent manner, and tumor volume shrink from 472.7 to 253.6 mm<sup>3</sup> on day 30 in xenograft model</p> <p>The tumor inhibition rate was 50.17% in the mice treated with formononetin</p> <p>Promoted lysosome biogenesis and autophagosome-lysosome fusion, relieving the blockade in autophagic flux and further induced lipophagy</p> <p>Ameliorated hepatic cholestasis by upregulating expression of SIRT1 and activating PPARα</p> <p>Reduced the levels of inflammation cytokines IL-1β and TNF-α and tau hyperphosphorylation in mice hippocampus</p>	<p>Wang et al. (2015)</p> <p>Kim et al. (2016)</p> <p>Qiu et al. (2017)</p> <p>Huang et al. (2017)</p> <p>Zhang et al. (2018)</p> <p>Et-Bekoush and Olajide (2018)</p> <p>Oza and Kulkarni (2018a)</p> <p>Huang et al. (2018)</p> <p>Huang et al. (2018)</p> <p>Lee et al. (2018)</p> <p>Wu et al. (2018)</p> <p>Zhou et al. (2019)</p> <p>Zhang et al. (2019)</p> <p>Wang et al. (2019)</p> <p>Yang et al. (2019)</p> <p>Fu et al. (2019)</p>	

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**TABLE 2 |** (Continued) Pharmacological activities of phytoconstituents of *Pueraria tuberosa*.

Purified compound studied	Model used for study (in silico/in vitro/in vivo)	Dose tested	Pharmacological activity	Conclusion	References
<p><b>Daidzin [12]</b> (C<sub>21</sub>H<sub>20</sub>O<sub>5</sub>) Daidzin, daidzein and their metabolites, O-desmethylyangolensin (O-DMA) and equol IUPAC name (Daidzin)-[3-(4-hydroxyphenyl)-7-[[[2S,3R,4S,5S,6R]-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy]chromen-4-one]</p>	<p><i>In vivo</i></p> <p>31.25 µg/ml</p>	Anti-inflammatory	LPS-induced inflammation in zebrafish was attenuated by formononetin mainly by restraining the MyD88 or TRIF-MAPK/ERK and MAPK/JNK pathways	Luo et al. (2019)	
<p><b>Isolirone [13]</b> (C<sub>21</sub>H<sub>20</sub>O<sub>5</sub>) IUPAC name-[5-(7-dihydroxy-6-methoxy-3-(4-methoxyphenyl)chromen-4-one)]</p>	<p><i>In vivo</i></p> <p>25 mg/kg b/w for 10 days</p>	Anti-stress	Reduced the neural excitability and the protective upregulation of GABA <sub>A</sub> receptors	Wang et al. (2019)	
	<p><i>In vivo</i></p> <p>10, 20, and 40 mg/kg b/w for 16 weeks</p>	Nephroprotective	Enhanced creatinine clearance and reduced oxidative stress burden along with increased SIRT1 expression in kidney tissues	Oza and Kulkarni (2019)	
<p><b>4-Methoxypuerarin [14]</b> (C<sub>22</sub>H<sub>22</sub>O<sub>5</sub>) IUPAC name-[7-hydroxy-3-(4-methoxyphenyl)-6-[[[2S,3R,4R,5S,6R]-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy]chromen-4-one]</p>	<p><i>In vivo</i></p> <p>10 mg/kg b/w</p>	Anticancer	Inhibited EGFR-Akt axis and promoted FBW7-mediated IκB-1 ubiquitination	Yu et al. (2020)	
	<p><i>In vitro</i></p> <p>5-100 µM</p>	Antioxidant	Stimulated catalase and total superoxide dismutase (CuZn- and Mn-SOD) activity, and mRNA and protein expression	Choi and Kim (2014)	
<p><b>Puerarone [15]</b> (C<sub>20</sub>H<sub>16</sub>O<sub>3</sub>) IUPAC name-[7-hydroxy-3-(7-hydroxy-2,5-dimethylchromen-6-yl)chromen-4-one]</p>	<p><i>In vitro/in vivo</i></p> <p><i>In vitro</i>: 1, 5, and 10 µM for 12 h; <i>In vivo</i>: 50, 100, and 200 mg/kg b/w for 30 days</p>	Anti-ischemia	<i>In vitro</i> , increased cell viability and attenuated apoptosis; <i>In vivo</i> , inhibited mitochondrial membrane potential (MMP) and increased total ATPase activity	Yin et al. (2016)	
	<p><i>In vitro/in vivo</i></p> <p><i>In vitro</i>: 5 or 10 µM for 30 min; <i>In vivo</i>: 20-50 mg/kg for 4 days</p>	Anti-gastric	Pre-treatment with iridodione decreased the area of hemorrhagic ulcerative lesions caused by ethanol and suppressed stomach myeloperoxidase activity, CXCL4 secretion, and NF-κB activation	Kang et al. (2017)	
	<p><i>In vivo</i></p> <p>20 mg/kg b/w</p>	Anti-colic	Alleviated colon shortening and myeloperoxidase activity in mice with TNBS-induced colitis	Jiang et al. (2019)	
<p><i>In silico</i></p> <p>—</p>	—	Weak DNA binding affinity	Glycosylation of 4'-methoxypuerarin, caused steric hindrance to weaken the DNA binding affinity and had no significant inhibition on DNA amplification	Chen et al. (2020)	
<p><i>In silico</i></p> <p>—</p>	—	Antidiabetic	Strong affinity to VEGFR-1 and VEGFR-2 along with 93.881% human intestinal absorption	Shvastava et al. (2017)	

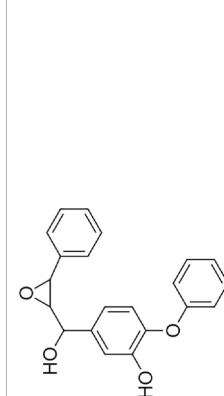
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**TABLE 2 | (Continued) Pharmacological activities of phytoconstituents of *Pueraria tuberosa*.**

Purified compound studied	Model used for study (in silico/in vitro/in vivo)	Dose tested	Pharmacological activity	Conclusion	References
 Quercetin [16] (C <sub>15</sub> H <sub>10</sub> O <sub>7</sub> ) IUPAC name-[3,3',4'-trihydroxyphenyl]-3,5,7-trihydroxychromen-4-one]	<i>In vivo</i> <i>In vitro/in vivo</i> <i>In vivo</i>	15 mg/kg b/w for 7 days <i>In vitro</i> : 5–100 µM; <i>In vivo</i> : 100 mg/kg b/w for 30 days 100 mg/kg b/w for 6 days	Hepatoprotective Neuroprotective Intestinal damage repair	Accelerated the regeneration after partial hepatectomy Protected neuronal cells from amyloid beta induced oxidative stress Increased intestinal and mucosal weight and prevented methotrexate-induced intestinal damage	Kanter et al. (2016) Li et al. (2017) Sukhotnik et al. (2018)
 Tectoridin [17] (C <sub>27</sub> H <sub>32</sub> O <sub>11</sub> ) IUPAC name-[5-hydroxy-3-(4-hydroxyphenyl)-6-methoxy-7-(β-D-3',4',5'-trihydroxy-6-(hydroxymethyl)oxan-2-yl)]oxychromen-4-one]	<i>In vivo</i>	25–400 mg/kg b/w	Anti-alcoholism	Strongest clearance rate of ethanol	Zhang et al. (2019)
 p-coumaric acid [18] (C <sub>9</sub> H <sub>8</sub> O <sub>3</sub> ) IUPAC name-[E]-3-(4-hydroxyphenyl)prop-2-enoic acid]	<i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i> <i>In vivo</i>	100 mg/kg b/w for 7 days 8 mg/kg b/w for 7 days 100 mg/kg b/w for 3 weeks 100 mg/kg b/w 30 mg/kg b/w 100 mg/kg b/w for 26 days 50 mg/kg b/w 100 mg/kg b/w for 2 weeks <i>In vitro</i> : 0–1,000 µmol/L for 24 and 72 h; <i>In vivo</i> : 100 mg/kg b/w for 30 weeks 50 and 100 µmol/L 50 mg/kg b/w for 6 weeks <i>In vitro</i> : 10–100 µM; <i>In vivo</i> : 50, 100, and 200 mg/kg b/w	Immunomodulatory Cardioprotective Nephroprotective Antidiabetic Neuroprotective Anti-arthritis Hepatoprotective Neuroprotective Anticancer Antioxidant Antidiabetic Hepatoprotective	Decreased the expression of inflammatory mediator TNF-α and circulating immune complexes Prevented cardiac hypertrophy, by virtue of its antihypertrophic, antidiabetic, and free radical scavenging Cadmium metal chelating activity Modulated glucose and lipid metabolism via GLUT2 activation in the pancreas Increased the total activity of IEP-SP, dose-dependently after high frequency stimulation and attenuated scopolamine-induced blockades of EP-SP in the hippocampal CA1 long-term potentiation area Suppressed the paw edema, body weight loss and inflammatory cytokines and chemokine levels (TNF-α, IL-1β, IL-6, and MCP-1) in serum and ankle joint of arthritic rats Suppressed hepatic apoptosis via ROS-mediated DNA damage and inflammation by modulating the mitogen-activated protein kinase (MAPK) signaling axis in an ROS-dependent manner Pretreatment with p-coumaric acid significantly reduced malondialdehyde (MDA) levels, whole-brain infarction volume, and hippocampal neuronal death together and increased catalase and superoxide dismutase activities Downregulated Grr7/8 and activated LPR mediated apoptosis both in <i>in vitro</i> and <i>in vivo</i> models of colon cancer Significantly increased the survival rate of <i>Caenorhabditis elegans</i> under the oxidative stress condition and also increased lifespan by 20% for both 50 and 100 µmol/L compared to the control Enhanced anti-inflammatory, anti-osteoclastogenic, and antioxidant defense systems in streptozotocin-treated mice No effect on cell viability up to 60–80 µM concentrations on HepG2 cells <i>In vitro</i> , p-coumaric acid at 200 mg/kg exhibited higher protection on ethanol-induced hepatic injury in rats	Pragasam et al. (2013) Roy and Prince (2013) Navaneethan and Rasooli (2014) Analan et al. (2016) Kim et al. (2017) Neogi et al. (2017) Cha et al. (2018) Sakamula and Thong-isa (2018) Sharma et al. (2018) Yue et al. (2019) Bhattarai et al. (2019) Sabitha et al. (2020)

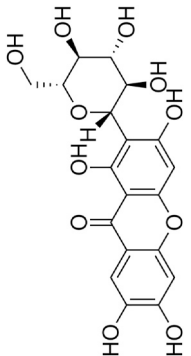
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**TABLE 2 |** (Continued) Pharmacological activities of phytoconstituents of *Pueraria tuberosa*.

Purified compound studied	Model used for study (in silico/in vitro/in vivo)	Dose tested	Pharmacological activity	Conclusion	References
 <p>Hydroxytuberone [19] (C<sub>20</sub>H<sub>26</sub>O<sub>4</sub>) IUPAC name: 1,14-dihydroxy-7,7-dimethyl-8,12,20-trioxapentacyclo [11,5,0,0<sup>2,11</sup>,0<sup>4,9</sup>,0<sup>4,13</sup>]pericosane-2-(11),3,5,9,15,18-hexaoxa-17-one</p>	In vivo	Topical application	Wound healing	Excision and incision wound model	Kamboja and Murthy (2007)
Pharmacological activity not reported					
 <p>Puerarosan [20] (C<sub>27</sub>H<sub>46</sub>O<sub>4</sub>) IUPAC name: [5-[[hydroxy-(3-phenyloxan-2-yl)methyl]-2-phenoxyphenyl]]</p>	In vivo	50 mg/kg b/w for 10 days	Cardioprotective	Modulation of TGF-β1 signaling pathway in doxorubicin-induced cardiac toxicity in Sprague Dawley rats	Janeesh and Abraham (2014)
	In vitro	6 µg/ml	Immunomodulatory	Inhibited TLR4-NF-κB signaling pathway	Janeesh et al. (2014)
	In vitro	0.125–0.50 mg/ml	Antioxidant	The total antioxidant capacity (TAC) in robbinin was significantly higher and best maintained the follicular morphology	Dos Santos Morais et al. (2019)
 <p>Robbinin [21] (C<sub>33</sub>H<sub>46</sub>O<sub>13</sub>) IUPAC name: [5-[[hydroxy-2-(4-hydroxyphenyl)-7-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxy-3-[(2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxy-methyl]oxan-2-yl]oxychromen-4-one]]</p>	In silico	–	Antidiabetic	In molecular docking study, tuberostan showed best interaction for GLP-1R with binding energy at 8.15 kcal/mol and dissociation constant at 1061624.125 pM	Shivastava et al. (2018)
 <p>Tuberostan [22] (C<sub>21</sub>H<sub>26</sub>O<sub>4</sub>) IUPAC name: [17-methoxy-7,7-dimethyl-8,12,20-trioxapentacyclo [11,5,0,0<sup>2,11</sup>,0<sup>4,9</sup>,0<sup>4,13</sup>]pericosane-1(13),2(11),3,5,9,14(19),15,17-octaan-21-one]</p>					

(Continued on following page)

**TABLE 2 |** (Continued) Pharmacological activities of phytoconstituents of *Pueraria tuberosa*.

Purified compound studied	Model used for study (in silico/in vitro/in vivo)	Dose tested	Pharmacological activity	Conclusion	References
 Isoorientin <b>[23]</b> (C <sub>27</sub> H <sub>30</sub> O <sub>11</sub> ) IUPAC name-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one]	In vitro In vitro/in vivo	0.1–100 μM In vitro: 25 nM and 100 μM for 16 hours; In vivo: 10 mg/kg and 20 mg/kg b/w for 24 h	Anti-inflammatory Anti-inflammatory	Inhibited COX-2 activity by 64% Inhibited the expression of COX-2 <i>in vitro</i> and decreased the expression of COX-2, TNF-α, IL-1β, iNOS, and 5-LXO in dose-dependent manner in carrageenan-induced inflammation in mice	Sumalatha et al. (2019) Anilkumar et al. (2017)
 Mangiferin <b>[24]</b> (C <sub>26</sub> H <sub>32</sub> O <sub>11</sub> ) IUPAC name-[1,3,6,7-tetrahydroxy-2-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]benzofuran-9-one]	In vitro In vitro/in vivo	100 μM In vitro: 20 and 40 μM for 16 h; in vivo: 10 mg/kg and 20 mg/kg b/w for 24 h	Anti-inflammatory Anti-inflammatory	Inhibited COX-1 and COX-2 activity by 79.4% and 45.9%, respectively Reduced expression of inflammatory mediator (COX-2, iNOS, and TNF-α) and increased anti-inflammatory cytokine (IL-10) and increased size of blood vessels were significantly reduced, and cell infiltration was less compared to mice treated with carrageenan alone	Sumalatha et al. (2019) Bulugonda et al. (2017)
 Stigmaastero <b>[25]</b> (C <sub>29</sub> H <sub>46</sub> O) IUPAC name-[3S,8S,9S,10R,13R,14S,17R]-17-(E)-2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta [a]phenanthren-3-ol]	In vivo	200 mg/kg and 400 mg/kg b/w	Chemo-preventive	Induced a significant decrease in 7,12-dimethylbenz[ <i>a</i> ]anthracene (DMBA)-induced skin tumor	Ali et al. (2015)

b/w: body weight.

parameters in the drug-induced myelosuppression model (Babu et al., 2016). Crude powder (3 g daily) of *P. tuberosa* tuber was given to a human patient with ischemic heart disease for twelve months. The case study demonstrated an overall significant cardioprotective effect; resting mean blood pressure was reduced from 96.66 to 90.00 mm Hg without affecting the resting heart rate, and the heart rate at peak exercise was also reduced, indicating better exercise tolerance (Verma et al., 2009).

*P. tuberosa* root extract, given to male Wistar rats (100 mg/rat per day) for 60 days, affected the fertility of rats as shown by a reduction in weight of testes, epididymis, prostate, and the seminal vesicle. Studies also showed a considerable decrease in the quantity of mature Leydig cells, cauda epididymis, and sperm motility (Gupta et al., 2005). The antioxidant-enriched fraction from the tuber extract of *P. tuberosa* against menopausal osteoporosis in ovariectomy-induced osteoporosis in rats was studied and found that it improved biochemical parameters, controlled the increased body weight, and decreased uterus weight following ovariectomy as well as restoration of typical bone structure and trabecular width of the femur (Satpathy et al., 2020). Incision and excision wounds were treated with methanolic and ethyl acetate tuber extract of *P. tuberosa*. The extracts showed potent wound healing property in comparison to the control and the group of rats treated with standard drugs, ibuprofen, and nitrofurazone ointment (Kambhoja and Murthy, 2007).

## Phytochemistry

The crude tuber extracts of *P. tuberosa* are known to contain alkaloids, anthracene, anthocyanidins, anthraquinone, glycosides, carbohydrates, catecholic compounds, coumarins, flavonoids, glycosides, hexose sugars, saponins, steroids, terpenoids, and volatile oils (Ratnam and Venkata Raju, 2009; Rawtal et al., 2019). Therefore, many studies have been undertaken to individually analyze and characterize the activities of different phytoconstituents of the plant. Vaishnav et al. could grow a callus culture of *P. tuberosa* and identified four isoflavonoids, viz., puerarin [1], daidzein [2], genistin [3], and genistein [4] (Vaishnav et al., 2006; Satpathy et al., 2017). Lupinose PA4 [5] was isolated from methanolic extract of *P. tuberosa* using HPLC, and its structure was determined by 1D, 2D NMR, and Q-TOF-MS (Dey et al., 2007). Pandey and Tripathi extracted tuberosin [6], 3-O-methylanhydrotuberosin [7], and puerarostan [8] from ethanolic tuber extract; the same was confirmed by UV, IR, and NMR spectral data (Pandey and Tripathi, 2010).  $\beta$ -Sitosterol [9] was quantified in the methanolic root extract of *P. tuberosa* by high-performance thin layer chromatography (HPTLC) method (Mhaske et al., 2009). Liquid chromatography–mass spectrometry (LC–MS) analysis of ethanolic extract was found to contain puerarin, daidzein, biochanin A [10], and biochanin B [11] (formononetin) (Chauhan et al., 2013). Daidzin [12], irisolidone [13], 4-methoxypuerarin [14], puerarone [15], quercetin [16], and tectoridin [17] are the flavonoid compounds and p-coumaric acid [18], which have been reported to be isolated from tuber of *P. tuberosa* (Maji et al., 2014) and aqueous tuber decoction shown to contain daidzein,

genistin, hydroxytuberosone [19], puerarin, puetuberosanol [20], robinin [21], tuberosin, and tuberosin [22] (Shukla et al., 2017). Mass spectrometry and 2D-NMR techniques were used to isolate isoorientin [23] and mangiferin [24] from methanolic extract from *P. tuberosa* (Sumalatha et al., 2015). Phytochemical analysis of *P. tuberosa* extract using HPTLC revealed the presence of carbohydrates, proteins, alkaloids, flavonoids, saponins, phenols, and tannins (Viji and Paulsamy, 2018). Satpathy et al. showed the presence of 23 bioactive molecules including stigmasterol [25],  $\beta$ -sitosterol, and stigmasta-3,5-dien-7-one by gas chromatography–mass spectrometry analysis of antioxidant-enriched fraction prepared from *P. tuberosa* (Satpathy et al., 2020). We have listed various phytoconstituents isolated from *P. tuberosa* and provided detailed information about their chemical structures, IUPAC names, and pharmacological activities, as well as associated references, in **Table 2**. The chemical structures of phytochemical compounds from *P. tuberosa* were drawn using “ChemDraw JS 19.0”; <https://chemdrawdirect.perkinelmer.cloud/js>. IUPAC (International Union of Pure and Applied Chemistry) names have been taken from PubChem database.

## Toxicology of *Pueraria tuberosa*

The acute (single dose of 2,000 and 5,000 mg/kg body weight) and repeated dose (250, 500, 1,000, and 2,000 mg/kg body weight for 28 days) toxicity studies with water extract of the tuber of *P. tuberosa* were conducted in rats as per OECD (Organization for Economic Co-Operation and Development) guidelines. The survival rate and biochemical and histological changes were studied. No adverse effect was reported in single-dose acute toxicity, but in repeated dose toxicity studies, 100% mortality was observed on day 21 at 2,000 mg/kg body weight, and histological examination of the visceral organs showed that this mortality could be due to hepatotoxicity (Pandey et al., 2018). However, histological evaluation of different organs using hematoxylin and eosin staining did not observe any morphological alterations in the spleen, adrenal glands, and heart. The size and shapes in crypts and villi of the intestine and seminiferous tubules were intact with normal spermatozoa count in testis (Pandey et al., 2019). In another experiment on acute toxicity study of poly-herbal formulation (containing *P. tuberosa*), “Dhatryadi Ghrita” methanolic extract did not show any untoward effects in mice (Pal and Mishra, 2019).

## CONCLUSION AND FUTURE DIRECTIONS

The scientific community worldwide has shown an interest in discovering the disease combating potential of natural flora and bioactive compounds therein. A wide pool of literature suggests that these phytochemicals hold the immense potential of eliminating diseases, and many such plant-based drugs have long been used in many parts of the world. Markedly, the tuber and leaf of *P. tuberosa* plant have been used from ancient times in the traditional practices. Previous literature has shown that leaf and tuber extracts of the plant contain several bioactive

constituents that possess an extensive range of pharmacological activities. Some of the isolated compounds, namely, puerarin, irisolidone, genistein, daidzein, biochanin A, biochanin B, isoorientin, and mangiferin, have been studied for various medicinal purposes and demonstrated several pharmacological activities like anticancerous, antidiabetic, anti-inflammatory, antioxidant, antiviral, cardioprotective, fibrinolytic, hepatoprotective, hypolipidemic, immunomodulatory, neuroprotective, nephroprotective, nootropic, vasodilatory, and wound healing. The bioactive constituents of *P. tuberosa* can individually or synergistically exert their therapeutic effects. Apart from puerarin, daidzein, genistein, irisolidone, and biochanin, many more compounds have been identified from *P. tuberosa*; however, underlying mechanisms of action of compounds isolated from this plant are not completely known. Thus, exploration of pharmacological mechanisms of individual bioactive constituents and their toxicity/clinical studies shall be the focus of future investigations. The extensive range of pharmacological properties of *P. tuberosa* could provide us a new interesting path for future research and may present new perspectives for the disease management.

## REFERENCES

- Adedapo, A. A., Fagbohun, O. A., Dawurung, C., Oyagbemi, A. A., Omobowale, T. O., and Yakubu, M. A. (2017). The aqueous tuber extract of *Pueraria tuberosa* (Willd.) D.C. caused cytotoxic effect on HT 29 cell lines with down regulation of nuclear factor-kappa B (NF- $\kappa$ B). *J. Compl. Integr. Med.* 16 (4), 1–8. doi:10.1515/jcim-2016-0119
- Ali, H., Dixit, S., Ali, D., Alqahtani, S. M., Alkahtani, S., and Alarifi, S. (2015). Isolation and evaluation of anticancer efficacy of stigmasterol in a mouse model of DMBA-induced skin carcinoma. *Drug Des. Dev. Ther.* 9, 2793–2800. doi:10.2147/DDDT.S83514
- Amalan, V., Vijayakumar, N., Indumathi, D., and Ramakrishnan, A. (2016). Antidiabetic and antihyperlipidemic activity of p-coumaric acid in diabetic rats, role of pancreatic GLUT 2: in vivo approach. *Biomed. Pharmacother.* 84, 230–236. doi:10.1016/j.biopha.2016.09.039
- Anilkumar, K., Reddy, G. V., Azad, R., Sastry Yarla, N., Dharmapuri, G., Srivastava, A., et al. (2017). Evaluation of anti-inflammatory properties of isoorientin isolated from tubers of *pueraria tuberosa*. *Oxid. Med. Cell. Longev.* 2017, 1–7. doi:10.1155/2017/5498054
- Aruna, M. R., Kumar, D. J. M., Senbagam, D., and Senthilkumar, B. (2016). Investigation on phytochemical and antimicrobial properties of tuber extracts of *pueraria tuberosa* linn. *J. Pure Appl. Microb.* 10 (2), 1573–1578.
- Aruna, M. R., Mukesh Kumar, D. J., Palani, P., Senbagam, D., and Senthilkumar, B. (2018). Effects of *pueraria tuberosa* linn hydroalcoholic tuber extract on expression of apoptosis associated proteins in HT-29 human colon carcinoma cell line. *Int. J. Curr. Microbiol. Appl. Sci.* 7 (6), 3863–3873. doi:10.20546/ijcmas.2018.706.455
- Ayurvedic pharmacopoeia of India (1999). *Ayurvedic pharmacopoeia of India*. Part-1, 2. New Delhi, India: Ministry of Health and Family Planning, Department of Health, Government of India, 1–190.
- Ayurvedic pharmacopoeia of India (2001). *Ayurvedic pharmacopoeia of India Part-1, 2*. New Delhi, India: Ministry of Health and Family Planning, Department of Health, Government of India, 183–184.
- Babu, P. V., Bandi, S., Raju, M., and Tiwari, V. K. (2016). Antioxidant and immunosuppressant activity of *pueraria tuberosa*. *IJPPR.* 8 (1), 23–34.
- Bagheri, M., Joghataei, M. T., Mohseni, S., and Roghani, M. (2011). Genistein ameliorates learning and memory deficits in amyloid  $\beta$ (1-40) rat model of

## AUTHOR CONTRIBUTIONS

RB was responsible for the methodology, writing the original draft, and data curation. BC and SR were responsible for data curation and reviewing and editing the manuscript. NK was responsible for conceptualization, data curation, writing, reviewing, and editing the manuscript.

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Alzheimer's disease. *Neurobiol. Learn. Mem.* 95 (3), 270–276. doi:10.1016/j.nlm.2010.12.001

- Basavaraj, P., Shivakumar, B., and Shivakumar, H. (2011). Evaluation of anticonvulsant activity of alcoholic extract of tubers of *Pueraria tuberosa* (Roxb). *Adv. in Pharm. and Toxicol.* 12 (1), 1–9.
- Berköz, M., Krośniak, M., Özkan-Yılmaz, F., and Özlüer-Hunt, A. (2020). Prophylactic effect of Biochanin A in lipopolysaccharide-stimulated BV2 microglial cells. *Immunopharmacol. Immunotoxicol.* 1. doi:10.1080/08923973.2020.1769128
- Bhattarai, G., Min, C. K., Jeon, Y. M., Bashyal, R., Poudel, S. B., Kook, S. H., et al. (2019). Oral supplementation with p-coumaric acid protects mice against diabetes-associated spontaneous destruction of periodontal tissue. *J. Periodontol. Res.* 54 (6), 690–701. doi:10.1111/jre.12678
- Bulugonda, R. K., Kumar, K. A., Gangappa, D., Beeda, H., Philip, G. H., Muralidhara Rao, D., et al. (2017). Mangiferin from *Pueraria tuberosa* reduces inflammation via inactivation of NLRP3 inflammasome. *Sci. Rep.* 7, 42683–42714. doi:10.1038/srep42683
- Cha, H., Lee, S., Lee, J. H., and Park, J. W. (2018). Protective effects of p-coumaric acid against acetaminophen-induced hepatotoxicity in mice. *Food Chem. Toxicol.* 121, 131–139. doi:10.1016/j.fct.2018.08.060
- Chauhan, N. S., Sharma, V., Thakur, M., Christine Helena Frankland Sawaya, A., and Dixit, V. K. (2013). *Pueraria tuberosa* DC extract improves androgenesis and sexual behavior via FSH LH cascade. *Sci. World J.* 2013, 1–10. doi:10.1155/2013/780659
- Chen, X., He, Z., Wu, X., Mao, D., Feng, C., Zhang, J., et al. (2020). Comprehensive study of the interaction between *Puerariae Radix* flavonoids and DNA: from theoretical simulation to structural analysis to functional analysis. *Spectrochim. Acta Mol. Biomol. Spectrosc.* 231. doi:10.1016/j.saa.2020.118109
- Choi, E. J., and Kim, G. H. (2014). The antioxidant activity of daidzein metabolites, O-desmethylangolensin and equol, in HepG2 cells. *Mol. Med. Rep.* 9 (1), 328–332. doi:10.3892/mmr.2013.1752
- Choi, E. M., Suh, K. S., Park, S. Y., Chin, S. O., Rhee, S. Y., and Chon, S. (2019). Biochanin A prevents 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced adipocyte dysfunction in cultured 3T3-L1 cells. *J. Environ. Sci. Heal.* 54 (9), 865–873. doi:10.1080/10934529.2019.1603746
- Choi, Y. R., Shim, J., and Kim, M. J. (2020). Genistin: a novel potent anti-adipogenic and anti-lipogenic agent. *Molecules* 25 (9). doi:10.3390/molecules25092042



- Croom, E. M. (2004). *Pueraria*. The Genus *pueraria*. *Econ. Bot.* 58 (3), 490. doi:10.1663/0013-0001(2004)058[0490:dfabre]2.0.co;2
- Dalal, P. K., Tripathi, A., and Gupta, S. K. (2013). Vajikarana: treatment of sexual dysfunctions based on Indian concepts. *Indian J. Psych.* 55, S273. doi:10.4103/0019-5545.105550
- De Luca, V., Salim, V., Atsumi, S. M., and Yu, F. (2012). Mining the biodiversity of plants: a revolution in the making. *Science* 336 (6089), 1658–1661. doi:10.1126/science.1217410
- Dey, D., Pal, B. C., Biswas, T., Roy, S. S., Bandyopadhyay, A., Mandal, S. K., et al. (2007). A lupinoid prevented fatty acid induced inhibition of insulin sensitivity in 3T3 L1 adipocytes. *Mol. Cell. Biochem.* 300 (1–2), 149–157. doi:10.1007/s11010-006-9378-1
- Dos Santos Morais, M. L. G., de Brito, D. C. C., Pinto, Y., Mascena Silva, L., Montano Vizcarra, D., Silva, R. F., et al. (2019). Natural antioxidants in the vitrification solution improve the ovine ovarian tissue preservation. *Reprod. Biol.* 19 (3), 270–278. doi:10.1016/j.repbio.2019.07.008
- El-Bakoush, A., and Olajide, O. A. (2018). Formononetin inhibits neuroinflammation and increases estrogen receptor beta (ER $\beta$ ) protein expression in BV2 microglia. *Int. Immunopharm.* 61, 325–337. doi:10.1016/j.intimp.2018.06.016
- Elmarakby, A. A., Ibrahim, A. S., Faulkner, J., Mozaffari, M. S., Liou, G. I., and Abdelsayed, R. (2011). Tyrosine kinase inhibitor, genistein, reduces renal inflammation and injury in streptozotocin-induced diabetic mice. *Vasc. Pharmacol.* 55 (5–6), 149–156. doi:10.1016/j.vph.2011.07.007
- Fu, X., Qin, T., Yu, J., Jiao, J., Ma, Z., Fu, Q., et al. (2019). Formononetin ameliorates cognitive disorder via PGC-1 $\alpha$  pathway in neuroinflammation conditions in high-fat diet-induced mice. *CNS Neurol. Disord. - Drug Targets* 18 (7), 566–577. doi:10.2174/1871527318666190807160137
- Gindi, S., Awen, B. Z., Baburao, C., and Khagga, M. (2010). Anti ulcerogenic & ulcer healing studies of aqueous extract of *Pueraria tuberosa* leaves on rats. *Int. J. Pharma Bio Sci.* 1 (4), 651–661.
- Gu, M., Zheng, A. B., Jin, J., Cui, Y., Zhang, N., Che, Z. P., et al. (2016). Cardioprotective effects of genistin in rat myocardial ischemia-reperfusion injury studies by regulation of P2X7/NF- $\kappa$ B pathway. *Evid. Based Complement Alternat. Med.* 2016, 5381290. doi:10.1155/2016/5381290
- Guo, C. J., Xie, J. J., Hong, R. H., Pan, H. S., Zhang, F. G., and Liang, Y. M. (2019). Puerarin alleviates streptozotocin (STZ)-induced osteoporosis in rats through suppressing inflammation and apoptosis via HDAC1/HDAC3 signaling. *Biomed. Pharmacother.* 115, 108570. doi:10.1016/j.biopha.2019.01.031
- Gupta, R. S., Sharma, R., Sharma, A., Choudhary, R., Bhatnager, A. K., Joshi, Y. C., et al. (2005). Antifertility effects of *Pueraria tuberosa*. Root extract in male rats. *Pharmaceut. Biol.* 42 (8), 603–609. doi:10.1080/13880200490902491
- Han, N. R., Kim, H. M., and Jeong, H. J. (2015). The potential anti-proliferative effect of  $\beta$ -sitosterol on human mast cell line-1 cells. *Can. J. Physiol. Pharmacol.* 93 (11), 979–983. doi:10.1139/cjpp-2015-0166
- He, Y., Wu, X., Cao, Y., Hou, Y., Chen, H., Wu, L., et al. (2016). Daidzein exerts anti-tumor activity against bladder cancer cells via inhibition of FGFR3 pathway. *Neoplasma.* 63 (4), 523–531. doi:10.4149/neo\_2016\_405
- Heinrich, M., Appendino, G., Efferth, T., Fürst, R., Izzo, A. A., Kayser, O., et al. (2020). Best practice in research - overcoming common challenges in phytopharmacological research. *J. Ethnopharmacol.* 246, 112230. doi:10.1016/j.jep.2019.112230
- Hua, F., Li, C. H., Chen, X. G., and Liu, X. P. (2018). Daidzein exerts anticancer activity towards SKOV3 human ovarian cancer cells by inducing apoptosis and cell cycle arrest, and inhibiting the Raf/MEK/ERK cascade. *Int. J. Mol. Med.* 41 (6), 3485–3492. doi:10.3892/ijmm.2018.3531
- Huang, D., Wang, C., Duan, Y., Meng, Q., Liu, Z., Huo, X., et al. (2017). Targeting Oct2 and P53: formononetin prevents cisplatin-induced acute kidney injury. *Toxicol. Appl. Pharmacol.* N. 326, 15–24. doi:10.1016/j.taap.2017.04.013
- Huang, Z., Liu, Y., and Huang, X. (2018). Formononetin may protect aged hearts from ischemia/reperfusion damage by enhancing autophagic degradation. *Mol. Med. Rep.* 18 (6), 4821–4830. doi:10.3892/mmr.2018.9544
- Hwang, J. S., Kang, E. S., Han, S. G., Lim, D. S., Paek, K. S., Lee, C. H., et al. (2018). Formononetin inhibits lipopolysaccharide-induced release of high mobility group box 1 by upregulating SIRT1 in a PPAR $\delta$ -dependent manner. *Peer J.* 6 (1), e4208. doi:10.7717/peerj.4208
- Indian Medicinal Plant Database Foundation for Revitalisation of Local Health Traditions (FRLHT). Available at: [http://www.medicinalplants.in/searchpage/showdetails/xplant\\_id/5e61a3ccb898ce34f62ec050b012b2f2/keywords/vidari/languages/HI](http://www.medicinalplants.in/searchpage/showdetails/xplant_id/5e61a3ccb898ce34f62ec050b012b2f2/keywords/vidari/languages/HI).
- Janeesh, P. A., and Abraham, A. (2014). Robinin modulates doxorubicin-induced cardiac apoptosis by TGF- $\beta$ 1 signaling pathway in Sprague Dawley rats. *Biomed. Pharmacother.* 68 (8), 989–998. doi:10.1016/j.biopha.2014.09.010
- Janeesh, P. A., Sasikala, V., Dhanya, C. R., and Abraham, A. (2014). Robinin modulates TLR/NF- $\kappa$ B signaling pathway in oxidized LDL induced human peripheral blood mononuclear cells. *Int. Immunopharm.* 18 (1), 191–197. doi:10.1016/j.intimp.2013.11.023
- Jang, H. M., Park, K. T., Noh, H. D., Lee, S. H., and Kim, D. H. (2019). Kakkalide and irisolidone alleviate 2,4,6-trinitrobenzenesulfonic acid-induced colitis in mice by inhibiting lipopolysaccharide binding to toll-like receptor-4 and proteobacteria population. *Int. Immunopharm.* 73, 246–253. doi:10.1016/j.intimp.2019.05.008
- Jiang, K., Chen, H., Tang, K., Guan, W., Zhou, H., Guo, X., et al. (2018). Puerarin inhibits bladder cancer cell proliferation through the mTOR/p70S6K signaling pathway. *Oncol Lett.* 15 (1), 167–174. doi:10.3892/ol.2017.7298
- Kambhoja, S., and Murthy, K. R. K. (2007). Wound healing and anti-inflammatory activity of *Pueraria tuberosa* (Roxb Ex wild) DC. *Biomed.* 2 (2), 229–232.
- Kang, G. D., Lee, S. Y., Jang, S. E., Han, M. J., and Kim, D. H. (2017). Irisolidone attenuates ethanol-induced gastric injury in mice by inhibiting the infiltration of neutrophils. *Mol. Nutr. Food Res.* 61 (2). doi:10.1002/mnfr.201600517
- Kanter, M., Tuncer, I., Erboga, M., Atanassova, P., Takir, M., and Kostek, O. (2016). The effects of quercetin on liver regeneration after liver resection in rats. *Folia Morphol.* 75 (2), 179–187. doi:10.5603/FM.a2015.0086
- Keung, W. M. (2002). *Pueraria. The Genus pueraria*. Boca Raton, FL: CRC Press. doi:10.1201/9780203300978
- Kim, H. B., Lee, S., Hwang, E. S., Maeng, S., and Park, J. H. (2017). p-Coumaric acid enhances long-term potentiation and recovers scopolamine-induced learning and memory impairments. *Biochem. Biophys. Res. Commun.* 492 (3), 493–499. doi:10.1016/j.bbrc.2017.08.068
- Kim, K. A., Lee, I. A., Gu, W., Hyam, S. R., and Kim, D. H. (2014).  $\beta$ -Sitosterol attenuates high-fat diet-induced intestinal inflammation in mice by inhibiting the binding of lipopolysaccharide to toll-like receptor 4 in the NF- $\kappa$ B pathway. *Mol. Nutr. Food Res.* 58 (5), 963–972. doi:10.1002/mnfr.201300433
- Kim, M., Choi, Y., Lee, J., Kim, K., and Yang, W. M. (2016). Topical treatment of hair loss with formononetin by modulating apoptosis. *Planta Med.* 82 (1–2), 65–69. doi:10.1055/s-0035-1557897
- Kirtikar, K. R., and Basu, B. D. (1935). *Indian medicinal plants*. Allahabad, India: Allahabad Lalit Mohan Basu.
- Kumar, P. G. (2016). Wild edible plants of Hassan District, Karnataka: a role in ayurvedic formulation. *Int. J. Herb. Med.* 4 (1), 16–24.
- Kumawat, R. B., Sharma, R. A., Mali, P. C., and Chandrawat, P. (2017). Ethnopharmacological screening of some selected medicinal plants. *Res. J. Recent Sci.* 6 (5), 32–41.
- Lee, H., Lee, D., Kang, K. S., Song, J. H., and Choi, Y. K. (2018). Inhibition of intracellular ROS accumulation by formononetin attenuates cisplatin-mediated apoptosis in LLC-PK1 cells. *Int. J. Mol. Sci.* 19 (3). doi:10.3390/ijms19030813
- legumes Available at: [http://www.legumes-online.net/ildis/aweb/td076/td\\_16078.htm](http://www.legumes-online.net/ildis/aweb/td076/td_16078.htm) (Accessed July 7, 2020).
- Li, S.-C. (2003). *Chinese medical herbs: a modern edition of a classic sixteenth-century manual*. Mineola, NY: Dover Publications Inc.
- Li, X., Zhu, Q., Zheng, R., Yan, J., Wei, M., Fan, Y., et al. (2020). Puerarin attenuates diabetic nephropathy by promoting autophagy in podocytes. *Front. Physiol.* 11. doi:10.3389/fphys.2020.00073
- Li, Y. L., Guo, H., Zhao, Y. Q., Li, A. F., Ren, Y. Q., and Zhang, J. W. (2017). Quercetin protects neuronal cells from oxidative stress and cognitive degradation induced by amyloid  $\beta$ -peptide treatment. *Mol. Med. Rep.* 16 (2), 1573–1577. doi:10.3892/mmr.2017.6704
- Likhitkar, M., and Pande, M. (2017). Antioxidant activity of methanolic and ethanolic extracts of *Pueraria tuberosa* plant. *Int J Ind Herbs Drugs* 2 (1), 1–5.
- Liu, D., Zhen, W., Yang, Z., Carter, J. D., Si, H., and Reynolds, K. A. (2006). Genistein acutely stimulates insulin secretion in pancreatic beta-cells through a cAMP-dependent protein kinase pathway. *Diabetes* 55 (4), 1043–1050. doi:10.2337/diabetes.55.04.06.db05-1089
- Liu, X., Zhao, W., Wang, W., Lin, S., and Yang, L. (2017). Puerarin suppresses LPS-induced breast cancer cell migration, invasion and adhesion by blockage NF- $\kappa$ B

- and Erk pathway. *Biomed. Pharmacother.* 92, 429–436. doi:10.1016/j.biopha.2017.05.102
- Luo, L., Zhou, J., Zhao, H., Fan, M., and Gao, W. (2019). The anti-inflammatory effects of formononetin and ononin on lipopolysaccharide-induced zebrafish models based on lipidomics and targeted transcriptomics. *Metabolomics* 15 (12), 153. doi:10.1007/s11306-019-1614-2
- Maji, A. K., Pandit, S., Banerji, P., and Banerjee, D. (2014). *Natural product research.*, 28. Abingdon, UK: Taylor & Francis, 2111–2127. doi:10.1080/14786419.2014.928291
- Maji, A. K., Mahapatra, S., and Banerjee, D. (2014). *In-vivo* immunomodulatory potential of standardized pueraria tuberosa extract and its isoflavonoids. *Int. J. Pharm. Pharmacol. Sci.* 6 (1), 861–867.
- Mhaske, H. P., Vaidya, V. V., Kekare, M. B., Champanerkar, P. A., and Parekh, S. A. (2009). Quantification of  $\beta$ -sitosterol and puerarin from *Pueraria tuberosa* DC. by using high performance thin layer chromatography. *Asian J. Chem.* 21 (5), 3449–3454.
- Migkos, T., Pourová, J., Vopršalová, M., Auger, C., Schini-Kerth, V., and Mladěnka, P. (2020). Biochanin A, the most potent of 16 isoflavones, induces relaxation of the coronary artery through the calcium channel and cGMP-dependent pathway. *Planta Med.* 86 (10), 708–716. doi:10.1055/a-1158-9422
- Nagwani, S., and Tripathi, Y. B. (2010). Amelioration of cisplatin induced nephrotoxicity by PTY: a herbal preparation. *Food Chem. Toxicol.* 48 (8–9), 2253–2258. doi:10.1016/j.fct.2010.05.057
- National Medicinal Plants Board, Government of India Retrieved from <https://www.nmpb.nic.in/about-us> July 7, 2020).
- Navaneethan, D., and Rasool, M. (2014). p-Coumaric acid, a common dietary polyphenol, protects cadmium chloride-induced nephrotoxicity in rats. *Ren. Fail.* 36 (2), 244–251. doi:10.3109/0886022X.2013.835268
- Neog, M. K., Joshua Pragasam, S., Krishnan, M., and Rasool, M. (2017). p-Coumaric acid, a dietary polyphenol ameliorates inflammation and cartilages erosion in the rheumatoid arthritis rat model. *Biofactors* 43 (5), 698–717. doi:10.1002/biof.1377
- Oza, M. J., and Kulkarni, Y. A. (2018b). Biochanin A improves insulin sensitivity and controls hyperglycemia in type 2 diabetes. *Biomed. Pharmacother.* 107, 1119–1127. doi:10.1016/j.biopha.2018.08.073
- Oza, M. J., and Kulkarni, Y. A. (2019). Formononetin attenuates kidney damage in type 2 diabetic rats. *Life Sci.* 219, 109–121. doi:10.1016/j.lfs.2019.01.013
- Oza, M. J., and Kulkarni, Y. A. (2018a). Formononetin treatment in type 2 diabetic rats reduces insulin resistance and hyperglycemia. *Front. Pharmacol.* 9, 73. doi:10.3389/fphar.2018.00739
- Pal, R. S., and Mishra, A. (2019). Evaluation of acute toxicity of the methanolic extract of dhatryadi ghrita in wistar rats. *Open Pharmacol. J.* 9 (1), 1–4. doi:10.2174/1874143601909010001
- Palanisamy, N., and Venkataraman, A. C. (2013). Beneficial effect of genistein on lowering blood pressure and kidney toxicity in fructose-fed hypertensive rats. *Br. J. Nutr.* 109 (10), 1806–1812. doi:10.1017/S0007114512003819
- Pandey, H., Srivastava, S., Singh, S., and Tripathi, Y. B. (2019). Histopathological study of different organs of charles foster strain rat under the exposure of *Pueraria tuberosa*. *BioRxiv.* 671529. doi:10.1101/671529
- Pandey, H., Srivastava, S., and Tripathi, Y. B. (2019). Herbal tablet of *Pueraria tuberosa* water extract suppresses the alloxan induced liver damage and hyperglycemia in rats. *BioRxiv.* 671594. doi:10.1101/671594
- Pandey, H., Srivastava, S., Tripathi, Y. B., and Kumar, R. (2018). Preclinical acute and repeated dose toxicity of *Pueraria tuberosa* (PTWE) on charles foster rats. *Int. J. Pharmacol. Sci. Res.* 9 (11), 4572. doi:10.13040/IJPSR.0975-8232.9(11).4572-81
- Pandey, N., and Tripathi, Y. B. (2010). Antioxidant activity of tuberodin isolated from *Pueraria tuberosa* Linn. *J. Inflamm.* 7, 47. doi:10.1186/1476-9255-7-47
- Pandey, N., Chaurasia, J. K., Tiwari, O. P., and Tripathi, Y. B. (2007). Antioxidant properties of different fractions of tubers from *Pueraria tuberosa* Linn. *Food Chem.* 105 (1), 219–222. doi:10.1016/j.foodchem.2007.03.072
- Pandya, K. B., Patel, H. B., Bhatt, P. R., Patel, U. D., and Modi, C. M. (2019). *In vitro* antibacterial activity of sixteen medicinal plants collected from nearby region of Junagadh, Gujarat (India). *J. Pharm. Innov.* 8 (3), 662–667.
- Park, C. E., Yun, H., Lee, E. B., Min, B. I., Bae, H., Choe, W., et al. (2010). The antioxidant effects of genistein are associated with AMP-activated protein kinase activation and PTEN induction in prostate cancer cells. *J. Med. Food.* 13 (4), 815–820. doi:10.1089/jmf.2009.1359
- Patel, J., Doshi, N., Bhalerao, A., and Bonagiri, R. (2016). Immunomodulatory activity of ethanolic extract of *Pueraria Tuberosa* Immunomodulatory activity of ethanolic extract of *Pueraria Tuberosa* D.C. *Int. J. Sci. Eng. Res.* 7 (11), 708–713.
- Patel, R. V., Mistry, B. M., Shinde, S. K., Syed, R., Singh, V., and Shin, H. S. (2018). Therapeutic potential of quercetin as a cardiovascular agent. *Eur. J. Med. Chem.* 155, 889–904. doi:10.1016/j.ejmech.2018.06.053
- Pragasam, S. J., Venkatesan, V., and Rasool, M. (2013). Immunomodulatory and anti-inflammatory effect of p-coumaric acid, a common dietary polyphenol on experimental inflammation in rats. *Inflammation* 36 (1), 169–176. doi:10.1007/s10753-012-9532-8
- Pramanik, S. S., Sur, T. K., Debnath, P. K., and Bhattacharyya, D. (2010). Effect of *Pueraria tuberosa* tuber extract on chronic foot shock stress in Wistar rats. *Nepal Med. Coll. J.* 12 (4), 234–238.
- Pramanik, S. S., Sur, T. K., Debnath, P. K., Pramanik, T., and Bhattacharyya, D. (2011). Effect of *Pueraria tuberosa* on cold immobilization stress induced changes in plasma corticosterone and brain monoamines in rats. *J. Nat. Remedies.* 11 (1), 69–75. doi:10.18311/jnr/2011/52
- Pueraria tuberosa*-Vikaspedia Available at: <https://vikaspedia.in/agriculture/crop-production/package-of-practices/medicinal-and-aromatic-plants/pueraria-tuberosa>. (Retrieved from September 21 2020).
- Puri, H. S. (2003). *Rasayana: Ayurvedic Herbs for Longevity and Rejuvenation.* 3 (2), (Hoboken, NJ: CRC Press). 303–307.
- Qian, Y., Guan, T., Huang, M., Cao, L., Li, Y., Cheng, H., et al. (2012). Neuroprotection by the soy isoflavone, genistein, via inhibition of mitochondria-dependent apoptosis pathways and reactive oxygen induced-NF- $\kappa$ B activation in a cerebral ischemia mouse model. *Neurochem. Int.* 60 (8), 759–767. doi:10.1016/j.neuint.2012.03.011
- Qiu, G., Tian, W., Huan, M., Chen, J., and Fu, H. (2017). Formononetin exhibits anti-hyperglycemic activity in alloxan-induced type 1 diabetic mice. *Exp. Biol. Med.* 242 (2), 223–230. doi:10.1177/1535370216657445
- Raghuwanshi, R., and Jain, B. (2011). Hypoglycemic effect of *Pueraria tuberosa* tubers in healthy and alloxan diabetic Rats. *J. Chem. Biol. Phys. Sci.* 2 (1), 270–272.
- Rani, V. U., Sudhakar, M., and Ramesh, A. (2017). Protective effect of *Pueraria tuberosa* Linn. in arsenic induced nephrotoxicity in rats. *Asian J. Pharmacol. Res.* 7 (1), 15. doi:10.5958/2231-5691.2017.00003.x
- Rao, N. V., Pujar, B., Nimbale, S. K., Shantakumar, S. M., and Satyanarayana, S. (2008). Nootropic activity of tuber extract of *Pueraria tuberosa* (roxb). *Indian J. Exp. Biol.* 46 (8), 591–598.
- Ratnam, V., and Venkata Raju, R. R. (2009). Preliminary phytochemical and antimicrobial properties of *pueraria tuberosa* (Willd.) DC: a potential medicinal plant. *Ethnobotanical Leaflets.* 13, 1051–1059.
- Rawtal, B., Sahatpure, N., and Sakharwade, S. (2019). *Pueraria tuberosa* (vidarikanda): an emerging cosmetic herb. *Int. J. Sci.* 4 (7), 130–137.
- Robinson, M. M., and Zhang, X. (2011). *The world medicines situation 2011, traditional Medicines : global situation , issues and challenges.* 3rd Edn. (Geneva, Switzerland: World Health Organization), 1–14.
- Roy, A. J., and Stanelly Mainzen Prince, P. (2013). Preventive effects of p-coumaric acid on cardiac hypertrophy and alterations in electrocardiogram, lipids, and lipoproteins in experimentally induced myocardial infarcted rats. *Food Chem. Toxicol.* 60, 348–354. doi:10.1016/j.fct.2013.04.052
- Sabitha, R., Nishi, K., Gunasekaran, V. P., Agilan, B., David, E., Annamalai, G., et al. (2020). p-Coumaric acid attenuates alcohol exposed hepatic injury through MAPKs, apoptosis and Nrf2 signaling in experimental models. *Chem. Biol. Interact.* 321, 109044. doi:10.1016/j.cbi.2020.109044
- Sadguna, V., Sarikha, K., Komuraiah, T. R., and Mustafa, M. (2015). Anti-microbial activity of *pueraria tuberosa* DC, an economically and medicinally important plant. *Int. J. Curr. Microbiol. App. Sci.* 4 (5), 152–159 Available at: <https://www.ijcmas.com/vol-4-5>.
- Sakamoto, Y., Naka, A., Ohara, N., Kondo, K., and Iida, K. (2014). Daidzein regulates proinflammatory adipokines thereby improving obesity-related inflammation through PPAR $\gamma$ . *Mol. Nutr. Food Res.* 58 (4), 718–726. doi:10.1002/mnfr.201300482
- Sakamula, R., and Thong-asa, W. (2018). Neuroprotective effect of p-coumaric acid in mice with cerebral ischemia reperfusion injuries. *Metab. Brain Dis.* 33 (3), 765–773. doi:10.1007/s11011-018-0185-7

- Satpathy, S., Patra, A., Ahirwar, B., and Hussain, M. D. (2018). Antioxidant and anticancer activities of green synthesized silver nanoparticles using aqueous extract of tubers of *Pueraria tuberosa*. *Artificial Cells. Nanomed. and Biotechnol.* 46 (Suppl. 3), S71–S85. doi:10.1080/21691401.2018.1489265
- Satpathy, S., Patra, A., Hussain, M. D., and Ahirwar, B. (2017). Simultaneous estimation of genistein and daidzein in *Pueraria tuberosa* (Willd.) DC by validated high-performance thin-layer chromatography (HPTLC) densitometry method. *J. Liq. Chromatogr. Relat. Technol.* 40 (10), 499–505. doi:10.1080/10826076.2017.1329743
- Satpathy, S., Patra, A., Hussain, M. D., and Kazi, M. (2020). Antioxidant enriched fraction from *Pueraria tuberosa* alleviates ovariectomized-induced osteoporosis in rats, and inhibits growth of breast and ovarian cancer cell lines *in vitro*. *BioRxiv*. doi:10.1101/2020.09.21.305953
- Sawale, P. D., Singh, R. B., Kapila, S., Arora, S., Rastogi, S., and Rawat, A. K. S. (2013). Immunomodulatory and antioxidative potential of herb (*Pueraria tuberosa*) in mice using milk as the carrier. *Int. J. Dairy Technol.* 66 (2), 202–206. doi:10.1111/1471-0307.12011
- Sharma, S., Agrawal, M., and Lal, M. (2018). Cultivation of “vidarikand” (*Pueraria tuberosa* dc): a drug of potential importance. *Int. J. Inf. Retr. Res. (IJIRR)*. 5 (5), 5460–5462.
- Sharma, S. H., Rajamanickam, V., and Nagarajan, S. (2018). Antiproliferative effect of p-Coumaric acid targets UPR activation by downregulating Grp78 in colon cancer. *Chem. Biol. Interact.* 291, 16–28. doi:10.1016/j.cbi.2018.06.001
- Sharmila, R., Sindhu, G., and Arockianathan, P. M. (2016). Nephroprotective effect of  $\beta$ -sitosterol on N-diethylnitrosamine initiated and ferric nitrilotriacetate promoted acute nephrotoxicity in Wistar rats. *J. Basic Clin. Physiol. Pharmacol.* 27 (5), 473–482. doi:10.1515/jbcp-2015-0085
- Shilpashree, V. K., Dang, R., and Das, K. (2015). Evaluation of phytochemical investigation and immunomodulatory activity of four different plant species of vidari by carbon clearance test on wistar rats. *Ann. Phytomed.* 4 (1), 94–98.
- Shukla, R., Banerjee, S., and Tripathi, Y. B. (2018a). Antioxidant and Antiapoptotic effect of aqueous extract of *Pueraria tuberosa* (Roxb. ex Willd.) DC. On streptozotocin-induced diabetic nephropathy in rats. *BMC Compl. Alternative Med.* 18 (1), 156. doi:10.1186/s12906-018-2221-x
- Shukla, R., Banerjee, S., and Tripathi, Y. B. (2018b). *Pueraria tuberosa* extract inhibits iNOS and IL-6 through suppression of PKC- $\alpha$  and NF- $\kappa$ B pathway in diabetes-induced nephropathy. *J. Pharm. Pharmacol.* 70 (8), 1102–1112. doi:10.1111/jphp.12931
- Shukla, R., Pandey, N., Banerjee, S., Tripathi, Y. B., and Tripathi, Y. B. (2017). Effect of extract of *Pueraria tuberosa* on expression of hypoxia inducible factor-1 $\alpha$  and vascular endothelial growth factor in kidney of diabetic rats. *Biomed. Pharmacother.* 93, 276. doi:10.1016/j.biopha.2017.06.045
- Shukla, S., Jonathan, S., and Sharma, A. (1996). Protective action of butanolic extract of *Pueraria tuberosa* DC. against carbon tetrachloride induced hepatotoxicity in adult rats. *Phytother Res.* 10 (7), 608–609. doi:10.1002/(SICI)1099-1573(199611)10:7<608::AID-PTR842>3.0.CO;2-1
- Srivastava, S., Pandey, H., Singh, S. K., and Tripathi, Y. B. (2019). Anti-oxidant, anti-apoptotic, anti-hypoxic and anti-inflammatory conditions induced by PTY-2 against STZ-induced stress in islets. *Biosci Trends* 13 (5), 382–393. doi:10.5582/bst.2019.01181
- Srivastava, S., Shree, P., Pandey, H., and Tripathi, Y. B. (2018). Incretin hormones receptor signaling plays the key role in antidiabetic potential of PTY-2 against STZ-induced pancreatitis. *Biomed. Pharmacother.* 97, 330–338. doi:10.1016/j.biopha.2017.10.071
- Srivastava, S., Shree, P., and Tripathi, Y. B. (2017). Active phytochemicals of *Pueraria tuberosa* for DPP-IV inhibition: in silico and experimental approach. *J. Diabetes Metab. Disord.* 16 (1), 46. doi:10.1186/s40200-017-0328-0
- Srivastava, S., Koley, T. K., Singh, S. K., and Tripathi, Y. B. (2015). The tuber extract of *pueraria tuberosa* Linn. competitively inhibits DPP-IV activity in normoglycemic rats. *Int. J. Pharm. Pharmacol. Sci.* 7 (9), 227–231.
- Sukhotnik, I., Moati, D., Shaoul, R., Loberman, B., Pollak, Y., and Schwartz, B. (2018). Quercetin prevents small intestinal damage and enhances intestinal recovery during methotrexate-induced intestinal mucositis of rats. *Food Nutr. Res.* 62. doi:10.29219/fnr.v62.1327
- Sumalatha, M., Munikishore, R., Rammohan, A., Gunasekar, D., Kumar, K. A., Reddy, K. K., et al. (2015). Isoorientin, a selective inhibitor of cyclooxygenase-2 (COX-2) from the tubers of *pueraria tuberosa*. *Nat Prod Commun.* 10 (10), 1703–1704. doi:10.1177/1934578x1501001017
- Tanaka, T., Moriyama, T., Kawamura, Y., and Yamanouchi, D. (2016). Puerarin suppresses macrophage activation via antioxidant mechanisms in a CaPO. *J. Nutr. Sci. Vitaminol.* 62, 425–431. doi:10.3177/jnsv.62.425
- Tanna, I., Aghera, H., Ashok, B., and Chandola, H. (2012). Protective role of Ashwagandharishta and flax seed oil against maximal electroshock induced seizures in albino rats. *Ayu.* 33 (1), 114–118. doi:10.4103/0974-8520.100327
- Tanwar, Y., Goyal, S., and Ramawat, K. (2008). Hypolipidemic effects of tubers of Indian kudzu (*Pueraria tuberosa*). *J. Herb. Med. Toxicol.* 2, 21–25.
- Tie, L., An, Y., Han, J., Xiao, Y., Xiaokaiti, Y., Fan, S., et al. (2013). Genistein accelerates refractory wound healing by suppressing superoxide and FoxO1/iNOS pathway in type 1 diabetes. *JNB (J. Nutr. Biochem.)*. 24 (1), 88–96. doi:10.1016/j.jnutbio.2012.02.011
- Tripathi, A. K., and Kohli, S. (2013). Anti-diabetic activity and phytochemical screening of crude extracts of *PuerariaTuberosa* DC. (FABACEAE) grown in India on STZ -induced diabetic rats. *Asian J. Med. Pharmaceut. Res.* 3 (3), 66–73.
- Tripathi, Y. B., and Aditi, P. (2020). Antioxidative and hypolipidemic effect of *pueraria tuberosa* water extract (ptwe) in rats with high fat diet induced non-alcoholic fatty liver disease (nafld). *Int. J. Pharmaceut. Sci. Res.* 11 (1), 378–386. doi:10.1017/CBO9781107415324.004
- Tripathi, Y. B., Nagwani, S., Mishra, P., Jha, A., and Rai, S. P. (2012). Protective effect of *Pueraria tuberosa* DC. Embedded biscuit on cisplatin-induced nephrotoxicity in mice. *J. Nat. Med.* 66 (1), 109–118. doi:10.1007/s11418-011-0559-1
- Tripathi, Y. B., Shukla, R., Pandey, N., Pandey, V., and Kumar, M. (2017). An extract of *Pueraria tuberosa* tubers attenuates diabetic nephropathy by upregulating matrix metalloproteinase-9 expression in the kidney of diabetic rats. *J. Diabetes.* 9 (2), 123–132. doi:10.1111/1753-0407.12393
- Tripathi, Y., Pandey, N., Yadav, D., and Pandey, V. (2013). Anti-inflammatory effect of *Pueraria tuberosa* extracts through improvement in activity of red blood cell anti-oxidant enzymes. *AYU.* 34 (3), 297. doi:10.4103/0974-8520.123131
- Umarani, V., Sudhakar, M., Ramesh, A., Lakshmi, B. V. S., and Sandhyarani, D. (2016). Protective effect of hydroalcoholic extract of *Pueraria tuberosa* against arsenic induced neurotoxicity in rats. *Int. J. Res. Pharm. Chem.* 6 (2), 350–362.
- Vaishnav, K., Goyal, S., and Ramawat, K. G. (2006). Isoflavonoids production in callus culture of *Pueraria tuberosa*, the Indian kudzu. *Indian J. Exp. Biol.* 44 (12), 1012–1017.
- Verma, S. K., Jain, V., and Singh, D. P. (2012). Effect of *Pueraria tuberosa* DC. (Indian Kudzu) on blood pressure, fibrinolysis and oxidative stress in patients with stage 1 hypertension. *Pakistan J. Biol. Sci.* 15 (15), 742–747. doi:10.3923/pjbs.2012.742.747
- Verma, S. K., Jain, V., Vyas, A., and Singh, D. P. (2009). Protection against stress induced myocardial ischemia by Indian kudzu (*Pueraria tuberosa*)-a case study. *Int. J. Herb. Med.* 3 (1), 59–63.
- Viji, Z., and Paulsamy, S. (2018). Preliminary phytochemical screening and HPTLC finger printing analysis of traditional medicinal plant *Pueraria tuberosa* (Roxb. ex Willd.) DC. *Kong. Res. J.* 5 (1), 56–59. doi:10.26254/kj254
- Viji, Z., and Paulsamy, S. (2015). In-Vitro antioxidant properties and total phenolic, flavonoid and tannin contents of *Pueraria tuberosa* (Roxb. ex Willd.) DC. *RJPBCS.* 7 (2428), 2428–2438.
- Wang, H., Zhang, D., Ge, M., Li, Z., Jiang, J., and Li, Y. (2015). Formononetin inhibits enterovirus 71 replication by regulating COX-2/PGE2 expression. *Virology.* 531 (1), 10–17. doi:10.1016/j.virus.2015.05.026
- Wang, X. S., Guan, S. Y., Liu, A., Yue, J., Hu, L. N., Zhang, K., et al. (2019). Anxiolytic effects of Formononetin in an inflammatory pain mouse model. *Mol. Brain* 12 (1). doi:10.1186/s13041-019-0453-4
- Wang, Y., Zhao, H., Li, X., Wang, Q., Yan, M., Zhang, H., et al. (2019). Formononetin alleviates hepatic steatosis by facilitating TFEB-mediated lysosome biogenesis and lipophagy. *J. Nutr. Biochem.* 73. doi:10.1016/j.jnutbio.2019.07.005
- WHO (2009). *WHO monographs on selected medicinal plants.*, Vol. 4. (Geneva, Switzerland: WHO)
- Wu, D., Wu, K., Zhu, Q., Xiao, W., Shan, Q., Yan, Z., et al. (2018). Formononetin administration ameliorates dextran sulfate sodium-induced acute colitis by inhibiting NLRP3 inflammasome signaling pathway. *Mediat. Inflamm.* 2018, 9878120. doi:10.1155/2018/9878120
- Xia, D. Z., Zhang, P. H., Fu, Y., Yu, W. F., and Ju, M. T. (2013). Hepatoprotective activity of puerarin against carbon tetrachloride-induced injuries in rats: a randomized controlled trial. *Food Chem. Toxicol.* 59, 90–95. doi:10.1016/j.fct.2013.05.055

- Xing, G., Dong, M., Li, X., Zou, Y., Fan, L., Wang, X., et al. (2011). Neuroprotective effects of puerarin against beta-amyloid-induced neurotoxicity in PC12 cells via a PI3K-dependent signaling pathway. *Brain Res. Bull.* 85 (3–4), 212–218. doi:10.1016/j.brainresbull.2011.03.024
- Xu, X., Zheng, N., Chen, Z., Huang, W., Liang, T., and Kuang, H. (2016). Puerarin, isolated from *Pueraria lobata* (Willd.), protects against diabetic nephropathy by attenuating oxidative stress. *Gene* 591 (2), 411–416. doi:10.1016/j.gene.2016.06.032
- Yadav, D., Sharma, A., Srivastava, S., and Tripathi, Y. B. (2016b). Nephroprotective potential of standardized herbals described in Ayurveda: a comparative study. *J. Chem. Pharmaceut. Res.* 8 (8), 419–427.
- Yadav, D., Kumar, M., and Tripathi, Y. B. (2016a). Methanolic extract of tubers of *Pueraria tuberosa* Linn. ameliorates glycerol induced acute kidney injury in rats. *J. Chem. Pharmaceut. Res.* 8 (2), 133–139.
- Yadav, D., Pandey, V., Srivastava, S., Tripathi, Y. B., and Kumar, M. (2019). Methanolic extract of *Pueraria tuberosa* Linn ameliorates renal injury and oxidative stress in rats with alloxan-induced diabetes. *J. emerg. technol.* 6, 557–574.
- Yang, S., Wei, L., Xia, R., Liu, L., Chen, Y., Zhang, W., et al. (2019). Formononetin ameliorates cholestasis by regulating hepatic SIRT1 and PPAR $\alpha$ . *Biochem. Biophys. Res. Commun.* 512 (4), 770–778. doi:10.1016/j.bbrc.2019.03.131
- Yin, M. S., Xu, S. H., Wang, Y., Jie, L., Zhang, Q., Zheng, W. M., et al. (2016). Methylamine irisolidone, a novel compound, increases total ATPase activity and inhibits apoptosis *in vivo* and *in vitro*. *J. Asian Nat. Prod. Res.* 18 (6), 562–575. doi:10.1080/10286020.2015.1133610
- Yu, Q., Han, W., Zhu, Y., and Zhai, H. (2017). Effect of puerarin on type II diabetes mellitus with orthopaedic footwear. *Pak. J. Pharm. Sci.* 30 (5), 1899–1903.
- Yu, X., Gao, F., Li, W., Zhou, L., Liu, W., and Li, M. (2020). Formononetin inhibits tumor growth by suppression of EGFR-Akt-Mcl-1 axis in non-small cell lung cancer. *J. Exp. Clin. Canc. Res.* 39 (1). doi:10.1186/s13046-020-01566-2
- Yue, Y., Shen, P., Xu, Y., and Park, Y. (2019). p-Coumaric acid improves oxidative and osmosis stress responses in *Caenorhabditis elegans*. *J. Sci. Food Agric.* 99 (3), 1190–1197. doi:10.1002/jsfa.9288
- Zhang, D., and Li, M. (2019). Puerarin prevents cataract development and progression in diabetic rats through Nrf2/HO-1 signaling. *Mol. Med. Rep.* 20 (2), 1017–1024. doi:10.3892/mmr.2019.10320
- Zhang, J., Liu, L., Wang, J., Ren, B., Zhang, L., and Li, W. (2018). Formononetin, an isoflavone from *Astragalus membranaceus* inhibits proliferation and metastasis of ovarian cancer cells. *J. Ethnopharmacol.* 221, 91–99. doi:10.1016/j.jep.2018.04.014
- Zhang, Q.-Y., Zheng, W., Gul Khaskheli, S., and Huang, W. (2019). *In Vivo* evaluation of tectoridin from puerariae flos on anti-alcoholism property in rats. *Journal of Food and Nutrition Research* 7 (6), 458–464. doi:10.12691/jfnr-7-6-8
- Zhang, Y., Chen, C., and Zhang, J. (2019). Effects and significance of formononetin on expression levels of HIF-1 $\alpha$  and VEGF in mouse cervical cancer tissue. *Oncol. Lett.* 18 (3), 2248–2253. doi:10.3892/ol.2019.10567
- Zheng, W., Sun, R., Yang, L., Zeng, X., Xue, Y., and An, R. (2017). Daidzein inhibits choriocarcinoma proliferation by arresting cell cycle at G1 phase through suppressing ERK pathway *in vitro* and *in vivo*. *Oncol. Rep.* 38 (4), 2518–2524. doi:10.3892/or.2017.5928
- Zhong, Y., Zhang, X., Cai, X., Wang, K., Chen, Y., and Deng, Y. (2014). Puerarin attenuated early diabetic kidney injury through down-regulation of matrix metalloproteinase 9 in streptozotocin-induced diabetic rats. *PLoS One* 9 (1). doi:10.1371/journal.pone.0085690
- Zhou, Q., Zhang, W., Li, T., Tang, R., Li, C., Yuan, S., et al. (2019). Formononetin enhances the tumoricidal effect of everolimus in breast cancer MDA-MB-468 cells by suppressing the mTOR pathway. *Evid. base Compl. Alternative Med.* 2019, 1–8. doi:10.1155/2019/9610629

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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