Jatrorrhizine: A Review of Sources, Pharmacology, Pharmacokinetics and Toxicity

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Jatrorrhizine, an isoquinoline alkaloid, is a bioactive metabolite in common medicinal plants, such as Berberis vernaef Schneid., Tinospora sagittata (Oliv.) Gagnep. and Coptis chinensis Franch. These plants have been used for centuries in traditional medicine for their wide-ranging pharmacological properties. This review emphasizes the latest and comprehensive information on the sources, pharmacology, pharmacokinetics and toxicity of jatrorrhizine. Studies on this alkaloid were collected from scientific internet databases, including the Web of Science, PubMed, ScienceDirect, Google Scholar, Elsevier, Springer, Wiley Online Library and Europe PMC and CNKI, using a combination of keywords involving “jatrorrhizine”, “sources”, “pharmacology”, “pharmacokinetics,” and “toxicology”. Jatrorrhizine exhibits anti-diabetic, antimicrobial, antiproteasomal, anticancer, anti-obesity and hypolipidemic properties, along with central nervous system activity and other beneficial activity. Studies of jatrorrhizine have laid the foundation for its application to the treatment of various diseases, but some issues still exist. Further investigations might emphasize 1) specific curative mechanisms of...

Abbreviations: 3OHase, tyrosine/tyramine 3-hydroxylase; 4-HNE, 4-hydroxynonenal; 4HPPDC, 4-hydroxyphenylpyruvate decarboxylase; 4′OMT, 3′-hydroxy-N-methyl-(S)-coclaurine 4′-O-methyltransferase; 53BP1, p53-binding protein 1; 5-HT, serotonin; 6OMT, (S)-norcoclaurine 6-O-methyltransferase; Aβ, amyloid β; AChE, acetylcholinesterase; Apaf-1, apoptotic protease activating factor 1; ALT, alanine aminotransferase; AR, aldose reductase; AST, aspartate aminotransaminase; Bax, BCL-2-associated X protein; BB, berberine bridge enzyme; Bcl-2, B cell lymphoma 2; BMD, bone mineral density; BVDV, bone volume/tissue volume; CDK, cyclin-dependent kinase; CNMT, (S)-coclaurine N-methyltransferase; CPT1A, carnitine palmitoyltransferase 1A; CPM, codeine-O-demethylase; CTR, calmodulin receptor; CTSK, cathepsin K; CYP7A1, cholesterol 7α-hydroxylase; eNOS, endothelial nitric oxide synthase; EMT, epithelial-mesenchymal transition; ERCC1, excision repair cross-complementation group 1; FAS, fatty acid synthase; GLUT4/1/2, glucose transporter 4/1/2; GSH, glutathione; GSK-3β, glycogen synthase kinase 3β; HDAC4, histone deacetylase 4; HDL-C, high-density lipoprotein cholesterol; HMGCR, 3-hydroxy-3-methyl glutaryl coenzyme A reductase; HO-1, heme oxygenase-1; hTERT, human telomerase reverse transcriptase; I-β, indoleamine 2, 3-dioxygenase 1; IL-1β, interleukin-1β; IRS2, insulin receptor substrate 2; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LDLR, low density lipoprotein receptor; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinases; MDA, lipid peroxidation; MHC, minimum inhibitory concentration; MMP (3/7), mitochondrial membrane potential; NA, neuraminidase; NCS, (S)-norcoclaurine synthase; NE, norepinephrine; NFATc1, T-cells cytoplasmic 1; NF-kB, nuclear factor kappa-B; NMMCh, (S)-N-methylcoclaurine-3′-hydroxylation; OCT, organic cation transporter; OMT, O-methyltransferase; p-4E-BP1, phosphorylated 4E-binding protein 1; PARP, ADP-ribose polymerase; p-AKT, phosphorylated protein kinase B; p-AMPK, phosphorylated AMP-activated protein kinase; p-ERK1/2, phosphorylated extracellular signal-regulated kinases 1/2; pH2AX, phosphorylated H2A histone X; PI3KR1, phosphoinositide-3-kinase regulatory subunit 1; p-JNK, phosphorylated c-Jun N-terminal kinases; PMAT, plasma membrane monoamine transporter; PPAR, peroxisome proliferator activated receptor; p-p38, phosphorylated p38; ROS, oxygen species; SOMT, (S)-scoulerine 9-O-methyltransferase; SREBP-1c, sterol regulatory element binding transcription factor 1c; STOX, (S)-tetrahydroprotoberberine oxidase; T2DM, type 2 diabetes mellitus; TBA, total bile acids; TC, total cholesterol; TRF1, TTAGGG repeat binding factor 1; TG, total triglyceride; TNF-α, tumor necrosis factor α; TRAP, tartrate-resistant acid phosphatase; TYDC, tyrosine decarboxylase; TyrAT, tyrosine aminotransferase.
INTRODUCTION

Plants are sources of metabolites with varied biological activities, clinical effectiveness. The therapeutical benefits and safety of plant-derived metabolites have been proven in long-standing traditional medicinal practices across the world (Gurib-Fakim, 2006; Porras et al., 2020). The bioactive metabolites and related derivatives are increasingly used for the production of new drugs and may have broad clinical applications.

Alkaloids are important natural products derived mostly from amino acids. These chemicals display substantial physiological and pharmacological activities. Jatrorrhizine is a well-known isoquinoline alkaloid of the protoberberine type. Its molecular structure is 2,9,10-trimethoxy-5,6-dihydroisoquinolin[2,1-b]isoquinolin-7-i um-3-ol (molecular formula: C_{20}H_{20}NO_{4}).

**Figure 1.** Jatrorrhizine is a major bioactive metabolite with wide distribution across plant families. Several species have been used medicinally for centuries, such as *Berberis verna* C.K.Schneid. (Li et al., 2020), *Mahonia bealei* (Fortune) Carrière (He and Mu, 2015), *Tinospora sagittata* (Oliv.) Gagnep. (Zhang et al., 2006), *Coptis chinensis* Franch. (Chen et al., 2017) and *Corydal dis yunnanu sso* (Y.H.Chou and Chun C. Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu (Xiao et al., 2011). One of the active constituents in herbal formulae, such as Zoujinwan, Jiaotai Pills and San-Huang decoction, is considered to be jatrorrhizine (Yan et al., 2012; Sun et al., 2018; Su et al., 2020). Modern pharmacological studies demonstrate that this alkaloid exhibits anti-diabetic, antimicrobial (Ali et al., 2013), antiprotozoal (Malebo et al., 2013), anticancer (Sun et al., 2019), anti-obesity and hypolipidemic properties (Yang et al., 2016). Central nervous system activities are also reported (Luo et al., 2011; Xiao et al., 2011; Bacq et al., 2012).

Jatrorrhizine has attracted the attention of researchers due to its wide distribution across a variety of plant species and its potential for clinical use certain diseases. We summarise and discuss, in this review, the latest and comprehensive information on the plant sources, synthesis, pharmacological effects, pharmacokinetics and toxicity of jatrorrhizine. This information will be beneficial for future examination of therapeutic potential of this active metabolite and subsequent development of clinical applications.

**Keywords:** jatrorrhizine, natural products, pharmacological properties, toxicology, pharmacokinetics

**SOURCES**

**Plant Sources of Jatrorrhizine**

Medicinal plants are major sources of jatrorrhizine. This metabolite is isolated from various plant families, such as Annonaceae, Berberidaceae, Menispermaceae, Papaveraceae, Ranunculaceae and Rutaceae (Table 1). Many species in these families are used in folk medicinal plants and Chinese herbal medicine. Several *Annnickia* species from the Annonaceae family, are multi-purpose medicinal plants used widely for the treatment of malaria and other ailments across tropical Africa. Protoberberine alkaloids (including jatrorrhizine and palmatine) are the major anti-protozoal agents in these plants (Malebo et al., 2013; Olivier et al., 2015; Odoh et al., 2018). Numerous species of the *Berberis, Mahonia, Tinospora, Corydalis, Coptis, Thalictrum* and *Phellodendron* genera are commonly used medicinal plants and important sources of jatrorrhizine (Alamzeb et al., 2015; Baijai et al., 2016; Du et al., 2018; Feng et al., 2018; Abdykerimova et al., 2020; Sharma et al., 2020). In China, the stems of *Mahonia bealei* (Fortune) Carrière and *Mahonia fortunei* (Lindl.) Fedde (named Mahoniae Caulis), rhizomes of *Coptis chinensis* Franch., *Coptis deltoidea* C.Y.Cheng and P.K.Hsiao and *Coptis teeta* Wall. (named Coptidis Rhizoma) and barks from *Phellodendron amurense* Rupr. (named Phellodendri amurensis Cortex) and *Phellodendron chinense* C.K.Schneid. (named Phellodendri Chinensis Cortex) are known for antipyretic and analgesic properties. These traditional medicines have been widely used to treat abdominal pain and diarrhea, inflammatory disorders and gastrointestinal diseases (Ryuk et al., 2012; He and Mu, 2015; Meng et al., 2018). However, the wild resources of the three *Coptis* species are almost endangered (Chen et al., 2017). Jatrorrhizine is also found in the Rutaceae stem barks of several *Zanthoxylum* species. The anti-cancer activity of these plants might be attributed to quaternary alkaloids (Tian et al., 2017).

**Synthesis of Jatrorrhizine**

Access to natural products with complex structures is a major challenge because of slow growth and limited production (Romanowski and Eustáquio, 2020). Chemical synthesis has thus become an effective way to obtain some plant metabolites. Total synthesis of jatrorrhizine has been achieved through an efficient

![Figure 1](image-url)
| Plant species                       | Family       | Used part          | References                        |
|------------------------------------|--------------|--------------------|-----------------------------------|
| Annickia affinis (Exell) Versteegh and Sosef | Annonaceae   | stem bark          | Olivier et al. (2015)             |
| Annickia chlorantha (Oliv.) Setten and Maas | Annonaceae   | stem bark          | Odoh et al. (2018), Olivier et al. (2015) |
| Annickia kummeriae (Engl. and Diels) Setten and Maas | Annonaceae | leaf               | Melebo et al. (2013)              |
| Duguetia triflora Maas and A.H.Gentry | Annonaceae   | leaf               | Fecchione et al. (2002), Pérez and Cassels (2010) |
| Xylopia parviflora Spruce          | Annonaceae   | bark and root      | Nishiyama et al. (2004)           |
| Berberis aristata DC.              | Berberidaceae| root               | Basera et al. (2021)              |
| Berberis brevissima Jafri          | Berberidaceae| cortex             | Ali et al. (2013)                 |
| Berberis dictyophylla Franch.      | Berberidaceae| cortex             | Feng et al. (2018)                |
| Berberis diaphana Maxim.           | Berberidaceae| cortex             | Feng et al. (2018)                |
| Berberis illenis Popov             | Berberidaceae| root, leaf and fruit | Abdykeranova et al. (2020)        |
| Berberis jaeschkeana C.K.Schneid.  | Berberidaceae| bark of root       | Alamzeb et al. (2015)             |
| Berberis kansuerisa C.K.Schneid.   | Berberidaceae| cortex             | Feng et al. (2018)                |
| Berberis parkeriiana C.K.Schneid.  | Berberidaceae| cortex             | Ali et al. (2013)                 |
| Berberis vernae C.K.Schneid.       | Berberidaceae| cortex             | Feng et al. (2018)                |
| Mahonia aquifolium (Pursh) Nutt.   | Berberidaceae| root               | Stobodniková et al. (2004)        |
| Mahonia beaute (Fortune) Carrière   | Berberidaceae| root, stem         | He and Mu (2015)                  |
| Mahonia fortunei (Lindl.) Fedde     | Berberidaceae| root, root bark stem | He and Mu (2015)                  |
| Mahonia leschenaultia (Wall. ex Wight and Am.) Takeda ex Gamble | Berberidaceae | root | Singh et al. (2017) |
| Mahonia napaulensis DC.             | Berberidaceae| root               | Singh et al. (2017)               |
| Mahonia owakensis Hayata            | Berberidaceae| root               | Chao et al. (2009)                |
| Nandina domestica Thunb.            | Berberidaceae| fruit, ground parts | Iwasa et al. (2008), Peng et al. (2014) |
| Burasaia australis Elliot           | Menispermaceae| root               | Da-Cunha et al. (2005)            |
| Burasaia congesta Decne.            | Menispermaceae| root               | Da-Cunha et al. (2005)            |
| Burasaia gracilis Decne.            | Menispermaceae| root               | Da-Cunha et al. (2005)            |
| Dioscoreophyllum cumminsii (Stapf) Diels | Menispermaceae | stem, leaf, tuber | Furuya et al. (1983) |
| Fibrakea recisa Pierre              | Menispermaceae| stem bark          | Su et al. (2007)                  |
| Fibrakea trinctoria Lour.           | Menispermaceae| stem bark          | Rao et al. (2009)                 |
| Penianthus zenkeri (Engl.) Diels    | Menispermaceae| leaf, root         | Achsenbach and Henrich (1991)     |
| Sphenocentrum jollyanum Pierre     | Menispermaceae| root               | Hussain et al. (1989)             |
| Stephania cambodica Gagnep.         | Menispermaceae| tuber              | Dary et al. (2017)                |
| Stephania rotunda Lour.             | Menispermaceae| stem, leaf, tuber  | Zhang and Rao (2009)              |
| Stephania yunnanensis H.S. Lo      | Menispermaceae| tuber              | Desgrous et al. (2014)            |
| Tinospora capillipes Gagnep.        | Menispermaceae| root               | Xiang et al. (2016)               |
| Tinospora cordifolia (Widl.) Hook.f. and Thomson | Menispermaceae | stem | Bapai et al. (2016) |
| Tinospora sagittata (olv.) Gagnep.  | Menispermaceae| stem               | Yuan et al. (2010)                |
| Corydalis decumbens (Thunb.) Pers. | Papaveraceae  | rhizome            | Mao et al. (2017)                 |
| Corydalis noliis (L.) Pers.         | Papaveraceae  | rhizome            | Slavik and Slavková (1989)        |
| Corydalis yanhusuo (Y.H.Chou and Chun C.Hsu) W.T.Wang ex Z.Y.Su and C.Y.Wu | Papaveraceae | tuber              | Du et al. (2018)                  |
| Eschscholzia californica Cham.      | Papaveraceae  | root               | Kuikula-Koch (2017)               |
| Aquilegia Fornosa Fisch.            | Ranunculaceae | root               | Constantine et al. (1966)         |
| Coptis chinensis Franch.            | Ranunculaceae | rhizome            | He et al. (2014)                  |
| Coptis deltoidea C.Y.Cheng and P.K.Hsiao | Ranunculaceae | rhizome            | He et al. (2014)                  |
| Coptis omeiensis (C.Chen) C.Y.Cheng | Ranunculaceae | rhizome            | He et al. (2014)                  |
| Coptis japonica (Thunb.) Makino     | Ranunculaceae | rhizome            | Ikuta et al. (1975)               |
| Coptis quinquefolia Miq.            | Ranunculaceae | rhizome            | Da-Cunha et al. (2005)            |
| Coptis quinquesecta W.T.Wang        | Ranunculaceae | rhizome            | Da-Cunha et al. (2005)            |
| Coptis teeta Wall.                  | Ranunculaceae | rhizome            | He et al. (2014)                  |
| Hydrastis canadensis L.             | Ranunculaceae | root               | Le et al. (2014)                  |
| Thalictrum angustifolium L.         | Ranunculaceae | root               | Ahowiriny et al. (2002)           |
| Thalictrum culturatum Wall.         | Ranunculaceae | root               | Lou et al. (1967)                 |
| Thalictrum foliolosum DC.           | Ranunculaceae | root               | Sharma et al. (2020)              |
| Thalictrum simplex L.               | Ranunculaceae | root               | Qin and Jiang (2011)              |
| Thalictrum squarrosum Stephan ex Wild. | Ranunculaceae | root               | Qin and Jiang (2011)              |
| Phellodendron amurense Rupr.        | Rutaceae     | stem bark          | Ryuk et al. (2012)                |
| Phellodendron chinense C.K.Schneid. | Rutaceae     | stem bark          | Ryuk et al. (2012)                |
| Zanthoxylum ailanthoides Siebold and Zucc. | Rutaceae | stem bark          | Tian et al. (2017)                |
| Zanthoxylum chalybeum Engl.         | Rutaceae     | stem bark          | Tian et al. (2017)                |
| Zanthoxylum simulans Hance          | Rutaceae     | stem bark          | Tian et al. (2017)                |
syntheses strategy in four steps (Figure 2). The alkaloid was synthesized from phenethylamine and 2,2-dimethoxyacetaldehyde using the Pictet–Spengler reaction to provide tetrahydroisoquinoline. This intermediate then reductively aminated with 2,3-dimethoxybenzaldehyde to afford the tertiary amine. Friedel–Crafts cyclization and subsequent oxidation deliver isomerically pure jatrorrhizine. This synthesis of jatrorrhizine displayed a 20% overall yield (Mori-Quiroz et al., 2018).

Microbial biosynthesis might become a fast and efficient way to obtain natural products. Identification and characterization of the biosynthetic pathway of jatrorrhizine is a prerequisite for its heterologous expression and production. Isoquinoline alkaloids are an important group of specialized plant metabolites. Biosynthesis proceeds by common early steps to form (S)-reticuline (Figure 3). This pivotal intermediate is the branch-point intermediate in the biosynthesis of many isoquinoline alkaloids (He et al., 2018). Sequentially, (S)-scoulerine is formed from (S)-reticuline by berberine bridge enzyme. Pyne et al. (2020) reported a yeast platform for high-level synthesis of tetrahydroisoquinoline alkaloids, and the production of the central intermediate (S)-reticuline increased to 4.6 g/L. However, the subsequent pathway leading to production of jatrorrhizine remains unknown. Hagel and Facchini proposed that 3-O-demethylation of (S)-scoulerine combined with 2-O- and 9-O-methylation might lead to jatrorrhizine (Hagel and Facchini, 2010); enzymes that might catalyse these reactions have not been identified to date. Hence, more research needed to clarify the biosynthetic pathway of jatrorrhizine.

PHARMACOLOGICAL ACTIVITIES OF JATRORRHIZINE

Anti-Obesity and Hypolipidemic Activity
Obesity is a challenging health problem worldwide. Plants and their active phytochemical constituents are used as natural anti-obesity agents and dietary supplements for weight loss. Jatrorrhizine increased the expression of hepatic low-density lipoprotein receptor (LDLR) in Hep G2 cells in vitro and produced a significant reduction in cellular lipid accumulation (Zhou et al., 2014). Jatrorrhizine (46.7 mg/kg×day) was administered to high-fat and high-cholesterol (HFHC)-induced hyperlipidemic hamsters. This treatment reduced the serum total cholesterol (TC) and total triglyceride (TG), decreased the low-density lipoprotein cholesterol (LDL-C) levels, reduced protein levels of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR) and significantly increased the expression of cholesterol 7α-hydroxylase (CYP7A1) and LDLR, as well as elevated fecal excretion of cholesterol and TBA (He et al., 2016). In addition, jatrorrhizine decreased body weights of C57BL/6 mice on a HFHC diet and increased HDL-C levels (Yang et al., 2016). The anti-obesity and hypolipidemic effect of jatrorrhizine may thus be related to regulating the expression of LDLR, CYP7A1 and HMGCR, increasing lipid metabolism, and promoting excretion of TBA. All of these effects would lead to increase metabolism and excretion of cholesterol. Jatrorrhizine ameliorated the pathophysiological changes observed in the livers of hyperlipidemic mice (e.g., swelling of hepatocytes, lipid accumulation, and so on) and caused in a significant decrease in serum aspartate transaminase (AST) and alanine aminotransferase (ALT) levels. Jatrorrhizine also downregulated the hepatic sterol regulatory element binding transcription factor 1c (SREBP-1c) and fatty acid synthase (FAS) levels and upregulated peroxisome proliferator activated receptor-α (PPAR-α) and carnitine palmitoyl transferase 1A (CPT1A) expression. Hence, jatrorrhizine may counter hyperlipidemia through inhibition of fatty acid synthesis and activation of fatty acid β oxidation (Yang et al., 2016). Obesity is a complex disorder that significantly increases the risk of multiple metabolic disorders, such cardiovascular disease and diabetes (Karri et al., 2019). The clinical use of jatrorrhizine might helpful in the management of obesity and associated disorders.
Anti-Diabetic Activity
Type 2 diabetes mellitus (T2DM), an expanding global health problem, is characterized by insulin resistance and impaired insulin secretion (DeFronzo et al., 2015). Some botanical drugs containing jatrorrhizine, such as Coptidis Rhizoma, are widely used in traditional Chinese medicine for treating diabetes (Ma et al., 2016; Meng et al., 2018).

The potential of jatrorrhizine as a hypoglycaemic agent was manifested by inhibition of α-glucosidase and aldose reductase (AR) (Patel MB. and Mishra S., 2012; Patel M. B. and Mishra S. M., 2012). Jatrorrhizine displayed anti-diabetic activity in vitro (RINm5F cells and HepG2 cells) and in vivo (glucose-loaded rats and hyperlipidemic mice) via promoting insulin secretion, improving glucose tolerance and insulin sensitivity and inhibiting hepatic gluconeogenesis, thus improve postprandial hyperglycemia (Patel and Mishra, 2011; Chen et al., 2012; Yang et al., 2016; Li et al., 2020).

Jatrorrhizine protected rats with induced diabetes mellitus and restored vascular endothelial dysfunction through upregulating the Akt/AMPK/eNOS signaling pathway and reducing IL-1β and 

FIGURE 3 | Putative biosynthetic pathway of jatrorrhizine in plants.
### TABLE 2 | Anti-diabetic, antimicrobial, antiprotozoal, and central nervous system activities and mechanisms of jatrorrhizine in in vitro and in vivo assays.

| Effect | Assay | Cell lines/model | Dosage | Type of biological activity | References |
|--------|-------|------------------|--------|----------------------------|------------|
| Anti-obesity and hypolipidemic activity | **In vitro** | HepG2 cells | 15 μM | Increased LDLR expression and decreased cellular lipid accumulation | Zhou et al. (2014) |
| | **In vivo** | high-fat and high-cholesterol (HFHC)-induced hyperlipidemic hamsters | 46.7 mg/kg | Decreased TC, TG, TBA and increased the fecal excretion of cholesterol; upregulation of LDLR, CYP7A1 and HMGCR | He et al. (2016) |
| | **In vivo** | C57BL/6 mice on a HFHC diet | 20 mg/kg; 100 mg/kg | Decreased body weight, TC, TG, LDL-C, AST, ALT and increased HDL-C; amelioration of liver pathophysiological changes (swelling of hepatocytes and lipid accumulation); downregulation of SREBP-1c and FAS; upregulation of PPAR-a and OPT1A | Yang et al. (2016) |
| Anti-diabetic activity | **In vitro** | RINm5F cells | 20 μg/ml | Increased insulin secretion | Patel and Mishra (2011) |
| | **In vitro** | Glucose-loaded rats | 40 μg/kg | Inhibition of hepatic gluconeogenesis | Chen et al. (2012) |
| | **In vivo** | HepG2 cells | 0.6 μM | Glucose-lowering effect | Wang et al. (2017) |
| | **In vivo** | Diabetes mellitus Wistar rats | 50, 100 mg/kg | Reduced IL-1β, TNF-α and upregulation of p-AKT, p-AMPK, eNOS | Zhu et al. (2018) |
| | **In vitro** | IR-3T3-L1 adipocytes | 0.5, 1, 5, 10, 20 μM/L | Amelioration of insulin resistance and upregulation of IRS2, PDK1, p-AKT, p-AMPK and GLUT4/1/2 | Patel and Mishra (2012b) |
| | **In vivo** | Hyperlipidemia model mouse | 100 mg/kg | Reduced the body weight and improved glucose tolerance and insulin sensitivity | Yang et al. (2016) |
| | **In vitro** | α-glucosidase | IC₅₀ = 36.25 μg/ml | Inhibitory activity against α-glucosidase | Patel and Mishra (2012a) |
| | **In vivo** | Wistar rats | 20 mg/kg | Increased insulin secretion Patel and Mishra | Patel et al. (2013) |
| | **In vitro** | Lens AR isolated from Wistar rats | IC₅₀ = 3.23 mg/ml | Inhibitory activity against aldose reductase Patel et al. (2013) |
| Anti-microbial activity | **In vitro** | Candida albicans SCS314 | MIC = 256 μg/ml | Inhibitory activity against Candida albicans and Candida auris Liu et al. (2020) |
| | **in vitro** | Candida auris 12372 | 16 μg/ml in Candida albicans and 64 μg/ml in Candida auris | Induced cell wall remodeling Slobodniková et al. (2004) |
| | **in vitro** | Propionibacterium acnes | MIC of 25–50 μg/ml in Propionibacterium acnes | Inhibitory activity against Propionibacterium acnes, coagulase-negative staphylococci and Candida tropicalis Ali et al. (2013) |
| | **in vitro** | Candida tropicalis | MIC of 100–250 μg/ml in coagulase-negative staphylococci | Inhibitory activity against Propionibacterium acnes, coagulase-negative staphylococci and Candida tropicalis Slobodniková et al. (2004) |
| | **in vitro** | Staphylococcus aureus SMRSA 106 and EMRSA 16 | 200 μg/ml | Inhibition of antibiotic resistant Staphylococcus aureus Ali et al. (2013) |
| | **in vitro** | Staphylococcus aureus (MRSA) SA1199B | MIC = 64 mg/L | Inhibitory activity against methicillin-resistant Staphylococcus aureus Yu et al. (2019) |
| | **in vivo** | Neutropenic murine thigh infection model | 25 or 50 mg/kg of jatrorrhizine and 100 mg/kg of NFX | Inhibitory activity against bacterial NA Kim et al. (2014) |
| | **in vitro** | Neumaminidase of Clostridium perfringens | IC₅₀ = 37.0 ± 1.8 μM | Anti-plasmodial, anti-trypanosomal and anti-leishmanial activity Malebo et al. (2013) |
| Anti-protozoal activity | **in vitro** | Plasmodium falciparum K1 | IC₅₀ = 0.24 ± 0.002 μg/ml | Anti-plasmodial, anti-trypanosomal and anti-leishmanial activity Malebo et al. (2013) |
| | **in vitro** | Trypanosoma brucei rhodesiense STIB 900 | IC₅₀ = 4.2 ± 0.002 μg/ml | Anti-plasmodial, anti-trypanosomal and anti-leishmanial activity Malebo et al. (2013) |
| | **in vitro** | Leishmania donovani axenic MHOM-ET-67/82 | IC₅₀ = 20.4 ± 0.03 μg/ml | Anti-plasmodial, anti-trypanosomal and anti-leishmanial activity Malebo et al. (2013) |
| Central nervous system activities | **in vitro** | Madin-Darby canine kidney cell line hOCT2-transfected cells | IC₅₀ = 2.31 ± 0.21 μM IC₅₀ = 4.09 ± 1.2 μM | Inhibition of OCT2 Li et al. (2016) |
| | **in vitro** | | IC₅₀ = 0.120 μM IC₅₀ = 0.819 μM | Inhibition of OCT3 Li et al. (2016) |
| | **in vitro** | | IC₅₀ = 0.278 μM | Decreased 5-HT and NE mediated by OCT2 (Continued on following page)
TABLE 2 | (Continued) Anti-diabetic, antimicrobial, antiprotozoal, and central nervous system activities and mechanisms of jatrorrhizine in in vitro and in vivo assays.

| Effect | Assay | Cell lines/model | Dosage | Type of biological activity | References |
|--------|-------|------------------|--------|----------------------------|------------|
| Anti-Alzheimer’s disease | **In vitro** | MAO-A from rat brain mitochondria | IC\textsubscript{50} = 4 μM | Inhibitory activity against MAO-A enzyme | Kong et al. (2001) |
|  | **In vitro** | Acetylcholinesterase | IC\textsubscript{50} = 0.57 μM | Inhibitory activity against AChE | Lin et al. (2020) |
| | **In vitro** | Recombinant human IDO-1 | IC\textsubscript{50} = 20 μM | Inhibitory activity against IDO-1 | Yu et al. (2010) |
| | **In vitro** | HT22 cells | IC\textsubscript{50} = 17.8 μM | Antioxidation and inhibition of the mitogen-activated protein kinases (MAPK) pathways | Jiang et al. (2015) |
| Neuroprotective effect | **In vitro** | H\textsubscript{2}O\textsubscript{2}-induced rat pheochromocytoma line PC12 injury | 0.01–10.0 μM | Increased cell viability and activities of SOD, HO-1; decreased LDH, MDA and ROS; inhibited apoptosis by inhibiting caspase-3 activation | Luo et al. (2011) |
| Treatment of ischaemic stroke | **In vitro** | mouse brain endothelial cells | 5, 10, 20 μM | Reduced t-BHP-induced apoptosis; decreased ROS, MDA and 4-HNE; inhibited bone destruction by the suppression of MAPKs signaling pathways and downregulation of NFATc1, TRAP, CTR and CTSK | Wu et al. (2020) |
| Anti-parkinsonian Effects on bones | **In vitro** | MAO-B from rat brain mitochondria | IC\textsubscript{50} = 62 μM | Inhibitory activity against MAO-B enzyme | Kong et al. (2001) |
|  | **In vitro** | Titanium Particle-induced murine calvarial osteolytic model (C57BL/6 mice) | 100 mg/kg | Increased BMD and BV/TV, reduced bone erosion and the number of osteoclasts | Li et al. (2018) |
|  | **In vitro** | bone marrow-derived macrophages | 5–20 μM | Inhibited RANKL-induced osteoclast formation and bone resorption by the suppression of MAPKs signaling pathways and downregulation of NFATC1, TRAP, CTR and CTSK | Qiu et al. (2018) |
| Other pharmacological activities | **In vitro** | collagen-induced arthritis (CIA) rats | 20 mg/kg; 50 mg/kg | Inhibited NF-αB and MAPKs stimulated by TNF-α and inhibited bone destruction | Qiu et al. (2018) |
| Effect on gastrointestinal tracts | **In vitro** | Gastrointestinal tract smooth muscles isolated from rat | 100 μM | Increased the amplitude of contractile responses of jejunum and ileum longitudinal muscles, antrum circular muscles and smooth muscles in distal colon, and activated acetylcholine receptors | Yuan et al. (2011) |
|  | **In vitro** | Male Wistar rats | 0.1, 0.3 and 1 mg/kg | Offset of postoperative ileus-induced delayed gastric emptying and intestinal transit | Zhang et al. (2012) |
| Hepatoprotective activity | **In vitro** | t-BHP-treated rat hepatocyte BRL-3A cells | EC\textsubscript{50} = 15.7 ± 3.3 μM | Decreased the release of LDH | Wang et al. (2016) |

Jatrorrhizine, a primary active component of Coptidis Rhizoma, displayed potent inhibition of gut microbiota modulation and decreased the release of glucose transporter 4/1/2 (GLUT4/1/2) (Zhu et al., 2018). Jatrorrhizine is thus considered to be an active ingredient with multiple manners that reduce hypoglycaemia (Table 2).
| Cancer type | Cells or tumor models | Application | Dosage | Suppressive effect | Mechanisms | References |
|-------------|----------------------|-------------|--------|-------------------|------------|------------|
| Melanoma    | C8161 human metastatic melanoma cell line | In vitro | 80, 160, 320 μmol/L, 48 h | Inhibition of cell proliferation and neovascularization | Cell cycle arrest, and upregulation of p21 and p27, p53 | Liu et al. (2013) |
| Colorectal cancer | Matrigel plug assay in BALB/C nude mice | In vivo | 50 μg, 14 days | Inhibition of cell proliferation and cell viability | Reduced numbers of blood vessels | Singh et al. (2016) |
| SW480 human colon cancer cell line | In vitro | 25–200 μg/ml, 24 and 48 h | Inhibition of cell proliferation and cell viability | Cell cycle arrest, and upregulation of p21 and p27, p53 | Liu et al. (2013) |
| SW620 colorectal cancer cell line | In vitro | 100 μM | Inhibition of cell proliferation | Formation of complexes with oncogene KRAS promoter NHE G-quadruplex | Wen and Xie (2017) |
| Human colorectal carcinoma cell lines HCT-116 and HT-29 | In vitro | IC_{50} of HCT-116: 6.90 ± 0.29 μM, 72 h; IC_{50} of HT-29: 5.46 ± 0.13 μM, 72 h 5, 10, 15 μM 24, 48, and 72 h | Suppression of cell growth and proliferation, inhibit migration and invasion | Promotion of apoptosis, induced nuclear morphological changes, block of cell cycle in S phase, repressed ΔΨm, reduced β-catenin, F-actin and N-cadherin, and increased GSK-3β and E-cadherin | Wang et al. (2019a) |
| HCT-116 nude mice xenograft model | In vivo | 5 mg/kg, 4 weeks | Inhibition of tumor growth and metastasis | Reduced tumor volume and weight, upregulation of GSK-3β and E-cadherin, and downregulation of β-catenin, F-actin and N-cadherin | Deng and Wan (2021) |
| Liver cancer | HepG2 and HCCLM3 liver cancer cells | In vitro | 0.5–16.0 μM, 48 h | Inhibition of cell viability, proliferation, invasion and migration | Promotion of apoptosis, downregulation of miR-221-3p and miR-15b-5p expression, and upregulation of Axin2 protein | Sun et al. (2019) |
| Breast cancer | MDA-MB-231 triple-negative breast cancer cell line, MCF-7 estrogen receptor positive breast carcinoma cell line, and 4T1 mouse mammarycarcinoma cells | In vitro | 10, 20, 30 μM 24 and 48 h | Inhibition of cell proliferation | Repressed ΔΨm, suppressed Wnt/β-catenin signaling and EMT expression via targeted TNIK, upregulation of GSK-3β and E-cadherin, and downregulation of β-catenin, F-actin and N-cadherin, upregulate Bax, downregulation of Bcl-2, decreased Procaspe-3, Procaspe-8, Procaspe-9 and PARP | Sun et al. (2019) |
| Orthotopic 4T1 tumour bearing mouse | In vivo | 2.5 mg/kg b.w 5 mg/kg b.w 4 weeks | Inhibition of the growth and metastasis | Reduced tumor growth rate and improve survival rate, upregulation of GSK-3β and E-cadherin, downregulation of TNK, p-TNIK, F-actin, β-catenin, and N-cadherin | Sun et al. (2019) |
| Thyroid cancer | SW1736, BHP7-13, and 8305C cell lines | In vitro | 1.5, 3, 6, 12, 24, 48 μM, 48 h | Inhibition of cell proliferation | Cell cycle arrest, increased accumulation of ROS, promoted the levels of cleaved caspase-3 and p-H2AX, suppressed pS6, p-ERK1/2, p-4E-BP1, p-AKT, KU70, ERO1L, RAD51 and KU80, downregulation of the PI3K/AKT/mTOR signaling pathway and promotion of DNA damage | Lu et al. (2020) |
| Female athymic nude mice | In vivo | 24.0 mg/kg, 14 days | Inhibition of tumor growth | Increased pH2AX and acetylated histone H3, histone H4 and cleaved caspase-3 | (Continued on following page) |
However, a comparative study of jatrorrhizine and existing anti-diabetic drugs is not available. Systematic clinical research and molecular studies of jatrorrhizine are still needed to elucidate definite mechanism of action. It is reported that other alkaloids in Coptidis Rhizoma also exhibit anti-diabetic effects, such as berberine, coptisine and palmatine (Lyu et al., 2021). The synergy between this natural metabolite with other alkaloids in Coptidis Rhizoma is of special interest, including interacts with berberine, coptisine and palmatine.

### Anti-Microbial and Anti-protozoal Activity

Jatrorrhizine, in plants such as Mahonia aquifolium (Pursh) Nutt., Berberis brevissima Jafri and Coptis chinensis Franch. (Slobodniková et al., 2004; Ali et al., 2013; Tseng et al., 2021), is a notable among natural products for its varied anti-microbial properties. This metabolite strongly inhibited the growth of some bacteria, such as Candida albicans SC5314 (MIC = 256 µg/ml), Candida auris 12372 (MIC = 256 µg/ml), Candida tropicalis (MIC = 125 µg/ml), Propionibacterium acnes (MIC between 25 and 50 µg/ml), coagulase-negative staphylococci (MIC between 100 and 250 µg/ml) and Staphylococcus aureus (200 µg/ml) (Slobodniková et al., 2004; Ali et al., 2013; Liu et al., 2020). This alkaloid induced cell wall remodeling at 16 µg/ml in Candida albicans and 64 µg/ml in Candida auris (Liu et al., 2020). The mechanism underlying the antinocytic effect was inhibition of drug efflux and expression of the NorA multi-drug efflux pump (Yu et al., 2019). Further, a combination of jatrorrhizine (25 or 50 mg/kg) and norfloxacin (NFX, 100 mg/kg) significantly decreased bacterial count in a murine thigh infection model, suggesting in vivo synergistic bacterial activity. Moreover, the combination of five berberine alkaloids (berberine: coptisine: jatrorrhizine: palmatine: epiberberine = 0.702 : 0.863 : 1: 0.491: 0.526) exhibited broad-spectrum antibacterial activity, and this activity was verified in vivo using cyclophosphamide-immunosuppressed mouse model and in vitro against Escherichia coli, Staphylococcus aureus, Staphylococcus dysenteriae, and Staphylococcus pneumoniae. Hence, jatrorrhizine may act synergistically with other alkaloids (Luo et al., 2013). Moreover, jatrorrhizine showed a synergistic effect with colistin antibacterial activity against carbapenem-resistant Klebsiella pneumoniae, exhibiting one-to two-fold reductions of colistin MIC (Tseng et al., 2021).

Neuraminidase (NA) is a novel target for the development of therapeutic agents to treat bacterial or viral infections (Kim et al., 2014; Luo et al., 2020). As documented in literature, jatrorrhizine showed inhibitory activity on bacterial NA with an IC_{50} value of 37.0 ± 1.8 µM and suppressed viral NA activity against rH1N1 and H5N1 with IC_{50} values of 66.2 ± 4.2 µM and 76.3 ± 2.1 µM (Kim et al., 2014). Molecular modelling and docking studies indicated that jatrorrhizine might be a potent agent against transmembrane protease serine 2 (TMPRSS2) enzyme for treating SARS-CoV-2 (Pooja et al., 2021). It bound to human immunodeficiency virus-1 (HIV-1) as an effective inhibitor of HIV (Namthabad and Mamidala, 2014). Therefore, jatrorrhizine is a promising therapeutic agent and a natural metabolite of the combination therapy for microbial diseases.

### Pharmacological Properties of Jatrorrhizine

**TABLE 3** | (Continued) The anti-cancer effects of jatrorrhizine and its complexes.

| Cancer type | Cells or tumor models | Application | Dosage | Suppressive effect | Mechanisms | References |
|-------------|-----------------------|-------------|--------|-------------------|------------|------------|
| HeLa cancer | Human cervical (HeLa) cell line | *In vitro* | Pt1: 15.01 ± 1.05 nM, Pt2: 1.00 ± 0.17 nM | Inhibition of cell proliferation | Targeting p53 and telomerase, repressed telomerase-related-proteins (c-myc and hTERT), promoted DNA damage (activation of 53BP1, H2AX, TRF1, and TRF2), decreased ΔΨm, sub-G1 phase arrest and cell apoptosis | Qin et al. (2019b) |
| Bladder cancer | Human cervical (HeLa)-xenograft model | *In vivo* | Pt2: 2.0 mg/kg per 2 days, 21 days | Inhibition of tumor growth | Induced TRF1- and TRF2-telomeres damage, decreased hTERT and c-myc levels, increased ROS, cytochrome c, caspase-9, caspase-3, Apaf-1, inhibited Bcl-2, and cell cycle arrest (suppression of cyclin D1 and CDK2) | Qin et al. (2019a) |
| Bladder cancer | Human bladder T-24 tumor cell | *In vitro* | Pt1: 100.0 nM, 6 h, Pt2: 10.0 nM, 6 h | Inhibition of cell proliferation | | | |
| | T-24 xenograft mouse models (nude mice) | *In vivo* | Pt1: 2.0 mg/kg per 2 days, Pt2: 2.0 mg/kg per 2 days | Inhibition of tumor growth | | | |
0.002 μg/ml) and anti-leishmanial activity against Leishmania donovani axenic MHOM-ET-67/82 strain (IC\textsubscript{50} = 20.4 ± 0.03 μg/ml) (Malebo et al., 2013).

In vivo validation of naturally occurring anti-microbials and the development of effective alternatives to anti-biotics is crucial in the current era of microorganism resistance. Several studies report anti-microbial and anti-protozoal activity of jatrorrhizine in vitro, but clinical efficacy, therapeutic doses, safety and mechanisms remain largely unknown.

**Effects on the Central Nervous System**

**Anti-depressant Activity**

Jatrorrhizine demonstrated anti-depressant activity via several targets in anti-depressant therapeutics. It showed strong inhibitory activity against monoamine oxidase A (MAO-A) (IC\textsubscript{50} = 4 μM). This inhibitory activity was greater than that of berberine (IC\textsubscript{50} = 126 μM), which lacks the phenolic hydroxyl of jatrorrhizine (Kong et al., 2001; Zhang et al., 2019). Furthermore, several studies have shown that organic cation transporters (OCTs) play roles in anti-anxiety and anti-depressant processes (Bacq et al., 2012) and plasma membrane monoamine transporter (PMAT) is a novel anti-depressant target. Jatrorrhizine was proved to be a high-affinity substrate for OCTs and a potent inhibitor of OCT2 (IC\textsubscript{50} = 2.31 ± 0.21 μM) and OCT3 (IC\textsubscript{50} = 4.09 ± 1.2 μM) (Li et al., 2016). Moreover, jatrorrhizine strongly reduced serotonin (5-HT) and norepinephrine (NE) uptake mediated by hOCT2, hOCT3, and hPMAT in vitro. Meanwhile, jatrorrhizine reduced 5-HT and NE uptake at 50 μM in mouse synaptosomes, and reduced the duration of immobility and reversed the effect of stress in tail suspension tests, consistent with an anti-depressant effect. However, more in vivo experiments are needed to verify and clarify the complex anti-depressant activity of jatrorrhizine.

**Anti-Alzheimer’s Disease**

The Alzheimer’s disease (AD) is currently attributed to extracellular aggregates of amyloid β (Aβ) plaques and intracellular neurofibrillary tangles in cortical and limbic areas of the human brain (Tiwari et al., 2019). Defects in acetylcholine and cholinergic neurotransmission can be observed along with the accumulation of β-amyloid. The use of acetylcholinesterase (AChE) inhibitors, which activate central cholinergic function, is a treatment strategy for AD. Jatrorrhizine demonstrated inhibitory activity against AChE with IC\textsubscript{50} values of 0.57 μM (Lin et al., 2020), 106.1 μM (Zhao et al., 2016) and 2.08 μM (Xiao et al., 2011), respectively. The differences in these values might be explained by the different sources and concentrations of the enzyme and substrate used for testing. Further, a jatrorrhizine derivative with -NH\textsubscript{2} linked at the 3-position (IC\textsubscript{50} = 0.301 μM) exhibited the greater AChE inhibitory activity than jatrorrhizine (IC\textsubscript{50} = 0.872 μM) (Jiang et al., 2017). Hence, structural modification of jatrorrhizine may be effective for modulating its activity.

Indoleamine 2, 3-dioxygenase 1 (IDO-1) is a rate-limiting enzyme in the kynurenine pathway of tryptophan metabolism. The accumulation of a downstream neurotoxic metabolite via overexpression or over activation of IDO1 is involved in neurodegenerative disease (Zhang et al., 2017; Rohrig et al., 2019). Jatrorrhizine was able to irreversibly inhibit IDO1, and had IC\textsubscript{50} values of 206 μM (recombinant human IDO-1) and 17.8 μM (in HEK 293-hIDO1 cells) (Yu et al., 2010).

In vivo treatment of APP/PS1 transgenic mice with 5 mg/kg or 10 mg/kg jatrorrhizine reduced levels of Aβ plaques in the cortex and hippocampus, and alleviated the learning and memory deficits (Wang S. et al., 2019). Learning and memory impairment in AD is related to dysfunction in gut microbiota (Vogt et al., 2017). Microbial colonies of APP/PS1 mice showed altered composition compared to C57BL/6 wild-type (WT) mice. High dose jatrorrhizine treatment modulated microbiota populations and enriched the numbers of beneficial bacteria, such as Faecalibaculum, Lactobacillus acidophilus and Bifidobacterium (Wang S. et al., 2019). Thus, jatrorrhizine might affect the learning and memory capabilities by regulating the intestinal flora.

Neuroprotective effects of jatrorrhizine are mainly attributed to its anti-oxidant property and anti-apoptosis activity. The alkaloid alleviates alleviated oxidative damage and suppresses neuronal apoptosis. Jatrorrhizine exhibited neuroprotective activity on okadaic acid (OA)-induced cytotoxicity and apoptosis in HT22 cells. This effect ascribed to increase cell viability, enhance anti-oxidant status (SOD and GSH) and maintenance of mitochondrial membrane potential (MMP). Reduced lactate dehydrogenase (LDH) release, lipid peroxidation (MDA) levels and reactive oxygen species (ROS) were also observed. Other responses included downregulation of expression of phosphorylated extracellular signal-regulated kinases 1/2 (p-ERK1/2), phosphorylated c-Jun N-terminal kinases (p-JNK) and phosphorylated p38 (p-p38), along with upregulation of B cell lymphoma 2 (Bcl-2), reduction in cleaved caspase-3 and BCL-2-associated X protein (Bax) levels, and inhibition of NF-κB p65 subunit activation (Jiang et al., 2015). A possible mechanism was inhibition of mitogen-activated protein kinase (MAPK) pathways. Similarly, jatrorrhizine was effective in mitigating hydrogen peroxide (H\textsubscript{2}O\textsubscript{2})-induced rat pheochromocytoma PC12 injury via reducing oxidative stress and inhibiting apoptosis (Luo et al., 2011). Furthermore, treatment with jatrorrhizine (10 mM) alleviated Aβ 25-35-induced nerve cell injury through upregulating miR-223-3p and inhibiting histone deacetylase 4 (HDAC4) expression. The alkaloid also suppressed apoptosis and oxidative stress (OS) and improved SH-SY5Y cell proliferation (Duan and Chen, 2021).

**Other Effects on the Central Nervous System**

Jatrorrhizine might have therapeutic potential for ischaemic stroke associated with endothelial dysfunction. The alkaloid produced protective effect in mouse brain endothelial cells (MBECs) treated with tert-butyl hydroperoxide (t-BHP) via reducing cell apoptosis, inhibiting oxidative damage and ameliorating mitochondrial dysfunction. Jatrorrhizine also prevented the expression of IL-1β, TNF-α and IL-6, and upregulated endothelial nitric oxide synthase (eNOS) and prevented decreases in PPAR-γ protein expression in MBECs (Wu et al., 2020). Jatrorrhizine also non-competitively inhibited MAO-B from rat brain mitochondria with an IC\textsubscript{50} value of 62 μM (Kong et al., 2001). This activity was intended to be helpful for the prevention and adjunct treatment of Parkinson’s disease.
Anti-Cancer Activity

Globally, cancer is one of the major diseases that cause a large number of deaths, and the incidence of cancer is increasing in recent years (Sharma et al., 2019). Inhibition of apoptosis, unlimited proliferation of cancer cells, invasion of normal organs and destruction of normal tissues are the main reasons that cancer threatens human health (Rosell and Karachaliou, 2015; Roy and Saikia, 2016). Over the past decades, development of anti-tumor agents from natural products has been one of the fresh approaches for therapeutic candidate discovery. Jatrorrhizine exhibited anti-cancer activity in various cancer cells (in vitro) and a few in vivo models (Table 3). Its multidirectional mechanisms involve in inhibiting cancer cell proliferation and tumor growth, preventing metastasis, while the important mechanism is promoting apoptosis of cancer cells (Figure 4).

Inhibition of Cell Proliferation

The rapid and unlimited proliferation of cancer cells is attributed to the loss or gene mutations of critical checkpoint controlling cycling of cell phase (Andrade-Tomaz et al., 2020). As an important process in cancer development, cell cycle modulation is a well-established therapeutic schedule. Jatrorrhizine (5–15 μM) affected human colorectal carcinoma HCT-116 and HT-29 cells proliferation by blocking cell cycle in S phase and it (5 mg/kg) could prolong the survival of nude mice xenografted HCT-116 cells (Wang P. et al., 2019). In C8161 human metastatic melanoma cells, jatrorrhizine (160 mmol/L) inhibited cell proliferation through inducing cell cycle arrest in the G0/G1 phases and upregulating expression of cyclin-dependent kinase (CDK) inhibitors (p21 and p27) and the tumor suppressor p53 (Liu et al., 2013). The derivative, Pt(II) complexes with jatrorrhizine blocked cell cycle at G1 phase in human bladder T-24 tumor cells, which was associated with inhibiting the levels of cyclin D1 and CDK2 (Qin et al., 2019a). microRNAs play a prominent role in modulation of cell proliferation by directly targeting cell cycle regulators, such as cyclin, c-myc, p27 and p57 (Yu et al., 2010). Jatrorrhizine (16.0 µM) inhibited cell viabilities of HepG2 and HCCLM3 liver cancer cells by down-regulating miR-221-3p and miR-15b-5p expressions (Deng and Wan, 2021).
Inhibition of Cancer Cell Metastasis
Abnormal vascularization and epithelial-mesenchymal transition (EMT) are essential for metastatic spread of cancer cells (Dewaguet et al., 2021). In BALB/C nude mice xenografted metastatic melanoma C8161 cell, jatrorrhizine (50 μg) reduced neovascularization of tumor, probably due to its suppression of CDH5 expression, which encodes the vascular endothelial cadherin (Liu et al., 2013). Traf2 and Nck interacting serine protein kinase (TNIK) has been considered as an important activator of Wnt signaling pathway to promote tumor progression and invasion (Yang et al., 2021). MDA-MB-231 human breast cancer cells targeted knockout of TNIK validated that the disruption of TNIK restrained the key proteins expression of Wnt/β-catenin signalling and EMT (Sun et al., 2019). Interestingly, jatrorrhizine exhibited good binding affinity and interaction with TNIK. The alkaloid effectively downregulated TNIK, p-TNIK, β-catenin, F-actin and N-cadherin expression levels, and upregulated GSK-3β and E-cadherin in in vitro (MDA-MB-231 cells and MCF-7 cells) and in vivo models (Orthotopic 4T1 tumour bearing mouse) (Sun et al., 2019). Moreover, jatrorrhizine (5 mg/kg) also reduced tumor volume and weight, and inhibited lung metastasis in nude mice xenografted HCT-116 colorectal carcinoma cells via suppressing Wnt signaling pathway and the process of EMT (Wang P. et al., 2019). Hence, jatrorrhizine is expected to be an anticancer drug targeting TNIK and EMT.

Promotion of Apoptosis
Apoptosis is considered as a major barrier for the development and progression of cancer (Boudreau et al., 2019). Jatrorrhizine (10–30 μM) triggered mitochondrial dysfunction and apoptosis in MDA-MB-231 breast cancer cells. The relevant mechanism was related to disruption of ΔΨm, upregulation of the pro-apoptotic protein Bax, and downregulation of the anti-apoptotic protein Bcl-2, as well
as decrease of apoptosis-related proteins including Procaspase-3, Procaspase-8, Procasc-pase-9 and PARP (Sun et al., 2019). Similarly, jatrorrhizine showed disruptive effect on ΔΨm and nuclear morphological changes in human colorectal carcinoma HCT-116 and HT-29 cells, indicating mitochondrial dysfunction and early apoptosis (Wang P. et al., 2019). Besides, jatrorrhizine-Platinum(II) complex promoted DNA damage of thyroid cancer SW1736 and BHP7-13 cells via increasing pH2AX protein (DNA damage protein) and decreasing DNA repair protein KU70, KU80 and RAD51, while activated apoptosis by upregulating ROS and cleaved caspase-3, and downregulating PI3K/akt/mTOR pathway (Ps6, p-ERK1/2, p-4E-BP1, and p-AKT levels) (Lu et al., 2020). In mice bearing SW1736 tumor xenografts, this derivative suppressed tumor growth and tumor tissues expression of pH2AX, which confirmed its anti-cancer activity in vivo (Lu et al., 2020). The complexes of jatrorrhizine with platinum (Pt1 and Pt2) induced apoptosis in HeLa cancer cells, which was manifested in that these derivatives target p53 and telomerase and further caused DNA damage via suppression of c-myc and human telomerase reverse transcriptase (htERT), and activation of 53BP1, pH2AX, TRF1, and TRF2 (Qin et al., 2019b). Consistent with that in HeLa cancer cells, a novel Pt(II) complex as well modulated telomerase related-proteins and DNA damage. It also successfully achieved the induction of apoptosis to decrease ΔΨm and Bcl-2, increase the release of ROS and cytochrome c, and up-regulate caspase-9, caspase-3 and apoptotic protease activating factor 1 (Apaf-1) (Qin et al., 2019a).

Several studies have illustrated that jatrorrhizine and its derivatives exert anti-cancer effect with low systemic toxicity in in vivo models, which inhibited tumor growth and metastasis and prolong the survival time for mice bearing tumor xenografts (Liu et al., 2013; Qin et al., 2019a; Wang P. et al., 2019; Sun et al., 2019). Additionally, the complexes of jatrorrhizine with platinum had good effects in the induction of cisplatin-resistant cancer SK-OV-3 cells and could reduce the side effects of anti-tumor drugs such as cisplatin (Qin et al., 2019a; Lu et al., 2020).

On the whole, jatrorrhizine and its derivatives may be a logical agent for tumor therapy. However, in the retrieved studies, the experiments also lacked the information on the selectivity index. More positive controls (anti-cancer drugs for clinical use) are required to further confirm the anticancer effects of jatrorrhizine. We observed that jatrorrhizine inhibited different types of cancer, but in vivo models of different cancer stages including tumorigenesis, development and metastasis were not fully considered. More importantly, elaborate consideration needs to be taken into the validation criteria of the models used. In addition, its clinical efficacy, specific targets and long-term drug safety during cancer treatment are critical issues to be addressed.

**Effects on Bones**

Jatrorrhizine inhibited osteolysis in titanium particle-induced murine calvarial osteolytic (C57BL/6 mice). Treatment with the alkaloid (100 mg/kg) significantly increased bone mineral density (BMD) as well as bone volume/tissue volume (BV/TV), and reduced bone erosion and the number of osteoclasts (Li et al., 2018). In bone marrow-derived macrophages, jatrorrhizine inhibited receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclast formation and bone resorption. Mechanism analysis revealed that these effects were mediated via suppression of MAPK (p38 and ERK) signaling and downregulation of nuclear factor of activated T-cells cytoplasmic 1 (NFATc1) and NFATc1-associated osteoclastic genes including tartrate-resistant acid phosphatase (TRAP), calcinon receptor (CTR) and cathepsin K (CTSK) (Li et al., 2018). Also, jatrorrhizine suppressed the activation of NF-κB and MAPK stimulated by TNF-α, thereby inhibiting inflammatory responses and bone destruction in collagen-induced arthritis (CIA) rats (Qiu et al., 2018). Bone protection and anti-inflammatory effects suggest that jatrorrhizine may be beneficial in reducing infection after orthopaedic titanium implantation. Overall, this natural product may be useful agents for treatment of bone disorders.

**Other Pharmacological Activities of Jatrorrhizine**

**Effects on Gastrointestinal Tracts**

Jatrorrhizine at concentrations from 1.0 to 300 μM increased the amplitude of spontaneous contractions of gastrointestinal tract smooth muscles isolated from rats in a concentration-dependent manner. Jatrorrhizine (100 μM) markedly increased contractile responses of jejenum and ileum longitudinal muscles, antrum circular muscles and smooth muscles in the distal colon. These effects were mediated by activation of acetylcholine receptors (probably M3 receptors) and associated with calcium agonistic effects, including enhancing Ca2+ influx through L-type Ca2+ channel and Ca2+ release via IP3 and ryanodine pathways (Yuan et al., 2011). Moreover, in vivo experiments in rats demonstrated that jatrorrhizine (0.1, 0.3 and 1 mg/kg) offset postoperative ileus-induced delayed gastric emptying and intestinal transit in a dose-dependent manner (Zhang et al., 2012). Hence, jatrorrhizine may be useful for treatment of functional disorders of the gastrointestinal tract.

**Hepatoprotective Activity**

Jatrorrhizine is one of the constituents in three traditional Chinese medicine formulae with hepatoprotective activity for treating jaundice, namely Zhi-Zi-Da-Huang-Tang, Yin-Chen-Hao-Tang and Da-Huang-Xiao-Shi-Tang. The alkaloid decreased the release of LDH (EC50 = 15.7 ± 3.3 μM) in a study on t-BHP-injured rat hepatocyte BRL-3A cells. LDH release is an indicator of liver damage and reduced release is evidence of a hepatoprotective effect against oxidative damage (Wang et al., 2016).

**PHARMACOKINETICS OF JATRORRHIZINE**

Pharmacokinetic evaluation of drugs provides increasingly important information for clinical research. The
| Route of administration | Inclusion of drug components | Species | Dose | Pharmacokinetic parameters | References |
|-------------------------|------------------------------|---------|------|----------------------------|------------|
| Oral                    | Jiaotai Pills extracts       | Rat (brain) | 300 mg/kg Rhizoma Coptidis extracts and 4.7 mg/kg cinnamon oil (equivalent to 15.52 mg/kg dose of jatrorrhizine) | $T_{\text{max}} = 2.17 \pm 1.11$ min $T_{1/2} = 2.89 \pm 1.76$ h $\text{AUC}_{0-t} = 16.96 \pm 1.57$ ng h$^{-1}$ mL$^{-1}$ $\text{AUC}_{0-\infty} = 24.45 \pm 1.73$ ng h$^{-1}$ mL$^{-1}$ $K_e = 0.98 \pm 1.79$ h$^{-1}$ $C_{\text{max}} = 5.56 \pm 2.40$ ng/ml | Zhang et al. (2018) |
|                         |                              | Insomnic rat (brain) | $T_{\text{max}} = 2.13 \pm 1.03$ min $T_{1/2} = 6.35 \pm 2.25$ h $\text{AUC}_{0-t} = 34.26 \pm 7.03$ ng h$^{-1}$ mL$^{-1}$ $\text{AUC}_{0-\infty} = 43.53 \pm 4.63$ ng h$^{-1}$ mL$^{-1}$ $K_e = 0.21 \pm 0.16$ h$^{-1}$ $C_{\text{max}} = 8.74 \pm 2.68$ ng/ml | He et al. (2014a) |
| Oral                    | Jiaotai Pills extracts       | Rat (plasma) | 300 mg/kg Rhizoma Coptidis extracts and 4.7 mg/kg cinnamon oil (equivalent to 15.52 mg/kg dose of jatrorrhizine) | $T_{\text{max}} = 5.25 \pm 2.22$ min $T_{1/2} = 3.88 \pm 1.46$ h $\text{AUC}_{0-t} = 10.36 \pm 4.28$ ng h$^{-1}$ mL$^{-1}$ $\text{AUC}_{0-\infty} = 13.22 \pm 4.63$ ng h$^{-1}$ mL$^{-1}$ $K_e = 0.20 \pm 0.08$ h$^{-1}$ $C_{\text{max}} = 1.04 \pm 0.67$ ng/ml | He et al. (2014a) |
|                         |                              | Insomnic rat (plasma) | $T_{\text{max}} = 0.53 \pm 0.30$ min $T_{1/2} = 8.94 \pm 15.99$ h $\text{AUC}_{0-t} = 9.47 \pm 2.25$ ng h$^{-1}$ mL$^{-1}$ $\text{AUC}_{0-\infty} = 13.22 \pm 4.63$ ng h$^{-1}$ mL$^{-1}$ $K_e = 0.33 \pm 0.20$ h$^{-1}$ $C_{\text{max}} = 8.64 \pm 2.17$ ng/ml | Shi et al. (2012) |
| i.v.                    | Jatrorrhizine                | Rat (plasma) | 0.1 mg/kg | $T_{\text{max}} = 0.50 \pm 0$ h $T_{1/2} = 8.5 \pm 2.6$ h $\text{AUC}_{0-t} = 7.6 \pm 2.9$ μg h$^{-1}$ L$^{-1}$ $\text{AUC}_{0-\infty} = 9.6 \pm 3.6$ μg h$^{-1}$ L$^{-1}$ $V_d = 188.9 \pm 121.7$ L/kg $CL = 11.6 \pm 3.8$ L/h/kg $\text{MRT}_{0-t} = 5.7 \pm 2.3$ h $T_{1/2} = 10.6 \pm 5.4$ h $\text{AUC}_{0-t} = 29.9 \pm 13.1$ μg h$^{-1}$ L$^{-1}$ $\text{AUC}_{0-\infty} = 32.1 \pm 13.4$ μg h$^{-1}$ L$^{-1}$ | Shi et al. (2012) |
|                         |                              | 0.3 mg/kg | $V_d = 149.9 \pm 74.4$ L/kg $CL = 10.6 \pm 3.9$ L/h/kg $\text{MRT}_{0-t} = 8.3 \pm 4.2$ h $T_{1/2} = 8.9 \pm 2.2$ h $\text{AUC}_{0-t} = 307.8 \pm 85.9$ μg h$^{-1}$ L$^{-1}$ $\text{AUC}_{0-\infty} = 308.9 \pm 85.7$ μg h$^{-1}$ L$^{-1}$ | |
|                         |                              | 3 mg/kg | $V_d = 137.0 \pm 57.5$ L/kg $CL = 10.3 \pm 2.8$ L/h/kg $\text{MRT}_{0-t} = 8.8 \pm 1.4$ h | |
| Oral                    | San-Huang decoction          | Rabbit (plasma) | 7.67 ml/kg (equivalent to 7.13 mg/kg dose of jatrorrhizine) | $T_{\text{max}} = 1.94 \pm 0$ h $T_{1/2} = 12.12 \pm 4.47$ h $\text{AUC}_{0-t} = 1,099.5 \pm 292.67$ ng/ml $C_{\text{max}} = 71.3 \pm 7.72$ ng/ml | Liu et al. (2011) |

(Continued on following page)
pharmacokinetic profile of jatrorrhizine after oral or intravenous administration was assessed in rats and rabbits using liquid chromatography-tandem mass spectrometry (LC-MS/MS), LC-MS/MS combined with brain micro-dialysis, ultra-high performance liquid chromatography-mass spectrometry (UPLC-MS/MS), UPLC-orbitrap mass spectrometry and liquid chromatography quadrupole time-of-flight mass spectrometry (LC-qTOF-MS) (Deng et al., 2008; Liu et al., 2011; Shi et al., 2012; He W. et al., 2014; Zhang et al., 2018). The pharmacokinetic parameters of these studies are shown in Table 4.

Cui et al. (2015) reported permeability and absorption of jatrorrhizine in rats after oral administration. An apparent permeability coefficient of jatrorrhizine (0.23–0.36 × 10⁻⁶ cm s⁻¹) indicated limited ability to cross cell membranes. P-glycoprotein (P-gp) efflux had a significant effect on the absorption of this compound, which may explain its poor bioavailability. Intestinal perfusion experiments confirmed absorption into the rat jejunum (8.98 ± 2.43% and ileum (7.54 ± 1.45%) (Cui et al., 2015). Jiaotai Pill extracts containing jatrorrhizine (15.52 mg/kg) was administered orally to rats and the pharmacokinetic parameters in rat brain were assessed using LC-MS/MS. The half-life of terminal elimination phase (T1/2), AUC (0-∞) and Cmax in insomnic rats were increased compared with normal controls (Zhang et al., 2018). Thus, the absorption and bioavailability of jatrorrhizine may increase under pathological conditions. A study on plasma pharmacokinetics reported similar results (He W. et al., 2014).

**Table 4** Pharmacokinetic parameters of jatrorrhizine.

| Route of administration | Inclusion of drug components | Species | Dose | Pharmacokinetic parameters | References |
|-------------------------|------------------------------|---------|------|-----------------------------|------------|
| Oral                    | Coptis-evodia powder (6:1, g/g) | Rat (plasma) | 1.086 g/kg (equivalent to 14.4 mg/kg dose of jatrorrhizine) | T_{max} = 90 ± 0 min  
T_{1/2} = 325.3 ± 8.0 min  
AUC_{0-∞} = 43,576.9 ± 4,767.8 ng min/mL  
C_{max} = 219.9 ± 12.8 ng/ml  
T_{max} = 0.67 ± 0.23 h  
T_{1/2} = 8.6 ± 2.61 h  
AUC_{0-∞} = 8.6 ± 0.80 ng/mL | Deng et al. (2008) |
| Oral                    | Coptis Root extract | Rat (plasma) | 800 mg/kg | T_{max} = 2.75 ± 0.25 h  
T_{1/2} = 7.0 ± 0.35 h  
AUC_{0-∞} = 6.6 ± 0.70 ng/mL  
C_{max} = 12.7 ± 0.84 ng/ml | Zhao et al. (2018) |
| Oral                    | Shuanghua Baihe tables powder | 3.13 g/kg | Oral Coptidis Rhizoma extract | Rat (plasma) | 1.08 g/kg | T_{max} = 1.53 ± 0.20 ng/ml  
AUC_{0-∞} = 33.35 ± 5.82 μg/L | Sun et al. (2018) |
| Oral                    | JinQi Jiangtang tablets | 0.4536 g/200 g | Oral Coptidis Rhizoma powder | Rat (plasma) | 1.08 g/kg | MRT_{0-∞} = 6.14 ± 0.30 h  
AUC_{0-∞} = 96.58 ± 21.69 μg/L | Yan et al. (2012) |
| Oral                    | Zoujinwan | Rhizoma coptidis powder | 1.08 g/kg and Evodia rutaecarpa powder 0.18 g/kg |  | | [**References**]

T_{max}: the time of maximum plasma concentration; T_{1/2}: the elimination half-life; AUC: area under the concentration-time curve; C_{max}: maximum plasma concentration; K_{e}: eliminate rate constant; Vd: apparent volume of distribution; CL: clearance; MRT: mean residence time; VRT: the variance of residence time.
TOXICITY OF JATRORRHIZINE

Toxicity and safety are critical for the assessment of clinical applications of natural products (Li et al., 2021). Jatrorrhizine is a bioactive metabolite in some commonly used medicinal plants and has been used for centuries in traditional medicine. However, analyses of the composition of traditional medicines and modern pharmacology research indicate that some natural products may produce adverse effects or even overt toxicity under certain conditions despite their beneficial pharmacological properties. Jatrorrhizine exhibited anti-cancer activity on SW480 cells (human colon cancer) and HepG2 cells (hepatocellular carcinoma) as discussed above. However, it also showed cytotoxicity against these cancer cells the at the concentrations of 200 μg/ml and 100 μM, respectively (Chen et al., 2012; Singh et al., 2016). Slight cytotoxicity was also reported in normal MCF10A normal breast epithelial cells in vitro (100 μM) (Sun et al., 2019). However, jatrorrhizine did not cause cytotoxicity to MCF-7 cells at the concentration below 10 μM (Lo et al., 2017). Additionally, Sun et al. (2019) reported that gross necropsy did not show signs of toxicity in the jatrorrhizine-treated (2.5 and 5 mg/kg) 4T1 tumour-bearing mice (Sun et al., 2019). Also, there was no significant changes in body weight and serum ALT and AST levels in jatrorrhizine (25 and 100 mg/kg)-treated Ti particle-induced mice, as compared with the untreated and control groups (Li et al., 2018). The alkaloid was also non-cytotoxic to rheumatoid arthritis-derived fibroblast-like synoviocyte MH7A cells, and no damage to liver function was observed in CIA rats at administered doses of 20 and 50 mg/kg (Qi et al., 2018).

Curative Mechanisms of Jatrorrhizine and Clinical Validity Confirmation

We recognise a potential for jatrorrhizine to be a therapeutic ingredient in medications, reflecting its impacts on multiple pathways and targets. However, its specific mechanisms of action against various diseases are not fully understood. Clarification the molecular targets of jatrorrhizine is conducive to a more scientific understanding and development of this natural metabolite. Currently, this natural metabolite is rarely alone used clinically to treat specific diseases even though it is the main active substance in some medicinal materials and extracts and has a role in the treatment of diabetes, gastrointestinal diseases, and Alzheimer’s disease in traditional medicine. Proper positive controls are necessary for future work to ensure the reproducibility and data quality for comparisons of therapeutic effects on various diseases and different disease stages. Sufficient evidence is available to support the detailed assessment of curative mechanisms of jatrorrhizine, structure-activity studies and clinical trials in humans. Such work...
should be approached systematically to fully explore the clinical utility of the alkaloid.

Jatrorrhizine is widely reported to exhibit pro-apoptotic effects in multiple cancer cells. However, it displays a protective role in AD and ischaemic stroke via reducing apoptosis. Mechanisms underlying these disparate effects require elucidation to understand actions on apoptosis in neuroprotection and cancer therapy, and subsequently improve targeting and specificity of jatrorrhizine through structural modification and dosage form optimization (e.g., as nanoparticles and liposome).

**Application Prospect of Jatrorrhizine in the Treatment of Metabolic Disorders**

Long-term metabolic disorders and hyperglycemia remain a challenge in medical practice. These conditions cause a series of complications, such as cardiovascular disease, retinopathy, neuropathy and nephropathy. Current therapeutics for metabolic diseases require a multi-drug regimen. However, major problems of this therapeutic method are poor patient compliance, side effects and drug-drug interactions (Lillich et al., 2021). Multi-target ligands and drugs have been proposed as promising approaches to developing therapies for complex diseases (González-Álvarez et al., 2021). Jatrorrhizine is a multi-purpose natural metabolite that affects multiple targets. The alkaloid effectively modulates glucose and lipid metabolism and exhibits anti-inflammatory, anti-oxidant and anti-cancer effects. It is also a safe and controllable natural product. Therefore, the use of jatrorrhizine, alone or as a supplement to other nutraceuticals, is a potential strategy to address multiple pathways and targets to delay metabolic disorders and affect the long-term treatment of related complications.

**Comprehensive Investigations of Toxicity Mechanisms**

We found that jatrorrhizine exerts cytotoxic effects under specific circumstances in vitro. High dose and long-term administration may lead to cytotoxicity in a few cancer cell lines, such as colon cancer and hepatocellular carcinoma cells and normal breast epithelial cells. However, there was no studies that report target-organ toxicity of jatrorrhizine in different disease models. The existing in vivo studies indicated that jatrorrhizine is non-cytotoxic and has no influence on liver function or other tissues. Therefore, further comprehensive investigation for mechanisms of toxicity is needed and further exploration of whether jatrorrhizine has target organ toxicity under special circumstances in vivo is of significance. Such studies will serve as a basis to further evaluate the safety of jatrorrhizine in the treatment of different diseases and for chronic administration.

**Interaction Mechanism of Jatrorrhizine With Other Compounds and Development of Derivatives**

Jatrorrhizine displays low permeability and poor bioavailability. Interestingly, jatrorrhizine may interact with other constituents and thereby alter its absorption and elimination. Additionally, different salt forms of quaternary ammonium compounds show varying physicochemical properties. Thus, salts of jatrorrhizine might exhibit different pharmacokinetic properties in vivo (Neef et al., 1984; Cui et al., 2019). Berberine, an alkaloid similar in chemical structure to jatrorrhizine, displays better bioavailability of its organic acid salts (fumarate, malate, succinate and citrate) than inorganic acid salts (hydrochloride) (Cui et al., 2019). The hydrochloride salt is commonly used in clinical practice and pharmacological research. However, almost no reports on the pharmacokinetics of other salts and comparative studies of different salt forms are available for jatrorrhizine. Therefore, the investigation of interactions between jatrorrhizine and other compounds and the effects of different salt forms on pharmacokinetics is crucial. The improvement of the bioavailability of jatrorrhizine and development of jatrorrhizine derivatives with high bioavailability and low toxicity also needs to be explored.

**AUTHOR CONTRIBUTIONS**

FZ and YM designed this work of review. FZ and YC collected the literatures related to jatrorrhizine. FZ, YC, JC, YL, and HL analyzed literatures and summarized results. FZ wrote the manuscript. HL, YM revised the manuscript.

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