**Supplementary materials**

**For**

**A Comprehensive Review on the Chemical Properties, Plant Sources, Pharmacological Activities, Pharmacokinetic and Toxicological Characteristics of Tetrahydropalmatine**

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**Table S1** The plant sources of tetrahydropalmatine.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Plant species** | **Effect** | **Area** | **Family** | **Used part** | **Extract** | **References** |
| *Stephania epigaea* H.S.Lo | N/A | The south of China{Xiao, 2021 #3}, especially in Yunnan and Guangxi province | Menispermaceae | Tuber | Ethanol and ammonium sulfate | (Sun et al., 2020; Xiao et al., 2021) |
| *Stephania venosa* (Blume) Spreng. | Treatment of cancer and diabetes, and as a blood-tonic and aphrodisiac | Southeast Asian countries | Menispermaceae | Root/Tuber | Methanol | (Kongkiatpaiboon et al., 2016; Le et al., 2017) |
| *Stephania cephalantha* Hayata | Used to treat lung cancer | China | Menispermaceae | Earthnut | 60% ethanol | (Wu et al., 2011; Xiao et al., 2019) |
| *Stephania cambodica* Gagnep. | Used to treat anxiety, malaria, fever, wounds, joint pains, fatigue and male sexual dysfunction | Cambodia and Vietnam | Menispermaceae | Tuber | hydroethanolic extract/52% ethanol | (Dary et al., 2017b) (Dary et al., 2017a) |
| *Stephania rotunda* Lour. | Used to treat asthma, headache, fever, and diarrhoea | Southeast Asia, Cambodian, Laos, Indian and Vietnamese | Menispermaceae | Root, Stem and Tuber | dichloromethanedichloromethane and aqueous extracts | (Baghdikian et al., 2013; Bory et al., 2013; Desgrouas et al., 2014) |
| *Stephania bancroftii* F.M.Bailey | N/A | N/A | Menispermaceae | Rhizome | Methanol | (Bartley et al., 1994) |
| *Stephania yunnanensis* H.S.Lo | N/A | Yunnan province | Menispermaceae | Tuber | N/A | (Ma et al., 2008) |
| *Stephania glabra* (Roxb.) Miers | Treatment of asthma, Tuberculosis, dysentery, hyperglycaemia, cancer, fever, intestinal complaints, sleep disturbances and inflammation | Asian countries | Menispermaceae | Young Leaves | methanol:water:acetic acid (50:50:0.1, v/v/v) | (Semwal and Semwal, 2015; Gorpenchenko et al., 2017) |
| *Tinospora cordifolia* (Willd.) Hook.f. & Thomson | immunomodulation, anticancer, hepatoprotective and hypoglycemic | Indian subcontinent and China | Menispermaceae |  | ethanol | (Bajpai et al., 2016; Singh and Chaudhuri, 2017; Chowdhury, 2021)  |
| *Corydalis yanhusuo* W. T. Wang | Drug addiction and pain relief, invigorate blood, invigorate qi and relieve pain | China | Papaveraceae | Tuber | 95% ethanol/methanol | (Xiao et al., 2011; Xu et al., 2015; Wu et al., 2018; Zhang et al., 2020)  |
| *Corydalis ternata* (Nakai) Nakai | Anticholinesterase, antiamnesic, and anti-inflammatory activities, and analgesic effects | Asian countries | Papaveraceae | N/A | N/A | (Yun, 2014; Kim et al., 2017a) |
| *Corydalis adunca* Maxim. | Clearing away heat and toxic matter, stop bleeding, anti-inflammatory, treat gallbladder disease, remove the stone, relive pain | China | Papaveraceae | Earthnut | Methanol | (Long X.Y., 2007) |
| *Corydalis decumbens* (Thunb.) Pers. | Removing blood stasis and freeing vessel, promote qi circulation to relieve pain, treatment of paralytic stroke, headache, rheumatic arthritis and sciatica | China | Papaveraceae | Earthnut/ Rhizome/ Bulb/ Seedling | Carbon dioxide supercritical CO2 fluid extraction/95% EtOH/90% ethanol | (Wang and Peng, 2002; Shen et al., 2011; Wu et al., 2013a; Wu et al., 2013b; Huang et al., 2018)  |
| *Corydalis racemosa* (Thunb.) Pers. | Antihypertensive | China | Papaveraceae | Whole plant /Root | 95% ethanol | (Wu et al., 2011) |
| *Corydalis bungeana* Turcz. | Anti-inflammatory, antibacterial activity and inhibition of the immune function of the host | China | Papaveraceae | Whole plant | 80% ethanol | (Zhai et al., 2016; Li et al., 2019) |
| *Corydalis bulbosa* (L.) DC. | N/A | Bulgaria | Papaveraceae | Tuber | MeOH | (Kiryakov and Iskrenova, 1984; Miyazawa et al., 1998) |
| *Corydalis saxicola* Bunting | Anti-inflammation, blood circulations improvement, hemostasis, and analgesia | China | Papaveraceae | Herb | Methanol | (Li et al., 2007; Kuai et al., 2020) |
| *Corydalis koidzumiana* Ohwi | N/A | N/A | Papaveraceae | N/A | N/A | N/A |
| *Corydalis cava* (L.) Schweigg. & Körte | Analgetic, sedating, narcotic, anti-inflammatory, anti-allergic and anti-tumour activities | Central and South Europe | Papaveraceae | Tuber | N/A | (Nawrot et al., 2010) |
| *Corydalis turtschaninovii* Besser | Treatment of abdominalgia, menorrhalgia, menostasia, and traumatic pain | China | Papaveraceae | N/A | Methanol andpurified water | (Tao et al., 2019; Tao et al., 2020) |
| *Corydalis ambigua* Cham. & Schltdl. | Analgesic and sedative agents | China | Papaveraceae | N/A | N/A | (Huang et al., 2021a) |
| *Glaucium corniculatum* (L.) Curtis | Memory-enhancing and neuroprotective properties | Turkey | Papaveraceae | Above-ground plant parts | Chloroform, methanol and water | (Nigdelioglu Dolanbay et al., 2021) |
| *Uvaria kweichowensis* P. T. Li | Cure inflammation and tumour | Southwest area of China | Annonaceae | Above-ground plant parts | 90% ethanol | (Zhao et al., 2006; Xu et al., 2007) |
| *Uvaria microcarpa* Champ. ex Benth. | N/A | N/A | Annonaceae | Leaves | 70% ethanol | (Liu et al., 2011) |
| *Annickia kummerae* (Engl. & Diels) Setten & Maas | Anti-plasmodia | Tanzania | Annonaceae | Leaves, Root-bark and Stem-bark | petroleum ether (PE), dichloromethane(DCM) and methanol (MeOH) | (Malebo et al., 2013) |
| *Embelia ribes* Burm.f. | Treatment of tumors, ascites, bronchitis, jaundice, diseases of the heart and brain | India | Myrsinaceae | Fruits |  hexane:dichloromethane (1:1) | (Shirole et al., 2015; Nuthakki et al., 2019) |
| *Phellodendron chinense* C.K.Schneid. | Remove damp heat, relieve consumptive fever, and cure dysentery and diarrhea | China | Berberidaceae | Cortex | N/A | (Kim et al., 2017b; Wang et al., 2019) |
| *Phellodendron amurense* Rupr. | Remove damp heat, relieve consumptive fever, and cure dysentery and diarrhea | China | Berberidaceae | Cortex | 30% ethanol | (Chen et al., 2012a) |
| *Berberis napaulensis* var. napaulensis | N/A | India（Todas of Nilgiris) | Berberidaceae | Root | ethanol (100%) | (Singh et al., 2017) |
| *Coptis deltoidea* C.Y.Cheng & P.K.Hsiao*/Coptis chinensis* Franch. | clear the damp-heat, quench the fire, and counteract the poison | Chongqing, Hubei, Guizhou, Shanxi provinces of China | Ranunculaceae | Rhizome |  Liquid-liquid extraction (LLE) and protein precipitation with methanol,acetonitrile | (Ho et al., 2014; Liu et al., 2016) |

**Table S2** Potential pharmacological action and mechanism of tetrahydropalmatine.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Pharmacological effect** | **Cell lines/model** | **Activity/mechanism(s)** | **Application** | **Dosage** | **References** |
| **Analgesic activity** | Partial sciatic nerve ligation (PSNL)-reduced chronic neuropathic pain mouse model | Antagonizes D2R | In vivo | 5 and 10 mg/kg | (Huang et al., 2021b) |
| Chronic constriction injury mice | Modulates spinal Sig-1R | In vivo | 0.2, 2, 20, 200nmol | (Kang et al., 2016) |
| Intraplantar injection of complete Freund's adjuvant | Increases dopamine D1 receptor-mediated dopaminergic transmission | In vivo | 1~4 mg/kg, i.p. | (Zhou et al., 2016) |
| Rats with bone cancer pain caused by tumor cell implantation (TCI) | Inhibits the activation of microglial cells and the increase of TNF-alpha and IL-18 | In vivo | 20, 40 and 60 mg/kg | (Zhang et al., 2015) |
| Oxaliplatin-induced mouse model in neuropathic pain | Modulates dopamine D-1 receptor | In vivo | 1~4 mg/kg, i.p. | (Guo et al., 2014) |
| Pretreatment of dl-THP in rats | Modulates the suprasipinal level | In vivo | 20, 40, 60 mg/kg, body weight | (Cao et al., 2011) |
| Adult female rats | Decreases immunoreactivity to all mediators involved in central sensitization and to HDAC2 in DRG, to TrkA and CGRP in ectopic endometrium, and to CGRP in eutopic endometrium | In vivo | 70 and 140 mg/kg | (Zhao et al., 2011) |
| Tamoxifen-induced female ICR mice Adenomyosis | Inhibits myometrial infiltration; Improves generalized hyperalgesia; Reduces the amplitude and irregularity of uterine contractions. | In vivo | 10 and 20 mg/kg | (Mao et al., 2011) |
| Wistar rat uterine contraction model | Inhibits the contraction of isolated uteri caused by Ach, PGF (2 alpha), and oxytocin; Affected the levels of NO, activation of NF-kappa B, up-regulated the expression of i-kappa B and down-regulated the expression of both iNOS and COX-2 | In vivo | 0.07 g/kg | (Chen et al., 2013) |
| Female Sprague-Dawley rats aged 6-7 weeks | Decreases MMP-2 and MMP-9, increasing TIMP-1; Promotes E-cadherin, and attenuated N-cadherin, Vimentin, Snail, Slug, ZEB1, ZEB2, Twist. | In vivo | N/A | (Chen et al., 2018) |
| **Antiaddiction activity** | METH-induced mice CPP | Inhibits the rewarding properties | In vivo | 1.25, 2.5, 5.0, 10.0 and 20.0 mg/kg | (Su et al., 2013) |
| Naive rat brain | Selectively activates the key brain regions of the dopaminergic, serotonergic and noradrenergic systems | In vivo | 5, 10, 20 and 40 mg/kg | (Liu et al., 2012) |
| Morphine-induced rats CPP;Aale adult Sprague-Dawley rats | Inhibits D-2R down-regulation and GluA1 AMPA receptor up-regulation | In vivo | 1.25, 2.5, 5 mg/kg | (Jiang et al., 2020) |
| Rat model of morphine-dependence | Antagonism of the dopamine autoreceptor | In vivo | 5mg/kg | (Ahn et al., 2020) |
| Human embryonic kidney-293 cells (HEK293) | Antagonistic potency on dopamine D1 receptors | In vitro | 0.6437uM | (Wu et al., 2018) |
| Rats | Modulates 5-HT neuronal activity and dopamine D3 receptor expression | In vivo | 10 and 15 mg/kg | (Yun, 2014) |
| Wistar rats | Up-regulates the level of plasma beta-endorphin and hypothalamic POMC | In vivo | 3, 5 and 10mg/kg | (Sushchyk et al., 2016) |
| Human neuronal nAChRs/Rats trained to self-administer nicotine | Blocks neuronal alpha 4 beta 2-nAChR function; Increases extracellular dopamine (DA) levels in the nucleus accumbens shell (nAcb) | In vitro and In vivo | 1.8×10−5M; 3 and 5 mg/kg | (Huang et al., 2021a) |
| L-THP treated mice | Modulates D2R-mediated PICA signaling in the CPu | In vivo | 2.5, 5, and 10 mg/kg | (Kim et al., 2013) |
| METH-induced mice CPP | Inhibits ERK phosphorylation in NAc and PFc; Decreases level of NAc and PFc  | In vivo | 10.0mg/kg | (Su et al., 2020) |
| Ketamine-induced rats CPP | Inhibits ERK and CREB phosphorylation in Hip and CPu | In vivo | 10 and 20mg/kg | (Du et al., 2017) |
| Fentanyl-induced rewarding behavior through conditioned place preference (CPP) in mice | Suppresses ERK and CREB phosphorylation in the Hip, NAc, and PFC of mice | In vivo | 5.0 and 10.0 mg/kg | (Du et al., 2021) |
| METH-induced mice locomotor sensitization | Inhibits ERK1/2 phosphorylation in the NAc and CPu | In vivo | 5 and 10 mg/kg | (Zhao et al., 2014) |
| Ketamine-induced learning and memory impairment in mice | Inhibits oxidative stress, inflammation and acetylcholinesterase activitydecreases acetylcholine levels | In vivo | 20, 40 and 80 mg/kg | (Zhang et al., 2018) |
| Mice | Reverses the impairment of acuquisition and retention of spatial memory | In vivo | 10.0 and 20 mg/kg | (Cao et al., 2018) |
| Male C57BL/6 mice | Modulates ERK1/2 expression in the PFC | In vivo | 5 and 10 mg/kg | (Chen et al., 2012b) |
| Male Sprague-Dawley rats | Decreases METH self-administration; Inhibits METH-induced reinstatement of METH-seeking behaviors; Conserves locomotor activity | In vivo | 0.00, 1.25, 2.50 and 5.00 mg/kg, i.p. | (Gong et al., 2016) |
| Abstinent rats | Inhibits heroin-induced reinstatement of heroin-seeking behavior;Conserves locomotion | In vivo | 0, 1.25, 2.5 and 5 mg/kg, i.p. | (Yue et al., 2012) |
| Male Sprague-Dawley rats | Conserves non-specific motor | In vivo | 3.0 or 10.0 mg/kg | (Figueroa-Guzman et al., 2011) |
| **Anti-inflammatory activity** | Bee Venom (BV)-induced persistent spontaneous pain-related behaviors in rats | Down-regulates P2X3 receptors and TRPV1 | In vivo | 20, 40, 60 mg/kg | (Wang et al., 2021) |
| Limb ischemia/reperfusion rat model;Male Sprague–Dawley rats | Inhibits PI3K/AKT/mTOR activity; | In vivo | 10, 20 and 40 mg/kg | (Wen et al., 2020) |
| BALB/c mice | Inhibits the activation of ERK/NF-kappa B signaling pathway | In vivo | 20 and 40 mg/kg | (Yu et al., 2019) |
| In vivo: lipopolysaccharide-induced DIC modelIn vitro: RAW 264.7 macrophages with LPS model | Inhibits TNF-alpha expression; Supresses the activation of NF-kappa B signaling pathway; Modifies coagulation indexes; Reduces the inflammatory cytokine production | In vivo and in vitro | vivo:30 and 60 mg/kgvitro:60 or 120 mM | (Zhi et al., 2020) |
| Rat model of myocardial ischaemia-reperfusioninjury | Decreases the accumulation of inflammatory factors, including TNF-alpha and MPO; Inhibits the extent of apoptosis | In vivo | 10, 20 or 40 mg/kg b.w. | (Han et al., 2012) |
| A (ConA-) induced hepatitis in Balb/c mice | Inhibits apoptosis and autophagy via the TRAF6/JNK pathway | In vivo | 20 or 40mg/kg | (Yu et al., 2018) |
| High-fat diet (HFD)-fed golden hamsters | Inhibits the accumulation of hepatic lipid | In vivo | 6.3, 12.6 and 25.2 g/kg/day | (Sun et al., 2018a) |
| Human umbilical vein endothelial cells (HUVECs) | Inhibits monocyte adhesion to vascular endothelial cell; Downregulates ICAM-1 and VCAM-1 in vascular endothelial cell | In vitro | 3, 10, 30 μmol/L | (Yang et al., 2015) |
| 4-5 weeks old BALB/c mice of either sex; Japanese encephalitis virus strain GP-78 infected mouse model | Decreases the level of viral population, caspase-2 expression, reactive oxygen and nitrogen species, microglial cells and proinflammatory mediators, stress linked protein molecules and neuronal apoptosis | In vivo | 2mg/kg | (Lixia et al., 2018) |
| Sprague-Dawley rats; Irradiation induced lung injuries in rats | Inhibits the pulmonary cells apoptosis; Decreases BALF cells recruitment, BALF protein levels and collagen content of lung tissues | In vivo | 40mg/kg | (Yu et al., 2016) |
| Sprague-Dawley rats | Inhibits inflammation, oxidative stress; Conserves vascular smooth muscle cells (VSMCs) | In vivo | 15mg/kg | (Wang et al., 2018) |
| D-gal induced memory impairment in rats | Decreases MDA, NO; Increases GSH, SOD, CAT, GPx; Reverses the abnormality of ACh and AChE; Inhibits the expression of NF-KB and GFAP | In vivo | 20, 40, 80mg/kg/d | (Qu et al., 2016) |
| **Neuroprotective activity** | Ischemic stroke model of Sprague Dawley male rats | Inhibits c-Abl overexpression | In vivo | 12.5, 25, and 50 mg/kg | (Sun et al., 2018b) |
| HEK293 cells | Inhibits the delayed rectifier Kv1.5 channels  | In vitro | 10 and 50uM | (Li et al., 2017) |
| Rat dorsal root ganglion (DRG) neurons | Inhibits the functional activity of ASICs in dissociated primary sensory neurons; Relieves acidosis-evoked pain in vivo | In vitroIn vivo | 10-5M | (Liu et al., 2015) |
| Single prolonged stress (SPS)-reduced rats of anxiety and depression | Reverses impairments of traumatic stress; Inhibits the decrease in neuropeptide Y (NPY) and the increase in corticotrophin-releasing factor (CRF) expression in the hypothalamus | In vivo | 10, 20, 50 mg/kg body weight | (Lee et al., 2014a) |
| Male Sprague-Dawley rats; Post-traumatic stress disorder-induced changes in rat | Changes transcriptional fold of dopamine, serotonin, acetylcholine, and gamma-aminobutyric acid neurotransmitter systems | In vivo | 20mg/kg | (Ceremuga et al., 2013) |
| Cisplatin-resistant A2780/DDP cell line | Modulates miR-93/PTEN/AKT pathway | In vitro | 0,50,100,150 and 200 µM | (Gong et al., 2019) |
| In vivo: tumor-bearing nude miceIn vitro: Mouse primary renal tubular cells (mPRTCs) and human primary renal tubular cells (hPRTCs) | Selectively inhibits OCT2; Maintains Pt concentration and Pt’s antitumor efficacy; Decreases cisplatin accumulation and cisplatin-induced cytotoxicity in human primary renal tubular cells | In vivo and in vitro | 5~40mg/kg | (Li et al., 2020) |
| ER alpha (+) BCa cells | Induces cell cycle arrest; Increases sensitivity to tamoxifen and fulvestrant;Promotes ER alpha degradation | In vitro | 25, 50, 100, 200 uM | (Xia et al., 2020) |
| **Other pharmacological activities** | MDCK-hOCT2/hMATE1 and MDCK-hOCT2/pcDNA3.1 cells | Reduces NC accumulation and cytotoxicity in MDCK-hOCT2, MDCK-hOCT2/hMATE1 and rPCPT cells | In vitro | 50 μM | (Li et al., 2016) |
| MDCK-hOCT1 or MDCK-hOCT3 and mock cells | Reduces the uptake of NC in MDCK-hOCT1 cells, MDCK-hOCT3 cells, and rat primary hepatocytes | In vitro | 50 mM | (Li et al., 2014) |
| Aorta of Male Wistar rats | Modulates PI3K/Akt/eNOS/NO/cGMP signaling pathway, Ca2+ channels and K+ channels | In vitro | 1, 3, 10, and 30, 100 µM | (Zhou et al., 2019) |
| In vitro: rat’s aorta In vivo: Male Wistar rats, Wistar Kyoto rats (WKY) and spontaneous hypertensive rats (SHR) | Modulates the activation of NO/cGMP pathway and calcium channel blockade | In vivo and in vitro | vivo: 20, 40 and 80 mg/kgvitro: 18.8, 37.6, 75.2, 150.4, 300.8 and 601.6 µg/mL | (Qu et al., 2015) |
| Quail chick chorioallantoic membrane (qCAM); HUVECs | Effects citrulline to arginine flux, arginine biosynthesis, and endothelial VEGFR2 expression sequentially | In vitro | 16, 32, and 64 µg20, 40, 80 µM | (Cui et al., 2021) |
| Myoblast C2C12 cells and embryonic fifibroblast 10T1/2 cells | Up-regulates p38MAPK and Akt; Modifies MyoD activation | In vitro | 100–1000 nM | (Lee et al., 2014b) |
| Mouse 3T3-L1 preadipocytes | Modulates the AMPK pathway | In vitro | 0, 10, 20 or 40 µM | (Piao et al., 2017) |
| In vitro: activated LX2 cell model induced by TGF-beta 1In Vivo: mouse hepatic fibrosis models (male C57 mice) | Inhibits ECM deposition and HSCs autophagy; Modulates PPAR gamma/NF-kappa B and TGF-beta 1/Smad pathway | In vitro and in vivo | 20 and 40 mg/kg | (Yu et al., 2021) |
| P.falciparum-type W2 | Antiplasmodial activity | In vitro | N/A | (Bory et al., 2013) |
| Trypanosoma brucei rhodesiense STIB 900 strain | Anti-trypanosomal activity | In vitro | N/A | (Malebo et al., 2013) |
| Strain of Plasmodium falciparum type W2 | Antiplasmodial activity | In vitro | N/A | (Baghdikian et al., 2013) |
| Cestode parasite, Raillietina echinobothrida | Interacts with active site residues of PEPCK from the parasite | In vitro | 0·25 mM | (Dutta et al., 2016) |
| Eight plant pathogenic fungi species, Rhizoctonia solani, Botrytis cinerea, Fusarium graminearum, Mycosphaerlla melonis, Fusarium oxysporum f. sp. Vasinfectum, Phyllosticta zeae, Sclerotinia sclerotiorum and Magnaporthe oryzae | Anti-phytopathogenic activity | In vitro | N/A | (Zhao et al., 2019) |

**Table S3** Tissue distribution of potential targets of tetrahydropalmatine.

|  |  |  |  |
| --- | --- | --- | --- |
| **Term** | **Count** | **%** | **P-Value** |
| Brain | 60 | 56.6 | 3.60E-03 |
| Blood | 11 | 10.4 | 8.60E-03 |
| Fetal brain | 11 | 10.4 | 1.10E-02 |
| Hippocampus | 9 | 8.5 | 4.00E-03 |
| Platelet | 9 | 8.5 | 1.40E-02 |
| Peripheral blood | 4 | 3.8 | 3.30E-02 |
| Corpus striatum | 3 | 2.8 | 2.90E-04 |
| Fetal lung | 3 | 2.8 | 5.30E-02 |
| Myeloid | 2 | 1.9 | 5.80E-02 |

**Table S4** Disease enrichment classification of potential targets of tetrahydropalmatine (Count%≥30).

|  |  |  |  |
| --- | --- | --- | --- |
| **Term** | **Count** | **%** | **P-Value** |
| Metabolic | 78 | 73.6 | 1.60E-12 |
| Pharmacogenomic | 65 | 61.3 | 9.40E-20 |
| Psych | 64 | 60.4 | 1.30E-26 |
| Cancer | 63 | 59.4 | 1.60E-14 |
| Chem-dependency | 60 | 56.6 | 4.30E-10 |
| Neurological | 55 | 51.9 | 2.00E-11 |
| Cardiovascular | 54 | 50.9 | 7.10E-05 |
| Immune | 49 | 46.2 | 1.10E-07 |
| Renal | 33 | 31.1 | 2.30E-08 |
| Reproduction | 33 | 31.1 | 1.10E-12 |

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