Acupuncture is a form of therapy practiced for more than 3000 years in Asia. Medical doctors practice acupuncture under the guidance of meridian theory to achieve “de qi” status [1]. To perform acupuncture, doctors use thin and sterile metal needles to penetrate specific stimulation points termed acupoints. Both manual and electroacupuncture (EA) are used in medical practice. Many studies have reported the benefits of acupuncture for treating diseases such as stroke, musculoskeletal disorders, chronic urticaria, irritable bowel syndrome, overactive bladder, cancer-related fatigue, and pain in humans [2–6]. Furthermore, few adverse effects have been observed when acupuncture is performed correctly, even in children and pregnant women [7, 8]. The widely known mechanism of acupuncture is that it results in the secretion of endorphins that exert an analgesic effect. With advances in understanding, more mechanisms of acupuncture have been determined, including the local segmental effect, somatoautonomic reflex, immune system regulation, neurotransmitter modulation, the neuroendocrine effect, and the functional connectivity neural network [9–11].

Nowadays, signal transduction has been applied for explaining acupuncture mechanisms. The signal transduction pathway of acupuncture has been mentioned with respect to many diseases, including neurological [12], cardiovascular [13], metabolic [14], and gynecological [15] diseases. Among the aforementioned diseases, nervous system diseases are the most common complaints in daily practice. When used to treat nervous system diseases, acupuncture enhances cell proliferation and neuroblast differentiation by increasing the levels of brain-derived neurotrophic factor (BDNF) and phosphorylated cyclic AMP response element-binding (CREB) protein [16]. Acupuncture was reported to exert a neuroprotective effect on dopaminergic neurons through anti-inflammatory and neurotrophic effects [17].
Other mechanisms, including antioxidation, antiapoptosis, and improved energy metabolism in the brain, have been reported [18–20]. Although many studies on the signal transduction pathway of acupuncture have been conducted, few reviews alone or in varied combination: acupuncture, molecular, signal transduction, genetic, cerebral ischemic injury, cerebral hemorrhagic injury, stroke, epilepsy, seizure, depression, Alzheimer’s disease (AD), dementia, vascular dementia (VD), and Parkinson’s disease (PD). In addition, we used Boolean operators (“not,” “and,” ”or”) to narrow or widen search results. All articles written in English or Chinese were manually screened, and relevant studies were identified. We included additional articles after performing a manual review of the reference lists of identified studies or review articles. Excluded articles included those with unavailable full text, those written in other languages, those not mainly related to the mechanism of the signal transduction pathway, or those with limited details of experimental methods or results. Flowchart of the search processes was as shown in Figure 1.

3. Cerebral Ischemic Injury

Ischemic injury of the brain, also known as cerebral infarction, is a crucial health issue in the modern world because of its associated disability and socioeconomic burden. Acupuncture has shown beneficial effects on ischemic stroke rehabilitation by exerting the antiapoptosis effect on the ischemic area, promoting neurogenesis and cell proliferation, and regulating cerebral blood flow [21, 22]. A retrospective cohort study reported that acupuncture was effective at reducing the stroke recurrence rate [23]. Ischemic stroke causes neural cell damage related to excitotoxicity, oxygen free radical injury, inflammatory status, and blood-brain barrier (BBB) damage [24]. Experimental pathways that can reverse apoptosis and improve cell proliferation and differentiation have been proposed.

Acupuncture causes an increase in the expression of neurotrophic factors, such as BDNF and glial-derive neurotrophic factor (GDNF), in the central nervous system (CNS), exerts a neuroprotective effect on hypoxic-ischemic insults, and results in neurogenesis after the reconstruction phase [25, 26]. In addition, acupuncture increased the vascular endothelial growth factor (VEGF) level in the hippocampus, promoting the proliferation and differentiation of neuronal stem cells [27]. Thus, acupuncture can be used to treat ischemic injury in the brain. Zhang et al. performed manual acupuncture on GV20 and Ex-HN 1 to increase GDNF and BDNF levels in a rat model [19]. The elevation of the BDNF level was related to the increased expression of BDNF/tyrosine receptor kinase B (TrkB) and the induction of neurogenesis [28].

Figure 1: Flow chart of the search processes. The 103 articles were summarized in Tables 1–7.
The mitogen-activated protein kinase (MAPK) family includes ERK1/2, JNK, and p38 MAPK proteins. In animals, the MAPK family is triggered by growth factors, stress, or an inflammatory environment and regulates cell functions, such as proliferation, division, differentiation, survival, and apoptosis. EA can trigger the MAPK family. ERK is believed to mediate reperfusion injury by inhibiting inflammatory reactions and promoting cell proliferation and growth [29]. However, equivocal results have been reported concerning the protective effect of ERK on ischemic brain injury [30, 31]. Some studies have demonstrated that EA protects against ischemic brain injury by reducing infarct volumes and improving neurological outcomes through activation of the ERK1/2 signaling pathway [29, 32–34]. EA is reported to be effective in neuroprotection and neural cell proliferation. The chosen acupoints in EA include GV20, GV14, ST36, and LI11. The activation of the ERK pathway is combined with an increase in BDNF and p-ERK1/2 levels [34]. Some studies have demonstrated that the application of EA on LU5, L14, ST36, and SP6 was effective in reducing neurogenic deficits and causing antiapoptosis in the brain cortex and hippocampus [35, 36].

Environmental stresses and inflammatory cytokines activate p38 MAPKs and induce apoptosis and inflammation [37]. In the acute phase of ischemic brain injury, the p38 MAPK signaling pathway induces neurotoxicity, whereas in the subacute phase, this pathway serves as a proinflammatory mediator in the neuroprotective antiapoptosis effect [38–40]. Some studies have reported that EA exerts the antiapoptosis effect on the peri-infarct cortex by modulating the ERK/JNK/p38 MAPK signaling pathway [41–44]. The chosen acupoints include GV14, GV20, GV24, GV26, LU5, L11L4, L11I, ST36, and SP6. Liu et al. reported that EA inhibits microglia-mediated neuroinflammation mediated by nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) cells, p38 MAPK, and myeloid differentiation primary response 88 (MYD88), as well as simultaneously reducing cytokine tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) levels [45].

The p38 MAPK pathway activates the expression of CREB protein and reduces the apoptosis of ischemic neural cells. Acupuncture on GV16, GV20, GV24, ST36, and HT7 also triggered the CREB pathway in the hippocampus and improved cognitive impairment in an animal model [46–51]. The CREB pathway is related to BDNF, p38 MAPK, and Ca2+/calmodulin-dependent protein kinase (CaMK) [46, 50, 52]. Lin et al. reported that EA exerted antioxidant and antiapoptosis effects by increasing superoxide dismutase and glutathione peroxidase levels and reducing the malondialdehyde level in the hippocampus and improved the learning and memory ability of rats [48]. A study reported that laser acupuncture on GV20 and HT7 for 14 days excited the cholinergic system and increased CREB, BDNF, and B-cell lymphoma 2 (Bcl-2) levels, thereby improving cognitive impairment in rats [51].

Being a cell cycle initiator, PI3K/AKT pathways are essential for cell survival [53]. However, interactions between transactivation of Raf/MAPK/ERK1/2 and PI3K/AKT systems were noted during ischemia and reperfusion phases. During ischemia, Akt reduces Raf/MAPK/ERK1/2 activity through phosphorylation of Raf-1. During reperfusion, abrupt reactive oxygen species (ROS) increases the phosphatase and tensin homolog and reactivates Raf/MAPK/ERK1/2 signaling [54]. For the modulation of the PI3K pathway, some studies have reported that EA on GV12, GV20, GV24, GV26, KII, LI1I, and ST36 activates the PI3K/AKT pathway and exerts antiapoptosis and neuroprotective effects [12, 55–60]. The effect of EA on the PI3K pathway can activate the downstream mTOR complex 1–UNC-51-like kinase 1 complex–Beclin-1 pathway, reduce caspase-3, caspase-8, and caspase-9 levels, and inhibit the autophagy process [61, 62]. EA also reduces nitric oxide (NO), neuronal NO synthase (nNOS), and inducible NO synthase (iNOS) levels by activating the PI3K pathway [58]. Xie et al. demonstrated that EA improved neurological deficit scores and increased the expression of p-AKT protein and bone marrow CD34+ endothelial progenitor cells in rats [63].

Because of the balance between Raf/MAPK/ERK1/2 and PI3K/AKT systems, some studies have included the pretreatment protocol [64, 65]. EA pretreatment in a rat model reduced the expression of p-Akt protein and prevented the downregulation of tight junction proteins, namely, claudin-5 and occludin, attenuating BBB disruption and brain edema [65].

NF-κB is another protein complex related to cell survival. Some studies have demonstrated that EA regulates the NF-κB-mediated apoptosis pathway and improves neuroprotection [66, 67].

Acupuncture improved neurogenic deficits and cognitive impairment in a cerebral ischemic/reperfusion animal model. In summary, acupuncture not only increases the levels of neurotrophic factors but also modulates signaling pathways, such as Raf/MAPK/ERK1/2 and PI3K/AKT and downstream CREB and NF-κB. Therefore, acupuncture results in cell proliferation, antiapoptosis, neuroprotection, and BBB maintenance. The most frequently chosen acupoints include GV20, GV14, and ST36. The mechanisms and main results of identified articles are summarized in Table I.

4. Cerebral Hemorrhagic Injury

Hemorrhagic stroke is less common than ischemic stroke. The causes of hemorrhagic stroke include high blood pressure, brain trauma, aneurysms, arteriovenous malformations, and brain tumors. In cerebral hemorrhagic injury, blood vessel spasms and oxidative stress caused by ischemia and reperfusion cause an injury to neural cells. Acupuncture could improve the hypoperfusion status and hematoma absorption, reduce brain edema, and promote neurogenesis in the brain [68]. Thus, some studies have reported that acupuncture is beneficial for treating cerebral hemorrhage because it results in functional improvements [69, 70]. Acupuncture also regulates inflammatory factors, such as IL-6, IL-1β, and NF-κB, prevents apoptosis by reducing the expression of p53 protein, and promotes neurogenesis by increasing the levels of BDNF and nerve growth factors [71].
Table 1: Signal transduction pathways of acupuncture in treating cerebral ischemic injury.

| Subjects                  | Location                        | Acupoint | Intervention       | Time of intervention | Signal pathway                      | Main results                                      | Author, reference |
|---------------------------|---------------------------------|----------|--------------------|----------------------|--------------------------------------|---------------------------------------------------|------------------|
| Male, SD rats, MCAO       | brain                           | GV20     | EA, 3mA, 2/20Hz    | 30min, QOD for 14 days | increase expression of BDNF/TrkB    | elevation of BDNF neuron proliferation            | Kim MW, et al. 2012[28] |
| Male, postnatal SD rats, MCAO | hippocampus                    | GV20, GV14 | EA, 2Hz            | 20min, QD for 10 days | increase VEGF and BDNF levels       | proliferation and differentiation of neuronal stem cells | Kim YR, et al. 2014[27] |
| Male, postnatal SD rats, CCAO | hippocampus                    | GV20, Ex-HN 1 | MA, 2Hz for 15 sec | 30min/time, 3 times | increase GDNF and BDNF levels       | proliferation and differentiation of neuronal stem cells | Zhang Y, et al. 2015[19] |
| Either sex, SD rats, CCAO combination with hypoxic treatment | cerebral cortex | MA: GV 20, GV 14, LI II, KI 1; EA: GV 14, LI 11 | MA and EA, 1mA, 1/20 Hz | 10 min, QD | activation of GDNF/RET/Akt pathway | neuroprotection | 
| Male, SD rats, MCAO       | brain                           | GV20     | EA, 1 mA, 2/15 Hz  | 30min                | activation of the ERK1/2 pathway    | elevation of CB1 neuron proliferation            | Du J, et al. 2010[32] |
| Male, SD rats, MCAO       | brain                           | ST36, LI11 | EA, 1/20 Hz        | 30 min, QD           | activation of the ERK pathway       | elevation of Ras, cyclin D1 and CDK4 neural cell proliferation | Xie G, et al. 2013[33] |
| Male, SD rats, MCAO       | brain                           | GV 20, GV14 | EA, 2.7-3.0 mA, 5Hz | 25min, QD for 2 days | activation of MAPK/ERK kinase, ERK1/2 pathway | elevation of BDNF, pRaf-1, pp90RSK, pBad depression of caspase-3 protein | Cheng CY, et al. 2014[34] |
| Male, SD rats, MCAO       | brain                           | LI11, ST36 | EA, 1-20 Hz        | 30min, QD for 3 days | activation of the ERK1/2 pathway    | elevation of p21 or p27 depression of cyclin D1, CDK4, cyclin E and CDK2 neural cell proliferation | Huang J, et al. 2014[29] |
| Male, SD rats, MCAO       | hippocampus                    | LU5, LI4, ST36, SP6 | EA, 2mA, 2/15 Hz  | 20 min, QD for 3 days | activation of the ERK pathway       | antiapoptosis                                      | Wu C, et al. 2015[35] |
| Subjects                           | Location                                           | Acupoint      | Intervention           | Time of intervention | Signal pathway                        | Main results                     | Author, reference |
|-----------------------------------|----------------------------------------------------|---------------|------------------------|----------------------|---------------------------------------|----------------------------------|------------------|
| Male, SD rats, MCAO               | brain                                              | LU5, LI4, ST36, SP6 | EA, 2 mA, 2/5Hz        | 20min, QD for 3 days and 7 days | activation of ERK pathway             | antiapoptosis                     | Wu C, et al. 2017[36] |
| Male, SD rats, ligation of common carotid artery and external carotid artery | hippocampus                                        | LU5, LI4, ST36, SP6 | EA, 2/50 Hz            | 20 min, QD            | regulation of p38 MAPK signal pathway | depression of phosphorylated p38 MAPK antiapoptosis | Lan X, et al. 2017[41] |
| Male, SD rats, MCAO               | brain                                              | GV20, GV14, GV26 | MA                     | 30min/time, 7 times   | Inactivation of MAPK/ERK pathway       | elevation of Bcl-2 depression of Bax anti-apoptosis | Lin Y, et al. 2017[42] |
| Male, SD rats, MCAO               | brain                                              | LI11, ST36    | EA, 1mA, 4/20 Hz       | 30min, QD for 3 days  | modulation of ERK/JNK/p38 signal pathway | depression of caspase-3, growth factor midkine depression of Bcl-2 anti-apoptosis | Xing Y, et al. 2018[43] |
| Male, SD rats, MCAO               | brain                                              | GV20, GV24    | EA, 1mA, 1/20 Hz       | 30min, QD for 10 days | modulation of p38MAPK/ERK1/2/JNK pathway | elevation of ERK1/2, Bcl-2/Bax ratio depression of JNK, p38 MAPK anti-apoptosis | Liu J, et al. 2018[44] |
| Male, SD rats, MCAO sensorimotor cortex | brain                                              | LI11, ST36    | EA, 0.2mA, 1/20Hz      | 30 min, QD for 3 days | inactivation of NF-κB, p38 MAPK and MYD88 pathway | depression of TNF-α, IL-1β, IL-6 inhibition of microglia-mediated neuroinflammation | Liu W, et al. 2016[45] |
| Subjects                               | Location          | Acupoint | Intervention | Time of intervention | Signal pathway                        | Main results                                           | Author, reference |
|----------------------------------------|-------------------|----------|--------------|----------------------|----------------------------------------|--------------------------------------------------------|-------------------|
| Male, SD rats, MCAO                    | brain             | GV20, GV16 | EA, 5 Hz and 25 Hz | 25 min, QD           | activation of p38 MAPK/CREB pathway     | decrease reactive astrocytosis                        | Cheng CY, et al. 2015[46] |
| Male, Wistar rats, homologous blood emboli injection of internal carotid artery | hippocampus       | ST36     | MA           | QD for 14 days        | activation of cAMP/PKA/CREB pathway     | activation of long-term potentiation                   | Li QQ, et al. 2015[47] |
| Male, SD rats, MCAO                    | hippocampus       | GV24, GV20 | EA, 1-3 mA, 5/20 Hz | 30 min, QD           | increase expression of p-CREB           | elevation of superoxide dismutase and glutathione peroxidase, Bcl-2 depression of malondialdehyde, Bcl2-xl anti-oxidase anti-apoptosis | Lin R, et al. 2015[48] |
| Male C57BL/6 mice, bilateral stenosis of the common carotid artery | corpus callosum   | GV20, GV14 | EA, 2 Hz     | 20 min, QD for 7 days | p-CREB pathway                         | oligodendrocyte regeneration                         | Ahn SM, et al. 2016[49] |
| Female, SD rats, MCAO                  | hippocampus       | GV20, GV24 | EA, 1/20 Hz  | 30 min, QD for 7 days | inactivation of CaM-CaMKIV-CREB pathway | inactivation of CaM-CaMKIV-CREB pathway               | Zhang Y, et al. 2016[50] |
| Male, SD rats, MCAO                    | hippocampus       | GV20, HT7   | MA LA, 30 mW, 100Hz | 14 days              | enhance cholinergic system             | elevation of CREB, BDNF, and Bcl-2 depression of Bax anti-apoptosis | Yun YC, et al. 2017[51] |
| Neonatal SD rats, CCAO                 | brain             | GV20, ST36 | EA, 1 mA, 2 Hz | 20 min               | activation of CREB/BDNF pathway        | oligodendrogenesis                                    | Pak ME, et al. 2018[52] |
| Subjects                               | Location                      | Acupoint       | Intervention     | Time of intervention | Signal pathway          | Main results                                      | Author, reference |
|----------------------------------------|-------------------------------|----------------|------------------|----------------------|-------------------------|--------------------------------------------------|-------------------|
| Male, Wistar rats, MCAO                | forebrain                     | GV20, GV26     | EA, 3mA, 3/20Hz | 60min                | activation of Akt       | depression of caspase-9 anti-apoptosis            | Wang SJ, et al. 2002 [55] |
| Male, SD rats, MCAO                    | brain                         | GV26, CV 24    | EA 1 mA, 4/16Hz  | 30min                | activation of PI3K pathway | neuroprotection                                 | Sun N, et al. 2005 [56] |
| Male, SD rats, MCAO                    | brain                         | GV26, CV24     | EA, 4/16Hz       | 30 min               | activation of TrkA-PI3K pathway | neuroprotection                                 | Zhao L, et al. 2007 [57] |
| Rats, modified intravascular suture technique | hippocampus, cerebral cortex | GV26, CV 24    | acupuncture      | -                    | activation of TrkA/PI3K pathway | depression of NO, nNOS and iNOS                    | Chen SX, et al. 2011 [58] |
| Male, SD rats, MCAO                    | brain                         | LI11, ST36     | EA, 1mA, 1/20 Hz | 30 min, QD           | activation of PI3K/Akt pathway | elevation of BDNF, GDNF, Bcl-2/Bax ratio anti-apoptosis | Chen A, et al. 2012 [59] |
| SD rats, left common carotid artery (LCCA) ligation | cerebral cortex | GV 20, GV 14, LI 11, KI 1 | MA and EA       | -                    | activation of PI3K/Akt pathway | depression of PI3K, p-Akt, p-Bad and Bcl-2, caspase 3-positive expression anti-apoptosis | Xu T, et al. 2014 [60] |
| Male, SD rats, MCAO                    | brain                         | LI11, ST36     | EA, 4/20 Hz      | 30 min, QD for 3 days| activation of PI3K/Akt pathway | depression of Bax anti-apoptosis                   | Xue X, et al. 2014 [12] |
| Male, SD rats, MCAO                    | brain                         | GV20, CV6      | EA, ImA, 2Hz     | 30min, BID           | activation of PI3K/Akt pathway | depression of caspase-3, -8 and -9 anti-apoptosis     | Kim YR, et al. 2013 [61] |
| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|----------|----------|----------|--------------|----------------------|----------------|--------------|------------------|
| Male, SD rats, MCAO | bone marrow | GV20, LI4, LR3 | EA, 3mA, 2/20Hz | 30min, QD | increase expression of p-Akt protein | elevation of CD 34+ endothelial progenitor cell | Xie CC, et al. 2014[63] |
| Male, SD rats, MCAO | brain | LI11, ST36 | EA, 0.2 mA, 1/20Hz | 30 min, QD for 3 days | activation of mTORC1-ULK1 complex-beclin1 pathway | depression of microtubule-associated protein 1 light chain 3 beta II/I, ULK1, autophagy related gene 13 and Beclin1 anti-autophagy | Liu W, et al. 2016[62] |
| Male, SD rats, MCAO | brain | GV20 | EA, 1mA, 2/15Hz | 30 min, QD for 3 days | phosphorylation of GSK-3β | anti-apoptosis | Wei H, et al. 2014[64] |
| Male, SD rats, MCAO | brain | GV20 | EA, 1mA, 2/15Hz | 30 min, QD for 5 days | decrease expression of p-Akt | elevation of Claudin-5, occludin decrease blood-brain barrier disruption | Zou R, et al. 2015[65] |
| Male, SD rats, MCAO | brain | GV20, GV24 | EA 1/20Hz | 30min, QD for 10 days | inhibition of NF-κB-mediated apoptosis pathway | depression of Bax and Fas anti-apoptosis | Feng X, et al. 2013[66] |
| Male, SD rats, MCAO | brain | LI11, ST36 | EA, 0.01mA, 1/20Hz | -- | regulation of TLR4/NF-κB pathway | depression of TNF-α, IL-1β and IL-6 neuroprotection | Lan L, et al. 2013[67] |

**Abbreviations**

--- not mentioned; Bax: Bcl-2 associated X; Bad: Bcl-2-associated death promoter; Bcl-2: B-cell lymphoma 2; BDNF: brain-derived neurotrophic factor; CaMK: Ca2+/calmodulin-dependent protein kinase; cAMP: cyclic adenosine monophosphate; CB1: cannabinoid receptor type 1; CCAO: occlusion of common carotid artery; CDK: cyclin-dependent kinase; CREB: phosphorylated cyclic AMP response element-binding protein; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; GDNF: glial-derived neurotrophic factor; IL: interleukin; JNK: c-Jun N-terminal kinases; MA: manual acupuncture; MAPK: mitogen-activated protein kinases; MCAO: occlusion of MCA; mTOR: mammalian target of rapamycin; MYD88: myeloid differentiation primary response 88; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; p38 MAPKs: p38 mitogen-activated protein kinases; PDHK: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA: protein kinase A; pp90RSK: phospho-90 kDa ribosomal S6 kinase; QD: daily; QOD: every other day; SD rat: Sprague Dawley rat; TLR4: Toll-like receptor 4; TNF-α: tumor necrosis factor-alpha; Trk: tyrosine receptor kinase; ULK: UNC-51-like kinase; VEGF: vascular endothelial growth factor.
Acupuncture increased the expression of endogenous GDNF and inhibited the early expression of VEGF, thus regulating nerve remodeling after cerebral hemorrhagic injury [72]. At the level of molecular signal transduction, acupuncture exerts a neuroprotective effect by increasing the angiopoietin level and reducing TNF-α and NF-κB levels [73, 74]. Li et al. reported that EA on GV20 and GB7 could reduce BBB permeability and improve brain edema by activating the caveolin-1/matrix metalloproteinase pathway [75]. Antia apoptosis is also an important pathway for neural preservation. Zhu et al. and Li et al. have demonstrated that EA activated the Bcl-2 pathway to increase hematoma absorption and antia apoptosis. This effect is combined with the suppression of caspase-3 and Bcl-2-associated X (Bax) proteins [76, 77]. However, the chosen acupoints were heterogeneous, including ST36, GV14, GV20, GV26, GB7, and PC6.

Taken together, acupuncture could improve neurogenic disability and reduce brain edema by increasing caveolin-1/matrix metalloproteinase levels and inducing antia apoptosis through the activation of the Bcl-2 pathway in a cerebral hemorrhagic model. The mechanisms and main results of identified articles are summarized in Table 2.

5. Seizure

Seizure is an abrupt, spontaneous, excessive, or synchronous neuronal activity in the brain that leads to various uncontrolled shaking movements or loss of consciousness. Seizure attack affects 8%–10% of the general population in their lifetime. The recurrence of seizure results in epileptic syndrome, which affects 2%–3% of the general population [78]. Epileptic seizures can be induced by metabolic imbalance, electrolyte imbalance, encephalitis, traumatic brain injury, brain tumor, stroke, and medication [78]. During the process of an epileptic seizure, changes occur in molecular, anatomical, or circuit development, including cell death, inflammatory cytokine production, and neurotransmitter dysregulation. This process is called epileptogenesis [79]. Involvement of BDNF–TrkB signaling, the mTOR pathway, and the repressor element 1-silencing transcription factor pathway was considered to be the underlying molecular mechanism [79].

In addition to the use of medication, some studies have reported that acupuncture reduced the frequency of seizures and improved the quality of life [80–82]. Some studies reported that acupuncture has effect on change of anatomical, neurotransmitter, inflammatory cytokines and molecular level. The augmentation of γ-aminobutyric acid neurotransmission, including the upregulation of glutamic acid decarboxylase 67 (GAD67), is a self-protective and anticonvulsive mechanism [83, 84]. Acupuncture reduced seizure attacks by enhancing GAD67 mRNA production in the dentate gyrus of epileptic rats [85]. Acupuncture changed the brain structure and reduced the mossy fiber sprouting in the dentate gyrus and exerted an antiepileptic effect [86]. Inflammation can increase neuronal excitability and result in the frequent onset of epilepsy, which is related to epileptogenesis [87]. Acupuncture also contributes to the antiepileptic effect accompanied by the anti-inflammatory effect of reducing IL-1β, TNF-α, and cyclooxygenase-2 (COX-2) levels in the hippocampus of an epileptic rat model [88, 89]. Wang et al. and Wang et al. have demonstrated that EA attenuated the seizure-induced increase in c-fos protein and preproenkephalin messenger ribonucleic acid (mRNA) levels in the hippocampus of a penicillin-induced seizure rat model [90, 91]. Yang et al. reported that EA on GV16 and GV8 exerted an anticonvulsant effect combined with a reduction in nNOS and iNOS levels [92].

With regard to molecular pathways, acupuncture on the auricular acupoint suppressed transient receptor potential ankyrin 1 (TRPA1) pathways by increasing the phosphorylated protein kinase C (pPKC)-α level and reducing pPKCe and pERK1/2 levels in a kainic acid-induced rat model [93]. Liao et al. used a similar rat model and reported that acupuncture exerted an antiepileptic effect by inactivating the Toll-like receptor 4 (TLR4) pathway, which was accompanied by a decrease in pCaMKIIα, pERK, pp38, pJNK, and pNFκB levels [94]. Yang et al. demonstrated that acupuncture on GV20 and GV14 reduced epileptic seizures by exerting a protective effect on the pyramidal cells of hippocampal CA1 and CA3. This effect was related to the activation of the PI3 K/Akt pathway [95]. The upregulation of glucose-regulated protein 78 (GRP78) and the downregulation of C/EBP homologous protein (CHOP) prevent neuronal cell death induced by endoreticulum stress. Acupuncture on GV20 and GV14 elevated the GRP78 level, reduced CHOP and caspase-12 levels, and exerted an antia apoptosis effect on the hippocampus, thus reducing epileptic seizure attacks [96, 97].

Taken together, acupuncture exerts the antiepileptic effect by changing anatomical, neurotransmitter, inflammatory cytokines and molecular level. With respect to signal transduction, acupuncture reduces seizure frequency by suppressing TRPA1/pERK and TLR4/ERK pathways and activating the PI3K/Akt pathway. Furthermore, acupuncture augments the antia apoptosis process and provides neuroprotection by increasing the GRP78 level and reducing the CHOP level. The mechanisms and main results of identified articles are summarized in Table 3.

6. Depression

Depressive disorders are common psychiatric disorders that affect approximately 17% of people in their lifetimes. A study reported that 12%–20% of depressed patients experience treatment-resistant depression, resulting in a considerable social burden [98]. In addition to medication and psychosocial support, acupuncture serves as an alternative option for patients with depression that exhibits promising effects and fewer side effects [99]. The mechanism of depression includes dysregulation of neuroinflammatory cytokines, neurotransmitters, neuroplasticity, and the neuroendocrine system [100, 101]. At the molecular level, dysregulation of striatal-enriched tyrosine protein phosphatase inactivates the neuronal signaling pathway, including ERK1/2, p38, Src family tyrosine kinases, and glutamate receptors. This process attenuates the neurogenesis effect of BDNF and causes depression [102].
| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|----------|----------|----------|--------------|----------------------|----------------|--------------|-----------------|
| Male, Wistar rats | brain | GV20, GB7 | MA | 30min, QD for 1,2,3,7,10 days | increase GDNF level and modulate VEGF level | elevation of GDNF, VEGF (early) depression of VEGF (late) modulate neuron remodeling | Zhang GW, et al. 2012[72] |
| Male, SD rats, collagenase-induced ICH | right globus pallidus | ST36 | EA, 2-20Hz | 30min, QD, 14 days | activation of Ang-1 and Ang-2 | elevation of Ang-1 and Ang-2 neuroprotection | Zhou HJ, et al. 2014[73] |
| Male, SD rats, autologous blood-induced ICH | right caudate nucleus | GV20, GB7 | MA, 3-4Hz, 5min | 30min, QD, 7 days | inactivation of TNF pathway | depression of TNF-α and NF-κB anti-inflammation | Liu H, et al. 2017[74] |
| Male, SD rats, collagenase-induced ICH | right caudate nucleus | GV20, GB7 | EA, 0.2mA, 2Hz | 30min, QD, 13,7 days | activation of caveolin-1/matrix metalloproteinase/blood-brain barrier permeability pathway | elevation of caveolin-1, matrix metalloproteinase-2/9 reduce blood-brain barrier permeability | Li HQ, et al. 2016[75] |
| Male, SD rats, collagenase and heparin-induced ICH | right caudate putamen | GV20, GV14 | EA, 1mA, 3Hz | 10min, QD, 14 days | activation of Bcl-2 pathway | elevation of Bcl-2 protein depression of caspase-3 and Bax proteins increase absorption of hematoma and anti-apoptosis | Zhu Y, et al. 2017[76] |
| Male, Wistar rats, autologous blood-induced ICH | caudate nucleus | PC6, GV26 | EA, 4Hz | 1min | balance of BCL-2 and Bax | elevation of BCL-2 mRNA anti-apoptosis | Li Z, et al. 2017[77] |

**Abbreviations**
- -: not mentioned; Ang: Angiopoietin; Bax: Bcl-2 associated X; Bcl-2: B-cell lymphoma 2; EA: electroacupuncture; GDNF: glial-derived neurotrophic factor; ICH: intracranial hemorrhage; MA: manual acupuncture; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; QD: daily; SD rat: Sprague Dawley rat; TNF-α: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor.
Table 3: Signal transduction pathways of acupuncture in treating seizure.

| Subjects                                      | Location                                      | Acupoint        | Intervention | Time of intervention | Signal pathway     | Main results                      | Author, reference          |
|-----------------------------------------------|-----------------------------------------------|-----------------|--------------|----------------------|--------------------|-----------------------------------|---------------------------|
| Male, SD rats, lithium-pilocarpine injection  | dentate gyrus                                 | ST36            | EA, 1-2mA, 4/20Hz | 30min, QD for 30, 45, 60 days | activation of GAD 67 mRNA | elevation of GAD67 mRNA anti-epileptic | Guo J, et al. 2008[85] |
| Male, SD rats, kainic acid injection          | prefrontal cortex, hippocampus, and somatosensory cortex | Auricular acupoint | Auricular EA, 2 and 15Hz | 20min, QD, 3 days/wk for 3 wks | inactivation of TLR4 pathway | depression of pCaMKIIa, pERK, pp38, pIjNK, pNF-κB anti-epileptic | Liao ET, et al. 2018[94] |
| Male, SD rats, intraperitoneal injection of pentylentetrazol | hippocampal CA 1 and CA 3 | GV20, GV14       | MA           | QD for 5 days        | activation of PI3 K/Akt pathway | increase pyramidal cells           | Yang, F, et al. 2013[95] |
| Male, SD rats, kainic acid injection          | hippocampal CA1 areas                         | Auricular acupoint | EA, 2Hz      | 20min, 3 days/wk for 6wks | Inactivation of TRPA1, pPKCα, pPKCε, and pERK1/2 pathways | elevation of PKCα depression of TRPA1, PKCα, pERK1/2 anti-epileptic | Lin YW, et al. 2014[93] |
| Male, SD rats, intraperitoneal injection of pentylentetrazol | hippocampal CA1 region                        | GV20, GV14       | MA           | 30min                 | balance of GRP78 and CHOP | elevation of GRP 78 protein depression of CHOP neuroprotection | Yang F, et al. 2014[96] |
| Male, newly-born SD rats, pentylentetrazol intraperitoneal injection | hippocampus                                   | GV20, GV14       | MA           | QD for 7 days         | balance of GRP78 and CHOP | elevation of GRP 78 protein depression of CHOP, caspase-12 anti-apoptosis | Zhang, H, et al. 2017[97] |

Abbreviations
Akt: protein kinase B; CaMK: Ca2+/calmodulin-dependent protein kinase; CHOP: C/EBP homologous protein; COX: cyclooxygenase; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; GAD67: glutamic acid decarboxylase 67; GRP78: glucose-regulated protein 78; IL: interleukin; JNK: c-Jun N-terminal kinases; MA: manual acupuncture; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; p38 MAPKs: p38 mitogen-activated protein kinases; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC: protein kinase C; QD: daily; QOD: every other day; SD rat: Sprague Dawley rat; TLR4: Toll-like receptor 4; TNF-α: tumor necrosis factor-alpha; TRPA: transient receptor potential ankyrin 1.
Acupuncture treats depression by regulating neurotransmitters, neuroinflammatory cytokines, the hypothalamic–pituitary–adrenal axis, and the hypothalamus–pituitary–sex gland axis [103]. Furthermore, acupuncture plays a role in molecular signaling pathways. Acupuncture elevated BDNF production and excitatory amino acid transporter levels and maintained neural regeneration of the hippocampus in a depressive rat model [104, 105]. The chosen acupoints include GV20, EX-HN3, and PC6 [104, 105]. Fan et al. demonstrated that acupuncture on LI4 and LR3 regulated the expression of soluble N-ethylmaleimide-sensitive factor attachment receptor protein, a fusion mediator, and promoted depression remission [106]. NO is a small molecule that freely diffuses across cell membranes and serves as a neurotransmitter in the CNS. NO initiates the NO-cyclic guanosine monophosphate (cGMP) pathway and activates protein kinases. Acupuncture regulates the NO-cGMP pathway by increasing nNOS and cGMP levels, which contribute to its effect on depression relief [107]. Shao et al. demonstrated that acupuncture on GV20 and PC6 inhibited the proinflammatory pathway of depression by reducing NF-kB protein and COX-2 levels [108].

Antidepressants alleviate the symptoms of depression by activating the MAPK/ERK pathway, which increases ERK1/2 and p-ERK1/2 expression. Many studies have reported that acupuncture activates the MAPK/ERK pathway and downstream CREB pathway and elevates BDNF production [109–114]. The most commonly chosen acupoints include GV20 and GV29, followed by EX-HN3, GB34, and PC6. The MAPK/ERK pathway induces neurogenesis and antiapoptosis of hippocampal neurons and eliminates the depression state. EA on GV20 and EX-HN3 also enhances the p-p38MAPK pathway [111]. Some studies have reported that EA on GV20 and GV29 reduced the hippocampal neural apoptotic rate by downregulating the hippocampal p-JNK pathway in depression rat model [115, 116]. Acupuncture also activated the adenyl cyclase (AC)–cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA)–CREB signaling pathway and elevated the BDNF level [117–120]. In the AC–cAMP–PKA–CREB signaling pathway, heterogeneous acupoints were chosen, including GV20, EX-HNI, EX-HN3, ST36, ST40, LI4, and LR3.

Molecular studies have reported that acupuncture plays a role in the neuroendocrine model of depression. Lu et al. demonstrated that acupuncture could relieve the symptoms of depression and increase cortisol, PAK, and PKC levels [117]. Oh et al. reported that acupuncture on HT8 elevated the serum corticosterone level and hippocampal nNOS phosphorylation, Akt, ERK, p70S6K, p4E-BP1, and CREB enhanced the effect of BDNF on neuroprotection and synaptic plasticity. Furthermore, acupuncture elevated the levels of synaptic proteins (e.g., PSD95, Syn1, and GluR1), which are crucial for neuronal synaptic plasticity [121].

The results of the Gene Ontology functional term and Kyoto Encyclopedia of Genes and Genomes database analysis indicated that the regulation of the Toll-like receptor signaling pathway, nucleotide-binding oligomerization domain-like receptor signaling pathway, MAPK/ERK pathway, PI3K/Akt pathway, neurotrophin signaling pathway, TNF pathway, and NF-kB pathway is the mechanism through which acupuncture treats depression. The aforementioned pathways cause cell survival, differentiation, antiapoptosis, and synaptic plasticity of neurons, thus alleviating depression symptoms and improving learning/memory dysfunction [122–124].

In summary, acupuncture can treat depression by upregulating MAPK/ERK and AC–cAMP–PKA–CREB pathways and downregulating JNK and NF-kB pathways. Because of the aforementioned mechanism, we observed an increase in neuron growth factor levels, neurogenesis, and antiapoptosis accompanied by the alleviation of depression symptoms. The mechanisms and main results of identified articles are summarized in Table 4.

7. Alzheimer’s Disease

AD is a progressive neurodegenerative disease that is presented with dementia, memory loss, disorientation, personality disorder, mood swings, behavior disturbance, and language problems. Because of patients’ cognitive decline, they withdraw from their family and society [125]. Risk factors for AD include genetic factors, a history of head trauma, depression, and hypertension [126]. The progression of AD is associated with the formation of amyloid plaques and neurofibrillary tangles in the brain [126]. Treatment of AD should be started immediately after the diagnosis to prevent cognitive decline. Both patients and their families are involved in administration of medication and psychosocial therapy for AD. Medication for AD includes cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), N-methyl-D-aspartate receptor antagonists (memantine), atypical antipsychotics, antidepressants, and anticonvulsants [126].

In addition to medication, acupuncture has been reported to improve cognitive function and the global clinical status of patients with AD without causing major adverse effects [127, 128]. Mechanisms through which acupuncture improves cognitive impairment in AD include attenuation of Aβ deposits, upregulation of BDNF expression, and regulation of cell proliferation and neural plasticity in the brain [129–131]. Acupuncture also regulates cytokine and growth factor levels associated with survival, proliferation, and differentiation of neural stem cells in the brain to promote the repair of damaged cells [130, 132].

Aβ deposits in the brain disturb BDNF signaling pathways, such as Ras/ERK, PI3K/Akt, and PKA/cAMP, which regulate BDNF expression and cause AD development [133, 134]. Acupuncture on GV20 reduces Aβ deposits in the brain, elevates the BDNF level, and exerts a neuroprotective effect on CNS cells [135, 136]. Lin et al. reported that the signaling pathway of BDNF elevation is mediated by the BDNF–TrkB pathway, which exerts an antiapoptosis effect [136]. The central cholinergic pathway is important for learning acquisition and synaptic plasticity in the mammalian limbic system; thus, increasing the acetylcholine level is a type of treatment strategy for AD. Lee et al. reported that acupuncture enhances the cholinergic system–CREB–BDNF pathway and exerts a neuroprotective effect [135].
| Subjects          | Location                        | Acupoint          | Intervention | Time of intervention | Signal pathway                      | Main results                                                                 | Author, reference |
|-------------------|---------------------------------|-------------------|--------------|----------------------|-------------------------------------|-------------------------------------------------------------------------------|-------------------|
| SD rats, CUMS     | hippocampus, frontal cortex     | GV20, EX-HN3, PC6 | --           | QOD for 28 days      | activation of BDNF mRNA and protein neural regeneration | elevation of BDNF mRNA and protein neural regeneration | Liang J, et al. 2012[104] |
| Male, SD rats, CUS | hippocampus                     | LI4, LR3          | EA           | QD for 21 days       | regulation of soluble N-ethylmaleimide-sensitive factor attachment receptor proteins | depression of SNAP25, VAMP1, VAMP2, VAMP7, and syntaxin1                       | Fan L, et al. 2016[106] |
| SD rats, CUMS     | hippocampus                     | GV20, EX-HN3      | EA, 0.6mA, 2Hz | 20min, QD for 21 days | activation of NO-cGMP pathway       | elevation of nNOS, cGMP normalize activity of the NO/cGMP pathway            | Han YI, et al. 2009[107] |
| Male, SD rats, CUS | hippocampus                     | GV20, PC6         | --           | QD for 28 days       | Inactivation of NF-κB inflammatory pathway | depression of NF-κB, COX-2, prostaglandin inhibition of pro-inflammatory pathway | Shao RH, et al. 2015[108] |
| Subjects                  | Location                        | Acupoint | Intervention                  | Time of intervention | Signal pathway                      | Main results                                                                 | Author, reference |
|--------------------------|---------------------------------|----------|-------------------------------|----------------------|-------------------------------------|------------------------------------------------------------------------------|--------------------|
| Male, SD rats, CUMS      | hippocampus, prefrontal cortex   | GV20, PC6| MA, rotated 2 Hz for 1 min and retained | 10 min, QOD for 28 days | activation of ERK-CREB pathway      | elevation of ratio of p-ERK1/2 to ERK1/2, ratio of p-CREB to CREB            | Lu J, et al. 2013[109] |
| Male, SD rats, CUMS      | hippocampus                     | GV20, GB34| EA, 0.3 mA, 2/100 Hz          | 30 min, QD for 14 days | activation of ERK pathway           | elevation of p-ERK neural stem cells proliferation                           | Yang L, et al. 2013[110] |
| Male, SD rats, CUMS      | hippocampus                     | GV20, EX-HN3| EA, 1-3 mA, 2 Hz             | 15 min, QD for 14 days | modulation of the p-ERK1/2 and p-p38MAPK pathway | elevation of p-ERK1/2, p-p38                                              | Xu J, et al. 2015[111] |
| Male, SD rats, CUMS      | hippocampus                     | GV20, GV29| MA, 2 Hz for 1 min           | 10 min, QD for 21 days | activation of ERK pathway           | elevation of -ERK1/2, CREB, and p-CREB neurotrophy and neurogenesis           | Zhang X, et al. 2016[112] |
| Male, SD rats, CUMS      | hippocampus                     | GV20, GV29| EA, 0.6 mA, 2 Hz             | 20 min, QD for 21 days | Activation of MAPK/ERK pathway      | elevation of BDNF, ERK, pERK, ribosomal s6 kinase augmentation of BDNF pathway, neurogenesis, anti-apoptosis | Li W, et al. 2017[113] |
| Subjects                                      | Location          | Acupoint         | Intervention | Time of intervention | Signal pathway | Main results                                                                 | Author, reference |
|----------------------------------------------|-------------------|------------------|--------------|----------------------|----------------|--------------------------------------------------------------------------------|-------------------|
| Male, specific pathogen-free SD rats, CRS    | hippocampus       | GV20, GV29       | EA, 1mA, 2Hz | pre-stress, 20 min, QD for 28 days | modulation of MAPK/ERK pathway | elevation of MAPT depression of PKC inhibition of cell differentiation and proliferation | Yang X, et al. 2017[114] |
| Male, SD rats, CUMS                         | hippocampus       | GV20, GV29       | EA           | 21 days              | inactivation of JNK pathway | depression of p-JNK anti-apoptosis | Dai W, et al. 2010[115] |
| Male, SD rats, CUMS                         | hippocampus       | GV20, GV29       | acupuncture  | 20 min, QD           | inactivation of JNK pathway | depression of p-JNK protein, MKK 4, MKK 7 protein | Guo Y, et al. 2016[116] |
| Male, SD rats                               | hippocampus, serum| GV20, EX-HN1, ST36, ST40 | EA           | QOD for 21 days      | regulation of hypothalamus-pituitary-adrenal axis | elevation of cortisol, PKA, PKC | Lu F, et al. 2008[117] |
| Subjects                          | Location          | Acupoint | Intervention | Time of intervention | Signal pathway                  | Main results                                                                 | Author, reference |
|----------------------------------|-------------------|----------|--------------|----------------------|---------------------------------|------------------------------------------------------------------------------|------------------|
| Male, SD rats, chronic mild stress | hippocampus       | LI4, LR3 | EA, 2/20 Hz  | 30min, QOD for 42 days | activation of AC-cAMP-PKA pathway | activation of AC-cAMP-PKA pathway                                           | Liu JH, et al. 2012[118] |
| Male, SD rats, CUMS               | hippocampus       | GV20, EX-HN3 | EA, 0.6mA, 2Hz | 30min, QD for 14, 28 days | activation of CREB and BDNF pathways | elevation of BDNF, TrkB, pCREB, and COX2 pathways                            | Duan DM, et al. 2016[119] |
| Male, SD rats, CUMS               | hippocampus       | GV20, EX-HN3 | MA,           | pre-stress, 30min for 21 days | Activation of PKA/CREB pathway | elevation of PKA-α and p-CREB                                               | Jiang H, et al. 2017[120] |
| Male, SD rats, Single prolonged stress | Hippocampus, serum | HT8       | MA, rotate 2Hz for 30sec | QD | activation of mTOR pathway | elevation of corticosterone(serum), corticotropin-releasing factor, mTOR phosphorylation of Akt, ERK, p70S6K, p4E-BP-1, CREB, PSD95, Synl, GluR increase synaptic plasticity | Oh JY, et al. 2018[121] |
| Male, Wistar rats, CUMS           | hippocampus and serum | GV20, EX-HN3 | EA, 1mA, 2Hz, pre-stress | 60min, QD for 28 days | Regulation of neurotrophin signaling pathway, MAPK/ERK pathway and PI3K/Akt pathway | depression of miR-383-5p and miR-764-5p activation of neurotrophy and inhibition of abnormal apoptosis | Duan DM, et al. 2017[122] |
Table 4: Continued.

| Subjects          | Location        | Acupoint       | Intervention  | Time of intervention | Signal pathway                                                                 | Main results                                                                 | Author, reference |
|-------------------|-----------------|----------------|---------------|----------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------|
| Male, SD rats, CRS| hippocampus     | GV20, EX-HN3   | not mentioned | 20min, QD for 28 days| down regulation of toll-like receptor signalling pathway and nucleotide-binding oligomerization domain-like receptor pathway | regulating inflammatory response, innate immunity and immune response          | Wang Y, et al. 2017[123] |
|                   |                 |                |               |                      |                                                                                  |                                                                              |                    |
| Male, SD rats, CRS| frontal cortex  | GV20, GV29     | MA            | pre-stress, 20min, QD for 28 days | Toll-like receptor pathway, TNF pathway, NF-κB pathway | inhibition of inflammatory process                                           | Wang Y, et al. 2017[124] |

Abbreviations
AC: adenyl cyclase; Akt: protein kinase B; BDNF: brain-derived neurotrophic factor; CaMK: Ca2+/calmodulin-dependent protein kinase; cAM: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; COX: cyclooxygenase; CREB: phosphorylated cyclic AMP response element-binding protein; CRS: chronic restraint stress; CUMS: chronic unpredictable mild stress; CUS: chronic unpredictable stress; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinases; MA: manual acupuncture; MAPK: mitogen-activated protein kinases; MAPT: microtubule-associated protein Tau; mRNA: messenger ribonucleic acid; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; nNOS: neuronal nitric oxide synthase; NO: nitric oxide; p38 MAPKs: p38 mitogen-activated protein kinases; PKA: protein kinase A; PKC: protein kinase C; QD: daily; QOD: every other day; SD rat: Sprague Dawley rat; TrkB: tyrosine receptor kinase B; VAMP: vesicle-associated membrane protein.
The p38 MAPKs are activated by environmental stresses and inflammatory cytokines and induce apoptosis and inflammation. In an AD animal model, acupuncture could improve cognitive impairment by reducing p38 MAPK levels, thus reducing neuroinflammation in the CNS [18, 137, 138]. Some studies have reported using Sanjiao acupuncture, which uses CV17, CV12, CV6, ST36, and SP10, as a standard regimen for AD [18, 139, 140]. A DNA microarray analysis demonstrated that Sanjiao acupuncture could reverse gene expression profiles related to aging in the hippocampus of senescence-accelerated mouse prone 10 (SAMP10) mice and reduce oxidative stress–induced damage [18]. Luo et al. reported that Sanjiao acupuncture attenuated cognitive deficits by regulating the G-protein/inositol trisphosphate/Ca2+–amplitude pathway and signal homeostasis [140]. In an Aβ-induced AD model, acupuncture on GV20 and BL23 reduced the level of peroxisome proliferator-activated receptor-γ (PPAR-γ) level and the deposition of Tau protein, thus reducing neuroinflammation [138].

Acupuncture regulated cell cycle and aging in an AD model. N-myc downregulated gene 2 (NDRG2) encodes a cytoplasmic protein that may play a role in neurite outgrowth. Wang et al. demonstrated that EA on GV20 suppressed the astrocyte NDRG2 expression and glial fibrillary acidic protein level, thereby treating memory impairment of amyloid precursor protein/presenilin-1 double transgenic mice [141]. P130, known as retinoblastoma-like protein 2 (RBL2), is a protein encoded by the RBL2 gene in humans and serves as a tumor suppressor signal. Acupuncture on CV17, CV12, CV6, SP10, and ST36 elevated the p130 level, caused cell proliferation in the brain, and treated dementia and aging-related diseases in SAMP10 mice [139]. Telomerase is a critical enzyme involved in aging and apoptosis. Lin et al. demonstrated that acupuncture on ST35 of telomerase-deficient mice activated the BDNF–TrkB signaling pathway along with elevating BDNF, TrkB, Akt, and ERK1/2 levels, which resulted in an increase in telomerase activity [142]. Acupuncture also modulates the balance of Bcl-2/Bax to regulate the cell cycle of neurons. However, the chosen acupoints were heterogeneous, including LI20, EX-HN3, GV20, BL23, and KI1 [143–145].

Metabolic stress modulates β-secretase gene transcription and β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) protein levels in AD through the sirtuin 1 (SIRT1)–PPARγ–proliferator-activated receptor γ coactivator 1 (PGC-1) pathway [146]. Aβ 25–35 suppresses mitochondrial biogenesis by inactivating the AMP-activated protein kinase (AMPK)–SIRT1–PGC-1α pathway in hippocampal neurons [147]. Therefore, brain energy metabolism impairment is considered an underlying pathogenesis of AD progression. Acupuncture on GV20 elevates glucose transporter (GLUT1 and GLUT3), p-AMPK, p-AKT, and mTOR levels in the hippocampus and cortex. Through regulation of brain energy metabolism, acupuncture has effect in decreasing Aβ deposits, suppressing autophagy process and relieving cognition deficits [148]. Acupuncture improved the spatial learning and memory ability of AD mice by increasing blood perfusion and glucose uptake in the bilateral amygdala, hippocampus, and left temporal lobe [149, 150]. For the molecular signaling pathway, Dong et al. demonstrated in two series studies that acupuncture in GV14 and BL23 exerted AMPK expression, activated SIRT1–PPARγ–PGC-1 pathway, and elevated ATP level. Because of the aforementioned mechanisms, acupuncture balances brain metabolism and improves cognition impairment of AD mice [20, 151]. Furthermore, the upregulation of SIRT1–PPARγ–PGC-1 suppresses BACE1 expression, thus reducing Aβ production in the hippocampus and improving cognitive decline in SAMP8 mice [152].

In summary, acupuncture treats AD by regulating neurotransmitter release, elevating the neurotrophic factor level, and exerting anti-inflammatory effects. Thus, many molecular signaling pathways involved in acupuncture were reported in the AD model, including the BDNF–TrkB pathway, the cholinergic system–CREB–BDNF pathway, G-protein regulation, and the p38 MAPK family. The aforementioned pathways are believed to exert antiapoptosis and anti-inflammatory effects and reduce Aβ deposits in the brain, thereby improving learning ability and memory in AD models. The most commonly chosen acupoints were GV20 and the Sanjiao regimen (CV17, CV12, CV6, ST36, and SP10). Acupuncture regulates cell cycle and aging by modulating NDRG2 and P130 expression, telomerase activity, and Bcl-2/Bax balance. Many studies have reported that acupuncture on GV14 and BL23 modulates brain energy metabolism impairment and treats cognitive impairment. The mechanisms and main results of identified articles are summarized in Table 5.

### 8. Vascular Dementia

VD, which accounts for 15% of dementia cases, is the second most common cause of dementia after AD. Multiple and recurrent ischemia of the brain caused by ischemia or hemorrhage has been found to be the main causes of VD [169]. Although the pathophysiology of VD remains unclear, approximately 15%–30% of patients develop dementia three months after the occurrence of stroke. Furthermore, approximately 20%–25% of patients develop delayed dementia [170]. Because of intricate coordination in the brain and, sometimes, the presence of other brain damage causes, the cognitive changes and declines in VD can be variable, including impairment of attention, information processing, and executive function [169]. Few medications have been approved specifically for the prevention or treatment of VD. Thus, treatment strategies for VD are similar to those for AD and include the use of cholinesterase inhibitors and memantine and providing psychosocial support.

Acupuncture can improve the scores on the Mini-Mental Status Examination, the revised Hasegawa’s dementia scale, and activities of daily living examination for VD patients [171, 172]. From the molecular viewpoint, acupuncture on GV20 and KI3 regulates the MAPK/ERK pathway by elevating the pERK level and reducing ionized calcium-binding adaptor molecule 1 (Iba-1), TLR4, and TNF-α levels [153]. Acupuncture reduced relevant proinflammatory factors, thus attenuating neuroinflammation and increasing neuronal synaptic plasticity.

Acupuncture exerted antioxidant and antiapoptosis effects in VD models. Zhu et al. reported that acupuncture on
| Subjects                                      | Location          | Acupoint    | Intervention | Time of intervention | Signal pathway                                      | Main results                                                                 | Author, reference |
|-----------------------------------------------|-------------------|-------------|--------------|----------------------|---------------------------------------------------|-------------------------------------------------------------------------------|-------------------|
| Male, SD rat, scopolamine injection           | brain             | GV20        | MA           | pretreatment for 5 min, QD for 14 days | enhance cholinergic system-CREB-BDNF pathway       | elevation of choline acetyltransferase, choline transporter 1, vesicular acetylcholine transporter, BDNF, CREB proteins neuroprotection | Lee B, et al. 2014[135] |
| APP/PS1 mice                                 | brain             | GV20        | EA, 1/20 Hz  | 30 min, QD for 4 weeks | modulation of BDNF-TrkB pathway                   | elevation of BDNF/proBDNF ratio, p-TrkB depression of β-amyloid (1-42), p75 anti-apoptosis | Lin R, et al. 2016[136] |
| Male, SAMP10                                 | hippocampus       | CV17, CV12, CV6, ST36, SP10 | MA           | QD                   | regulation of aging gene                          | elevation of p53, Mad related protein 2, Nucleoside diphosphate kinase B, AT motif-binding factor, Hsp84, Hsp86 depression of p38 MAPK, retinoblastoma-associated protein 1 anti-oxidation | Ding X, et al. 2006[18] |
| SD rat, Aβ1-40 injection                      | hippocampus, frontal cortex | GV20, KI3, ST36 | EA, 1mA, 2Hz | 15 min, QD for 12 days | inactivation of p38 MAPK pathway                  | depression of p-p38 MAPK protein, IL-1beta mRNA decrease neuroinflammation | Fang JQ, et al. 2013[137] |
| Subjects                              | Location                        | Acupoint | Intervention | Time of intervention | Signal pathway                              | Main results                                                                 | Author, reference |
|--------------------------------------|---------------------------------|----------|--------------|----------------------|---------------------------------------------|-------------------------------------------------------------------------------|-------------------|
| Male, SD rat, Aβ1-40 injection        | hippocampus CA1                 | GV20, BL23 | EA, 2mA, 2-4V, 2Hz | 20min, QD, 6 days/wk for 4 weeks | activation of PPAR-γ pathway               | elevation of PPAR-γ depression of p-p38MAPK, Aβ, p-Tau Ser404 protein decrease neuroinflammation | Zhang M, et al. 2017[138] |
| SAMP 10 mice                         | neocortex and hippocampus       | CV17, CV12, CV6, SP10, ST36 | not mentioned | QD for 14 days         | p130 pathway                               | elevation of p130 cell proliferation                                           | Liu T, et al. 2008[139] |
| Male, SAMP8 mice                     | cortex and hippocampus          | CV17, CV12, CV6, ST36, SP10 | MA, >2Hz      | 30sec per acupoint, QD, 21 days | regulation of G protein/ IP3/ Ca2+ amplitude pathway | elevation of physiologically coupled activation rate and maximal coupled activation rate of Gα and Gαi signal homeostasis | Luo B, et al. 2017[140] |
| Male, APP/PS1 mice                   | brain                           | GV20     | EA, 1mA, 2/15Hz | 30min, QD, 5 days/wk for 4 weeks | suppression of astrocytic NDRG2 pathway    | depression of Glial fibrillary acidic protein, NDRG2 increase astrocytic reactivity | Wang F, et al. 2014[141] |
| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|----------|----------|----------|--------------|----------------------|----------------|--------------|------------------|
| telomerase-deficient mice (TERC-/-) mice | hippocampus and dentate gyrus | ST36 | MA | 30 min, QD for 4 days | activation of BDNF pathway | elevation of BDNF, TrkB, p75NTR, Akt, and ERK1/2 increase telomerase activity | Lin D, et al. 2015 [142] |
| SD rat, beta-amyloid (Abeta)(1-40) injection | hippocampal | LI20, EX-HN3 | EA, 1-3mA, 80-100Hz | 10min, QD, 5 days/wk for 6 weeks | regulation of Bcl-2/Bax | elevation of Bcl-2, depression of Bax anti-apoptosis | Liu ZB, et al. 2011 [143] |
| Male, SD rat, Aβ1-40 injection | hippocampus CA1 | GV20, BL23 | EA, <2mA, 20Hz | 30 min, QD, 6 days/wk for 4 weeks | downregulation of Notch pathway | elevation of Bcl-2, synapsin-1, synaptophysin depression of Bax, Notch1 mRNA, Hes1 mRNA anti-apoptosis | Guo HD, et al. 2015 [144] |
Table 5: Continued.

| Subjects          | Location                  | Acupoint   | Intervention | Time of intervention | Signal pathway                         | Main results                                                                 | Author, reference |
|-------------------|---------------------------|------------|--------------|----------------------|----------------------------------------|------------------------------------------------------------------------------|--------------------|
| Male, APP/PS1 mice | hippocampus               | GV20, KI1  | EA, 1mA, 2/100Hz | 15min, QD for 3 days | inactivation of caspase-3/ Bax pathway | elevation of Bcl-2/Bax ratio depression of caspase-3-positive cell number and Bax protein anti-apoptosis | Li XY, et al. 2016[145] |
| APP/PS1 mice      | hippocampus, cortex       | GV20       | EA, 1/20Hz   | 30min, QD, 5 days/wk for 4 weeks | regulation of AMPK/mTOR pathway       | elevation of GLUT1, GLUT3, p-AMPK, p-Akt, mTOR decrease Aβ (1-42) deposition, decrease autophagy process | Liu W, et al. 2017[148] |
| Male, SAMP8 mice  | hippocampus CA1           | GV14, BL23 | EA, 1mA, 2Hz | 20min, QD, 8 days' treatment and 2 days' rest for 3 cycles | activation of AMPK pathway            | elevation of ATP levels, SIRT1, PGC-1α expression improved brain energy metabolism | Dong W, et al. 2015[20] |
| Male, SAMP8 mice  | hippocampus and frontal cortex | GV14, BL23 | EA, 1mA, 2Hz | 20min, QD, 8 days' treatment and 2 days' rest for 3 cycles | activation of SIRT1-dependent PGC-1α expression pathway | elevation of ATP levels, SIRT1, PGC-1α expression improved brain energy metabolism | Dong W, et al. 2015[151] |

Abbreviations
Akt: protein kinase B; AMPK: AMP-activated protein kinase; APP/PS1: amyloid precursor protein (APP)/presenilin-1 (PS1) double transgenic; Bax: Bcl-2 associated X; Bcl-2: B-cell lymphoma 2; BDNF: brain-derived neurotrophic factor; CREB: phosphorylated cyclic AMP response element-binding protein; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; GLUT: glucose transporter; IL: interleukin; IP3: Inositol triphosphate; MA: manual acupuncture; MAPK: mitogen-activated protein kinases; NDRG2: N-myc downregulated gene 2. NMCA: N-methyl-D-aspartate; PGC1: proliferator-activated receptor γ coactivator 1; PPAR-γ: peroxisome proliferator-activated receptors γ; QD: daily; QOD: every other day; RBL2: Retinoblastoma-like protein 2; SAMP: senescence-accelerated mouse prone; SD rat: Sprague Dawley rat; SIRT1: sirtuin 1; TrkB: tyrosine receptor kinase B.
GV20 and ST36 inactivated the apoptosis signal-regulating kinase 1 (ASK1)–JNK/p38 pathway and elevated thioredoxin-1 and thioredoxin reductase-1 levels [154]. The p38 MAPK pathway activates the expression of CREB and reduces the apoptosis of ischemic neural cells. Some studies have reported that acupuncture activates the cAMP/PKA/CREB pathway and elevates the CREB level [47, 48, 50, 51]. The elevated CREB level upregulates Bcl-2 activity and downregulates Bcl-2x1 and Bax activities, consequently preventing the apoptosis of neurons injured by vascular events [48, 51]. The most discussed acupoint was GV20, followed by GV24. Scalp and Sanjiao acupuncture techniques (CV17, CV12, CV6, ST36, and SP10) have been reported to affect the balance between Bcl-2 and Bax expression and antiapoptosis [155, 156]. VD rats had lower expression of mTOR and eukaryotic translation initiation factor 4E (eIF4E) in CA1 accompanied with decreased spatial memory [173]. Zhu et al. demonstrated that EA on GV20, GV14, and BL23 activates the mTOR pathway and increases mTOR and eIF4E levels, thus modulating cell growth, proliferation, and synaptic plasticity [157].

Taken together, acupuncture treats VD by activating MAPK/ERK and ASK1–JNK/p38 pathways; increasing CREB, mTOR, and Bcl-2 levels; and reducing the Bax level. In addition, through the aforementioned mechanism, acupuncture exerts an effect on antioxidant activity, antiapoptosis, and synaptic plasticity. The most commonly chosen acupoints were GV20, GV24, and ST36. The mechanisms and main results of identified articles are summarized in Table 6.

9. Parkinson’s Disease

PD is a chronic neural degenerative disorder that mainly affects the motor system. Patients with PD experience shaking, rigidity, and walking difficulty. In advanced stages of the disease, behavioral disturbance, depression, poor sleep, and cognitive dysfunction are noted [174]. Treatments such as the administration of L-dopa, dopamine agonists, catechol-O-methyl transferase inhibitors, and monoamine oxidase inhibitor and deep brain stimulation are suggested for treating motor problems of patients with PD. However, dyskinesias and motor fluctuations that develop after a long-term use or high dose use of L-dopa and nonmovement-related symptoms, such as sleep disturbances and psychiatric problems, become problems for patients with PD [174].

Both manual acupuncture and EA help alleviate some motor symptoms in patients with PD and some nonmotor symptoms, such as psychiatric disorders, sleep disorders, and gastrointestinal symptoms. Acupuncture also improved the therapeutic efficacy of levodopa, lowering the necessary dosage [175–177]. Reducing dopaminergic neurons in the substantia nigra (SN) results in PD. Acupuncture has been reported to exert neuroprotective effects that increase the levels of endogenous neurotransphins and modulate the apoptosis and neuroinflammation of dopaminergic neurons in the SN [178, 179]. Neuroimaging findings of the human brain showed that acupuncture on GB34 and the scalp significantly increased glucose metabolism bilaterally in the frontal and occipital lobes and improved motor dysfunction in patients with PD [179, 180].

In light of signal transduction, EA at 2 Hz on GV16 and LR3 inactivate the ERK 1/2 signaling pathway and p38/MAPK signaling pathway, causing an increase in tyrosine hydroxylase–positive neurons and a decrease in COX-2, TNF-α, and IL-1β levels. The regulation of cytokines reduces the neuroinflammation of the SN and alleviates PD symptoms [158, 159]. Acupuncture also activates the PI3K/Akt pathway, which elevates the Bcl-2 level and reduces dopamine- and cAMP-regulated phosphoprotein of 32 kDa and Fos B. Through the activation of the PI3K/Akt pathway, acupuncture increases the dopamine turnover rate and availability in the synapse of the SN and striatum and regulates the tyrosine hydroxylase–positive cell cycle, thus improving motor function [160–162]. Lu et al. demonstrated that EA on KI3 inactivates pPKA/pPKC/CaMKIIα signaling pathways and reduces neuronal excitotoxicity in the hippocampus [163].

Rapamycin, an inhibitor of mTOR, is a potent inducer of autophagy and has an effect on PD [181]. However, rapamycin-based treatments for PD show adverse effects, including dyslipidemia, proliferative dysregulation, and renal dysfunction [182]. Acupuncture on GB34 affected the downstream autophagy–lysosome pathway through the m-TOR independent pathway; this effect was comparable to that observed in the rapamycin treatment group [164]. Acupuncture induced autophagic clearance of α-syn, caused recovery of DA neurons in the SN, and improved motor function of an animal model without any notable adverse effect [164].

Oxidative stress and inflammation both contribute to the neural toxicity and development of PD [183]. Many studies have indicated the use of high-frequency EA for treating PD motor symptoms in animal models [184, 185]. Kim et al. reported that high-frequency EA on GB34 and GB39 increased tyrosine hydroxylase–positive neurons and cytochrome c oxidase subunit Vb and reduced cytosolic malate dehydrogenase, munc18-1, and hydroxyacylglycathione hydratase levels, thus exerting an antioxidative effect on the SN [165]. Lv et al. demonstrated that EA at 100 Hz on ST36 and SP6 exerted a neuroprotective effect on PD mice and reversed the increase in the levels of Iba-1 and proinflammatory cytokines, including TNF-α, IL-6, and IL-1β, induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), thus suppressing the neuroinflammatory process [166]. The nuclear factor erythroid 2-related factor 2 (Nrf2)–antioxidant response element (ARE) pathway regulates oxidative stress and inflammatory responses. EA enhances the Nrf2–ARE pathway and regulates the expression of antioxidants, such as the ARE-driven reporter gene, nicotinamide adenine dinucleotide phosphate quinone oxidoreductase, and heme oxygenase-1 (HO-1), thus relieving PD symptoms [166]. Similarly, Deng et al. reported that EA at 100 Hz on ST36 and SP6 elevated HO-1 and glutamate–cysteine ligase modifier subunits and reduced astrogliosis and neuroinflammation through the Nrf2–ARE pathway [167].

PD symptoms were relieved through the modification of TLR/NF-κB and Nrf2/HO-1 pathways [186]. EA on GV16 and
| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|----------|----------|----------|--------------|----------------------|----------------|--------------|------------------|
| Male, Wistar rats, homologous blood emboli injection of internal carotid artery | hippocampus | ST36 | MA | QD for 14 days | activation of cAMP/PKA/CREB pathway | activation of long-term potentiation | Li QQ, et al. 2015[47] |
| Male, SD rats, MCAO | hippocampus | GV24, GV20 | EA, 1-3mA, 5/20Hz | 30min, QD | increase expression of p-CREB | elevation of superoxide dismutase and glutathione peroxidase, Bcl-2 depression of malondialdehyde, Bcl2-xl anti-oxidase and anti-apoptosis | Lin R, et al. 2015[48] |
| Female, SD rats, MCAO | hippocampus | GV20, GV24 | EA, 1/20Hz | 30min, QD for 7 days | inactivation of CaM-CaMKIV-CREB pathway | anti-apoptosis | Zhang Y, et al. 2016[50] |
| Male, SD rats, MCAO | hippocampus | GV20, HT7 | MA, LA, 30 mW, 100Hz | 14 days | enhance cholinergic system | elevation of CREB, BDNF and Bcl-2 depression of Bax anti-apoptosis | Yun YC, et al. 2017[51] |
| Mongolian gerbils, CCAO | hippocampal CA1 | K13, GV 20 | EA, 1mA, 2Hz | 20 min, 4 times/ 2 days | regulate MAPK/ERK pathway | elevation of p-ERK depression of ionized calcium-binding adaptor molecule 1, TLR4, TNF-α decrease neuroinflammation, regulate the synaptic plasticity | Yang EJ, et al. 2016[153] |
| Male Wistar rats, two-vessel occlusion model | hippocampus | GV20, ST36 | MA | QD for 14 days | inactivation of ASK1-JNK/p38 pathway | elevation of thioredoxin-1 and thioredoxin reductase-1 anti-oxidase and anti-apoptosis | Zhu W, et al. 2018[154] |
### Table 6: Continued.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|----------|----------|----------|--------------|----------------------|----------------|--------------|------------------|
| Male, Wistar rat, homoblood injection | hippocampal CA1 | CV17, CV12, CV6, ST36, SP10 | MA, 2Hz | 30sec for each acupoint, QD, 6 days/ wk for 3 weeks | balance Bcl-2 and Bax expression | elevation of Bcl-2 depression of Bax anti-apoptosis | Wang T. et al. 2009[155] |
| Male, SD rat, using modified Pulsinelli 4-vessel-occlusion method | hippocampal CA1 | Scalp-acupuncture | MA | 30min, QD for 10 days | activation of Bcl-2 pathway | elevation of Bcl-2 anti-apoptosis of astrocytes | Tian WJ, et al. 2015[156] |
| Female, SD rat, CCAO | hippocampus | GV20, GV14, BL23 | EA, 2mA, 4Hz | 30min, QD for 30 days | activation of mTOR pathway | elevation of mTOR and eIF4E modulates cell growth, proliferation and synaptic plasticity | Zhu Y, et al. 2013[157] |

**Abbreviations**
- ASK1: apoptosis signal-regulating kinase 1
- Bax: Bcl-2 associated X
- Bcl-2: B-cell lymphoma 2
- BDNF: brain-derived neurotrophic factor
- CaMK: Ca2+/calmodulin-dependent protein kinase
- cAMP: cyclic adenosine monophosphate
- CCAO: occlusion of common carotid artery
- CREB: phosphorylated cyclic AMP response element-binding protein
- EA: electroacupuncture
- eIF4E: eukaryotic translation initiation factor 4E
- ERK: extracellular signal-regulated kinase
- JNK: c-Jun N-terminal kinases
- MA: manual acupuncture
- MAPK: mitogen-activated protein kinases
- MCAO: occlusion of middle cerebral artery
- mTOR: mammalian target of rapamycin
- PKA: protein kinase A
- QD: daily
- TLR4: Toll-like receptor 4
### Table 7: Signal transduction pathways of acupuncture in treating Parkinson's disease.

| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|----------|----------|----------|--------------|----------------------|----------------|--------------|------------------|
| Male SD rats, rotenone injection | substantia nigra | GV16, LR3 | EA, 1mA, 2Hz | 20min, QD for 14 days | inactivation of p38-MAPK pathway | elevation of tyrosine hydroxylase-positive neuron, depression of phosphorylated p38-MAPK, COX-2 decrease neuroinflammation | Wang SJ, et al. 2013[158] |
| Male SD rats, rotenone injection | substantia nigra | GV16, LR3 | EA, 2mA, 2Hz | 20min, QD for 14 days | inactivation of ERK 1/2 pathway | elevation of tyrosine hydroxylase protein, depression of p-ERK 1/2, TNF-α, IL-1β decrease neuroinflammation | Wang SJ, et al. 2014[159] |
| Male C57BL/6 mice, MPTP injection | substantia nigra, striatum | GB34 | MA, 2Hz for 15sec | QD for 7 days | activation of PI3K/Akt pathway | elevation of pAkt prevents MPTP-induced dopaminergic neuron degeneration | Kim SN, et al. 2011[160] |
| Male C57BL/6 mice, MPTP injection | substantia nigra pars compacta, striatum | GB34 | MA, 2Hz for 15sec | QD for 12 days | activation of PI3K/Akt pathway | elevation of dopamine depression of dopamine- and cAMP-regulated phosphoprotein of 32 kDa, Fos increase dopamine turnover rate | Kim SN, et al. 2011[161] |
| Male, C57BL6 mice (MPTP intraperitoneal injection) and SD rats (Sigma-Aldrich injection into substantia nigra) | substantia nigra | GB34, LR3 | EA, 1mA, 50Hz | QD for 5(mice)/7(rats) days | activation of Akt pathway | elevation of BDNF, Bcl-2, tyrosine hydroxylase regulation of cell cycle | Lin JG, et al. 2017[162] |
| Subjects                                                                 | Location          | Acupoint | Intervention     | Time of intervention | Signal pathway                                                                 | Main results                                                                                                                                                                                                 | Author, reference |
|------------------------------------------------------------------------|-------------------|----------|------------------|----------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Imprinting control region mouse pups, systemic 6-hydroxydopamine injection | hippocampus       | KI3      | EA, 1mA, 2Hz     | 15min, QD, 5 days/wk for 6wks | inactivation of pPKA/pPKC/CaMKIIα signaling pathways | depression of pNR1, pNR2B, pPKA, pPKC, pCaMKIIα, pERK, pCREB reduce neuronal excitotoxicity                                                                                                                | Lu KW, et al. 2017[163] |
| Male C57BL/6 mice, MPTP injection                                      | substantia nigra par compacta | GB34     | MA, 2Hz for 15sec every 5min | 10min, QD for 7 days | m-TOR independent pathway | depression of α-synuclein induces autophagic clearance of α-syn, dopaminergic neurons protection                                                                                                              | Tian T, et al. 2016[164] |
| Male C57BL/6 mice, MPTP injection                                      | substantia nigra, striatum | GB34, GB39 | EA, 1mA, 100Hz   | 20min, QD for 12 days | regulation of glyoxalase system | elevation of tyrosine hydroxylase-positive neurons, cytochrome c oxidase subunit Vb, depression of cytosolic malate dehydrogenase, munc18-1, hydroxyacylglutathione hydrolase, anti-oxidative effect | Kim ST, et al. 2010[165] |
| Male C57BL/6 mice, MPTP injection                                      | midbrain, striatum  | ST36, SP6 | EA, 1-1.4mA, 100Hz | 30min, QD for 12 days, except day 7 | activation of Nrf2-ARE pathway | elevation of tyrosine hydroxylase, ARE-driven reporter gene, NQO1, HO-1, depression of ionized calcium-binding adaptor molecule 1, TNF-α, IL-6, IL-1β, anti-oxidative effect | Lv E, et al. 2015[166] |
| Subjects | Location | Acupoint | Intervention | Time of intervention | Signal pathway | Main results | Author, reference |
|----------|----------|----------|--------------|---------------------|----------------|--------------|------------------|
| GFAP-tTA/tetO-α-syn double transgenic mice | midbrain, striatum | ST36, SP6 | EA, 1-1.2mA, 100Hz | 30min, QD for 28 days | activation of Nrf2-ARE pathway | elevation of Nrf2, HO-1, glutamate-cysteine ligase modifier subunits depression of α-syn decrease astrogliosis and neuroinflammation | Deng J, et al. 2015[167] |
| Male C57BL/6 mice, MPTP injection | striatum, substantia nigra | GB34 | MA, 2Hz, 15sec | QD for 12 days | activation of p53 signaling pathways | elevation of p53 dopaminergic neuron protection | Park JY, et al. 2015[168] |

**Abbreviations**

Akt: protein kinase B; ARE: antioxidant response element; CaMK: Ca2+/calmodulin-dependent protein kinase; cAMP: cyclic adenosine monophosphate; COX: cyclooxygenase; CREB: phosphorylated cyclic AMP response element-binding protein; EA: electroacupuncture; ERK: extracellular signal-regulated kinase; HO-1: heme oxygenase-1; IL: interleukin; MA: manual acupuncture; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mTOR: mammalian target of rapamycin; NQO1: nicotinamide adenine dinucleotide phosphate quinone oxidoreductase; Nrf2: nuclear factor erythroid 2-related factor 2; p38 MAPKs: p38 mitogen-activated protein kinases; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA: protein kinase A; PKC: protein kinase C; pNR: phosphorylated N-methyl-D-aspartate receptor; QD: daily; SD rat: Sprague Dawley rat; TNF-α: tumor necrosis factor-alpha.
LR3 upregulated NFKB protein expression and downregulated 26S proteasome protein expression in rotenone-induced PD rats [187]. P53 plays a role in DNA repair or cell death depending on the nature and extent of stress and damage [188]. P53 dysfunction was reported in neurodegenerative diseases and cancers [189]. Park et al. demonstrated that acupuncture on GB34 activated the p53 signaling pathway, protected dopaminergic neurons in the SN and striatum, and treated PD symptoms [168].

At the gene level, Choi et al. demonstrated that EA regulated gene expression in the striatum and exerted a neuroprotective effect on MPTP parkinsonism mice [190, 191]. Yeo et al. performed a microarray analysis study of acupuncture on GB34 and LR3 in an MPTP mouse model of parkinsonism and reported that acupuncture reversed the downregulation of five annotated genes and upregulation of three annotated genes through MPTP intoxication [192].

In summary, acupuncture improved motor dysfunction and memory of PD. These effects were accompanied by the regulation of gene expression. Acupuncture modulates neuroinflammation by inactivating ERK 1/2 and p38/MAPK signaling pathway and reduces neuronal excitotoxicity through the pPKA/pPKC/CaMKIIα signaling pathway. Acupuncture also regulates apoptosis by balancing the Bcl-2 and m-TOR-independent pathway. The most chosen acupoints include GB34, LR3, and GV16. Moreover, high-frequency EA (100
Hz) on ST36 and SP6 reduces neuroinflammation through the Nrf2–ARE pathway. The mechanisms and main results of identified articles are summarized in Table 7.

10. Conclusion

Acupuncture treats nervous system diseases through many signal transduction pathways. Besides increasing the neurotrophic factors level, acupuncture influences pathways including p38 MAPKs, Raf/MAPK/ERK1/2, TLR4/ERK, PI3K/AKT, AC/cAMP/PKA, ASK1–JNK/p38, and downstream CREB, JNK, m-TOR, NF-κB, and Bcl-2/Bax balance. We summarized the common signal transduction pathways through which acupuncture treats nervous system diseases (Figure 2). Through the aforementioned pathways, acupuncture affects synaptic plasticity, elevates neurotrophic factors, and results in neuroprotection, cell proliferation, antiapoptosis, antioxidant activity, anti-inflammation, and maintenance of the BBB.

Data Availability

The data in this study are available to other researchers upon request.

Conflicts of Interest

We declare that there are no conflicts of interest associated with this manuscript, and no significant financial support was received that would influence our findings.

Authors’ Contributions

Hsiang-Chun Lai collected data and wrote the manuscript, Qwang-Yuen Chang participated in discussions and provided suggestions, and Ching-Liang Hsieh provided an informed opinion and revised the manuscript.

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