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Chapter

Therapeutic Potential of Baicalein in Parkinson's Disease: Focus on Inhibition of α-Synuclein Oligomerization and Aggregation

Hayate Javed and Shreesh Ojha

Abstract

Parkinson's disease (PD) is the most common neurodegenerative diseases, which affects the people in old age. The neuropathological symptoms of PD include the degeneration of dopaminergic neurons in the substantia nigra pars compacta, and presence of intracellular inclusions of α-synuclein (α-syn) aggregates. α-Syn, a natively unfolded protein, has been found to play a key role in PD pathology. Several mechanistic studies revealed the numerous aspects of α-syn fibrillation and aggregation process that lead to dopaminergic neurodegeneration in PD. Till to date, there is no complete cure of PD, but some therapeutic agents are able to halt the disease progression. Scutellaria baicalensis Georgi is a traditional Chinese medicine commonly used to treat the central nervous system diseases. Recently, it has been confirmed that root of S. baicalensis Georgi contains baicalein (5,6,7-trihydroxyflavone) as a major bioactive flavone constituent. Baicalein possess numerous pharmacological properties such as antiaggregation of amyloid proteins including α-syn, antioxidant, anti-inflammatory, and antiapoptotic. In the light of these properties, baicalein has potential therapeutic efficacy for PD. In this chapter, we explored the pharmacological protective actions of baicalein against α-syn fibrillation and aggregation that make it suitable for PD treatment and also discussed the possible mechanisms underlying the effects.

Keywords: Parkinson's disease, α-Synuclein, baicalein, flavonoids, dopaminergic neurons

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease involving movement disorders [1, 2]. Worldwide, about 10 million people are living with PD and it affects 3–4% of individuals over the age of 65 years [3, 4]. Symptomatically, PD is characterized by the movement and behavioral disorders and pathologically characterized by the deterioration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies [5, 6]. The diagnosis of PD, in general, includes motor disorders such as bradykinesia, cogwheel rigidity, resting tremors, postural instability, and slowness or absence of voluntary movements along with neuropsychiatric manifestations [7, 8]. The Lewy bodies in PD result from accumulation of intracellular α-synuclein (α-syn) inclusions in neurons,

and aggregates of α-syn spread through the brain following a specific pattern [9]. The neuron-to-neuron transfer of α-syn is considered critical for the propagation of Lewy body pathology. The definitive postmortem diagnosis and pathological character of PD constitute the presence of aggregated (i.e., fibrillar, spherical, and oligomeric) forms of α-syn protein in the soma and processes including axons and dendrites of affected neurons. The familial form of PD is caused by mutations in the *SNCA* gene, which is the first determinant of PD [10]. Moreover, inherited forms of PD result from the genetic overexpression *via* gene duplication or triplication [11, 12]. Importantly, more α-syn gene copies result in highly aggressive form of the disease, which suggests a direct relationship between disease severity and the expression level of α-syn [13]. The fibrillated form of α-syn protein is the abundant component of Lewy bodies, which are the pathological hallmarks of sporadic form of PD and present as cytoplasmic inclusions [14]. Consequently, α-syn is believed to play a crucial and significant causative role in most, if not all, forms of PD.

In the last 30 years, the approach in the treatment of PD is based on enhancing the deteriorating levels of dopamine neurotransmitter through administering dopamine precursor L-dopa. Until now, the replacement of dopamine by L-dopa administration is the standard treatment for PD management [15]. However, L-dopa appears to provide only symptomatic relief in correcting the motor abnormalities and did not inhibit or reverse the PD progression [16]. However, the long-term use of dopamine precursor drugs found to produce numerous adverse effects and induce complications that ultimately flop to treat PD patients if disease progresses [17]. Thus, there is a great requirement to develop new drugs for the management of PD, which are not only therapeutic but can also prevent the initiation or delay or stop the progression of the disease.

In the past few years, there is an enormous emphasis on the medicinal use of plant extracts, which are also reputed for their therapeutic claims in a variety of traditional medicines. The traditional preparations usually contain many medicinal plant extracts that have been shown better therapeutic efficacy on neurological diseases, such as cerebral stroke, dementia, and paralysis, in clinical setup for decades [18, 19]. Though all these herbs-based medicinal preparations are used in the traditional practice of medicine with perceived safety and efficacy, the precise pharmacological and molecular mechanisms involved in the therapeutic efficacy of these traditional Chinese medicines remain unclear. Majority of the mechanisms purported behind the clinical efficacy of these herbal medicines are based on generalized antioxidant and anti-inflammatory property, rather a well-established pharmacological target. They are therefore not well accepted in modern medicine, which is based on rigorously documented evidence-based randomized clinical data. It is challenging to systematically identify these mechanisms with modern biochemical and pharmacological techniques [20]. Simultaneously, medicinal plants are well acknowledged as a source of modern drugs, which provides a drug discovery approach and further leads to drug development. It is well documented that enhanced dietary consumption of herbal medicines reduces the risk of developing neurodegenerative diseases [21].

In an approach to identify a novel molecule form of traditional medicine, the root of *Scutellaria baicalensis* Georgi garnered enormous attention in drug discovery for neurodegenerative diseases. *Scutellaria baicalensis* Georgi, widely grown in Mongolia, Korea, Siberia, China, Japan, and the Russian Far East, represents one of the important ingredients in the decoction of traditional herbal preparation employed for the treatment of CNS diseases [21]. Pharmacokinetic study confirmed that baicalein, a flavone chemically known as 5,6,7-trihydroxyflavone, is one of the prominent bioactive components of the roots of *Scutellaria baicalensis* Georgi [22]. Baicalein is one of the widely studied compounds and

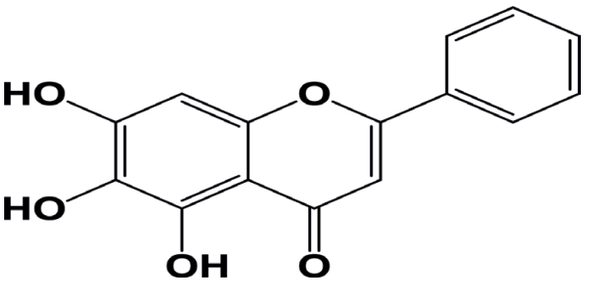


Figure 1.
The chemical structure of baicalein.

reputed for its multiple pharmacological actions including antibacterial, antiviral, anticarcinogenic, and anti-inflammatory activities in traditional Chinese medicine [23–26]. Baicalein has a wide safety of margin and appears to be able to cross the blood-brain barrier [27]. Several studies based on animal model of AD and PD have shown that baicalein exhibits neuroprotective properties [26–29]. Therefore, baicalein has been the central molecule to investigate its versatility as therapeutic agent for neurological diseases [21]. In this chapter, we will describe the therapeutic importance of baicalein against the PD with a focus in the amelioration of α-syn, which is central protein in the pathogenesis of PD. In addition, we will also highlight the potential underlying biochemical mechanisms of action of baicalein (**Figure 1**).

2. α-Syn a major mediator in PD pathogenesis

α-Syn is a 140 amino acid protein, which is encoded by *SNCA* gene located on human chromosome 4 and most abundantly expressed in presynaptic terminals and helps in the maintenance of neurotransmitter systems in CNS [28]. Regardless of its abundant distribution in numerous areas intricated in multifaceted activities, α-syn pathology exists in selectively vulnerable areas rather than its site of expression in the brain [28, 29]. Furthermore, red blood cells are also abundant in α-syn [30] and many other CNS tissues [31, 32], which indicates broader range of α-syn functions throughout the body. Almost two decades have been spent to find out the exact role of α-syn physiology; its mechanism of action is still unknown, and complex dynamics of this protein is characterized by its ability to achieve the toxic effect as well as flexibility to adapt. α-Syn has gained much consideration as important factor in PD pathophysiology. α-Syn exists in a dynamic equilibrium from monomeric to oligomeric states, and this equilibrium prevents formation of fibrils in physiological conditions. Importantly, multifunctional properties of α-syn are predicted by its structure that has been attributed to this protein [33]. The structure flexibility property of α-syn allows it to accept a wide range of conformations depending on binding partners and environment [34, 35]. Because of its abundant presence at presynaptic terminals, chaperone function of α-syn is the key cellular function, which controls the exocytosis through trafficking and organizing the synaptic vesicle pool. Mutations in α-syn coding gene *SNCA* lead to functional changes of SNAP REceptor (SNARE) protein, which is a receptors family that binds soluble N-ethylmaleimide sensitive fusion attachment proteins (SNAP) receptor (SNARE) proteins and controls its assembly [36]. Moreover, α-syn also targets presynaptically dopamine active transporter (DAT) [37].

Several approaches occur to prevent the oligomerization of α-syn [39], which includes hydrophobic interactions between C- and N-terminals of α-syn [40]. Interestingly, α-syn exhibits a polar C-terminal tail, which can bind to

hydrophobic region of other denatured protein, having functional and structural homology with different molecular chaperones. Therefore, the flexibility of α-syn depends on the capacity of this protein to autoassemble and function as intramolecular chaperone [41]. Autochaperone property was found absent in C-terminus of truncated α-syn and that will increase the formation of α-syn aggregates compared with the full-length α-syn [39]. At present, the exact biological functions of α-syn are unknown; but there is a substantial amount of ongoing research that helps us to understand this gap in our knowledge. The functional repertoire of α-syn is largely studied through determining the irregularities following overexpression, expression of mutant forms of α-syn, or loss of expression. The number of studies indicates α-syn involved in the formation of synaptic vesicles, mitochondrial function, and/or dopamine synthesis and metabolism. Furthermost characteristics strongly argue for important role in synaptic plasticity and neurotransmitter release. Chaperone plays an important role in the folding of polypeptide during proteins translation, and assembly misfolding is common with aging yet they are generally partial by numerous quality control machineries that degrade the misfolded and denatured proteins [42]. With the complex organization of α-syn expression and its function of great adaptability, homeostatic functions failures do not bring to uneven function gain, instead trigger a sequence of neurodegenerative process in the intracellular system.

Several studies conducted in PD patients and animal models support the idea that the proteostasis of α-syn has a critical role in the PD pathogenesis. This concept backs to two decades when two discoveries provided the evidence that PD is linked to α-syn mutations. The first report published by Polymeropoulos and colleague for the identification of a missense mutation in α-syn gene causing early onset of familial form of PD [9]. In the same year, an experimental report showed that Lewy bodies contain higher amount of α-syn that appears as intracytoplasmic inclusion of α-syn aggregates and considered as classical pathological hallmarks of PD [14]. Soon after these discoveries, the presence of Lewy body in the brain parenchyma of sporadic idiopathic forms of PD was also found [43]. To examine the probable causal links, pathological and physiological functions of α-syn and different misfolding proteins have been investigated in relative with documented features of PD. Several risk factors for PD have been explored that are genetic and environmental. Point mutations, mitochondrial dysfunctions, oxidative stress, neuroinflammation, multiplications, and specific polymorphisms are the genetic causes that may lead to develop suitable environment for progressing PD. Remarkably, these factors are equally responsible to exert α-syn toxicity. Despite having good quality control structures to confirm a precise α-syn assembly and the capability to control α-syn oligomerization, this protein also expresses its neurotoxic effects upon formation of oligomers from soluble monomers, and then gradually formed protofibrils to large α-syn aggregates which eventually leads to Lewy body formation [44]. A greater chance of α-syn aggregation is accessible by various posttranslational covalent modifications including conformational changes, which direct α-syn more vulnerable to aggregation [35]. α-Syn truncation at the C-terminus and tyrosine nitration (Tyr125) are usually observed in α-syn aggregates and often found to enhance its in vitro fibrillation [45]. Additionally, aging diminishes the proteolytic efficiency that plays an important additive role in the accumulation of α-syn. These finding supporting the data showing enhanced α-syn levels in nigral neurons in aged brain. In the normal brain, intracellular homeostasis of α-syn is confirmed by the accumulative functions of lysosomal autophagy, and ubiquitin-proteasome systems with the previous one play a key role in the clearance of oligomeric α-syn. Irregularities in both systems lead to excessive production and accumulation of α-syn that eventually end up to formation of α-syn aggregates.

3. Abnormal accumulation of α-syn causes dopaminergic neurodegeneration

In PD, decreased striatal dopamine occurred following selective neurodegeneration of dopaminergic neurons of the substantia nigra par compacta (SNc) and impairment of several basal ganglia functions. It is still unknown through which mechanism α-syn causes dopaminergic neurons vulnerable and it needs to be fully elucidated. α-Syn is associated to dopamine neurons for its capability to control homeostasis of dopamine in the synapses and effects DAT activity, but the exact mechanism is still debatable [46]. α-Syn plays a key role as a modulator for dopamine synthesis and metabolism by decreasing the tyrosine hydroxylase phosphorylation and stabilizes in inactive state [47]. Therefore, α-syn absence employs considerable effect on dopaminergic systems because it reduces dopamine levels in the striatum and decreased DAT functions. Absence of α-syn is also linked with reduced striatal dopamine uptake, decreased number of TH-positive nigral dopaminergic neurons, and nerve terminals in the striatum [48]. However, the sensitivity of dopaminergic neurons also conferred to intrinsic and excitotoxic insult and does not rely on absence of dopamine metabolism. There are two characteristic features of dopaminergic neurons which makes them especially more susceptible to excitotoxic challenge. First dopamine neurons show a prolonged axonal branch, which offer extensive neurotransmitter release sites. Enhanced mitochondrial impairment is observed in the axons of dopaminergic neurons and this is one of the reasons to show elevated susceptibility. Second, dopamine neurons act as autonomous pacemakers and display spontaneous activity. The activity of dopaminergic neurons is considered through oscillations in intracellular calcium (Ca^{2+}) levels, which is operated by voltage-dependent L-type Ca^{2+} channels opening to maintain a rhythmic (2–10 Hz) spiking [49]. This capability is connected to decreased intrinsic Ca^{2+} levels and required a strict quality control for Ca-mediated processes from intracellular reservoir, endorsing Ca^{2+} entry into the mitochondria and ATP production by oxidative phosphorylation [50]. All these processes are required to complete the requirements of bioenergetics and to prevent the unnecessary activation of ATP-sensitive potassium channels that may inhibit the spontaneous activity of neurons. Nigral dopaminergic neurons and different brain nuclei neurons involved in sensorimotor integration are capable with mechanisms that maintain to rapidly implement a correct strategy upon environmental stress. As a result, for this adaptive ability is the vulnerability of the system to environmental toxins, age, and genetic mutations or that can increase the reactive oxygen species production which ca warrant the proteostasis, DNA damages, especially in mitochondria. Impairment in mitochondria ultimately leads to cause impaired mitophagy and also compromised. Recently, Burbulla and colleagues [51] showed inactivation of DJ-1 causes additive toxic effect of elevated α-syn levels, mitochondrial dysfunction, and stimulation of dopaminergic receptors in mice. Remarkably, overexpression of human α-syn A53T [52] in dopaminergic neurons and constitutive DJ-1 deficiency in mice showed enhanced levels of oxidized dopamine in dopaminergic neurons and decreased lysosomal activity.

4. Baicalein as a potential molecule of natural origin to target α-syn

In the recent years, a growing effort has been taken in the development of innovative neuroprotective molecules of natural origin with high efficacy and low side effects to prevent neuronal deaths [10, 19]. Several studies have been attempted to

examine the effects of extracted components from different plants on neurotoxicity. Among the numerous compounds from plants, flavonoids are the utmost effective components with a broader range of pharmacological and health-promoting properties [20, 21]. To date, almost 8000 different flavonoid compounds have been discovered and are classified into various subgroups, including flavonols, flavones, flavanols, flavanones, isoflavones, etc. [22]. Numerous vegetables and fruits, flavonoid compounds are the major classes of natural polyphenols. The consumption of flavonoid-rich fruits and vegetables significantly reduces the risk of many diseases in humans [23, 24].

Baicalein (5,6,7-trihydroxyflavone; $C_{15}H_{10}O_5$) is an important flavonoid compound mainly isolated from the roots of *S. baicalensis* Georgi (Labiatae). Earlier studies clearly showed that baicalein has various pharmacological properties such as antioxidant, anti-inflammatory, antidiabetic, anticancer, antiulcerative colitis, antithrombotic, antiviral, eye protective, cardioprotective, neuroprotective, and hepatoprotective properties [25]. It also possesses anticonvulsive, anxiolytic, and mild sedative actions [26]. Many studies have clearly demonstrated that baicalein protected 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenylpyridinium (MPP+), glutamate, amyloid-β (Aβ), hydrogen peroxide (H_2O_2), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and methamphetamine-induced neurotoxicity in animal models and cell lines [27–33]. Earlier, some authors clearly reviewed the anticancer, anti-inflammatory, cardioprotective properties, ocular disorders, and mitochondrial function [34–37]. Li et al. [38] briefed the therapeutic properties of baicalein against PD. Baicalein halts PD progression by reducing oxidative stress, inhibiting excitotoxicity, inhibiting aggregation of disease-specific amyloid proteins, and stimulating neurogenesis and antiapoptosis as well as anti-inflammatory properties. In addition, Gasiorowski et al. [21] reviewed the neuroprotective actions of flavones (baicalein, oroxylin A, and wogonin) from the root of *S. baicalensis*. However, scientific literature review on the neuroprotective effects of baicalein is still missing.

5. Baicalein inhibits aggregation of α-syn protein

PD develops with the aggregation of disease-specific proteins in amyloid nature. Amyloid proteins are predominantly rich in β-sheet fibrillar aggregates composed of self-assembly of different proteins including α-syn. Abnormally folded aggregates of α-syn are the key component of Lewy bodies and present as intracellular inclusions in nigral dopaminergic neurons in the PD brain [14].

Familial early-onset PD is potentially linked with α-syn mutations [53]. Therefore, α-syn is the potential therapeutic target for PD therapy to prevent the progression and development of this devastating disease. It is well evidenced that preformed α-syn fibrils, oligomeric α-syn, are considered more toxic than mature fibrils in arbitrating α-syn-induced neurotoxicity [54, 55]. The underlying mechanism for protein aggregation remains to be elucidated; phytochemicals or molecules of natural origin that can halt or slow down the fibrillation process of α-syn could be potentially important as new therapeutic strategy for the prevention of PD. Remarkably, reports have shown that aggregation of disease-specific α-syn protein can be inhibited by baicalein. Baicalein, as well as its oxidized forms in lower micromolar concentrations, inhibits formation of α-syn fibrils. Moreover, baicalein also showed the ability to disaggregate the existing α-syn fibrils [56]. Biophysical and experimental (in vitro/in vivo) studies showed that baicalein is capable of modifying α-syn aggregation and decreasing the cytotoxicity [57, 58]. In cellular as well as cell-free systems, baicalein was found to inhibit the α-syn oligomerization

and effectively inhibits α-syn fibrillation. It has been reported that inhibition of α-syn oligomer formation was achieved by baicalein treatment in Hela cells and SH-SY5Y cells and later was protected from the toxicity induced by α-syn oligomer [57]. Further, inhibition of aggregation and cytotoxicity of wild-type α-syn and baicalein showed decreased aggregation of different mutant form (E46K A30P and A53T) of α-syn in vitro and represented a neuroprotective effect in N2A cellular model of familial forms of parkinsonism [58, 59]. Moreover, α-syn aggregation was augmented by baicalein in the nigrostriatal dopaminergic system of MPP+-treated rat brain [60]. In the intragastrically rotenone-injected chronic mouse model of PD, baicalein did not decrease the expression of α-syn mRNA, but significant decrease

Experimental model system	Effects/mechanisms observed	References
α-Syn aggregation assay	• Inhibits formation of α-syn fibrils • Disaggregates α-syn fibrils after binding to Tyr residues in α-syn	[56]
Dopaminergic cell lines (SN4741) overexpressing wild-type α-syn or A53T mutant-type α-Syn	• Inhibits α-syn fibrillation by covalent binding • Promotes degradation of α-syn fibrils and polymerization to reduce its propagation and transmission • Enhances cell viability and increases macroautophagy	[76]
Intranigral infusion of MPP+ in rat brain	• Attenuates α-syn aggregation • Inhibits inflammasome activation and cathepsin B production • Inhibits apoptosis (caspases 9 and 12), and autophagy (LC3-II)	[60]
α-Syn aggregation in infused substantia nigra of rats	• S/B formulation containing *Scutellaria baicalensis* Georgi attenuates inflammation, apoptosis, oxidative, mitochondrial and ER stress and preserves glutathione • Attenuates astrocytosis/microgliosis, improves dopamine levels • Inhibits α-syn aggregation in SNc	[77]
PC12 and primary dopaminergic neurons	• Dichloromethane and n-butanol extract of *Scutellaria pinnatifida* reduces α-SN aggregation and scavenges free radicals	[78]
Biophysical and biochemical assays on 39 polyphenols including baicalein	• Inhibits α-syn aggregation	[79]
Biophysical and biochemical assays on 14 polyphenols including baicalein	• Inhibits α-syn aggregation	[80]
Biophysical and biochemical assays on 12 polyphenols including baicalein	• Inhibits α-syn aggregation	[59]
Biophysical and biochemical assays on four polyphenols including baicalein	• Inhibits α-syn aggregation	[81]

Table 1.
The experimental studies showing the effect of baicalein in PD.

of α-syn oligomers was observed in the thoracic spinal cord, midbrain, and ileum. In the light of this, baicalein could be able to prevent the PD progression through inhibiting the aggregation and formation of α-syn oligomers [61]. Although, the exact molecular mechanism of baicalein through which inhibition of aggregation of α-syn proteins takes place is yet to be elucidated, but characteristic molecular structure-based mechanism of baicalein has been proposed. It is well known that polyphenols, including baicalein or other flavonoids, are readily oxidized to quinones by oxygen because of their reductive nature, although quinones are readily reactive with the side-chain amino groups of proteins. Oxidized form of baicalein, that is, baicalein quinones, plays a key role in carrying α-syn inhibitory reactions, and the resulting product is mostly soluble α-syn oligomers. In this process, baicalein quinone covalently modified the protein molecules to form a Schiff base with a lysine side chain in α-syn, and Tyr is involved in the interaction of α-syn with baicalein [56]. Moreover, analysis of structure-activity demonstrated that quinone formation required vicinal dihydroxyphenyl moieties of baicalein to bind α-syn, and for maximum inhibitory effects of baicalein on α-syn fibrillation, three vicinal hydroxyl groups are more beneficial compared with two vicinal hydroxyl groups [59]. The in vitro inhibitory effects of baicalein on α-syn fibrillation are correlated with its antioxidant activities [62]. Recent study showed that non-baicalein-treated α-syn oligomers fibrillation can be inhibited by baicalein-stabilized α-syn oligomers. This suggests that some forms of soluble oligomer formation can be beneficial because baicalein-stabilized α-syn oligomers do not disrupt the integrity of the biological membrane [63]. Hence, these results indicated that baicalein would be a therapeutic agent for PD treatment through inhibition of α-syn accumulation and aggregation (**Table 1**).

6. Blood-brain barrier (BBB) penetrating ability

The BBB is an important network that plays a key role in maintaining homeostasis of the central nervous system, and its disturbance is prominently recognized for many neuronal disorders [27]. The BBB is made up of microvessel endothelial cells, in the arrangement of basement membrane, pericytes, neurons, and astrocytes. The BBB brings a hard barrier between the blood and brain parenchyma cells. However, several transport systems help to ease the channel of selective constituents across the BBB. Tsai et al. [64] reported that baicalein crosses the BBB 20–30 min following injection. Wang et al. [65] showed that baicalein remarkably decreased the BBB permeability after 24 hours in animal model of subarachnoid hemorrhage.

7. Bioavailability of baicalein

The deprived oral bioavailability and aqueous solubility are the major drawback for the pharmaceutical formulations and clinical practice of baicalein. Previous reports showed that baicalin and baicalein 6-O-sulfate are the metabolic product of baicalein in the blood [66, 67]. Several studies have demonstrated that oral administration of baicalein endures widespread glucuronidation within the wall of intestine and liver in humans and rats [68]. Additionally, baicalein was found less absorbed by colon when compared to stomach and small intestine [69]. Lai et al. [70] reported that 75.7% of the baicalein dose injected intravenously was found to be circulating in the form of conjugated metabolites in rats. Based on the earlier studies, it was documented that intravenous and oral administration of baicalein is instantly metabolized into baicalin in the animal's blood [71, 72].

In another study, conducted on monkeys, it has been reported that the different doses of baicalein bioavailability range 23.0 and 13.1% through intravenous and oral routes, respectively [73].

8. Clinical trials with baicalein

Baicalein has been shown a novel potential therapeutic agent for the treatment of neurological diseases. Therefore, clinical trials are essential for baicalein in order to confirm the potential therapeutic efficacy against neurodegenerative diseases. Two phase I clinical trials have been done based on chewable tablets of baicalein in Chinese healthy adult volunteers.

A phase I (2014), randomized, double-blind test for pharmacokinetic properties of baicalein with single-dose trail (100–2800 mg) was investigated on 72 healthy Chinese adults [74]. Without any additional treatment, mild adverse effects were fixed. Blood pressure and electrocardiogram were found normal during the entire period of study. No sign of toxicity observed in liver and kidney or any other serious adverse effects were not observed [74].

In 2016, another study in Chinese subjects based on placebo-controlled, single-center, and double-blind parallel group investigated the pharmacokinetics, safety, and tolerability of baicalein following multiple-ascending-dose protocol [75]. Volunteers were randomly divided to get placebo treatment (n = 2 per dose regimen) or baicalein (n = 8 per dose regimen). The selected dose regimens (200, 400, and 800 mg) were given once daily on days 1 and 10, and twice on days 3–9. High-performance liquid chromatography–tandem mass spectrometry methods were employed to assay the baicalein and its metabolite in urine, feces, and plasma samples. On day 8, plasma samples are given steady-state concentration of analytes after repeated dosing. The analytes concentration increased with increasing dose. The dose proportionality constant (b) for the area under the plasma concentration-time curves of baicalein and baicalin was 0.922 (90% confidence interval 0.650–1.195) and 0.942 (90% confidence interval 0.539–1.345), respectively.

Phase I clinical trials of baicalein showed that oral administration is safe to humans. But additional studies of baicalein are needed in the patients of neurodegenerative diseases to strengthen its therapeutic importance.

9. Conclusion

In the recent years, the pathophysiological understanding of α-syn has advanced rapidly from small unfolded protein located into nerve terminals and possesses the quality to self-aggregate into fibrils, resembling to Lewy bodies, a characteristic pathological hallmark of PD. Moreover, the endpoints of PD are not this long structure but an intermediate and transferable agent of the disease and is the most potent therapeutic target for PD prevention/treatment. Baicalein has showed the neuroprotective effects against PD in both in vitro/in vivo studies. Baicalein possesses the antioxidant activity and inhibition of α-syn aggregation. This suggests baicalein to be considered as solid treatment tool for neurodegenerative diseases including PD. Importantly, baicalein is safe and sufficiently well tolerated by healthy volunteers as evidenced by two phase I clinical trials based on Chinese healthy adult volunteers [74, 75]. Therefore, the abovementioned properties of baicalein indicate its potential therapeutic implications in slowing down/halting the progression of PD.

Conflict of interests

The authors declare that there is no conflict of interest.

Author's contribution

HJ wrote and revised the chapter; SO critically proofread the final version and provided the important inputs to prepare the final version of the chapter.

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Author details

Hayate Javed[1*] and Shreesh Ojha[2]

1 Department of Anatomy, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

2 Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

*Address all correspondence to: h.javed@uaeu.ac.ae

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