ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal, multisystemic neurodegenerative disease with evidence of motor neuron loss in the brain and spinal cord. The factors behind the ALS are genetic, oxidative stress, glutamate excitotoxicity, protein aggregation, apoptosis, autoimmunity, production of inflammatory cytokines, alteration in a cellular process, metabolic impairment, mitochondrial damage, glial activation, and disruption in axonal transport. The multiple pathogeneses behind the development and progression of ALS make a challenge to find out an effective therapy for this disease. This study aims to unravel the mechanisms behind the neuroprotective effects of wedelolactone and gallic acid against aluminium-induced neurodegeneration and thereby to unlock a platform to find a cure for sALS.

In this study, we evaluated the neuroprotective effects of wedelolactone and gallic acid on the pathogenesis of sporadic ALS (sALS). Hence, we used the glutamateinduced neurotoxicity *in vitro* model, and aluminium-induced and quinolinic acidinduced neurotoxicity *in vivo* models to study the effects of wedelolactone and gallic acid on the pathogenesis behind the sALS. The results from the *in vitro* study demonstrated that wedelolactone and gallic acid could improve the antioxidant status and inhibit proinflammatory cytokine production in neurons. The wedelolactone and gallic acid also maintained the Ca^{2+} homeostasis, IGF-1 expression, and protected the neurons from glutamate-induced neuronal toxicity. The results of the NAA and MAP-2 expression support the neuroprotective effects of wedelolactone and gallic acid.

The results of *in vivo* studies propose that the treatment with wedelolactone and gallic acid could protect the motor neurons from the toxicity that caused by aluminium and quinolinic acid via improving the antioxidant status, inhibiting proinflammatory cytokine production, by modulating NF-| B pathway, and by preventing glutamate excitotoxicity via maintaining Ca^{2+} homeostasis. Also, wedelolactone and gallic acid are found to be effective in inhibiting caspase-3 activation and in upregulating BDNF, and Growth factors like VEGF and IGF-1. The results of NAA and LDH from the quinolinic acidinduced model support the neuroprotective activities of wedelolactone and gallic acid.
The treatment with wedelolactone and gallic acid also found effective in improving the motor learning abilities and motor coordination in rats in both *in vivo* models. Histopathological results further confirmed the protective effects of wedelolactone and gallic acid. Wedelolactone and gallic acid prevent the neurofibrillary tangle formation and neuronal damage. The study concluded that the wedelolactone and gallic acid were dose-dependently effective in managing the $AlCl_3$-induced and quinolinic acid-induced neurodegeneration.