Our primary focus in this research was to identify and characterize its bioactive compounds for potential therapeutic use. Twenty-seven metabolites of *Polygonum orientale* were identified using LC-QTOF tandem mass spectrometry. Interestingly, *P. orientale* extracts included several highly oxygenated flavonoids were isolated from *P. orientale* by column chromatography. ^{13}C NMR data of highly oxygenated flavonoids (**1–7**) are reported here for the first time. In addition, nitric oxide, 1,1-diphenyl-2-picrylhydrazyl, and water-soluble tetrazolium salt assays were carried out on the isolated compounds to investigate their anti-inflammatory, anti-oxidant, and neuroprotective activities, respectively. Compounds **1**, **2**, **3**, **5**, **7**, and **8** significantly attenuated lipopolysaccharide-stimulated NO production in BV2 cells without affecting cell viability. Compounds **9–12** exhibited significant antioxidant activity, while compounds **8**, **9,** and **12** exhibited protective effects against glutamate-induced neurotoxicity in HT22 cells. Our results indicate that *P. orientale* is a promising source of natural agents for the potential treatment of inflammation and neurodegenerative diseases.

Chemical profile of *Polygonum orientale*.