Chemical Structures and Biological Activities of Neuroprotective Compounds from Korean Medicinal Mushroom

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The hyperactivity of ionotropic glutamate receptors has been implicated in the development of the neuronal cell death seen in many neurodegenerative processes including ischemic stroke, traumatic brain injury, and epilepsy. Thus neuronal protection against glutamate-induced neurotoxicity is considered an appropriate therapeutic strategy for preventing and treating neurodegenerative diseases.

In search for novel neuroprotective compounds from medicinal mushrooms against excitatory neurotoxins including glutamate, *N*-methyl-D-aspartate (NMDA), *a*-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA), and kainate using mouse primary cortical cell culture, named curtisians from *paxillus curtisii*, leucomentins from *Paxillus panuoides*, and dictyoquinazols from *Dictyophora indusiata* were isolated.

The structures of compounds isolated were determined by the spectroscopic studies including mainly mass and NMR analysis. Curtisians and leucomentins were assigned as novel *p*-terphenyl compounds, and dictyoquinazols were identified as a novel quinazoline class, which are very rare in nature.

Curtisians and leucomentins protected mouse cortical neurons from glutamate-induced toxicity in a dose dependent manner. of the glutamate receptor subtypes, curtisians and leucomentins were found to block NMDA receptor-mediated but not AMPA/kainate mediated cell death. In addition, we found that curtisians and leucomentins exhibited potent antioxidative activity against iron-mediated oxidative damage which was generated by H2O2neurotoxocity and lipid peroxidation, but no activity was detected in the superoxide, DPPH and ABTS radical scavenging systems, and in protection of N18-RE-105 cells subjected to glutamate-induced glutathione depletion. This effect was likely due to the iron chelating properties of curtisians and leucomentins. The iron chelation testing of curtisians and leucomentins was then further investigated on DNA single strand breakage (SSB) induced by the addition of iron and H2O2,

and they prohibited DNA SSB like iron chelator desferrioxamine. These results suggest that the neuroprotective action of curtisians and leucomentins is dependent on their ability to chelate iron, and they may be useful as neuroprotective agents against neurological disorder, which result in neuronal cell death.

Dictyoquinazols protected neurons from glutamate-induced neurotoxicity to a significant degree at concentration ranging from 5 to 10 *u*M. Also these compounds protected neurons from toxicity induced by NMDA, in a dose-dependent manner at concentration ranging from 10 to 30 *u*M. However, they did not protect cortical neurons damaged by non-NMDA receptor agonist. Dictyoquinazol A was structurally similar to methaqualone, which was known as a psychotropic substance. Recently, methaqualone derivatives with a C-2 enol side chain have been reported as a potent noncompetitive AMPA receptor antagonist whereas its derivatives without a C-2 enol side chain did not block AMPA receptor function. Our results are in accorance with the results in that dictyoquinazols without a C-2 enol side chain did not protect cortical cells against AMPA neurotoxicity. Thus dictyoquinazols were suggested as a novel glutamate receptor antagonists.

References

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