Can *Glycyrrhiza glabra* L. Reduce Delirium after Coronary Artery Bypass Graft Surgery?

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**Keywords**

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Coronary artery bypass graft (CABG) surgery is one of the most commonly performed invasive procedures worldwide [1, 2]. Since the introduction of cardiopulmonary bypass (CPB), the neurological consequence of CABG surgery has been an important subject [2]. Delirium is a major problem after CABG surgery with the approximate reported incidence rate of 20–80% [2]. This complication is associated with increased mortality, longer hospital stay, increased hospital costs, and long-term care [2–4]. Regarding the high incidence of delirium in patients undergoing CABG surgery, prophylactic treatment is preferable. Hence, pharmacological neuroprotective strategies have been developed for these patients [3, 4]. A meta-analysis indicated that preoperative low-dose and short-term administration of haloperidol or risperidone may modestly reduce delirium occurrence in high-risk patients that need intensive care unit (ICU) [4]. Other clinical trials have not reported any decreases in the incidence rate of delirium in patients receiving pharmacologic prophylactic (haloperidol, donepezil [5], citicoline [6], and rivastigmine) [7–9].

Acute inflammation and reduced serotonin neurotransmitter are the most important causes of delirium in these patients [10, 11]. In a meta-analysis, Peng et al. [12] showed the role of peripheral inflammatory markers, such as interleukin-6 and S-100β, in postoperative delirium [13]. Although some studies indicated that use of compounds with brain protective activities (such as propofol, aprotinin and lidocaine) can prevent delirium after CABG surgery, no sufficient evidence was presented to make a change in standard clinical practice.

Licorice (*G. glabra*, species: Leguminosae) is a worldwide popular herbal medicine. Just 3 out of the numerous species of licorice are usually used as commercial drugs, including *G. glabra*, *Glycyrrhiza echinata* L., and *Glycyrrhiza uralensis* Fisch. In traditional medicine, the roots and rhizomes (underground stems) of licorice are currently used as therapeutic compounds in many Asian and European countries. Licorice mainly consists of a mixture of glycyrhrizinic acid, glycyrhrizic acid, glycyrrhizin, isoflavones, isoliquiritigenin, hispaglabridin B, paratocarpin B, and glabridin. Furthermore, this plant has been used as an antiplatelet and demulcent, expectorant, antioxidant, antiulcer, laxative, antipyretic, antimicrobial, and anti-inflammatory agent [14]. Glabridin, a major active flavonoid in licorice, has anti-atherosclerotic, anti-inflammatory, anti-nephritis, radical scavenging activities and antidepressant-like effects [15]. Moreover, this compound has been reported to be useful for renovascular and cardiovascular diseases [16]. Ojha et al. [16] evaluated the cardioprotective effect of licorice against ischemia-reperfusion injury induced by ligation of left anterior descending coronary artery in rats. Their results confirmed the cardioprotective activity of licorice by alleviating oxidative stress in myocardial ischemia-reperfusion injury [16].

Safe brain-protective agents, such as licorice, could be utilized to reduce the neuroinflammation and delirium caused by CPB in these patients. Muralidharan et al. [14] investigated the cerebroprotective effect of 250 and 500 mg/kg of licorice roots in hypoxic rats and indicated that licorice has a cerebro-
protective effect. This effect may be mediated by its antioxid-
ant activities. Results of this in-vitro study showed that the 
licorice extract administration could significantly reverse the 
decreased levels of glutamate and dopamine and reduced ace-
tylcholinesterase (AChE) activity. Moreover, antioxidant en-
zyme levels (superoxide dismutase, glutathione peroxidase, 
glutathione reductase, and catalase) were restored close to 
normal range [14].

In-vitro and in-vivo analyses demonstrated that glabridin 
has neuroprotective effects by enhancing the survival of neu-
rons and preventing their death and apoptosis [15]. Glabridin 
is a type of isoflavonoid (isoflavane) derived from the extract 
of licorice root. Yu et al. [15] showed that 25mg/kg (higher 
dose) of glabridin significantly decrease the focal infarct vol-
ume, cerebral histological damage, and apoptosis induced by 
middle cerebral artery occlusion in rats. Glabridin was pur-
chased from the National Institute for the Control of Pharma-
cutical and Biological Products (NICPBP) (purity 99.0%). It 
was dissolved in dimethyl sulfoxide (DMSO), and freshly pre-
pared for this study. That study presented primary evidence 
that glabridin exhibits neuroprotective effects via inhibition of 
oductive stress. These findings indicate that glabridin had 
nuroprotective effects by modulation of multiple pathways 
associated with apoptosis.

Although the majority of potent antioxidants demonstrate 
suitable efficacy in animal studies, there are only few studies 
showing the therapeutic effects of this extract on humans. 
Thus, further studies are warranted to further investigate the 
biological mechanisms underlying the protective effect of 
glabridin on brain and to collect evidence for clinical use of 
licorice in delirium management.

In conclusion, licorice could theoretically be used as a sin-
gle supplement or in combination with other drugs to de-
crease delirium after cardiac surgery with CPB. Although 
licorice and its major constituent glabridin have positive ther-
apeutic effects on human health, there are only few clinical 
trials that investigate the ability of these compounds on cere-
bral protection, clinical efficacy, and the mechanism responsi-
ble for their pharmacological activities. Further research ad-
ressing the preventive role of licorice and glabridin on delir-
ium after cardiac surgery with CPB is recommended.

**Disclosure Statement**

The authors declare that they have no conflict of interest concerning 
this manuscript.

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    glabridin, a major active isoflavane from Glycyr-
    Glycyrrhiza glabra protects from myocardial is-
    chemia-reperfusion injury by improving hemody-
    namic, biochemical, histopathological and ventricular 