*Ho J.H., Chen Y.F., Ma W.H., Tseng T.C., Chen M.H., Lee O.K.* 2011. Cell contact accelerates replicative senescence of human mesenchymal stem cells independent of telomere shortening and p53 activation: Roles of Ras and oxidative stress. Cell Transplant. 20 : 1209–1220.

*Ip F.C., Ng Y.P., An H.J., Dai Y., Pang H.H., Hu Y.Q., Chin A.C., Harley C.B., Wong Y.H., Ip N.Y.* 2014. Cycloastragenol is a potent telomerase activator in neuronal cells: Implications for depression management. Neurosignals. 22 : 52–63.

*Jiang K., Lu Q., Li Q., Ji Y., Chen W., Xue X.* 2017. Astragaloside IV inhibits breast cancer cell invasion by suppressing Vav3 mediated Rac1/MAPK signaling. Int. Immunopharmacol. 42 : 195–202.

*Khavinson V.Kh., Malinin V.V.* 2005. Gerontological aspects of genome peptide regulation. Basel: Karger AG. 104 p.

*Kim N.W., Piatyszek M.A., Prowse K.R., Harley C.B., West M.D., Ho P.L., Coviello G.M., Wright W.E., Weinrich S.L., Shay J.W.* 1994. Specific association of human telomerase activity with immortal cells and cancer. Science. 266 : 2011–2015.

*Lafferty-Whyte K., Cairney C.J., Will M.B., Serakinci N., Daidone M.G., Zaffaroni N., Bilsland A., Keith W.N.* 2009. A gene expression signature classifying telomerase and ALT immortalization reveals an hTERT regulatory network and suggests a mesenchymal stem cell origin for ALT. Oncogene. 28 : 3765–3774.

*Li M., Li H., Fang F., Deng X., Ma S.* 2017. Astragaloside IV attenuates cognitive impairments induced by transient cerebral ischemia and reperfusion in mice via anti-inflammatory mechanisms. Neurosci. Lett. 639 : 114–119.

*Liu Y., Zhang H.G., Li X.H.* 2011. A Chinese herbal decoction, Danggui Buxue Tang, improves chronic fatigue syndrome induced by food restriction and forced swimming in rats. Phytother. Res. 25 : 1825–1832.

*Mazzolini R., Gonzàlez N., Garcia-Garijo A., Millanes-Romero A., Peiró S., Smith S., García de Herreros A., Canudas S.* 2018. Snail1 transcription factor controls telomere transcription and integrity. Nucleic Acids Res. 46 : 146–158.

*Molgora B., Bateman R., Sweeney G., Finger D., Dimler T., Efffros R.B., Valenzuela H.F.* 2013. Functional assessment of pharmacological telomerase activators in human T cells. Cells. 2 : 57–66.

*Qi Y., Gao F., Hou L., Wan C.* 2017. Anti-inflammatory and immunostimulatory activities of astragalosides. Am. J. Chin. Med. 45 : 1157–1167.

*Qin C.D., Ma D.N., Ren Z.G., Zhu X.D., Wang C.H., Wang Y.C., Ye B.G., Cao M.Q., Gao D.M., Tang Z.Y.* 2017. Astragaloside IV inhibits metastasis in hepatoma cells through the suppression of epithelial-mesenchymal transition via the Akt/GSK-3β/β-catenin pathway. Oncol. Rep. 37 : 1725–1735.

*Ren S., Zhang H., Mu Y., Sun M., Liu P.* 2013. Pharmacological effects of Astragaloside IV: A literature review. J. Tradit. Chin. Med. 33 : 413–416.

*Salvador L., Singaravelu G., Harley C.B., Flom P., Suram A., Raffaele J.M.* 2016. A natural product telomerase activator lengthens telomeres in humans: A randomized, double blind, and placebo controlled study. Rejuvenation Res. 19 : 478–484.

*Shen C.Y., Jiang J.G., Yang L., Wang D.W., Zhu W.* 2017. Anti-ageing active ingredients from herbs and nutraceuticals used in traditional Chinese medicine: Pharmacological mechanisms and implications for drug discovery. Br. J. Pharmacol. 174 : 1395–1425.

The state pharmacopoeia commission of China. Pharmacopoeia of the People's Republic of China. V. 1. Beijing: China Medicine Science and Technology Press. P. 283–284.

The United States Pharmacopeial Convention: USP39–NF34, 2016.

*Wang H.L., Zhou Q.H., Xu M.B., Zhou X.L., Zheng G.Q.* 2017. Astragaloside IV for experimental focal cerebral ischemia: Preclinical evidence and possible mechanisms. Oxid. Med. Cell Longev. 2017 : 1–13.

WHO monographs on selected medicinal plants. 1999. Geneva: WHO Press. 1 : 50–58.

# INFLUENCE OF GEROPROTECTORS ASTRAGALOSIDE IV, CYCLOASTRAGENOL, AND PEPTIDE COMPLEX "TIMOVIAL–EPIVIAL" ON THE TELOMERE LENGTH AND TELOMERASE ACTIVITY IN HUMAN MESENCHYMAL STROMAL CELLS AND SENESCENT FIBROBLASTS

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An active search for non-tumorigenic geroprotectors affecting telomere length and/or telomerase activity is in progress now. The use of various extracts of a plant *Astragalus* (Fabaceae) for medical purposes was described for the first time in 200 AD. However, scientific studies on the components of these extracts, cycloastragenol and astragaloside IV, have only recently been initiated. The aim of the present work was to study the effect of the composition consisting of astragaloside IV, cycloastragenol and the "Timovial–Epivial" dipeptide and its components on the length of telomeres and the telomerase activity in human umbilical cord mesenchymal stromal cells and the senescent human

fibroblasts. Telomerase activity was estimated by telomeric repeats amplification (TRAP). The length of telomeres was measured as the intensity of fluorescent *in situ* hybridization signals by flow cytometry (Flow-FISH). None of the composition components alone caused a significant change in the estimated parameters. Only cycloastragenol had low effect on telomere length in fibroblasts. The combination of a key compound astragaloside IV, core astragaloside (CAG) and a complex of biopeptides made it possible to achieve a significant change in telomere length and telomerase activity more than in the case of using each component separately. Further research is needed to determine the cause of this effect of the combined drug.

***Keywords:*** telomeres, *Astragalus sp*, cycloasragenol, telomerase, mesenchymal stromal cells, fibroblasts, geroprotectors