EXCLI Journal 2021;20:1453-1457 – ISSN 1611-2156
Received: August 16, 2021, accepted: September 13, 2021, published: September 27, 2021

Letter to the editor:

A RECENT OVERVIEW ON GINSENOSIDES AS MICRORNA MODULATORS IN THE TREATMENT OF HUMAN DISEASES

Tae Kyung Hyun*

Department of Industrial Plant Science and Technology, College of Agricultural, Life and Environmental Sciences, Chungbuk National University, Cheongju 28644, Republic of Korea; Phone: +82-43-261-2520, Fax: +82-43-271- 0413.
E-mail: taekyung7708@chungbuk.ac.kr

http://dx.doi.org/10.17179/excli2021-4200

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

Dear Editor,

MicroRNAs (miRNAs) are short (20-22 nucleotides) and highly conserved noncoding transcripts that play a crucial role in the regulation of gene expression, guiding the RNA-induced silencing complex to target mRNAs (Treiber et al., 2019). Under normal physiological conditions, miRNAs are involved in feedback and feedforward loops, which have widespread functions in diverse biological processes, including cell proliferation, differentiation, and apoptosis (Tsang et al., 2007; Reddy, 2015). Since the human disease-related miR15 and miR16, located at chromosome 13q14, were first characterized in chronic lymphocytic leukemia (Calin et al., 2002), much attention has been directed towards the function of miRNAs in a number of disorders such as cancer, viral infections, diabetes, immune-related diseases, and neurodegenerative disorders (Condrat et al., 2020). In addition, accumulating evidence suggests that miRNA-mediated control of gene expression is important for the treatment of various diseases (Ali Syeda et al., 2020; Condrat et al., 2020; Zhang et al., 2020; Wang et al., 2021a).

Ginsenosides are a class of steroid glycosides and triterpene saponins that account for the medical effects of ginseng (*Panax ginseng*). Among more than a hundred ginsenosides in ginseng, the most abundant ginsenosides are Rb1, Rb2, Rc, Rd, Re, and Rg1, all of which belong to the protopanaxadiol or protopanaxatriol saponins (Chen et al., 2019a). A growing body of evidence indicates that ginsenosides act as antioxidant, antimicrobial, anti-inflammatory, anticancer, anti-diabetic, and anti-aging agents, although each ginsenoside exhibits a different pharmacological action (Bai et al., 2018; Zheng et al., 2018b; Wang and Roh, 2020). The molecular targets of these effects contain various signaling pathways, including the Ras/Raf/MEK/ERK, PI3K/Akt, NF-κB, and PPARγ/HO-1 signaling pathways (Bai et al., 2018; Zheng et al., 2018a). In addition, increasing focus on ginsenosides as miRNA modulators continues to contribute to advances in clinical trials.

In this letter, we present a review of recent clinical findings on the miRNA-mediated pharmacological role of ginsenosides (Table 1). We believe that this letter provides a solid foundation for further evaluation of ginsenosides as miRNA modulators in the prevention and treatment of a number of chronic diseases in humans.

EXCLI Journal 2021;20:1453-1457 – ISSN 1611-2156
Received: August 16, 2021, accepted: September 13, 2021, published: September 27, 2021

Table 1: Recent studies on the modulation of microRNAs by ginsenosides as potential therapeutics

Ginseno-side	Key regulation	Reference
Rb1	Rb1-mediated upregulation of miR-208 improves erythropoiesis in models of Diamond Blackfan Anemia by targeting Nemo-like kinase.	Wilkes et al., 2021
	Rb1 up-regulates miR-210, resulting in repression of oxidative damage in H_2O_2-treated human endothelial cells via the inhibition of BCL2/adenovirus E1B 19-kDa interacting protein 3.	Jia et al., 2019
	Rb1 protects rats from spinal cord injury through reducing activated microglia-induced proinflammatory responses and neuronal injury via the miR-130b-5p/TLR4/nuclear factor-κB (NF-κB) axis.	Wang et al., 2021b
	Rb1 up-regulates miR-21 expression and down-regulates programmed cell death protein 4 (target gene of miR-21), leading to the protection of cardiomyocytes from oxygen-glucose deprivation injuries.	Yang et al., 2019
Rb2	Rb2 binds to miR-216a, and further attenuates the senescent status and inflammatory process induced by miR-216a via enhancement of the Smad3/IκBα signaling pathway in the primary human umbilical vein endothelial cells.	Chen et al., 2021
Rd	Rd up-regulates the tumor-suppressive miR-144-5p and down-regulates Toll-like receptor 2 (target of miR-144-5p) in glioblastoma cells, resulting in the inhibition of glioblastoma cell proliferation.	Liu et al., 2020
Rg1	Rg1 exhibits antidepressant-like effects in chronic unpredictable mild stress-exposed rats via the induction of miR-134 expression in the basolateral amygdala.	Yu et al., 2018
	Rg1 up-regulates miR-26a, leading to protection of human retinal pigment epithelial ARPE-19 cells against high glucose-induced injury through inhibition of the ERK and Wnt/β-catenin pathways.	Shi et al., 2019
	Rg1 promotes wound closure of diabetic foot ulcers through elevation of nitric oxide production via the miR-23a/interferon regulatory factor 1 axis.	Cai et al., 2019
	Rg1 protects rat bone marrow mesenchymal stem cells against ischemia induced apoptosis through miR-494-3p/Rho associated coiled-coil containing the protein kinase 1/Bcl-2 signaling pathway.	Zheng et al., 2018a
	Treatment of Rg1 with Acori graminei Rhizoma, the dry rhizome of *Acorus gramineus* Solander (Araceae), significantly attenuates neuron cell apoptosis by promoting the expression of miR-873-5p in senescence-accelerated prone mice.	Shi et al., 2018
	Tail vein administration of Rg1 in combination with geniposide (an active component of *Gardenia*) protects against focal cerebral ischemia in rats through inhibition of microglial miR-155-5p.	Wang et al., 2018
	Rg1 protects the rat pheochromocytoma PC12 cells against oxygen glucose deprivation/re-oxygenation induced neurotoxicity via promoting the antioxidative stress defenses of the Nrf2/ARE pathway at the post-translational level by inhibiting miR-144 activity.	Chu et al., 2019
	Rg1 inhibits high glucose-induced mesenchymal activation and fibrosis via up-regulating miR-2113 and down-regulating RP11-982M15.8 in Müller cells.	Xue et al., 2018
	Rg1 defenses pheochromocytoma PC-12 cells against hydrogen peroxide-caused damage via up-regulation of miR-216a-5p, which is known as an oncogene.	Yi et al., 2019
Rg3	Rg3 down-regulates long noncoding RNA ATXN8OS that inhibits the tumor-suppressive miR-424-5p, leading to the downregulation of the oncogenic target genes (EYA1, DACH1, and CHRM3) in breast cancer cells.	Kim et al., 2021
	Rg3 protects mouse Leydig cells against triptolide by downregulation of miR-26a, which suppresses GSK-3β expression.	Liang et al., 2019

	Rg3 decreases the fibrotic and invasive nature of endometriosis by reducing miRNA-27b expression in human endometrial stromal cells and mouse endometriosis models.	Kim et al., 2017
	Rg3 suppresses proliferation and epithelial-mesenchymal transition of human oral squamous carcinoma cells by down-regulating miR-221, which negatively regulates the level of the tumor inhibitor of metalloproteinases-3.	Cheng and Xing, 2019
	Rg3 protects human umbilical vein endothelial cells against γ-d-glutamyl-meso-diaminopimelic acid-induced endothelial-to-mesenchymal transition by upregulating miR-139-5p expression.	Lee et al., 2020
20(S)-Rg3	20(S)-Rg3 enhances the expression of miR-532-3p via suppressing DNMT3A-mediated DNA methylation, resulting in the inhibition of aerobic glycolysis in ovarian cancer cells by suppressing the expression of HK2 (hexokinase-2, the target of miR-532-3p).	Zhou et al., 2018
	20(S)-Rg3 suppresses cell viability in esophageal squamous cell carcinoma via induction of miR-324-5p, which targets the 3'-UTR of proteasome activator subunit 3.	Jiang et al., 2021
Rg6	Rg6 significantly induces miR-146a, which is responsible for the inhibition of the LPS-induced production of pro-inflammatory cytokines in bone marrow-derived macrophages.	Paik et al., 2019
Rh2	Rh2 inhibits proliferation but promotes apoptosis and autophagy by miR-638-mediated up-regulation of p53 and inactivation of the PI3K/AKT/mTOR pathway in human retinoblastoma cells.	Li et al., 2019
	Rh2 inhibits cell survival and colony formation via the induction of miR-146a-5p expression in the liver cancer cell line HepG2.	Chen et al., 2018a
	Rh2 inhibits prostate cancer cell growth through inhibition of miR-4295, which binds to the 3'-UTR of the cyclin-dependent kinase Inhibitor 1A.	Gao and Zheng, 2018
	Rh2 inhibits proliferation and migration of medulloblastoma Daoy via down-regulation of miR-31 to inactivate the Wnt/β-catein signaling pathway.	Chen et al., 2018b
	Rh2 inhibits hypoxia-induced A549 cell migration via upregulation of miR-491, which can inhibit matrix metalloproteinase-9 expression in A549 cells.	Chen et al., 2019b

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

Ali Syeda Z, Langden SSS, Munkhzul C, Lee M, Song SJ. Regulatory mechanism of microRNA expression in cancer. Int J Mol Sci.2020;21:1723.

Bai L, Gao J, Wei F, Zhao J, Wang D, Wei J. Therapeutic potential of ginsenosides as an adjuvant treatment for diabetes. Front Pharmacol. 2018;9:423.

Cai HA, Huang L, Zheng LJ, Fu K, Wang J, Hu FD, et al. Ginsenoside (Rg-1) promoted the wound closure of diabetic foot ulcer through iNOS elevation via miR-23a/IRF-1 axis. Life Sci. 2019;233:116525.

Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, et al. Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A. 2002;99:15524-9.

Chen W, Chu S, Li H, Qiu Y. MicroRNA-146a-5p enhances ginsenoside Rh2-induced anti-proliferation and the apoptosis of the human liver cancer cell line HepG2. Oncol Lett. 2018a;16:5367-74.

Chen Y, Shang H, Zhang S, Zhang X. Ginsenoside Rh2 inhibits proliferation and migration of medulloblastoma Daoy by down-regulation of microRNA-31. J Cell Biochem. 2018b;119:6527-34.

Chen W, Balan P, Popovich DG. Analysis of ginsenoside content (*Panax ginseng*) from different regions. Molecules 2019a;24:3491.

Chen Y, Zhang Y, Song W, Zhang Y, Dong X, Tan M. Ginsenoside Rh2 inhibits migration of lung cancer cells under hypoxia via miR-491. Anticancer Agents Med Chem. 2019b;19:1633-41.

Chen Y, Wang S, Yang S, Li R, Yang Y, Chen Y, et al. Inhibitory role of ginsenoside Rb2 in endothelial senescence and inflammation mediated by microRNA-216a. Mol Med Rep. 2021;23:415.

Cheng Z, Xing D. Ginsenoside Rg3 inhibits growth and epithelial-mesenchymal transition of human oral squamous carcinoma cells by down-regulating miR-221. Eur J Pharmacol. 2019;853:353-63.

Chu SF, Zhang Z, Zhou X, He WB, Chen C, Luo P, et al. Ginsenoside Rg1 protects against ischemic/reperfusion-induced neuronal injury through miR-144/Nrf2/ARE pathway. Acta Pharmacol Sin. 2019;40:13-25.

Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, Cretoiu D, et al. miRNAs as biomarkers in disease: Latest findings regarding their role in diagnosis and prognosis. Cells. 2020;9:276.

Gao Q, Zheng J. Ginsenoside Rh2 inhibits prostate cancer cell growth through suppression of microRNA-4295 that activates CDKN1A. Cell Prolif. 2018;51: e12438.

Jia F, Mou L, Ge H. Protective effects of ginsenoside Rb1 on H_2O_2-induced oxidative injury in human endothelial cell line (EA.hy926) via miR-210. Int J Immunopathol Pharmacol. 2019;33:2058738419866021.

Jiang M, Zhu Y, Yu H. Ginsenoside 20(S)-Rg3 suppresses cell viability in esophageal squamous cell carcinoma via modulating miR-324-5p-targeted PSME3. Hum Exp Toxicol. 2021; epub ahed of print.

Kim H, Ji HW, Kim HW, Yun SH, Park JE, Kim SJ. Ginsenoside Rg3 prevents oncogenic long noncoding RNA ATXN8OS from inhibiting tumor-suppressive microRNA-424-5p in breast cancer cells. Biomolecules. 2021;11:118.

Kim MK, Lee SK, Park JH, Lee JH, Yun BH, Park JH, et al. Ginsenoside Rg3 decreases fibrotic and invasive nature of endometriosis by modulating miRNA-27b: In vitro and in vivo studies. Sci Rep. 2017;7:17670.

Lee A, Yun E, Chang W, Kim J. Ginsenoside Rg3 protects against iE-DAP-induced endothelial-to-mesenchymal transition by regulating the miR-139-5p-NF-κB axis. J Ginseng Res. 2020;44:300-7.

Li M, Zhang D, Cheng J, Liang J, Yu F. Ginsenoside Rh2 inhibits proliferation but promotes apoptosis and autophagy by down-regulating microRNA-638 in human retinoblastoma cells. Exp Mol Pathol. 2019;108: 17-23.

Liang H, Zhang S, Li Z. Ginsenoside Rg3 protects mouse leydig cells against triptolide by downregulation of miR-26a. Drug Des Devel Ther. 2019;13:2057-66.

Liu GM, Lu TC, Sun ML, Jia WY, Ji X, Luo YG. Ginsenoside Rd inhibits glioblastoma cell proliferation by up-regulating the expression of miR-144-5p. Biol Pharm Bull. 2020;43:1534-41.

Paik S, Choe JH, Choi GE, Kim JE, Kim JM, Song GY, et al. Rg6, a rare ginsenoside, inhibits systemic inflammation through the induction of interleukin-10 and microRNA-146a. Sci Rep. 2019;9:4342.

Reddy KB. MicroRNA (miRNA) in cancer. Cancer Cell Int. 2015;15:38.

Shi R, Zhang S, Cheng G, Yang X, Zhao N, Chen C. Ginsenoside Rg1 and Acori graminei rhizoma attenuates neuron cell apoptosis by promoting the expression of miR-873-5p in Alzheimer's disease. Neurochem Res. 2018;43:1529-38.

Shi Q, Chen X, Sun G, Wang L, Cui L. Ginsenoside Rg1 protects human retinal pigment epithelial ARPE-19 cells from toxicity of high glucose by up-regulation of miR-26a. Life Sci. 2019;221:152-8.

Treiber T, Treiber N, Meister G. Regulation of microRNA biogenesis and its crosstalk with other cellular pathways. Nat Rev Mol Cell Biol. 2019;20:5-20.

Tsang J, Zhu J, van Oudenaarden A. MicroRNA-mediated feedback and feedforward loops are recurrent network motifs in mammals. Mol Cell. 2007;26:753-67.

Wang D, Zhao S, Pan J, Wang Z, Li Y, Xu X, et al. Ginsenoside Rb1 attenuates microglia activation to improve spinal cord injury via microRNA-130b-5p/TLR4/NF-κB axis. J Cell Physiol. 2021b;236:2144-55.

Wang F, Roh YS. Mitochondrial connection to ginsenosides. Arch Pharm Res. 2020;43:1031-45.

Wang J, Li D, Hou J, Lei H. Protective effects of geniposide and ginsenoside Rg1 combination treatment on rats following cerebral ischemia are mediated via microglial microRNA-155-5p inhibition. Mol Med Rep. 2018;17:3186-93.

Wang S, Shen L, Luo H. Identification and validation of key miRNAs and a microRNA-mRNA regulatory network associated with ulcerative colitis. DNA Cell Biol. 2021a;40:147-56.

Wilkes Mc, Jung K, Lee BE, Saxena M, Sathianathen RS, Mercado JD, et al. The active component of ginseng, ginsenoside Rb1, improves erythropoiesis in models of Diamond Blackfan Anemia by targeting Nemo-like Kinase. J Biol Chem. 2021;297(3):100988.

Xue LP, Fu XL, Hu M, Zhang LW, Li YD, Peng YL, et al. Rg1 inhibits high glucose-induced mesenchymal activation and fibrosis via regulating miR-2113/RP11-982M15.8/Zeb1 pathway. Biochem Biophys Res Commun. 2018;501:827-32.

Yang C, Li B, Liu Y, Xing Y. Ginsenoside Rb1 protects cardiomyocytes from oxygen-glucose deprivation injuries by targeting microRNA-21. Exp Ther Med. 2019;17:3709-16.

Yi G, Liu L, Lv C, Wei Y, Yan T. Ginsenoside Rg1 defenses PC-12 cells against hydrogen peroxide-caused damage via up-regulation of miR-216a-5p. Life Sci. 2019;236:116948.

Yu H, Fan C, Yang L, Yu S, Song Q, Wang P, et al. Ginsenoside Rg1 prevents chronic stress-induced depression-like behaviors and neuronal structural plasticity in rats. Cell Physiol Biochem. 2018;48:2470-82.

Zhang B, Tian L, Xie J, Chen G, Wang F. Targeting miRNAs by natural products: A new way for cancer therapy. Biomed Pharmacother. 2020;130:110546.

Zheng HZ, Fu XK, Shang JL, Lu RX, Ou YF, Chen CL. Ginsenoside Rg1 protects rat bone marrow mesenchymal stem cells against ischemia induced apoptosis through miR-494-3p and ROCK-1. Eur J Pharmacol. 2018a;822:154-67.

Zheng M, Xin Y, Li Y, Xu F, Xi X, Guo H, et al. Ginsenosides: A potential neuroprotective agent. Biomed Res Int. 2018b;2018:8174345.

Zhou Y, Zheng X, Lu J, Chen W, Li X, Zhao L. Ginsenoside 20(S)-Rg3 inhibits the warburg effect via modulating DNMT3A/ MiR-532-3p/HK2 pathway in ovarian cancer cells. Cell Physiol Biochem. 2018;45: 2548-59.