https://doi.org/10.17221/149/2020-CJFS

Alteration in ginsenoside and cordycepin content by solid-state fermentation of red ginseng with *Cordyceps militaris*

*Young Suk Kim[1], Jong Min Lim[1], Bon-Hwa Ku[1], Hyung-Rae Cho[1], Jae-Suk Choi[2]**

[1]*Glucan Corp., Jinju-si, Republic of Korea*
[2]*Department of Food Biotechnology, College of Medical and Life Sciences, Silla University, Busan, Republic of Korea*

**Corresponding author: jsc1008@silla.ac.kr*

Citation: Kim Y.S., Lim J.M., Ku B.-H., Cho H.-R., Choi J.-S. (2021): Alteration in ginsenoside and cordycepin content by solid--state fermentation of red ginseng with *Cordyceps militaris*. Czech J. Food Sci., 39: 487–492.

Abstract: We aimed to increase the ginsenosides present in fermented red ginseng and enhance cordycepin production by *Cordyceps militaris* using solid-state fermentation. After 50 days of fermentation, red ginseng solid-state fermented with *C. militaris* demonstrated considerably higher contents of Rb3 (9.16%), Rd (513.93%), Rg2 (63.12%), Rg3 (20R; 112.53%), and Rg3 (20S; 101.17%) than untreated red ginseng. As the fermentation time increased, the production of cordycepin gradually increased, yielding approximately 34.8 mg kg^{-1} of cordycepin after 50 days of fermentation. In conclusion, red ginseng fermented by *C. militaris* could be used as natural herbal medicine or dietary supplement with several health-beneficial effects.

Keywords: steamed and dried root of *Panax ginseng*; *Cordyceps* spp.; natural herbal medicine; health-beneficial activities

The therapeutic potential of red ginseng (steamed and dried root of *Panax ginseng* C.A. Meyer, family Araliaceae) has been extensively investigated (Park et al. 2012), and ginsenosides, the active components present in red ginseng, are involved in the modulation of multiple physiological activities (Leung and Wong 2010). Ginsenosides are triterpene saponins, and most are composed of a dammarane skeleton (17 carbons in a four-ring structure) with various sugar moieties, such as glucose, xylose, rhamnose, and arabinose, attached to the C-3 and C-20 positions (Leung and Wong 2010). To date, more than 30 ginsenosides have been identified and largely classified into two categories: *i*) 20(S)-protopanaxadiol (such as Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, and Rs1) and *ii*) 20(S)-protopanaxatriol (such as Re, Rf, Rg1, Rg2, and Rh1) (Matsuura et al. 1984; De Smet 2002; Leung and Wong 2010). Red ginseng has a unique saponin profile, with emerging ginsenosides Ra1, Ra2, Ra3, Rf2, Rg4, Rg5, Rg6, Rk1, Rs1, and Rs2 possibly resulting from heat transformation and deglycosylation of naturally occurring ginsenosides (Kasai et al. 1983; Kwon et al. 2001; Leung and Wong 2010).

The fermentation of medicinal herbs improves their pharmacological efficacy and/or increases the absorption rates in the body. Reportedly, fermented red ginseng has enhanced functionality, increased amounts of physiologically active substances, and an increased absorption rate in the body as reported by various microorganisms, *Bifidobacterium* H-1 (Bae et al. 2004), *Bifidodoterium* (Trinh et al. 2007), *Lactobacillus plantarum* M1 (Kim et al. 2010), and red-koji (Kim et al. 2013).

Cordyceps militaris is a useful source of bio-metabolites for herbal medicines, with extensive data supporting its health-beneficial activities since ancient times. Notably, the active principles of *C. militaris* possess

https://doi.org/10.17221/149/2020-CJFS

antioxidant, anti-inflammatory, anti-microbial, immunomodulatory, anticancer, hypolipidemic, hypoglycemic, anti-diabetic, anti-fatigue, hepatoprotective, and neuroprotective activities (Das et al. 2010).

Cordycepin (3-deoxyadenosine), an active ingredient of *C. militaris* (Cunningham et al. 1950), is a class of compounds exhibiting significant therapeutic potential, including anticancer, antitumor, anti-inflammatory, antioxidant, insecticidal, antiviral, and antimicrobial activities (Tuli et al. 2013; Qin et al. 2019).

Reportedly, *C. militaris* has enhanced the functionality and increased the amount of physiologically active substances in several raw herbal and food materials, including *Undaria pinnatifida* (Kim et al. 2015), buckwheat, embryo rice (Huang et al. 2017), and rice (Xu et al. 2019).

Solid-state fermentation consists of microbial growth and product formation on solid particles in the absence (or near absence) of water; however, the substrate contains sufficient moisture to allow microbial growth and metabolism (Pandey 2003). Notably, solid-state fermentation offers numerous advantages over submerged fermentation, such as a simpler technique and lower cost. However, several problems may be encountered in terms of controlling parameters such as pH, temperature, aeration, oxygen transfer, and moisture. In addition, regulating the environment within the bioreactors can be difficult to achieve, particularly temperature and moisture (Couto and Sanromán 2006; Sadh et al. 2018).

It has been reported that fermentation of red ginseng extract with *C. militaris* can be achieved via a liquid fermentation process (Bae et al. 2011); however, evidence supporting this process is lacking. Therefore, in this study, we aimed to increase the ginsenosides present in fermented red ginseng, along with the cordycepin production of *C. militaris*, by utilising solid-state fermentation.

MATERIAL AND METHODS

Material. The red ginseng and *C. militaris* (strain No. KCCM 60304) used in this study were purchased from Chungok Korean Ginseng (Geumsan-Gun, Chungcheongnam-Do, Korea) and the Korean Agricultural Culture Collection (Wanju-gun, Jeollabuk-do, Korea), respectively. Baeksul white sugar was purchased from CJ Cheil Jedang Corp. (Seoul, Korea) and unpolished brown rice powder was purchased from the Munsan local market (Jinju, Gyeongsangnam-do, Korea).

Preparation of red ginseng fermented by *C. militaris* mycelia. To prepare the seed culture, *C. militaris* (1% of inoculum) was cultured in potato dextrose broth (PDB) (25 g L^{-1}; VentechBio Co., Ltd., Eumseong, Chungcheongbuk-do, Korea) at 24 ± 1 °C for 168 h using an incubator (VS-1203P1; Vision Scientific Co., Ltd., Daejeon-si, Korea).

Solid-state fermentation of red ginseng by *C. militaris*. After immersing 1 kg of red ginseng in 100 °C water for 30 s, the red ginseng was dried to ensure a 25% moisture content (hot air dryer OF-21; Jeio Tech Co., Ltd., Daejeon, Korea). After mixing the sugar and brown rice powder as a carbon source in a 2 : 8 ratio, this mixture [5% (w/w) of red ginseng] was coated onto the red ginseng. The coated red ginseng was sterilised at 121 °C and 1.1 kg cm^{-2} for 30 min (DA-AC-80 autoclave; Donga Science, Siheung-si, Korea) and then cooled to 25 °C at a rate of 7 °C min^{-1} (HB-402 clean bench; Han Baek Scientific, Bucheon, Korea). The cooled red ginseng was incubated at 25 °C (VS-1203P1 incubator; Vision Scientific Co., Ltd., Daejeon-si, Korea). After 2 days, the *Cordyceps* mycelia (*C. militaris*) were inoculated on the surface of the red ginseng in an amount equivalent to 5% of the weight of red ginseng and solid-state fermentation was performed at 24 °C for 50 days (VS-1203P1 incubator; Vision Scientific Co., Ltd., Daejeon-si, Korea).

Determination of ginsenoside content. The saponin content was measured by pulverising the prepared red ginseng using a grinder (HMF-3250S; Hanil Electric Co., Ltd., Seoul, Korea), followed by hot water extraction for 4 h using an autoclave (DA-AC-80; Donga Science, Siheung-si, Korea) at 100 ± 5°C, filtration using a 110 nm filter (No. 2; Advantec Toyo Kaisha, Ltd., Tokyo, Japan), vacuum concentration using a vacuum evaporator (RE-2000E; Dooyoug HI-TECH, Seoul, Korea), and lyophilised powder preparation using a freeze dryer (Lyovapor L200; BÜCHI Labortechnik AG, Flawil, Switzerland) and a vibrating body (GY-200; Guan Yeu Machinery Factory, Chang-Hua Hsien, Taiwan) with a 60-mesh according to the methods provided by the Health Functional Food Code (KFDA 2012) and Lim et al. (2019). In this study, the ginsenoside standards used were ginsenoside Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1, Rg2, Rg3 (20R), and Rg3 (20S) (Ambo Institute, Daejeon-si, Korea).

Determination of the cordycepin content. The cordycepin content was measured by pulverising the prepared red ginseng, followed by hot water extraction, filtration, vacuum concentration, and lyophilised powder preparation according to the slightly modified method reported by Wang et al. (2016). The standard cordycepin (C3394) was purchased from Sigma-Aldrich Co., Ltd. (St. Louis, Missouri, US).

https://doi.org/10.17221/149/2020-CJFS

RESULTS AND DISCUSSION

During the solid-state fermentation process, the growth of *C. militaris* mycelia increased. After 50 days of fermentation, approximately 95% of the red ginseng surface was covered by *C. militaris* mycelia (Figure 1). In the untreated red ginseng, the contents of Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1, Rg2, Rg3 (20R), and Rg3 (20S) were 7.448, 1.915, 0.284, 3.916, 0.567, 1.753, 3.599, 0.610, 0.399, and 0.257 mg g^{-1}, respectively (Table 1). The total ginsenoside content was 20.748 mg g^{-1}. In red ginseng solid-state fermented with *C. militaris,* the contents of Rb1, Rb2, Rb3, Rc, Rd, Re, Rg1, Rg2, Rg3 (20R), and Rg3 (20S) were 2.996, 1.713, 0.310, 2.934, 3.481, 1.312, 2.255, 0.995, 0.848, and 0.517 mg g^{-1}, respectively (Table 1). The total ginsenoside content was 17.361 mg g^{-1}. The red ginseng solid-state fermented with *C. militaris* demonstrated considerably higher contents of Rb3, Rd, Rg2, Rg3 (20R), and Rg3 (20S) than the untreated red ginseng (9.16, 513.93, 63.12, 112.53, and 101.17%, respectively). The higher content of these specific ginsenosides, including Rb3, Rd, Rg2, Rg3(20R), and Rg3(20S), is known to afford beneficial effects on the human body as follows: Rb3 has hypoglycemic, antidepressant-like, and protective properties against cell injury and oxidative stress (Cui et al. 2012; Oh et al. 2016; Meng et al. 2017; Wang et al. 2018); Rd has neuroprotective effects and attenuates oxidative damage (Yokozawa et al. 2004; Ye et al. 2009); Rg2 has protective effects against neurotoxicity, ultraviolet B (UV-B)-induced DNA damage, and memory impairment (Li et al. 2007; Zhang et al. 2008; Ha et al. 2010); Rg3(20R) and Rg3(20S) enhance human intestinal bacteria activities and possess anticancer and anti-obesity effects (Bae et al. 2002; Hwang et al. 2009; Sun et al. 2017). It could be postulated that the *Cordyceps* mycelium induced a change in the ginsenoside content through the bioconversion of the ginsenoside components while growing on the surface of the red ginseng, which contains the ginsenosides. Although a liquid fermentation process rather than solid-phase fermentation, the ginsenoside content of red ginseng extract was 13 786.5 μg mL^{-1} according to Bae et al. (2011), whereas red ginseng extract fermented by *C. militaris* showed high levels of total ginsenosides (17 501.6 μg mL^{-1}). Among various ginsenosides, levels of Rg1 and Rb1, fermented with *C. militaris,* were higher (2 981.4 μg mL^{-1}) than the content in red ginseng extract (2 774.1 μg mL^{-1}).

After 10, 20, 30, and 40 days of fermentation, the content of cordycepin in red ginseng solid-state fermented with *C. militaris* was 1.8, 10.7, 25.3, and 31.1 mg kg^{-1}, respectively. As shown in Figure 2, 0 days of fermentation produced no cordycepin; however, as the fermentation time increased, the production of cordycepin gradually increased, yielding approximately 34.8 mg kg^{-1} of cordycepin at 50 days of fermentation (Figure 2).

Red ginseng contains several components with various physiological activities (Park et al. 2012). Secondary fermentation has been evaluated using specific strains to enhance the specific components or physiological activities of red ginseng. According to the results of Bae et al. (2004), when red ginseng is fermented for 5 days with *Bifidobacterium* H-1, its main components are compound K (CK) > ginsenoside Rg3 ≥ ginsenoside Rh2. Notably, while the orally administered red ginseng extract fails to protect against ischemia-reperfusion brain injury, fermented red ginseng provides significant protection (Trinh et al. 2007). Red ginseng powder (RGP) fermented by *Lactobacillus plantarum* M1 possesses a higher total content of ginsenosides (142.4 mg g^{-1}) than the control (121.8 mg g^{-1}) (Kim et al. 2010). Particularly, the ginsenosides Rg3, Rg5, Rk1, CK, Rh1, and Rg2 are present in the fermented RGP to a greater extent (65.5 mg g^{-1}) than the control (32.7 mg g^{-1}). In everted intestinal sacs of rats, red ginseng displayed a higher transportation level

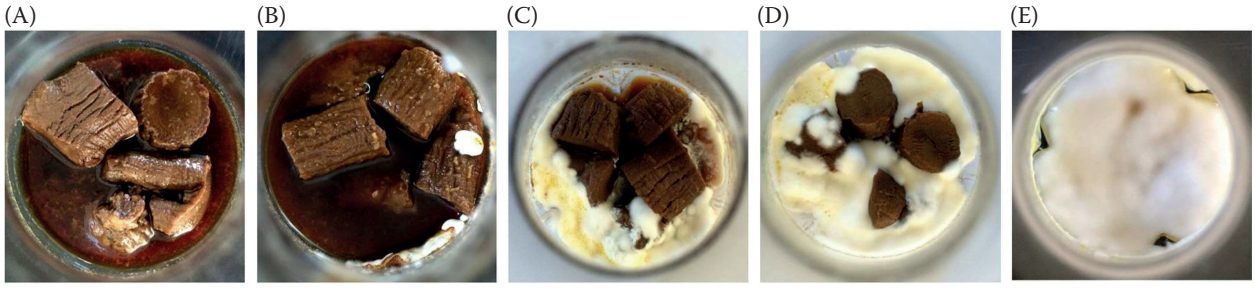

Figure 1. Solid-state fermented red ginseng after (A) 0, (B) 10, (C) 25, (D) 40, and (E) 50 day-fermentation by *Cordyceps militaris*

Solid-state fermentation was performed at 24 °C

https://doi.org/10.17221/149/2020-CJFS

Table 1. Changes in ginsenoside contents in red ginseng solid-state fermented with *Cordyceps militaris* after a 50-day fermentation

Ginsenosides	Red ginseng (mg g^{-1})	Fermented red ginseng (mg g^{-1})	Rate of change (%)
Rb1	7.448	2.996	–59.77
Rb2	1.915	1.713	–10.55
Rb3	0.284	0.310	9.16
Rc	3.916	2.934	–25.08
Rd	0.567	3.481	513.93
Re	1.753	1.312	–25.16
Rg1	3.599	2.255	–37.34
Rg2	0.610	0.995	63.12
Rg3(20S)	0.399	0.848	112.53
Rg3(20R)	0.257	0.517	101.17
Total ginsenosides	20.748	17.361	–16.33

(10.3 mg of polyphenols g^{-1} sac) than non-fermented red ginseng (6.67 mg of polyphenols g^{-1} sac) after 1 h. Additionally, Kim et al. (2013) reported that the alleviation of obesity-mediated metabolic disorders in mice -fed a high-fat diet by red ginseng is enhanced by red-koji fermentation.

C. militaris, a medicinal and edible mushroom, has been used as herbal medicine (Das et al. 2010). Additionally, this strain has been used to alter the quantity of raw material constituents, as well as to improve the related physiological activities. Reportedly, the free radical scavenging activity of the *U. pinnatifida* extract

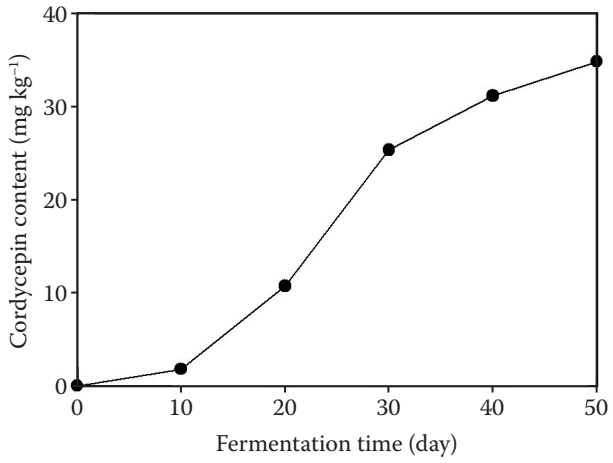

Figure 2. Increase in cordycepin content in solid-state fermented red ginseng with *Cordyceps militaris* during a 50-day fermentation

fermented with *C. militaris* mycelia using solid culture extracts is higher than that of *C. militaris* mycelia or *U. pinnatifida* alone. In the *U. pinnatifida* extract fermented with *C. militaris*, the 2,2-diphenylpicrylhydrazyl (DPPH), alkyl, and hydroxyl radical scavenging activities significantly increased ($P < 0.05$) up to 35, 10, and 16 times, respectively (Kim et al. 2015). Huang et al. (2017) reported that UV-B light-irradiated samples of buckwheat and embryo rice fermented with *C. militaris* showed a significant increase in the vitamin D_2 content when compared with fresh embryo rice fermented by *C. militaris*. Furthermore, in the irradiated dry samples fermented using *C. militaris,* the adenosine, cordycepin, and polysaccharide contents were higher than in the irradiated fresh samples fermented by *C. militaris*. Samples fermented by *C. militaris* had lower effective concentration $(EC)_{50}$ values and higher content of antioxidants than the unfermented samples. Xu et al. (2019) have studied the increase in *C. militaris* polysaccharide production and the antioxidant activities of fermented rice by solid-state fermentation. Under optimised conditions, the maximal *C. militaris* polysaccharide content and free radical scavenging ratio are 68.3 mg g^{-1} dry substrate and 98.9%, respectively.

However, evidence supporting the potential of red ginseng fermented with *C. militaris* is lacking in a solid phase fermentation. Therefore, in this study, we aimed to increase the ginsenosides present in fermented red ginseng and the cordycepin production of *C. militaris* using solid-state fermentation. Solid-state fermentation refers to a method of fermenting that involves growing a microorganism on a solid substrate containing a certain amount of water. Unlike liquid fermentation, solid-state fermentation enables the convenient extraction and purification of the target compound(s) from the fermented products (Shuler et al. 2017). In this study, the production of several ginsenosides in fermented red ginseng and the cordycepin production of *C. militaris* was demonstrated through solid-state fermentation (Table 1 and Figure 2). In this solid-state fermentation, the fermentation process was stopped when the moisture content was less than 12%; additionally, when the moisture content was 80–85% or more, free water appeared and inhibited the fermentation (data not shown). Additionally, red ginseng fermented by *C. militaris,* which carries out the solid-state fermentation, does not use water unlike liquid fermentation and thus has several process advantages, including a simplified fermentation process and convenient separation and purification. Moreover, the rate of production of the target ginsenosides and cordyce-

https://doi.org/10.17221/149/2020-CJFS

pin was high. To the best of our knowledge, this is the first study demonstrating the development of a solid-state fermentation process to increase the ginsenosides present in fermented red ginseng, as well as the cordycepin production by *C. militaris*.

To confirm the bioactive effects of red ginseng fermented by *C. militaris*, it is necessary to evaluate the potential synergistic effects of ginsenosides and cordycepin on specific bioactivities in future investigations.

CONCLUSION

In conclusion, red ginseng fermented by *C. militaris* may be used as natural herbal medicine or dietary supplement with various beneficial effects on human health.

REFERENCES

Bae E.A., Han M.J., Choo M.K., Park S.Y., Kim D.H. (2002): Metabolism of 20(S)- and 20(R)-ginsenoside Rg3 by human intestinal bacteria and its relation to *in vitro* biological activities. Biological and Pharmaceutical Bulletin, 25: 58–63.

Bae E.A., Hyun Y.J., Choo M.K., Oh J.K., Ryu J.H., Kim D.H. (2004): Protective effect of fermented red ginseng on a transient focal ischemic rats. Archives of Pharmacal Research, 27: 1136–1140.

Bae S.H., Lee H.S., Kim M.R., Kim S.Y., Kim J.M., Suh H.J. (2011): Changes of ginsenoside content by mushroom mycelial fermentation in red ginseng extract. Journal of Ginseng Research, 35: 235–242.

Couto S.R., Sanromán M.A. (2006): Application of solid-state fermentation to food industry – A review. Journal of Food Engineering, 76: 291–302.

Cui J., Jiang L., Xiang H. (2012): Ginsenoside Rb3 exerts antidepressant-like effects in several animal models. Journal of Psychopharmacology, 26: 697–713.

Cunningham K.G., Manson W., Spring F.S., Hutchinson S.A. (1950): Cordycepin, a metabolic product isolated from cultures of *Cordyceps militaris* (Linn.) link. Nature, 166: 949–949.

Das S.K., Masuda M., Sakurai A., Sakakibara M. (2010): Medicinal uses of the mushroom *Cordyceps militaris*: Current state and prospects. Fitoterapia, 81: 961–968.

De Smet P.A.G.M. (2002): Herbal remedies. New England Journal of Medicine, 347: 2046–2056.

Ha S.E., Shin D.H., Kim H.D, Shim S.M., Kim H S., Kim B.H., Lee J.S., Park J.K. (2010): Effects of ginsenoside Rg2 on the ultraviolet B-induced DNA damage responses in HaCaT cells. Naunyn-Schmiedeberg's Archives of Pharmacology, 382: 89–101.

Huang S.J., Huang F.K., Li Y.S., Tsai S.Y. (2017): The quality improvement of solid-state fermentation with *Cordyceps militaris* by UVB irradiation. Food Technology and Biotechnology, 55: 445–453.

Hwang J.T., Lee M.S., Kim H.J., Sung M.J., Kim H.Y., Kim M.S., Kwon D.Y. (2009). Antiobesity effect of ginsenoside Rg3 involves the AMPK and PPAR-γ signal pathways. Phytotherapy Research, 23: 262–266.

Kasai R., Besso H., Tanaka O., Saruwatari Y., Fuwa T. (1983): Saponins of red ginseng. Chemical and Pharmaceutical Bulletin (Tokyo), 31: 2120–2125.

KFDA (2012). Ginseng/Red Ginseng Saponins. Health Functional Food Code. Korea Food & Drug Administration. Available at https://foodsafetykorea.go.kr/foodcode/01_03.jsp?idx=110921 (accessed May 4, 2020).

Kim B.G., Choi S.Y., Kim M.R., Suh H.J., Park H.J. (2010): Changes of ginsenosides in Korean red ginseng (*Panax ginseng*) fermented by *Lactobacillus plantarum* M1. Process Biochemistry, 45: 1319–1324.

Kim C.M., Yi S.J., Cho I.J., Ku S.K. (2013): Red-koji fermented red ginseng ameliorates high fat diet-induced metabolic disorders in mice. Nutrients, 5: 4316–4332.

Kim Y.S., Kim E.K., Hwang J.W., Han Y.K., Kim S.E., Jeong J.H., Moon S.H., Jeon B.T., Park P.J. (2015): Radical scavenging activities of *Undaria pinnatifida* extracts fermented with *Cordyceps militaris* mycelia. Journal of Microbiology and Biotechnology, 25: 820–827.

Kwon S.W., Han S.B., Park I.H., Kim J.M., Park M.K., Park J.H. (2001): Liquid chromatographic determination of less polar ginsenosides in processed ginseng. Journal of Chromatography A, 921: 335–339.

Leung K.W., Wong A.S.T. (2010): Pharmacology of ginsenosides: A literature review. Chinese Medicine, 5: 1–7.

Li N., Liu B., Dluzen D.E., Jin Y. (2007): Protective effects of ginsenoside Rg2 against glutamate-induced neurotoxicity in PC12 cells. Journal of Ethnopharmacology, 111: 458–463.

Lim J.M., Kim Y.D., Kim Y.S., Cho H.R., Lee K.H., Yoon I.J., Kim S.K., Kim M.S., Choi J.S. (2019): Sea cucumber *Stichopus japonicus* hydrolysate alleviates late-onset-hypogonadism in aged SD rats. Toxicology and Environmental Health Sciences, 11: 312–319.

Matsuura H., Kasai R., Tanaka O., Saruwatari Y., Kunihiro K., Fuwa T. (1984): Further studies on the dammarane-saponins of ginseng roots. Chemical and Pharmaceutical Bulletin (Tokyo), 32: 1188–1192.

Meng F., Su X., Li W., Zheng Y. (2017): Ginsenoside Rb3 strengthens the hypoglycemic effect through AMPK for inhibition of hepatic gluconeogenesis. Experimental and Therapeutic Medicine, 13: 2551–2557.

Oh S.J., Oh Y., Ryu I.W., Kim K., Lim C.J. (2016): Protective properties of ginsenoside Rb3 against UV-B radiation-

https://doi.org/10.17221/149/2020-CJFS

-induced oxidative stress in HaCaT keratinocytes. Bioscience, Biotechnology, and Biochemistry, 80: 95–103.

Pandey A. (2003): Solid state fermentation. Biochemical Engineering Journal, 13: 81–84.

Park Y.C., Lim J.D., Kim J.B., Lee S. (2012): Review of red ginseng in terms of mechanisms for pharmacodynamics and toxicity. Journal of Korean Medicine, 33: 200–230.

Qin P., Li X., Yang H., Wang Z.Y., Lu D. (2019): Therapeutic potential and biological applications of cordycepin and metabolic mechanisms in cordycepin-producing fungi. Molecules, 24: 2231.

Sadh P.K., Duhan S., Duhan J.S. (2018): Agro-industrial wastes and their utilization using solid state fermentation: A review. Bioresources and Bioprocessing, 5: 1–15.

Shuler M.L., Kargi F., DeLisa M. (2017): Bioprocess Engineering: Basic Concepts. 3rd Ed. Upper Saddle River, New Jersey, US, Prentice Hall: 656.

Sun M., Ye Y., Xiao L., Duan X., Zhang Y., Zhang H. (2017): Anticancer effects of ginsenoside Rg3. International Journal of Molecular Medicine, 39: 507–518.

Trinh H.T., Han S.J., Kim S.W., Lee Y.C., Kim D.H. (2007): *Bifidus* fermentation increases hypolipidemic and hypoglycemic effects of red ginseng. Journal of Microbiology and Biotechnology, 17: 1127–1133.

Tuli H.S., Sharma A.K., Sandhu S.S., Kashyap D. (2013): Cordycepin: A bioactive metabolite with therapeutic potential. Life Sciences, 93: 863–869.

Wang M., Chen X., Jin W., Xu X., Li X., Sun L. (2018): Ginsenoside Rb3 exerts protective properties against cigarette smoke extract-induced cell injury by inhibiting the p38 MAPK/NF-κB and TGF-β1/VEGF pathways in fibroblasts and epithelial cells. Biomedicine & Pharmacotherapy, 108: 1751–1758.

Wang X., Liu F., Li F., Cai H., Sun W., Chen X., Gao H., Shen W. (2016): Determination of cordycepin content of *Cordyceps militaris* recombinant rice by high performance liquid chromatography. Tropical Journal of Pharmaceutical Research, 15: 2235–2239.

Ye R., Li N., Han J., Kong X., Cao R., Rao Z., Zhao G. (2009): Neuroprotective effects of ginsenoside Rd against oxygen-glucose deprivation in cultured hippocampal neurons. Neuroscience Research, 64: 306–310.

Yokozawa T., Satoh A., Cho E.J. (2004): Ginsenoside-Rd attenuates oxidative damage related to aging in senescence-accelerated mice. Journal of Pharmacy and Pharmacology, 56: 107–113.

Xu L., Wang F., Zhang Z., Terry N. (2019): Optimization of polysaccharide production from *Cordyceps militaris* by solid-state fermentation on rice and its antioxidant activities. Foods, 2019: 590.

Zhang G., Liu A., Zhou Y., San X., Jin T., Jin Y. (2008): Panax ginseng ginsenoside-Rg2 protects memory impairment via anti-apoptosis in a rat model with vascular dementia. Journal of Ethnopharmacology, 115: 441–448.

Received: June 7, 2020
Accepted: November 30, 2021