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An overview of the bioactivity of monacolin K / lovastatin

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ABSTRACT

Monacolin K (MK) is the principal active substance in *Monascus*-fermentation products (*e.g.* red yeast rice). MK is effective in reducing cholesterol levels in humans and has been widely used as a lipid-lowering drug. The mechanism for this is through a high degree of competitive inhibition of the rate-limiting enzyme HMG-CoA reductase (HMGR) in the cholesterol synthesis pathway. In addition to lowering blood lipid levels, MK also prevents colon cancer, acute myeloid leukemia and neurological disorders such as Parkinson's disease and type I neurofibromatosis. The aim of this manuscript is to comprehensively review the progress in the study of the biological activity of MK and its imechanism of action in reducing blood lipid concentration, prevention of cancer and its neuroprotective, anti-inflammatory and antibacterial properties. This review provides a reference for future applications of MK in functional foods and medicine.

1. Introduction

Monacolin K (MK), also known as lovastatin, is the major active component in red yeast rice (RYR) (Lin et al., 2008). Japanese Professor Akira Endo first isolated an active substance capable of inhibiting cholesterol synthesis from *Monascus ruber*, which was termed monacolin K (Endo, 1979). MK is a transparent, white, needle-shaped crystal under normal laboratory conditions, with low solubility in water, but highly soluble in organic solvents such as methanol, ethanol, acetone, chloroform and benzene. MK has the molecular formula $C_{24}H_{36}O_5$ with a molecular weight of 404.55. Under acidic conditions, it adopts one of two forms, acidic or lactone. The acidic form plays a role in reducing blood lipid concentration (Halpin et al., 1993).

RYR is recognized as a functional food, proven to be effective in controlling hypercholesterolemia. The key active substance in RYR is MK (Lin et al., 2008; Perez-Jimenez et al., 2018). Researchers from around the world have conducted in-depth research on MK to investigate additional physiological properties that MK may have, such as anti-cancer (Agarwal et al., 2002; Chen et al., 2015a,b; Klawitter et al., 2010; Lin et al., 2006), neuroprotection (Divsalar et al., 2018; Ghanizadeh et al., 2014; Lin et al., 2015), and anti-inflammatory and antibacterial effects (Zhou et al., 2018).

This paper comprehensively reviews the research progress on RYR and MK in terms of biological activity and mechanisms of action. We review their anti-inflammatory and antibacterial properties and capability towards reducing blood lipid concentration, prevention of cancer and neuroprotection. This review provides a reference for future applications of RYR and MK in functional foods and medicine.

2. Reduction in blood lipids

2.1. Mechanism of action of MK in lowering blood lipid concentration

The mechanism by which MK lowers blood lipid concentration is complex, acting through various components and different pathways in human blood. The main lipid-lowering mechanism is through reducing endogenous lipid synthesis, absorption of exogenous lipids and by promoting their transport and excretion.

The principal components of blood lipids are triglycerides and cholesterol. In the cholesterol synthesis pathway, acetyl-CoA (CoA) synthesizes HMG-CoA, which in turn then synthesizes mevalonate (MVA). Cholesterol is synthesized through a series of reactions. In this reaction sequence, HMG-CoA reductase (HMGR) acts as the rate-limiting enzyme. Because MK has a similar structure to HMGR, it operates

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through a high degree of competitive inhibition of HMGR, which can effectively inhibit cholesterol synthesis in the blood, thereby reducing blood lipid content (Endo, 1980; Istvan and Deisenhofer, 2001; Perez-Jimenez et al., 2018).

Low-density lipoprotein (LDL) is also a key substance controlling blood cholesterol concentration, its principal function being to transport cholesterol in the circulation to peripheral tissues. LDL is mostly degraded and transformed by LDL receptors. MK can increase LDL receptor production, thereby lowering LDL levels in the body, thus lowering the content of cholesterol in blood. Studies have confirmed that RYR as a functional food is effective in reducing blood LDL concentration. The main active substance in RYR is MK. Compared with purified lovastatin, MK in RYR extract has higher bioavailability, rendering its cholesterol-lowering properties more effective (Poli et al., 2018).

2.2. Hypolipidemic effects of MK

Hypercholesterolemia is a dangerous form of cardiovascular disease, for which statins are generally prescribed as the main therapeutic drug. However, in some patients, statins can cause serious side effects such as muscle pain. Ezetimibe is often used as adjunctive therapy to statins but can also be used as a monotherapy for patients with statin intolerance. Nevertheless, ezetimibe may cause elevated transaminases within the liver (Stefanutti et al., 2017). Research has shown that when RYR is used as a food supplement for patients with hypercholesterolemia, it significantly reduces their symptoms (Anagnostis et al., 2018).

Studies have confirmed the efficacy and tolerability of RYR in patients intolerant to conventional statins. Stefanutti et al. (2017) selected 55 patients with familial hypercholesterolemia who discontinued statin use due to muscle pain. They received a cholesterol-lowering diet containing 300 mg of RYR (containing 10 mg MK) daily. LDL cholesterol levels in patients decreased significantly after 6 months of treatment (17% for men, 16% for women; $p < 0.005$). After 12 months, levels had decreased by 24% and 27% in men and women, respectively. No patient experienced elevated levels of serum aminotransferase or C-reactive protein.

Liu et al. (2006) conducted a meta-analysis to evaluate the efficacy and safety of RYR preparations to achieve lipolyzation in primary hyperlipidemia. The study consisted of three randomized trials, using 9625 participants, in which three RYR formulations were tested. The combined results demonstrated a significant decrease in levels of total cholesterol, triglycerides and LDL in the serum of participants, and a significant increase in high density lipoprotein cholesterol (HDL) concentrations. The results of this study indicate that RYR has a short-term positive effect on lipolyzation.

Gerards et al. (2015) also performed a meta-analysis of 20 trials to verify the safety and efficacy of RYR extract to lower LDL cholesterol. Compared with a placebo, it was found that RYR extract could significantly reduce LDL, as effective as treatment using statins. The study therefore indicated that RYR may be a safe and effective option for statin-intolerant patients in the treatment of dyslipidemia and in reducing the risk of cardiovascular disease.

Researchers have collected clinical data from a large number of patients with hypercholesterolemia, including some who have used RYR as a therapy, for a follow-up survey. This highlighted that RYR can lower blood cholesterol levels and can also serve as an alternative acceptable to patients intolerant of other drugs (Becker et al., 2010; Stefanutti et al., 2017; Venero et al., 2010). Stefanutti et al. (2017) demonstrated that RYR has good efficacy and safety in patients with hypercholesterolemia who are intolerant to statins, while MK from RYR is the key active ingredient providing therapeutic activity in patients with moderate hypercholesterolemia.

3. Anti-cancer

Statins have potential utility as a therapeutic drug against cancer (Abdullah et al., 2018; Aguirre-Vidal et al., 2015; Altwairgi, 2015). Moon et al. (2019) demonstrated that in a mouse model of liver cancer that have a *p53* gene mutation, atorvastatin inhibited cholesterol synthesis by suppressing the expression of genes involved in the mevalonate pathway, significantly inhibiting tumor growth. A combination of statins and chemotherapeutic drugs can improve the efficacy of chemotherapy. Statins can also be used directly as chemotherapeutic drugs. Their positive effects in combination with other chemotherapeutic drugs are principally due to their cytostatic (cytotoxic) properties towards cancer cells (Ahmadi et al., 2018).

Lovastatin, an important type of statin, has been shown to significantly inhibit the growth of cancer cells and promote their apoptosis (Agarwal et al., 2002; Chen et al., 2015a,b; Hong et al., 2008; Klawitter et al., 2010; Laezza et al., 2008; Lin et al., 2006; Sanli et al., 2011; Ukomadu and Dutta, 2003; Zhang et al., 2019) when used in the treatment of many types of cancer, including colon (Agarwal et al., 2002; Hong et al., 2008; Lin et al., 2006; Ukomadu and Dutta, 2003), acute myeloid leukemia (Chen et al., 2015a,b), gastric (Zhang et al., 2019), breast (Klawitter et al., 2010), lung (Sanli et al., 2011) and thyroid cancers (Laezza et al., 2008).

3.1. Prevention and treatment of colon cancer

A growing number of reports suggests that statins (including lovastatin) can inhibit colon cancer cell growth, thereby reducing the incidence of colon cancer (Agarwal et al., 2002; Lin et al., 2006; Ukomadu and Dutta, 2003).

Hong et al. (2008) compared RYR with purified MK in the inhibition of colon cancer. Purified MK reduces the proliferation of HCT-116 and HT-29 human colon cancer cells and induces apoptosis in cancer cells. RYR inhibits HCT-116 tumor cell growth and increases cell apoptosis. In this study, RYR was purified into two components: pigment-rich (P-RYR) and MK-rich (M-RYR) fractions. M-RYR exhibited properties similar to those of purified MK, while P-RYR acted in a similar manner to that of the whole RYR extract.

3.2. Prevention and treatment of acute myeloid leukemia

Chen et al. (2015) demonstrated that MK was capable of inhibiting the spread of acute myeloid leukemia (AML). The study demonstrated that MK exhibited a significant inhibitory effect on the proliferation of the U937 human AML cell line in a dose-dependent manner. The mechanism by which MK induces apoptosis in U937 cells appears related to inhibition of the Ras/Raf/ERK and Ras/PI3K/Akt signaling pathways and the down-regulation of HMGR and GLO1 gene expression by MK.

The mechanism of MK-induced apoptosis in HL-60 cancer cells was studied by the same research team (Chen et al., 2015a). A large quantity of cholesterol is required for cell membrane synthesis during the rapid proliferation of cancer cells. The *Ras* gene is the most common mutant oncogene in human cancer. Fig. 1 shows that MK, as an inhibitor of HMGR, inhibits the synthesis of farnesyl pyrophosphate (FPP) in the cholesterol synthesis pathway, inhibits the isoprenylation of Ras, reduces the concentration of Ras in cell membranes and consequently results in the inactivation of the *Akt* and *Erk* genes, resulting in transport of the NF-κB transcription factor from the cytoplasm to the cell membrane. As a result, the expression levels of the glyoxalase 1 (*GLO*1) gene decreased. Methylglyoxal (MG) is a by-product of glucose decomposition, which is strongly cytotoxic, can prevent cell proliferation and induce cell apoptosis. GLO1 is the key enzyme that protects cancer cells from apoptosis by eliminating excessive MG. Therefore, decreased expression of GLO1 will lead to the accumulation of MG in cancer cells, resulting in cancer cell apoptosis (Chen et al., 2015a,b).

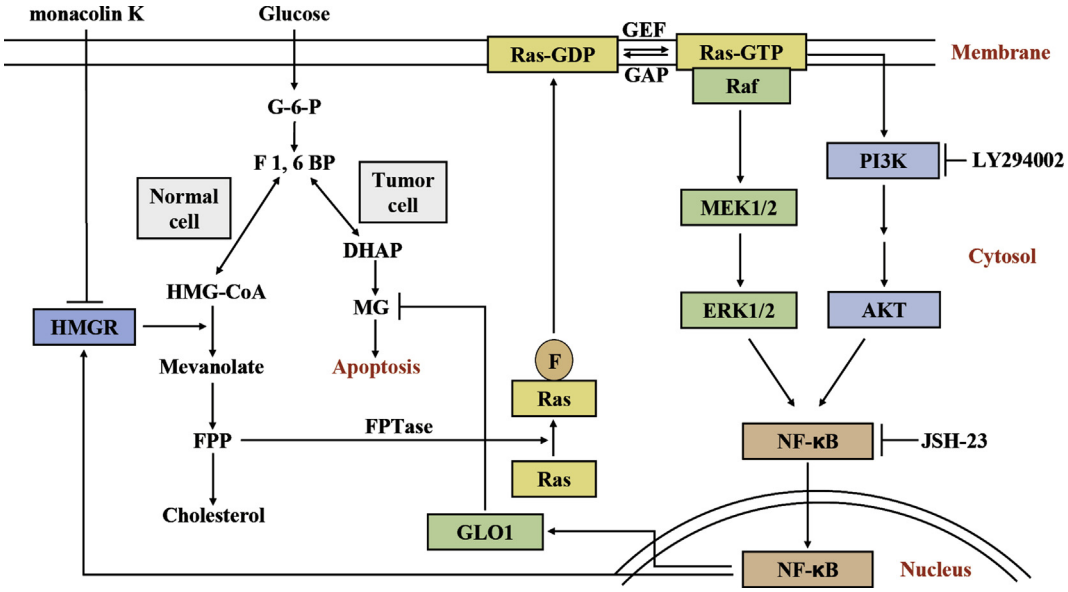

Fig. 1. Overview of the mechanism of cancer cell apoptosis induced by MK (Chen et al., 2015a,b). MK down-regulates the expression of the *HMGR* and *GLO*1 genes by inhibition of Ras/Raf/ERK/NF-κB and Ras/PI3K/Akt/NF-κB pathways in cancer cells. G-6-P: glucose 6-phosphate; F1,6 BP: fructose 1,6-bisphosphate; DHAP: dihydroxyacetone phosphate; FPP: farnesyl pyrophosphate; FPTase: farnesyl prenyl transferase; GLO 1: glyoxalase 1; GEF: guanine nucleotide exchange factor; GAP: GTPase-activating protein.

3.3. Prevention and treatment of gastric cancer

Zhang et al. (2019) utilized WGCNA and CMap software to identify two compounds that could potentially provide a positive therapeutic effect in gastric cancer patients: valproic acid (VPA), a histone deacetylase (HDAC) inhibitor and lovastatin. *In vitro* experiments revealed that VPA and lovastatin exhibit dose-dependent inhibition of the growth of gastric cancer cells. HDAC2 is overexpressed in gastric cancer cell lines and both VPA and lovastatin induce gastric cancer cell apoptosis by inhibition of HDAC2 expression. The study highlighted that lovastatin may show potential as a therapy for treatment of gastric cancer.

4. Neuroprotection

In terms of neuroprotection, MK and other statins have demonstrated significant efficacy in the prevention and treatment of neurological disorders such as Parkinson's disease (Lin et al., 2015), in improvement in memory (Lee et al., 2007), schizophrenia (Shen et al., 2018), depression (Divsalar et al., 2018) and type I neurofibromatosis (Acosta et al., 2011).

4.1. Prevention and treatment of Parkinson's disease

Lee et al. (2007) found that RYR was capable of improve memory and reducing learning impairment in rats. Researchers have since studied improvements in the symptoms of Parkinson's disease in humans associated with the administration of RYR and MK.

Lin et al. (2015) studied the protective effects of six lovastatin derivatives on nerve growth factor (NGF)-differentiated PC12 cells. The results demonstrated that four of the six derivatives, termed 3a, 3d, 3e and 3f, enhanced cell viability significantly. Compound 3f in particular exhibited excellent neuroprotective properties and reduced the 6-OHDA-induced apoptosis of PC12 cells. Furthermore, compound 3f also reduced the activity of caspase (CASP) 3, CASP 8 and CASP 9, in a concentration-dependent manner. Compound 3f was also able to increase intracellular calcium concentration by increasing 6-OHDA activity without inhibiting the production of reactive oxygen species. The results of JC-1 staining demonstrated that compound 3f also stabilized mitochondrial membrane potential. Therefore, compound 3f has potential as a protective agent for nerve cells.

4.2. Prevention and treatment of schizophrenia

Shen et al. (2018) conducted a meta-analysis to demonstrate that statins can be used as an adjuvant drug in schizophrenia. Statins can improve both positive and negative schizophrenic symptoms. However simvastatin is the sole statin associated with improvement in only negative symptoms. There is currently no evidence to show that lovastatin has a significant positive effect in the treatment of schizophrenia.

Ghanizadeh et al. (2014) utilized a placebo-controlled trial to evaluate the efficacy and safety of lovastatin as an adjuvant treatment for patients with schizophrenia. However, this study did not demonstrate that lovastatin significantly relieved schizophrenic symptoms.

The results of the studies described above do not confirm whether MK has a significant effect in schizophrenia, or that it contributes to improving schizophrenia as an adjuvant therapy. Therefore, the therapeutic effect of MK in schizophrenia remains unclear.

4.3. Prevention and treatment of depression

Divsalar et al. (2018) studied the efficacy of RYR in 50 patients with major depression. All patients had undergone coronary angioplasty and were divided into placebo and treatment groups, comprising sertraline plus placebo or RYR capsules containing MK. The primary outcome of the trial approached significance with a significant time × treatment interaction effect. This study was the first to report the use of RYR as a treatment for depression.

Since lipophilic statins are more likely to cross the blood-brain barrier and directly affect mood (Fong, 2014), Dave et al. (2018) suggested that statins may increase the risk of depression. Statistical and analytical results demonstrate however, that the use of lipophilic statins (including lovastatin) has not been associated with a significant increase in the risk of developing depression. Therefore, MK is unlikely to increase the risk of depression, and may even have a positive therapeutic effect.

4.4. Prevention and treatment of type I neurofibromatosis

Type I neurofibromatosis is a common neurological disease that is associated with the development of learning disabilities (Brewer et al., 1997) and attention deficit disorders (Koth et al., 2000). In experiments with mice, Li et al. (2005) found that treatment with lovastatin could enhance spatial learning and reduce attention deficit. The study indicated that lovastatin can treat type I neurofibromatosis. Guimarães et al. (2015) also concluded that treatment with lovastatin had no negative effects on cognition or memory, such cognitive capabilities shown to improve in rats after treatment with lovastatin and α-tocopherol.

The most common neurological complication of neurofibromatosis in children is cognitive dysfunction (North et al., 2002). Based on the mouse experiments described above, Acosta et al. (2011) administered lovastatin to 24 children with type I neurofibromatosis, the results showing that their speech and non-verbal memory improved.

These two studies demonstrated that lovastatin causes a clear improvement in type I neurofibromatosis and its associated cognitive dysfunction, but specific efficacy and methods of clinical use require further study.

5. Anti-inflammatory and antibacterial effects

Song et al. (2003) discovered that lovastatin and fluconazole have synergistic effects on the inhibition of planktonic *Candida albicans* cells *in vitro* and can affect gene expression in the ergosterol and prenylation pathways.

Zhou et al. (2018) demonstrated that a combination of lovastatin and itraconazole is an effective synergistic therapy against planktonic *C. albicans* cells and biofilms, even in itraconazole-resistant strains. Strains with dysregulated ERG11 and ERG3 genes are resistant to itraconazole, but sensitive to lovastatin monotherapy. The results of this study indicate that the drug combination is effective in overcoming resistant fungal pathogens.

The results of the studies above indicate that lovastatin has a clear antibacterial effect against *C. albicans* when used in combination with other antibacterial agents. Lovastatin alone has also demonstrated antibacterial activity in specific circumstances, but whether it has a broader antibacterial action and suppress other strains requires further study.

6. Conclusions and outlook

Over recent years, researchers have conducted in-depth research on the hypolipidemic effects of MK, widely recognized as a lipid-lowering drug. The proportion of hyperlipidemia patients with statin intolerance is high and MK can achieve comparable or even greater lipid-lowering effects than statins. MK is therefore a suitable adjuvant therapy or a potential substitute for statins and has thus gained increased attention.

In addition, many reports have highlighted the positive effect that MK has in the treatment of cancer and neurological diseases. However, due to its lipid-lowering properties, the focus on MK's ability to prevent and treat cancer and neurological diseases is rather low. Most studies have not progressed beyond the stage of *in vitro* or animal testing, lacking in-depth research in clinical settings. In the future, comprehensive studies of the mechanism of action of MK and its efficacy in treating diseases such as hyperlipidemia, cancer, neurological disorders and inflammation, will significantly promote further application of MK in functional foods and medicine.

Declaration of interests

The authors declare that they have no known competing financialinterestsor personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Acknowledgments

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Conflicts of interest

The authors declare no conflicts of interest.

Transparency document

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References

Abdullah, M.I., de Wolf, E., Jawad, M.J., Richardson, A., 2018. The poor design of clinical trials of statins in oncology may explain their failure – lessons for drug repurposing. Cancer Treat Rev. 69, 84–89. https://doi.org/10.1016/j.ctrv.2018.06.010.

Acosta, M.T., Kardel, P.G., Walsh, K.S., Rosenbaum, K.N., Gioia, G.A., Packer, R.J., 2011. Lovastatin as treatment for neurocognitive deficits in neurofibromatosis type 1: phase I study. Pediatr. Neurol. 45, 241–245. https://doi.org/10.1016/j. pediatrneurol. 2011.06.016.

Agarwal, B., Halmos, B., Feoktistov, A.S., Protiva, P., Ramey, W.G., Chen, M., Pothoulakis, C., Lamont, J.T., Holt, P.R., 2002. Mechanism of lovastatin- induced apoptosis in intestinal epithelial cells. Carcinogenesis 23, 521–528. https://doi.org/10.1093/carcin/23.3.521.

Aguirre-Vidal, Y., Montes, S., Tristan-López, L., Anaya-Ramos, L., Teiber, J., Ríos, C., Baron-Flores, V., Monroy-Noyola, A., 2015. The neuroprotective effect of lovastatin on MPP+-induced neurotoxicity is not mediated by PON2. Neurotoxicology 48, 166–170. https://doi.org/10.1016/j.neuro.2015.03.012.

Ahmadi, Y., Karimian, R., Panahi, Y., 2018. Effects of statins on the chemoresistance-The antagonistic drug-drug interactions versus the anti-cancer effects. Biomed. Pharmacother. 108, 1856–1865. https://doi.org/10.1016/j.biopha.2018.09.122.

Altwairgi, A.K., 2015. Statins are potential anticancerous agents (review). Oncol. Rep. 33, 1019–1039. https://doi.org/10.3892/or.2015.3741.

Anagnostis, P., Paschou, S.A., Goulis, D.G., Athyros, V.G., Karagiannis, A., 2018. Dietary management of dyslipidaemias. Is there any evidence for cardiovascular benefit? Maturitas 108, 45–52. https://doi.org/10.1016/j.maturitas.2017.11.011.

Becker, D.J., Gordon, R.Y., Halbert, S.C., French, B., Morris, P.B., Rader, D.J., 2010. Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial. Ann. Intern. Med. 152, 135–136. https://doi.org/10.7326/0003-4819-150-12-200906160-00006.

Brewer, V.R., Moore, B.D.R., Hiscock, M., 1997. Learning disability subtypes in children with neurofibromatosis. J. Learn. Disabil.-Us 30, 521–533. https://doi.org/10.1177/002221949703000508.

Chen, C.C., Liu, T.Y., Huang, T.C., Huang, S.P., Ho, C.T., 2015a. Differentiation and apoptosis induction by lovastatin and γ-tocotrienol in HL-60 cells via Ras/ERK/NF-κB and Ras/Akt/NF-κB signaling dependent down-regulation of glyoxalase 1 and HMG-CoA reductase. Cell. Signal. 27, 2182–2190. https://doi.org/10.1016/j. cellsig.2015.07.014.

Chen, C.C., Wu, M.L., Ho, C.T., Huang, T.C., 2015b. Blockade of the ras/Raf/ERK and ras/PI3K/Akt pathways by monacolin K reduces the expression of GLO1 and induces apoptosis in U937 cells. J. Agric. Food Chem. 63, 1186–1195. https://doi.org/10.1021/jf505275s.

Dave, C.V., Winterstein, A.G., Park, H., Cook, R.L., Hartzema, A.G., 2018. Comparative risk of lipophilic and hydrophilic statins on incident depression: a retrospective cohort study. J. Affect. Disord. 238, 542–546. https://doi.org/10.1016/j.jad. 2018.06.021.

Divsalar, P., Noorbala, A.A., Moazen-Zadeh, E., Jafarinia, M., Shakiba, M., Shahmansouri, N., Ghazizadeh-Hashemi, M., Etesam, F., Akhondzadeh, S., 2018. Red yeast rice as an adjunct to sertraline for treatment of depression in patients with percutaneous coronary intervention: placebo-controlled trial. Advances in Integrative Medicine 5, 69–74. https://doi.org/10.1016/j.aimed.2018.01.001.

Endo, A., 1979. Monacolin K, a new hypocholesterolemic agent produced by a Monascus species. J. Antibiot. 32, 852–854. https://doi.org/10.7164/antibiotics. 32.852.

Endo, A., 1980. Monacolin K, a new hypocholesterolemic agent that specifically inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase. J. Antibiot. 33, 334–336.

Fong, C.W., 2014. Statins in therapy: understanding their hydrophilicity, lipophilicity, binding to 3-hydroxy-3-methylglutaryl-CoA reductase, ability to cross the blood brain barrier and metabolic stability based on electrostatic molecular orbital studies. Eur. J. Med. Chem. 85, 661–674. https://doi.org/10.1016/j.ejmech. 2014.08.037.

Gerards, M.C., Terlou, R.J., Yu, H., Koks, C.H.W., Gerdes, V.E.A., 2015. Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but

safety is uncertain - a systematic review and meta-analysis. Atherosclerosis 240, 415–423. https://doi.org/10.1016/j.atherosclerosis.2015.04.004.
Ghanizadeh, A., Rezaee, Z., Dehbozorgi, S., Berk, M., Akhondzadeh, S., 2014. Lovastatin for the adjunctive treatment of schizophrenia: a preliminary randomized double-blind placebo-controlled trial. Psychiatr. Res. 219, 431–435. https://doi.org/10.1016/j.psychres.2014.06.039.
Guimarães, M.R.M., Murad, L.B., Paganelli, A., de Oliveira, C.A.B., Vianna, L.M.A., 2015. Effects of alpha-tocopherol associated with lovastatin on brain tissue and memory function in SHRSPs. Physiol. Behav. 149, 303–309. https://doi.org/10.1016/j.physbeh.2015.06.025.
Halpin, R.A., Ulm, E.H., Till, A.E., Kari, P.H., Vyas, K.P., Hunninghake, D.B., Duggan, D.E., 1993. Biotransformation of lovastatin. V. Species differences in in vivo metabolite profiles of mouse, rat, dog, and human. Drug Metab. Dispos.: the biological fate of chemicals 21, 1003–1011.
Hong, M.Y., Seerarn, N.P., Zhang, Y.J., Heber, D., 2008. Anticancer effects of Chinese red yeast rice versus monacolin K alone on colon cancer cells. J. Nutr. Biochem. 19, 448–458. https://doi.org/10.1016/j.jnutbio.2007.05.012.
Istvan, E.S., Deisenhofer, J., 2001. Structural mechanism for statin inhibition of HMG-CoA reductase. Science 292, 1160–1164. https://doi.org/10.1126/science.1059344.
Klawitter, J., Shokati, T., Moll, V., Christians, U., Klawitter, J., 2010. Effects of lovastatin on breast cancer cells: a proteo-metabonomic study. Breast Cancer Res. 12, R16. https://doi.org/10.1186/bcr2485.
Koth, C.W., Cutting, L.E., Denckla, M.B., 2000. The association of neurofibromatosis type 1 and attention deficit hyperactivity disorder. Child Neuropsychol. : a journal on normal and abnormal development in childhood and adolescence 6, 185–194. https://doi.org/10.1076/chin.6.3.185.3155.
Laezza, C., Fiorentino, L., Pisanti, S., Gazzerro, P., Caraglia, M., Portella, G., Vitale, M., Bifulco, M., 2008. Lovastatin induces apoptosis of k-ras-transformed thyroid cells via inhibition of ras farnesylation and by modulating redox state. J. Mol. Med. 86, 1341–1351. https://doi.org/10.1007/s00109-008-0396-1.
Lee, C., Kuo, T., Wang, J., Pan, T., 2007. Red mold rice ameliorates impairment of memory and learning ability in intracerebroventricular amyloid beta-infused rat by repressing amyloid beta accumulation. J. Neurosci. Res. 85, 3171–3182. https://doi.org/10.1002/jnr.21428.
Li, W.D., Cui, Y.J., Kushner, S.A., Brown, R., Jentsch, J.D., Frankland, P.W., Cannon, T.D., Silva, A.J., 2005. The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. Curr. Biol. 15, 1961–1967. https://doi.org/10.1016/j.cub.2005.09.043.
Lin, C., Lin, Y., Lin, R., Huang, W., Lee, M., 2015. Neurocytoprotective effects of aliphatic hydroxamates from lovastatin, a secondary metabolite from monascus-fermented red mold rice, in 6-hydroxydopamine (6-OHDA)-treated nerve growth factor (NGF)-Differentiated PC12 cells. ACS Chem. Neurosci. 6, 716–724. https://doi.org/10.1021/cn500275k.
Lin, W., Song, C., Pan, T., 2006. Proteomic analysis of Caco-2 cells treated with monacolin K. J. Agric. Food Chem. 54, 6192–6200. https://doi.org/10.1021/jf061060c.
Lin, Y.L., Wang, T.H., Lee, M.H., Su, N.W., 2008. Biologically active components and nutraceuticals in the Monascus-fermented rice: a review. Appl. Microbiol. Biotechnol. 77, 965–973. https://doi.org/10.1007/s00253-007-1256-6.
Liu, J.P., Zhang, J., Shi, Y., Grimsgaard, S., Alraek, T., Fonnebo, V., 2006. Chinese red yeast rice (Monascus purpureus) for primary hyperlipidemia: a meta-analysis of randomized controlled trials. Chin Med-Uk 1, 4. https://doi.org/10.1186/1749-8546-1-4.
Moon, S.H., Huang, C.H., Houlihan, S.L., Regunath, K., Freed-Pastor, W.A., Morris, J.P.T., Tschaharganeh, D.F., Kastenhuber, E.R., Barsotti, A.M., Culp-Hill, R., Xue, W., Ho, Y.J., Baslan, T., Li, X., Mayle, A., de Stanchina, E., Zender, L., Tong, D.R., D'Alessandro, A., Lowe, S.W., Prives, C., 2019. p53 Represses the mevalonate pathway to mediate tumor suppression. Cell 176, 1–17. https://doi.org/10.1016/j.cell.2018.11.011.
North, K., Hyman, S., Barton, B., 2002. Cognitive deficits in neurofibromatosis 1. J. Child Neurol. 17, 605–612. https://doi.org/10.1177/088307380201700811.
Perez-Jimenez, F., Pascual, V., Meco, J.F., Perez, M.P., Delgado, L.J., Domenech, M., Estruch, R., Leon-Acuna, A., Lopez-Miranda, J., Sanchez-Ramos, A., Soler, I.F.C., Soler-Rivas, C., Sola, A.R., Valdivielso, P., Ros, E., 2018. Document of recommendations of the SEA 2018. Lifestyle in cardiovascular prevention. Clín. Invest. Arterioscler. 30, 280–310. https://doi.org/10.1016/j.arteri.2018.06.005.
Poli, A., Barbagallo, C.M., Cicero, A.F.G., Corsini, A., Manzato, E., Trimarco, B., Bernini, F., Visioli, F., Bianchi, A., Canzone, G., Crescini, C., de Kreutzenberg, S., Ferrara, N., Gambacciani, M., Ghiselli, A., Lubrano, C., Marelli, G., Marrocco, W., Montemurro, V., Parretti, D., Pedretti, R., Perticone, F., Stella, R., Marangoni, F., 2018. Nutraceuticals and functional foods for the control of plasma cholesterol levels. An intersociety position paper. Pharmacol. Res. 134, 51–60. https://doi.org/10.1016/j.phrs. 2018.05.015.
Sanli, T., Liu, C., Rashid, A., Hopmans, S.N., Tsiani, E., Schultz, C., Farrell, T., Singh, G., Wright, J., Tsakiridis, T., 2011. Lovastatin sensitizes lung cancer cells to ionizing radiation: modulation of molecular pathways of radioresistance and tumor suppression. J. Thorac. Oncol.: official publication of the International Association for the Study of Lung Cancer 6, 439–450. https://doi.org/10.1097/JTO.0b013e3182049d8b.
Shen, H., Li, R., Yan, R., Zhou, X., Feng, X., Zhao, M.J., Xiao, H., 2018. Adjunctive therapy with statins in schizophrenia patients: a meta-analysis and implications. Psychiatr. Res. 262, 84–93. https://doi.org/10.1016/j.psychres.2018.02.018.
Song, J.L., Lyons, C.N., Holleman, S., Oliver, B.G., White, T.C., 2003. Antifungal activity of fluconazole in combination with lovastatin and their effects on gene expression in the ergosterol and prenylation pathways in Candida albicans. Med. Mycol. 41, 417–425. https://doi.org/10.1080/1369378031000137233.
Stefanutti, C., Mazza, F., Mesce, D., Morozzi, C., Di Giacomo, S., Vitale, M., Pergolini, M., 2017. Monascus purpureus for statin and ezetimibe intolerant heterozygous familial hypercholesterolaemia patients: a clinical study. Atherosclerosis Suppl. 30, 86–91. https://doi.org/10.1016/j.atherosclerosissup.2017.05.021.
Ukomadu, C., Dutta, A., 2003. p21-dependent inhibition of colon cancer cell growth by mevastatin is independent of inhibition of G(1) cyclin-dependent kinases. J. Biol. Chem. 278, 43586–43594. https://doi.org/10.1074/jbc.M307194200.
Venero, C.V., Venero, J.V., Wortham, D.C., Thompson, P.D., 2010. Lipid- lowering efficacy of red yeast rice in a population intolerant to statins. Am. J. Cardiol. 105, 664–666. https://doi.org/10.1016/j.amjcard.2009.10.045.
Zhang, L., Kang, W.Q., Lu, X.L., Ma, S.Y., Dong, L., Zou, B.C., 2019. Weighted gene co-expression network analysis and connectivity map identifies lovastatin as a treatment option of gastric cancer by inhibiting HDAC2. Gene 681, 15–25. https://doi.org/10.1016/j.gene.2018.09.040.
Zhou, Y.J., Yang, H., Zhou, X.D., Luo, H.K., Tang, F., Yang, J., Alterovitz, G., Cheng, L., Ren, B., 2018. Lovastatin synergizes with itraconazole against planktonic cells and biofilms of Candida albicans through the regulation on ergosterol biosynthesis pathway. Appl. Microbiol. Biotechnol. 102, 5255–5264. https://doi.org/10.1007/s00253-018-8959-8.