AFSSAAE

Advances in Food Science, Sustainable Agriculture and Agroindustrial Engineering 2023 | Special Issue | 51-64
ISSN 2622-5921

ORIGINAL RESEARCH Open Access

Angkak (red mold rice) as an antihypercholesterolemic and antihypertensive effect: A review

Primanita Setyowati*, Elok Zubaidah and Aji Sutrisno

Department of Food Science and Technology, Faculty of Agricultural Technology, Universitas Brawijaya, Malang, Indonesia

KEYWORDS

GABA
Hypercholesterolemia
Hypertension
Monacolin K
Red mold rice

ABSTRACT

Red Mold Rice (RMR) or angkak is a fermented product of cooked rice by *Monascus* mold. RMR mainly contains pigments, monacolins (Monacolin K), and *γ-aminobutyric acid* (GABA). Monacolin K (MK) is also popular as lovastatin (natural statin). MK are inhibitors of enzyme 3 hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the main enzim for regulating cholesterol synthesis and exerting potent serum cholesterol demoting effect. GABA is a prominent inhibitory neurotransmitter found in the central nervous system. It functions as an antihypertensive, anti-inflammation, and antioxidant. This paper provides a review of factors influencing the *Monascus* fermentation process on the synthesis of the pigments, MK, and GABA, which can relieve hypercholesterolemia and hypertension. The information reviewed for this paper was obtained from the SciFinder, Elsevier, NCBI, Science Direct, Google Scholar, Frontier, MDPI, and M.Sc. and Ph. D dissertations published in August 2021. Maximizing RMR bioactive yield obtained by optimizing the selection of optimal *monascus* strain, substrates, and fermentation factor (pH, inoculum dimension, temperature, fermentation time). Comparison between collaboration RMR bioactive activities (MK, GABA) and statin activities are also examined. Other bioactive of RMR and their health benefits have been discussed. However, little information about the relationship between RMR bioactive and their effects on reducing hypercholesterolemia and hypertension is available.

Introduction

RMR is a naturally fermented product by microorganisms that are grown in a wide variety of natural substrates. The process of carbohydrate complex decomposition creates monosaccharides and energy in aerobic conditions (Silbir & Goksungur, 2019; Voidarou et al., 2021). RMR produce secondary metabolite during RMR fermentation, such as pigments, monacolin K, and GABA (Zhu et al., 2019)

RMR has been an omnipresent ingredient of ancient Chinese medicine and is popular as traditional food medicine in East Asian Countries like China, Japan, Korea, and Thailand (Patel, 2016). Approximately more than one billion was RMR consumer (Yang et al., 2015). RMR is widely used as a food preservative, flavor enhancer, and food colorant agent for meat (cured meat and sausages), fish, soybean products, and beverages (yogurt, rice wine, vinegar) (Husakova et al., 2021; Song et al., 2019; Zhu et al., 2019)

Hypercholesterolemia is also known as elevated blood cholesterol (Vourakis et al., 2021). It is responsible for 4,4 million fatalities globally (IHME, 2019). Cholesterol levels are categorized as normal if total cholesterol levels are <200 mg/dl, thresholds 200-239 mg/dl, and high >240 mg/dl (Nantsupawat et al., 2019). Hypercholesterolemia is a risk factor for hypertension (Ivanovic & Tadic, 2015). Egan et al. (2013) concluded from 3 reports (1988-1994, 1999-2004, 2005-2010) of the National Health and Nutrition Examination Surveys that 60,7-64,3% of hypertensive patients also had hypercholesterolemia. In 2009, hypertension was responsible for 10,8 million mortalities globally (IHME, 2019).

American Heart Association (AHA) in 2018 issued a handbook on the management of blood cholesterol, in which statins are recommended for

*Corresponding author
E-mail address: primanitata@student.ub.ac.id

use in a population of patients with clinical atherosclerotic CVD, diabetes mellitus, and hyperlipidemia with a target cholesterol reduction of ≥50% (Grundy et al., 2019). Lipid-relieving therapy with statins notably decreases blood pressure through the pleiotropic effect system (Ivanovic & Tadic, 2015). RMR has become an alternative to statin therapies; this therapy has been declared to be tolerated in patients who developed myalgia and poor drug-drug interaction (Childress et al., 2013).

RMR was popular because of its content of pigments, monacolin K, and GABA. Previous studies on RMR provided some information about RMR related to raw materials (substrates), microorganisms, the fermentation process, and secondary metabolites (especially pigments, monacolin, and GABA. In addition, comparisons between RMR bioactive (MK, GABA) and statin activities have been discussed thoroughly.

Red mold rice: A fermented food

RMR is the most potent cholesterol-relieving compound obtained by fermenting mold *Monascus purpureus* (Cicero et al., 2019). Fermentation using *Monascus purpureus* has been traditionally practiced for centuries in Asian countries. Variants of substrates influenced pigment's yield and RMR composition (I. Srianta et al., 2020)

In previous studies, besides rice, some substrates of various sources have been observed, such as *dioscorea*, *finger millet*, *brown seaweed*, *glycine max*, red ginseng, cassava, and adlay (Hong et al., 2011; Suraiya et al., 2018; Yanli & Xiang, 2020). In addition, recent studies reported that agricultural-industrial wastes could be used for substrates that demand less water, such as durian seed, jackfruit seed, corn cob, corn and sugarcane bagasse (Chaudhary et al., 2021; Hamdiyati et al., 2016; Raja Rajeswari et al., 2014; Ignatius Srianta et al., 2012; Velmurugan et al., 2011). Among the substrates mentioned above, substrates rich in starch or protein (rice, soybean flour, dioscorea) are compatible with *Monascus* fermentation (Yanli & Xiang, 2020).

RMR fermentation process

In the early stage, extracellular enzymes are secreted to break down starch into simple compounds as the supply of nutrients for monascus growth. The main metabolic products, such as ethanol, reducing sugar, succinic acid, gluconic acid, oxalic acid, citric acid, and ester, are produced during the growth of *Monascus* (Kraboun et al., 2019).

In the common fermentation process, the mold enhances the rice of polyketides with clinically noticeable anticholesterol, the monacolin (Cicero et al., 2021). At some point, the quantity of metabolites produced is low and cannot be delivered. The standard for Chinese Medicine Yinpian Processing of Zhejiang and Sichuan Provinces (2015) suggested that the amount of MK lactone should present as the quality control of RMR, the minor MK content should be 0.4% (in Zhejiang) and 0.3% (in Sichuan) (Yanli & Xiang, 2020).

Then to obtain sufficient secondary metabolite, the parameter for RMR production, such as initial moisture, pH, temperature, and fermentation time, must be optimized (Song et al., 2019; Yanli & Xiang, 2020). The quality of common RMR is measured by the color and quantity of secondary metabolites (Song et al., 2019). The RMR should be dryish. A moist mushy substrate is unpreferable (Manan, 2017).

Several researchers have attempted to increase MK production by optimizing the medium. For example, using rice as substrates, the optimal yield of MK was 2.50 mg/g below optimized conditions (Yu et al., 2013). In addition, using glutinous rice as a substrate, the optimal yield of MK was obtained to be five times higher after optimization fermentation conditions (Kanpiengjai et al., 2018).

Furthermore, the solid-state fermentation of *Monascus purpureus* TISTR 3541 was optimized by statistical technique to attain a yield of MK that was about three times higher than in the common fermentation (C. Zhang et al., 2019).

Factors influencing RMR fermentation

a. ***Initial moisture of the substrate***

The moisture content of the substrate influenced the *Monascus* growth and secondary metabolite production. Substrates with higher or lower moisture content are undesirable because they may affect the *Monascus purpureus* growth (for new cell synthesis) (I. Srianta & Harijono, 2015)

Rice as the substrate has a moisture content of 50-60% for the optimal condition of *Monascus purpureus* growth, and 55-75% was the optimal condition of *Monascus pilosus* M12-69 strain growth (Subsaendee et al., 2014). The yield increased to 56% (optimal moisture content), with yield sagging due to the appearance of substrates' agglomeration and the danger risk of bacterial defilement (Chaudhary et al., 2021).

b. ***pH***

Secondary metabolites yield was more stable at pH 7 than pH 3 because high initial pH containcontainslectrons (H+) than pH 7. Low pH strongly attacks the chromophore group from pigment and significantly reduces the production of secondary metabolites (Fatimah et al., 2014; Tedjautama & Zubaidah, 2014).

c. ***Inoculum dimension***

Previous studies showed that the size of the inoculum or specific surface inoculum area affects microorganism growth and secondary metabolite yields because of the influence on mass transfer and filament attachment (B. B. Zhang et al., 2018). The excessive inoculum dimension (>20%) from the initial substrate could trigger an excessive pile of biomass and rapidly depleted nutrients, which is disadvantageous to the afterwards synthesis of secondary metabolites (Wen et al., 2020; B. B. Zhang et al., 2018).

d. ***Time and temperature***

RMR is produced after several weeks because of the utilization of pure *Monascus sp*. inoculum (Zubaidah et al., 2015). Secondary metabolites were undetected in the early phase (less than five days) because of the process of mycelial growth (Chen et al., 2019). The fermentation metaphase (14-17 days) was recommended for optimal secondary metabolite yield production (Chen et al., 2019; Saithong et al., 2019; Wen et al., 2020). Incubation temperature at 25-30 ºC (7-14 days), room temperature higher at 32-35 ºC and lower at 25 ºC could reduce MK concentration (Saithong et al., 2019).

e. ***Secondary metabolite of RMR***

RMR consists of monacolin, pigment, organic acid, sterols, amino acid, decalin derivative, flavonoid, lignan, and polysaccharide. Pigment and MK are the most bioactive compounds in RMR (Zhu et al., 2019). Bioactive of RMR have many functional effects which beneficial for human health, such as antioxidant, anticancer, anti-cardiovascular, antibacterial, antidiabetic, anticholesterol, and antihypertensive (Fukami et al., 2021; Lin et al., 2019; Mostafa & Saad Abbady, 2014; Musselman et al., 2012).

f. ***Red Mold Rice (RMR) pigment***

Monascus produced some advantageous secondary metabolites, *Monascus* pigments (MP). They are commonly used in the food industry as a color booster, flavor enhancer, and nitrite replacements in process, natural dye in cosmetic products and garment industries (Agboyibor et al., 2018). MP has abundant antioxidant activities such as a peroxidation inhibitor, scavenging agent on DPPH, and chelating capability on Fe^{2+} (Kraboun et al., 2019). Currently, the MP industry scale in China is estimated to produce more than 1000 tons (Ignatius Srianta et al., 2012).

Monascus purpureus started to generate pigments at the end of the logarithmic phase (Ignatius Srianta et al., 2016). The most important of *Monascus* is its capability to degrade pigments from polyketide chromophore and β-keto acid by esterification (Silbir & Goksungur, 2019).

The pigments generated by *Monascus* are classified into six kinds of azaphilone pigments: rubropunctatin and monascorubrin (orange); ankaflavin and monascin (yellow); rubropunctamin and monascorubramin (purple-red) (Mapari et al., 2010; Nakbanpote, Woranan & Majeti, 2016).

Orange MP, including monascorubrin and rubropunctatin, are the ultimate color of *Monascus* fermentation. Orange MP is water-insoluble pigment that restrains the usage of orange MP as a food colorant. Moreover, red MP is also a type of limited water-insoluble. However, only the solid state of RMR can be used traditionally as a food colorant (Liu et al., 2018).

Factors influencing pigment production

a. ***Carbon***

The main carbon source throughout *Monascus* growth in rice is starch. Starch must be degraded to monosaccharide or disaccharide before microorganisms can apply it. At the first week of fermentation, a common carbon starvation stage appeared; the tricarboxylic acid cycle, amino acid synthesis, and fatty acid elongation, which contend with pigments synthesis for precursor, were all down-regulated. Otherwise, acetate synthesis and fatty acid breakage, which provide the acetyl-CoA pool, were upregulated. In this atmosphere, the strain intends to generate more yields, including variants of pigments. Pigment is significantly increased when rice is used as the major carbon source (Yang et al., 2015)

Supplementation of carbon source (sorbitol, fructose, sucrose, maltose) on substrates effectively increases MP production (Ignatius Srianta et al., 2012). Affiliation of glucose and sucrose significantly increased the spore and cell mass of *Monascus* (Ajdari et al., 2011).

b. *Nitrogen*

Nitrogen is an important nutrient in hyphae growth (Wen et al., 2020). The addition of several forms of nitrosourcesurce, such as monosodium glutamate, glutamic acid, peptone, chitin, and glycine by 1%, can enhance the production of pigments. Glutamic acid may stimulate the growth of the mycelium and showed to proliferate the permeability of the cell membranes (C. Zhang et al., 2019). Monosodium glutamate can postulate the uppermost growth in the production of red and yellow pigments (V. L. Da Silva et al., 2021; Ignatius Srianta et al., 2021).

The water solubility level of *Monascus* pigments can increase by supplementation of nitrogen. The oxygen atom in rubropunctatin and monascorubrin will be substituted by a nitrogen atom of an amino group, such as amino acid, protein, or peptide, signed by the color alteration from orange to purple-red (Kraboun et al., 2019).

c. *Mineral*

Pigment yield can also be increased by adding magnesium, zinc, phosphate, and potassium. *Monascus* pigment was produced during polyketides pathway and demands Acetyl CoA from the glucose pathway by pyruvate acid (Danuri, 2008)

Mg^{2+} and Zn^{2+} have the most abundant beneficial effect on MK output (Wen *et aI.*, 2020). Zinc might promote glucose intake, mycelial growth inhibitor, and trigger pigment production (Silbir & Goksungur, 2019). Supplementation of excessive zinc (>5%) can reduce the production of pigments (Zubaidah & Dewi, 2014).

d. *Temperature*

In microorganisms, the best temperature for the different enzymes was varied. In previous studies, researchers discovered that temperature has a significant influence on MK yield from *Monascus* (Wen et al., 2020). Optimal temperatures for various *Monascus* strains were at 25-37 ºC (Manan, 2017).

RMR pigments consist of several chromophores and double bonds. When these groups are exposed to higher temperatures, they will be defective because of the release of the functional groups that make up the chromophore groups. The pigment production would decrease at a temperature >150 ºC for 1-hour exposure (Tedjautama & Zubaidah, 2014).

e. *Aeration*

Monascus usually vary in its oxygen demand. The major usage of oxygen demand through the growth of aerobic mold was respiration. Oxygen is a final electron recipient for oxidative response to supply energy for cellular function (Manan, 2017).

Adequate aeration supplies optimal yield of pigments and slight citrinins production. Commonly, *Monascus* develop the optimal pigments in blackness (Nakbanpote, woranan and Majeti, 2016).

f. *Monacolin K (MK) syntesis*

RMR has become prevalent in alternative natural components for hypercholesterolemia because it contains monacoin K (lovastatin or natural statin) and is declared to have a specific advantage in relieving cholesterol in humans and animals (Kanpiengjai et al., 2018; Nannoni et al.). Besides *Monascus*, MK is also obtained from other fungi, such as *Penicillium, Gymnoascus, Trichoderma,* and *Pleorotus ostreatus* (Kraboun et al., 2019; B. B. Zhang et al., 2018).

MK requires it to be altered from lactone form (close loop) to *β-hydroxy acid* (open loop), which is active, bioavailable, and easier to absorb. The lactone of MK was more lipophilic than the hydroxy acid form. Open loop MK can bond with HMG CoA reductase to utilize as an inhibitor of HMG CoA reductase in the cholesterol metabolism pathway, thereby relieving cholesterol production (Banach et al., 2019; Chen et al., 2019).

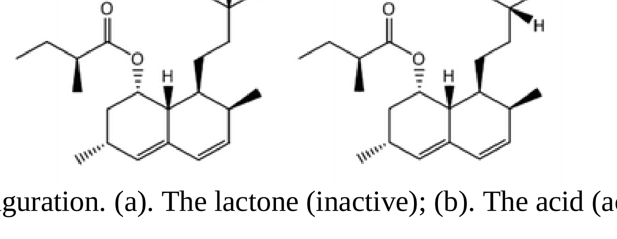

Figure 1. Monacolin K configuration. (a). The lactone (inactive); (b). The acid (active) (Song et al., 2019)

Table 1 informed that the major substrate which influenced the MK yield of *Monascus* fermentation was rice (Chen et al., 2019; Pengnoi et al., 2017; B. B. Zhang et al., 2018). White rice is a well-known substrate for *Monascus* because it is abundant in nutrients (such as carbohydrates, proteins, and minerals) (Subsaendee et al., 2014; Sun et al., 2015). Pengnoi *et al*. (2017) reported that the effect of the purple rice variety on MK yield influenced the MK production, showing that MK was produced at the highest level, 13,48 mg/kg, from Doi Muser variety.

Chen *et al*. (2019) reported, MK production from refined rice increased 2,7-fold compared to glutinous rice as substrate and produced 6.5-fold higher MK than commercial RMR "Gutian". However, glutinous rice is not suitable as a substrate because after being cooked, the texture is compelled into masses, and the deprived aeration permeability inhibits the mycelial growth of *Monascus*, in fact diminishing MK yield (Chen et al., 2019).

In addition, different substrate and strains have produced different amounts of MK yields. To establish novel substrate for MK production besides rice, scholars tend to observe numerous substrates for Monascus fermentation, such as corn, millet, wheat, barley, and brown seaweed (Kanpiengjai et al., 2018; Suraiya et al., 2018; B. B. Zhang et al., 2018). The crucial obstacle with non-pellet substrates is that the production of MK is too small and not sufficient for manufacturing purposes (B. B. Zhang et al., 2018)

Several papers have observed that supplementing carbon (sucrose, glycerol, lactose) and nitrogen (peptone, glutamic acid, sodium nitrate, ammonium sulfate, yeast extract) could extensively multiply MK production because nitrogen and carbon was crucial nutrient for the development of hyphae and thallus (Wen et al., 2020). Other studies show that supplementation of glucose and soluble starches for 3% (w/w) extensively enhanced MK production. In contrast, the supplementation of sucrose has no meaningful outcome on MK production. Soluble starch is pricier than glucose. Therefore glucose can be chosen as an alternative carbon source in concern of the production budget. The 4% (w/w) of nitrogen supplementation, such as sodium nitrate, ammonium sulfate, peptone, and yeast, can also multiply MK production (Chen et al., 2019).

During fermentation, *Monascus* can generate several enzymes which absorb the starchy substrate (such as amylase, protease, glucoamylase, maltase, and pectinase) (Kraboun et al., 2019). Starch can be converted to pyruvate acid by glycolysis. Pyruvate acid will be degraded to decarboxylase oxidation to produce acetyl-CoA and malonyl-CoA, which are responsible as precursors of pigment production and involved in MK production (Yang et al., 2015). Throughout several studies, MK yield was influenced by appropriate *Monascus* strain, substrate selection, and optimization of parameters in fermentation such as pH, temperature, aeration, nutrients, carbon and nitrogen supplementation, and inoculum dimension) (Mulder et al., 2015; Velmurugan et al., 2011; Wen et al., 2020)

Table 1. Monacolin K production in different substrates

Indicator	Strain	Optimal Parameter	Additional Nutrition	Monacolin K yield	References
MIllet	*M. ruber*	25 ^{0}C; 18 days	carbon and nitrogen source MK (19,81 mg/g) (Substrate: rice, millet, corn)	7,25 mg/g	(B. B. Zhang et al., 2018)
Purple rice (Doi muser)	*M. purpureus CMU002U* (UV mutant strain)	5 days at 30 ^{0}C, 30 days at 25 ^{0}C, pH 5		13,48 mg/kg	(Pengnoi et al., 2017)
Brown seaweed (*S. japonica*)	*M. purpureus KCCM 60168*	14, 49 days, 25,6 ^{0}C	glucose (1,32%)	13.40 mg /$g_{dfs}{}^{-1}$)	(Suraiya et al., 2018)
Glutinous rice	*M. purpureus* CMU002UXX-32-44 (X-Ray mutant strain)	14 hari, 30 ^{0}C	Mineral. carbon source	6,428 mg/g (5,1-fold increase in MK yield before X-ray exposure)	(Kanpiengjai et al., 2018)
Rice "1a825" Variety	*M. purpureus*	17 days, 30 ^{0}C, pH 5		4,64 mg/g	(Chen et al., 2019)

g. GABA (*γ-aminobutyric acid*)

GABA is a nonprotein type of amino acid which exists in the human brain, plants, animals, and vertebrates (Dikshit & Tallapragada, 2015). Generally, GABA is synthesized by glutamic acids. L-glutamic acid is developed by α-ketoglutarate in the tricarboxylic acid (TCA) cycle by glutamic acid dehydrogenase (GDH) (Sahab et al., 2020).

GABA was reported due to antihypertensive, antidiabetes, anticancer, antioxidant, and anti-inflammation functions. Furthermore, GABA was also described as a protector of the kidney, hepar, and intestines against contaminants, also a regulator of hormone production (Dikshit & Tallapragada, 2015; Ngo & Vo, 2019) (Rashmi et *al.,* 2 .018; Ngo dan Vo, 2019).

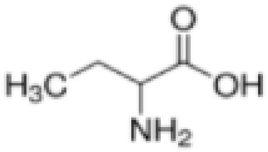

Figure 2. Chemical configuration of GABA (Pereira et al., 2021)

The total GABA production from several fermented foodstuff products is insignificant (Sahab et al., 2020). Table 2 shows that GABA yield quantity is influenced by several various substrates (Khan et al., 2019; Kusdiyantini et al., 2021; Wang et al., 2010). Rice is the best substrate for producing GABA compared to barley, cassava, oat, and sweet potato. Rice has proven to have the most excessive content of GABA, and this is expected because of the glutamic acid content inside rice which is a GABA precursor (Khan et al., 2015)

The optimal production of GABA, influenced by supplementation of nutrients, such as carbon (glucose, lactose), nitrogen (alanine), and inorganic salt ($ZnSO_4$), can produce a 25-fold GABA yield compared to the controlled substrate without having optimized nutrients (Fadillah et al., 2020; Khan et al., 2019). Alanine and malt extract were selected as the best nitrogen sources, with assist 18,64% and 16,41% for GABA yield. Lactose was observed as the best option for carbon source, assist 44,93% of GABA yield (Khan et al., 2015)

Fermentation parameters such as cultivation time, pH, and temperature are the foremost parameters for optimizing GABA production (Dikshit & Tallapragada, 2015). The GABA yield increased, with the culture time occurring about day 20, and gradually decreased afterwards (Fukami et al., 2021).

Furthermore, on the 14th day of culture, the highest average GABA was 6,1085 mg/ml, and the smallest on the 9th day was 3,7812 mg/ml (Fadillah et al., 2020). Previous studies showed that the highest GABA yield was above 88,21% when 3 mg/mL of RMR was conditioned at 80 ºC, pH 3,4, for 15 minutes. Moreover, above 70% of GABA production can be retrieved by constraining the heat exposure of RMR below 80 ºC (Khan et al., 2015).

Table 2. GABA production in different substrates

Strain Monascus	Optimal Parameter	Additional Nutrition	GABA	Note	References
M. purpureus MTCC 369	14 days**,** 30 ^{0}C	lactose 0,054 g/g, alanin 2 mg/g, malt extract 37,4 mg/g, $ZnSO^4$ 0,3 mg/g	24 mg/g	can produce a 25-fold GABA yield compared to a controlled substrate	(Khan et al., 2019)
M. purpureus NTU 803	Ethanol extract method (dried RMR extract in 95% ethanol) at 37 ^{0}C, 18 hours		16,01 mg/g	Total phenol: 58,13 mg/g; total flavonoid: 70,55 mg/g; monacolin K: 36,52 mg/g (dried extract).	(Wang et al., 2010)
M. purpureus	14 days**,** 28 ^{0}C		0,332 mg/mL	GABA in commercial RMR: 0,0203 mg/mL	(Kusdiyantini et al., 2021)
M. purpureus	14 days, pH 6	MSG 12,6; KCl 0,5; KH_2PO_4 2,4; K_2HPO_4 2,4; $FeSO_4$.$7H_2O$ 0,01	6,1085 mg/ml	Significant in incubation time	(Fadillah et al., 2020)

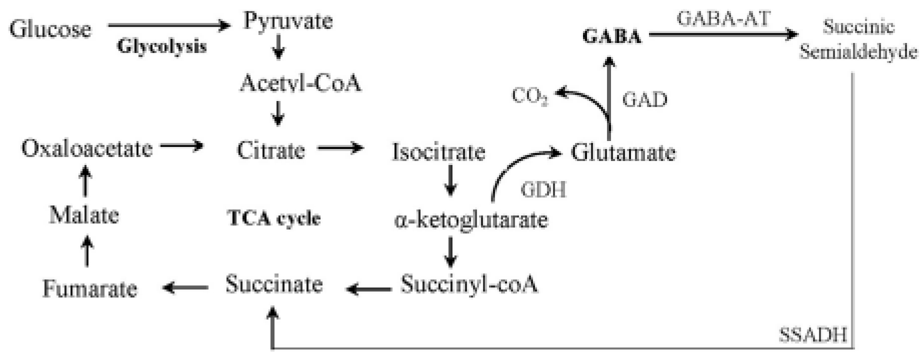

Figure 3. Pathway of GABA (Sahab et al., 2020)

As shown in figure 3, glucose metabolism in microorganisms creates some metabolites; one of them is GABA. In glycolysis, glucose is transformed into pyruvate. Subsequently, pyruvate is transferred into acetyl-CoA, which bonds with oxaloacetate and passes into the developing TCA cycle. Citrate is transferred into isocitrate and α-ketoglutarate, then by some microorganisms changed to GABA via glutamic acid dehydrogenase (GDH) and glutamate decarboxylase (GAD) (Sahab et al. 2020). The decrease in GABA yield might be due to the transformation of GABA to succinic acids by GABA transaminase and succinic semialdehyde dehydrogenase separately (Long et al., 2016).

RMR for hypercholesterolemia and hypertension

Cholesterol is the main element in the cell membrane, which regulates their permeability and stability; used as a precursor for sex hormones (testosterone and estrogen), for producing bile acids, and to produce vitamin D (Kapourchali et al., 2016). Lipids are fatty substances; to dissolve in the blood, lipid molecules must be attached to protein molecules known as apolipoproteins (apo). From total cholesterol, LDLC distributes 60-70% apolipoprotein, known as ApoB100. ApoB100 is distinctive since the hefty size and sensible hydrophobicity, and capability to transform among lipoproteins (Behbodikhah et al., 2021). LDL Cholesterol (LDLC) is an atherogenic lipoprotein and has become the main target for the management of dyslipidemia (PERKENI, 2019).

Reactive oxygen inactivates NO (nitrite Oxide) and, at the same time,e harms vascular endothelial cells and decreases NO production. Plasma LDL suppresses NOS (Nitric Oxide Synthase) activity in vascular endothelial cells by hydroxyl radicals, thereby reducing NO production and promoting arteriosclerosis. Several studies have shown that the decrease NO in production can cause vasomotor dysfunction, induce apoptosis, and reorganize the cellular matrix, which could interfere with vasorelaxation, initiate vasoconstriction and afterwards create hypertension (Fukami et al., 2021).

RMR contains an importance active substance, Monacolin K (MK), which inhibits cholesterol synthesis by aggressively restraining the action of the speed-regulating enzyme in cholesterol uptake, 3hydroxy-3methylglutaryl co-enzymeA (CoA) reductase, which can reduce Low-Density Lipoprotein Cholesterol (LDLC) quantity inside the blood (Wen et al., 2020). MK inhibits the oxidation of LDL and improves vascular endothelial function (vasoconstrictor reaction). Furthermore, RMR also produces GABA. GABA is known to have a blood pressure-regulating effect, antioxidant, and anti-inflammation effect (Fukami et al., 2021).

The pathophysiology of hypertension is correlated with sympathetic overactivity, angiotensin transformation, endothelial cell deprivation, insulin resistance, vascular remodelling, and ion channel deterioration (Hu et al., 2020). GABA inhibits sympathetic nerve activity, raises sodium levels in urine, and decreased blood pressure (Nishimura et al., 2016).

Increased levels of total cholesterol (TC) and low-density lipoprotein (LDL) are correlated with a more significant possibility of coronary heart disease (CHD) (Colantonio et al., 2016). Monacolin K (MK) and statin (synthetic hypercholesterolemia-lower drug) have a similar structure, however dissimilar in pharmacokinetic profile and bioavailability (Cicero et al., 2019).

Table 3 shows that statin and RMR have similar pleiotropic effects (Cicero & Colletti, 2015; Fukami et al., 2021). Pleiotropic effects of the drug are unrelated actions from a drug that was specifically developed, but the case with HMGR (statin and RMR) has other beneficial effects such as anti-inflammation, anti-oxidant, anti-proliferate, anti-microbial (Murphy et al., 2020; Wei & Popovich, 2012). Analysis of the efficiency and security of RMR and simvastatin in the management of dyslipidemia (hence, only in Chinese populations) indicated that RMR and simvastatin have identical effects in diminishing TC, LDL, and TG and enhancing HDL. In addition, adverse events testified in the included tests were minor (Ong & Aziz, 2016).

RMR in XZK 1.2 or 2.4 g/day for three months is considered to have lowered 27% LDLC compared with placebo (Moriarty et al., 2014). RMR can reduce 10-15% apolipoprotein B, 5-10% TG, and enhanc HDLC by 5-10% (Bule et al., 2018; Cicero et al., 2021). In addition, RMR with Monacolin K at 3 mg/day shows compressing LDLC level (Banach et al., 2019). Hence, Table 3 shows that decreased level of LDLC and TC is associated with adverse events such as benign muscle pain, an increase ofinlood glucose, hepar dysfunction, and neuropathy (Ivanovic & Tadic, 2015). Moreover, it is reported that RMR had an identical lipid-reducing components to simvastatin and might stimulate lower fatigue side effects compared to simvastatin (Xue et al., 2017).

Table 3. Benefits and risks of statin and red mold rice effect

Function	Statin	References	Red Yeast Rice	References
Hypercholesterolemia	Pleiotropic effects	(Fukami et al., 2021)	Pleiotropic effects Lifestyle intervention	(Cicero et al., 2021; Cicero & Colletti, 2015)
	↓ TC, LDL (can cause muscle pain) vasodilation and endothelial improvement ↓ oxidation of LDLC (↑ Blood glucose) Stabilize atherosclerotic plaque (risk of neuropathy) ↑ NO, ↓ aldosteron (Risk of hepar disfunction) ↓ Vascular inflammation	(Ivanovic & Tadic, 2015; Wen et al., 2020)	↓ significant 27% LDLC	(Moriarty et al., 2014)
			↓ 10-15 % Apolipoprotein B ↓ TG 5-10%, ↑ HDL C (5-10%)	(Cicero et al., 2021)
			↓ intracellular ROS	(Bule et al., 2018)
Hypertension	↓ RAAS activity ↓ Angiotensin II synthesis, ↓ ATRs1 expression, ↓ aldosteron ↓ Stress oxidative, ↓ inflammation, ↓ artery blood pressure	(Drapala et al., 2014)	↓ inflammation, ↓ lipid peroxidation ↑ endothelial function (↓ adhesion of monocytes and endothelial cells) ↓ Artery rigidity, adjust systemic arterial compliance.	(Xiong et al., 2017)
Conclusion	↓ Significant: hypercholesterolemia, hypertension	(Ivanovic & Tadic, 2015; Murphy et al., 2020)	↓ significant: TC, LDLC. insignificant change in systolic, diastolic blood pressure, TG, HDLC RMR + statin: ↓ systolic blood pressure, mo serious adverse event	(Xiong et al., 2017)
	Long-term effect of statin: ↓ CoEnzym Q10	(Alves Peres et al., 2017)	Long-term effect of RMR: significant ↓ CHD mortality risk by 29,2%	(Cicero et al., 2021)
			Risk of citrinin residue	(Twarużek et al., 2021)

(↑): enhancement; (↓): reduction; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease;

GABA performs a vital part in blood vascular amelioration, for example, reducing large artery stiffness, inflammation, and lipid peroxidation (Xiong et al., 2017). GABA may induce increased sodium excretion in the kidney through urine (Nishimura et al., 2016). GABA was implied as an inflammation inhibitor through proinflammatory mediator reduction and improvement of inflammatory indication. The anti-inflammatory activity of GABA was through limiting the release of IL-1β, iNOS, and TNF-α (Ngo & Vo, 2019). In addition, GABA contributed to angiotensin I-converting enzyme (ACE) limiting action, which could alleviate hypertension (Li et al., 2011).

Small differences in LDLC, for 25-30 mg/dl (0,6-0,8 mmol/L), which hold over prolonged period (13-15 years), would expect CVD possibility reduction compared to 5-year medium-high intensity outcome (Cicero et al., 2021). RMR is considered able to decrease the prevalence of CHD mortality by 29.2%.

RMR was acceptable for lipid-lowering functional food, in fact, in patients intolerant to statin therapy. This achievement could be attained with the application of a healthy lifestyle, such as an unsaturated fat dietary habit and moderate to high-intensity of physical activity (Cicero et al., 2019). Finally, RMR is safe as long as it is prepared and used appropriately.

Potential toxicity

Throughout fermentation with *Monascus purpureus*, there was a vulnerability that hazardous mycotoxin could be produced from the process: citrinin (Cicero et al., 2021).

Citrinin is also delivered by numerous species of *Penicillium, Aspergillus*, and *Monascus*; this mycotoxin is nephrotoxic, hepatotoxic, and carcinogenic (Ostry et al., 2017; Tangni et al., 2021; Twarużek et al., 2021). Citrinin is an antibiotic that could protect against gram-positive bacteria; nonetheless, because of its hepatotoxic and nephrotoxic properties, it is forbidden to apply in medicine—previously, primarily named citrinin monascidinA (Pan & Hsu, 2014).

The European Food Safety Society in 2012 issued that the optimal dosage of citrinin that can be digested in individuals without suffering serious nephro injuriousness is 0.2 µg citrinin/kg body weight for each day. Inside RMR, Japan and China have regulated maximum thresholds of Citrinin were 200 and 50 µg/kg (Younes et al., 2018). Citrinin is concerned with heat and has minimal quantity in processed foods (L. J. G. Silva et al., 2021).

Table 4 shows different strains of *Monascus* influenced citrinin yield in RMR (Yuliana et al., 2019). In China, 12 commercial RMR products from 6 areas (powder and grain form), citrinin was spotted in 10 RMR brands (appearing in 83%), and the noxius concentration aligned from 0.14 to 44.24 mg/kg (Ji et al., 2015). Citrinin yield can be minimize or eliminate to enhance the quality of RMR. Numerous methods have been applied , involving purification of citrinin, gene manipulation, optimization of fermentation conditions, and application of nanoparticles in the RMR industry (Agboyibor et al., 2018; Kang et al., 2014).

Table 4. Citrinin in red mold rice products

Researched Material	Object	Yield	LOD	LOQ	Detected Citrinin	References
15 RMR products in the Poland market	capsules, tablet, *sachet*s	Monacolin K : 1,5%-4%	16 ng/g	26 ng/g	None above LOD	(Twarużek et al., 2021)
Citrinin with 1,2,10,20, 200 ppm variation	90 days at male wistar rats	100 mg/kg of body weight	-	-	Two ppm Citrinin in RMR be a safe concentration	(Lee et al., 2010)
12 RMR commercial brands	Powder and grain		1 µg/kg	3 µg/kg	in 10 RMR products, from 0.14 to 44.24 mg/kg.	(Ji et al., 2015)
RMR with 5 difference isolate *Monascus purpureus*	RMR 100-200 g		-	-	LipiF147: 3,59 ng/mL ITB: 70,48 ng/mL IPBB: 790,17 ng/ mL LipiF01: 0,85 ng/ mL IPBA: 369,97 ng/mL	(Yuliana et al., 2019)

Conclusion

Nowadays, RMR is prevalent as the most impressive natural relieving cholesterol level. Several parameters and variables are required to be optimized in the fermentation process, for example, pH, temperatures, inoculum dimension, fermentation period, and supplementary nutrition (nitrogen and carbon). The strain of *Monascus*, sufficient substrate, and optimization of parameters in the fermentation process are vital factors in the production of RMR secondary metabolites (Pigmen, monacolin K, GABA) and particularly in minimizing citrinin yield.

RMR reported it can relieve blood LDLC in patients with mild hypercholesterolemia and improve blood vascular function in patients with hypertension. The optimal dose of RMR also depends on the needs of each individual. Moreover, the safe dose which is issued is 3-10 mg/day with no citrinin content or with a minimum dose of citrinin of 0.2 g/kg body weight per day.

The effect of RMR on each individual can vary, influenced by the condition of the consumer (frail or healthy consumer), varieties of composition in each RMR product, and each individual lifestyle which is heterogeneous.

Declarations

Conflict of interests The authors declare no competing interests.

References

Agboyibor, C., Kong, W. B., Chen, D., Zhang, A. M., and Niu, S. Q. (2018) ‘Monascus pigments production, composition, bioactivity and its application: A review’, *Biocatalysis and Agricultural Biotechnology*, 16, pp. 433–447

Ajdari, Z., Ebrahimpour, A., Abdul Manan, M., Hamid, M., Mohamad, R., and Ariff, A. B. (2011) ‘Assessment of monacolin in the fermented products using Monascus purpureus FTC5391’, *Journal of Biomedicine and Biotechnology*, 2011, pp. 1-9

Alves Peres, H., Freitas Foss, M. C., and Leira Pereira, L. R. (2017) ‘The role of coenzyme Q10 supplementation with statin drug use and chronic diseases’, *Journal of Ancient Diseases & Preventive Remedies*, 5(2), pp. 5–7

Banach, M., Bruckert, E., Descamps, O. S., Ellegård, L., Ezhov, M., Föger, B., Fras, Z., Kovanen, P. T., Latkovskis, G., März, W., Panagiotakos, D. B., Paragh, G., Pella, D., Pirillo, A., Poli, A., Reiner, Ž., Silbernagel, G., Viigimaa, M., Vrablík, M., and Catapano, A. L. (2019) ‘The role of red yeast rice (RYR) supplementation in plasma cholesterol control: A review and expert opinion’, *Atherosclerosis Supplements*, *39*, pp. 1–8

Behbodikhah, J., Ahmed, S., Elyasi, A., Kasselman, L. J., De Leon, J., Glass, A. D., and Reiss, A. B. (2021) ‘Apolipoprotein b and cardiovascular disease: Biomarker and potential therapeutic target’, *Metabolites*, 11(10), pp. 690

Bule, M., Khan, F., & Niaz, K. (2018). Red Yeast Rice (Monascus purpureus). In *Nonvitamin and Nonmineral Nutritional Supplements*. Elsevier Inc

Chaudhary, V., Katyal, P., Poonia, A. K., Kaur, J., Puniya, A. K., and Panwar, H. (2021) ‘Natural pigment from Monascus: The production and therapeutic significance’, *Journal of Applied Microbiology*, *August*, pp. 1–21

Chen, Z., Zhu, Y., Cao, X., Wen, Q., Xiong, Z., Cheng, Z., Long, C., Lin, S., Huang, X., Liu, J., and Huang, Z. (2019) ‘Isolation, screening and fermentation optimization of monascus strains with high monacolin K yield and the cholesterol lowering effect of red yeast rice’, *International Journal of Agriculture and Biology*, 22(2), pp. 223–233

Childress, L., Gay, A., Zargar, A., & Ito, M. K. (2013) ‘Review of red yeast rice content and current food and drug administration oversight’, *Journal of Clinical Lipidology*, 7(2), pp. 117–122

Cicero, A. F. G., & Colletti, A. (2015). Combination Therapy In Dyslipidemia. *Combination Therapy In Dyslipidemia*, *January*

Cicero, A. F. G., Fogacci, F., and Banach, M. (2019) ‘Red yeast rice for hypercholesterolemia’, *Methodist DeBakey Cardiovascular Journal*, 15(3), pp. 192–199

Cicero, A. F. G., Fogacci, F., and Zambon, A. (2021) ‘Red yeast rice for hypercholesterolemia: JACC focus seminar’, *Journal of the American College of Cardiology*, 77(5), pp. 620–628

Colantonio, L. D., Bittner, V., Reynolds, K., Levitan, E. B., Rosenson, R. S., Banach, M., Kent, S. T., Derose, S. F., Zhou, H., Safford, M. M., and Muntner, P. (2016) ‘Association of serum lipids and coronary heart disease in contemporary observational studies’, *Circulation*, 133(3), pp. 256–264

Da Silva, V. L., Ienczak, J. L., and Moritz, D. (2021) ‘Agro-industrial residues for the production of red biopigment by Monascus ruber: Rice flour and sugarcane molasses’, *Brazilian Journal of*

Microbiology, 52(2), pp. 587–596

Danuri, H. (2008) ‘Optimizing angkak pigments and lovastatin production By *Monascus purpureus*’, *HAYATI Journal of Biosciences*, 15(2), pp. 61–66

Dikshit, R., and Tallapragada, P. (2015) ‘Screening and optimization of γ-aminobutyric acid production from *Monascus sanguineus* under solid-state fermentation’, *Frontiers in Life Science*, 8(2), pp. 172–181

Drapala, A., Sikora, M., and Ufnal, M. (2014) ‘Statins, the renin-angiotensin-aldosterone system and hypertension - A tale of another beneficial effect of statins’, *JRAAS - Journal of the Renin-Angiotensin-Aldosterone System*, 15(3), pp. 250–258

Egan, B. M., Li, J., Qanungo, S., and Wolfman, T. E. (2013) ‘Blood pressure and cholesterol control in hypertensive hypercholesterolemic patients: National health and nutrition examination surveys 1988-2010’, *Circulation*, 128(1), pp. 29–41

Fadillah, M. S., Kusdiyantini, E., and Wijanarka. (2020) ‘Produksi pigmen dan asam γ-Aminobutirat (GABA) oleh *Monascus purpureus*. *Saintek*, 25(1), pp. 72–83

Fatimah, S., Suprihadi, A., and Kusdiyantini, E. (2014) ‘Produksi dan kestabilan pigmen merah kapang *Monascus sp.* menggunakan media tepung kulit singkong dengan penambahan bekatul pada konsentrasi yang berbeda’, *Jurnal Biologi*, 3(3), pp. 49–59

Fukami, H., Higa, Y., Hisano, T., Asano, K., Hirata, T., and Nishibe, S. (2021) ‘A review of red yeast rice, a traditional fermented food in japan and east asia: Its characteristic ingredients and application in the maintenance and improvement of health in lipid metabolism and the circulatory system. *Molecules*, 26(6), pp.1-9

Grundy, S. M., Stone, N. J., Bailey, A. L., Beam, C., Birtcher, K. K., Blumenthal, R. S., Braun, L. T., de Ferranti, S., Faiella-Tommasino, J., Forman, D. E., Goldberg, R., Heidenreich, P. A., Hlatky, M. A., Jones, D. W., Lloyd-Jones, D., Lopez-Pajares, N., Ndumele, C. E., Orringer, C. E., Peralta, C. A., and Yeboah, J. (2019) ‘2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines’, *Journal of the American College of Cardiology*, 73(24), pp. 285–350

Hamdiyati, Y., Kusnadi, K., & Yuliani, L. A. (2016). ‘Effect of *Monascus purpureus* inoculum concentration on pigment production in jackfruit seed flour substrate’, *AIP Conference Proceedings*, 1708, pp. 1–6

Hong, S. Y., Oh, J. H., and Lee, I. (2011) ‘Simultaneous enrichment of deglycosylated ginsenosides and monacolin K in red ginseng by fermentation with monascus pilosus’, *Bioscience, Biotechnology and Biochemistry*, 75(8), pp. 1490–1495

Hu, J., Wang, J., Gan, Q. X., Ran, Q., Lou, G. H., Xiong, H. J., Peng, C. Y., Sun, J. L., Yao, R. C., and Huang, Q. W. (2020) ‘Impact of red yeast rice on metabolic diseases: A review of possible mechanisms of action’, *Journal of Agricultural and Food Chemistry*, 68(39), pp. 10441–10455

Husakova, M., Plechata, M., Branska, B., & Patakova, P. (2021) ‘Effect of a *Monascus sp.* red yeast rice extract on germination of bacterial spores’, *Frontiers in Microbiology*, 12(432), pp. 1–10

IHME. (2019). *The Lancet : Estimasi - estimasi penyakit global terbaru mengungkapkan badai “ sempurna ” dari penyakit - penyakit kronis yang timbul dan kegagalan kesehatan publik yang memperbesar intensitas pandemi COVID - 19*.

Ivanovic, B., and Tadic, M. (2015) ‘Hypercholesterolemia and hypertension: Two sides of the same coin’, *American Journal of Cardiovascular Drugs*, 15(6), pp. 403–414

Ji, X., Xu, J., Wang, X., Qi, P., Wei, W., Chen, X., Li, R., and Zhou, Y. (2015) ‘Citrinin determination in red fermented rice products by optimized extraction method coupled to liquid chromatography tandem mass spectrometry (LC-MS/MS)’, *Journal of Food Science*, 80(6), pp. 438–444

Kang, B., Zhang, X., Wu, Z., Wang, Z., and Park, S. (2014) ‘Production of citrinin-free Monascus pigments by submerged culture at low pH’, *Enzyme and Microbial Technology*, *55*, pp. 50–57

Kanpiengjai, A., Mahawan, R., Pengnoi, P., Lumyong, S., and Khanongnuch, C. (2018) ‘Improving the monacolin K to citrinin production ratio in red yeast rice by an X-ray-induced mutant strain of Monascus purpureus’, *Biotechnologia*, 99(2), pp. 109–118

Kapourchali, F. R., Surendiran, G., Goulet, A., and Moghadasian, M. H. (2016) ‘The role of dietary cholesterol in lipoprotein metabolism and related metabolic abnormalities: A Mini-review’, *Critical Reviews in Food Science and Nutrition*, 56(14), pp. 2408–2415

Khan, W., Bhatt, P. C., and Panda, B. P. (2015) ‘Degradation kinetics of gamma amino butyric acid in monascus-fermented rice’, *Journal of Food Quality*, 38(2), pp. 123–129

Khan, W., Regmi, O., Hasan, M., and Panda, B. P. (2019) ‘Response surface modeling for the enrichment of gamma-aminobutyric acid with a minimum content of citrinin in monascus - fermented rice’, *EFood*, 1(2), pp. 181

Kraboun, K., Kongbangkerd, T., Rojsuntornkitti, K., and Phanumong, P. (2019) ‘Factors and advances on fermentation of Monascus sp. for pigments and monacolin K production: A review’, *International Food Research Journal*, 26(3), pp. 751–761.

Kusdiyantini, E., Nurhayati, and Ferniah, R. S. (2021) ‘Production of γ- Aminobutyric Acid (GABA) by Monascus Purpureus isolated from Angkak, a mold isolated from Angkak in Semarang, Indonesia', *Journal of Physics: Conference Series*, 1943(1), pp. 1-10

Lee, C. H., Lee, C. L., and Pan, T. M. (2010) 'A 90-D Toxicity study of monascus-fermented products including high citrinin level', *Journal of Food Science*, 75(5). pp. 1-15

Li, X. M., Shen, X. H., Duan, Z. W., and Guo, S. R. (2011) 'Advances on the pharmacological effects of red yeast rice', *Chinese Journal of Natural Medicines*, 9(3), pp. 161–166

Lin, C., Hur, H., and Lin, C. (2019) 'Antioxidant properties and antibacterial activity of fermented Monascus purpureus extracts', *MOJ Food Processing & Technology*, 7(2), pp. 49–54

Liu, L., Zhao, J., Huang, Y., Xin, Q., & Wang, Z. (2018) 'Diversifying of chemical structure of native Monascus pigments', *Frontiers in Microbiology*, 9(December), pp. 1–13

Long, K., Danial, A., and Peng, K. (2016) 'Enrichment of Mung Bean with L-DOPA, GABA, essential amino acids via controlled biofermentation strategy', *International Journal of Biotechnology for Wellness Industries*, *4*(4), pp. 114–122

Manan, M. A. (2017) 'Monascus spp.: A source of Natural Microbial Color through Fungal Biofermentation', *Journal of Microbiology & Experimentation*, 5(3), pp. 1-9

Mapari, S. A. S., Thrane, U., and Meyer, A. S. (2010) 'Fungal polyketide azaphilone pigments as future natural food colorants?', *Trends in Biotechnology*, *28*(6), pp. 300–307

Moriarty, P. M., Roth, E. M., Karns, A., Ye, P., Zhao, S. P., Liao, Y., Capuzzi, D. M., Bays, H. E., Zhang, F., Liu, S., Reichman, A. J., Brusco, O. A., Lu, G., Lerman, S., Duan, Z., Guo, S., Liu, P. L., Zhao, J., Zhang, Y., and Li, S. (2014) 'Effects of Xuezhikang in patients with dyslipidemia: A multicenter, randomized, placebo-controlled study', *Journal of Clinical Lipidology*, 8(6), 568–575

Mostafa, M. E., and Saad Abbady, M. (2014) 'Secondary metabolites and bioactivity of the monascus pigments review article', *Global Journal of Biotechnology & Biochemistry*, 9(1), pp. 1–13

Mulder, K. C. L., Mulinari, F., Franco, O. L., Soares, M. S. F., Magalhães, B. S., and Parachin, N. S. (2015) 'Lovastatin production: From molecular basis to industrial process optimization', *Biotechnology Advances*, 33(6), pp. 648–665

Murphy, C., Deplazes, E., Cranfield, C. G., and Garcia, A. (2020) 'The role of structure and biophysical properties in the pleiotropic effects of statins', *International Journal of Molecular Sciences*, 21(22), pp. 1–29

Musselman, M. E., Pettit, R. S., and Derenski, K. L. (2012) 'A review and update of red yeast rice', *Journal of Evidence-Based Complementary and Alternative Medicine*, 17(1), pp. 33–39

Nakbanpote, woranan and Majeti, P. (2016). *Increasing the Value of Rice by Transformation into Red Yeast Rice Increasing the Value of Rice by Transformation into Red Yeast Rice*. *May 2015*.

Nannoni, G., Alì, A., and Di Pierro, F. (2015) 'Development of a new highly standardized and granulated extract from Monascus purpureus with a high content of monacolin K and KA and free of inactive secondary monacolins and citrinin', *Nutrafoods*, 14(4), pp. 197–205

Nantsupawat, N., Booncharoen, A., Wisetborisut, A., Jiraporncharoen, W., Pinyopornpanish, K., Chutarattanakul, L., and Angkurawaranon, C. (2019) 'Appropriate total cholesterol cut-offs for detection of abnormal LDL cholesterol and non-HDL cholesterol among low cardiovascular risk population', *Lipids in Health and Disease*, 18(1), pp. 1–8

Ngo, D. H., and Vo, T. S. (2019) 'An updated review on pharmaceutical properties of gamma-aminobutyric acid', *Molecules*, 24(15), pp. 2678

Nishimura, M., Yoshida, S. I., Haramoto, M., Mizuno, H., Fukuda, T., Kagami-Katsuyama, H., Tanaka, A., Ohkawara, T., Sato, Y., and Nishihira, J. (2016). Effects of white rice containing enriched gamma-aminobutyric acid on blood pressure. *Journal of Traditional and Complementary Medicine*, 6(1), pp. 66–71

Ong, Y. C., and Aziz, Z. (2016) 'Systematic review of red yeast rice compared with simvastatin in dyslipidaemia', *Journal of Clinical Pharmacy and Therapeutics*, *41*(2), pp. 170–179

Ostry, V., Malir, F., Toman, J., and Grosse, Y. (2017) 'Mycotoxins as human carcinogens—the IARC Monographs classification', *Mycotoxin Research*, *33*(1), pp. 65–73

Pan, T. M., and Hsu, W. H. (2014) 'Monascus-fermented products. In *Encyclopedia of Food Microbiology: Second Edition* (Second Edi, Vol. 2, Issue i). Elsevier

Patel, S. (2016) 'Functional food red yeast rice (RYR) for metabolic syndrome amelioration: a review on pros and cons', *World Journal of Microbiology and Biotechnology*, 32(5), pp. 1-9

Pengnoi, P., Mahawan, R., Khanongnuch, C., and Lumyong, S. (2017) 'Antioxidant properties and production of monacolin K, citrinin, and red pigments during solid state fermentation of purple rice (*Oryzae sativa*) varieties by Monascus purpureus', *Czech Journal of Food Sciences*, *35*(1), pp. 32–39

Pereira, C., Lourenço, V. M., Menezes, R., and Brites, C. (2021) 'Rice compounds with impact on diabetic control', *Foods*, 10(9), pp. 1–18

PERKENI. (2019) *Pedoman Pengelolaan Dislipidemi di Indonesia 2019* (*Guidelines for the Management of Dyslipidemia in Indonesia 2019)* PB. Perkeni, 9 [In Indonesian]

Raja Rajeswari, T., Ponnusami, V., & Sugumaran, K. R. (2014) 'Production of Monascus pigment in low cost fermentation', *International Journal of ChemTech Research*, *6*(5), pp. 2929–2932

Sahab, N. R. M., Subroto, E., Balia, R. L., & Utama, G. L. (2020) ‘γ-Aminobutyric acid found in fermented foods and beverages: current trends’, *Heliyon*, 6(11), pp. e05526

Saithong, P., Chitisankul, W. T., and Nitipan, S. (2019) ‘Comparative study of red yeast rice with high monacolin K, low citrinin concentration and pigments in white rice and brown rice’, *Czech Journal of Food Sciences*, 37(1), pp. 75–80

Silbir, S., and Goksungur, Y. (2019) ‘Natural red pigment production by monascus purpureus in submerged fermentation systems using a food industry waste: Brewer’s spent grain’, *Foods*, *8*(5). pp. 11-20

Silva, L. J. G., Pereira, A. M. P. T., Pena, A., and Lino, C. M. (2021) ‘Citrinin in foods and supplements: A review of occurrence and analytical methodologies’, *Foods*, 10(1), pp. 1-7

Song, J., Luo, J., Ma, Z., Sun, Q., Wu, C., and Li, X. (2019) ‘Quality and authenticity control of functional red yeast rice—a review’, *Molecules*, 24(10), pp. 1944

Srianta, I., and Harijono. (2015) ‘Monascus-fermented sorghum: Pigments and monacolin K produced by Monascus purpureus on whole grain, dehulled grain and bran substrates’, *International Food Research Journal*, 22(1), pp. 377–382

Srianta, I., Ristiarini, S., and Nugerahani, I. (2020) ‘Pigments extraction from monascus-fermented durian seed’, *IOP Conference Series: Earth and Environmental Science*, 443(1), pp. 1-7

Srianta, Ignatius, Kusdiyantini, E., Zubaidah, E., Ristiarini, S., Nugerahani, I., Alvin, A., Iswanto, N., and Zhang, B. B. (2021) ‘Utilization of agro-industrial by-products in Monascus fermentation: A review’, *Bioresources and Bioprocessing*, 8(1), pp. 1-9

Srianta, Ignatius, Novita, Y., and Kusumawati, N. (2012) ‘Production of monascus pigments on durian seed: Effect of supplementation of carbon source’, *Journal of Pure and Applied Microbiology*, 6(1), pp. 59–63

Srianta, Ignatius, Zubaidah, E., Estiasih, T., Yamada, M., and Harijono. (2016) ‘Comparison of Monascus purpureus growth, pigment production and composition on different cereal substrates with solid state fermentation’, *Biocatalysis and Agricultural Biotechnology*, 7, pp. 181–186

Subsaendee, T., Kitpreechavanich, V., and Yongsmith, B. (2014) ‘Growth, glucoamylase, pigments and monacolin K production on rice solid culture in flask and koji chamber using monascus sp. KB9’, *Chiang Mai Journal of Science*, 41(5–1), pp. 1044–1057

Sun, H., Wu, Y., Wang, X., Liu, Y., Yao, X., and Tang, J. (2015) ‘Effects of dietary supplementation with red yeast rice on laying performance, egg quality and serum traits of laying hens’, *Italian Journal of Animal Science*, 14(3), pp. 532–537

Suraiya, S., Kim, J. H., Tak, J. Y., Siddique, M. P., Young, C. J., Kim, J. K., and Kong, I. S. (2018) ‘Influences of fermentation parameters on lovastatin production by Monascus purpureus using Saccharina japonica as solid fermented substrate’, *LWT - Food Science and Technology*, 92, pp. 1–9

Tangni, E. K., Van Hove, F., Huybrechts, B., Masquelier, J., Vandermeiren, K., and Van Hoeck, E. (2021) ‘Citrinin determination in food and food supplements by LC-MS/MS: Development and use of reference materials in an international collaborative study’, *Toxins*, 13(4), pp. 1–14

Tedjautama, E., and Zubaidah, E. (2014) ‘Peningkatan Produksi Pigmen Merah Angkak Tinggi Lovastatin menggunakan ko-kultur *Monascus purpureus* dan *Saccharomyces cerevisiae*’, *Jurnal Pangan dan Agroindustri*, 2(4), pp . 78-88

Twarużek, M., Ałtyn, I., and Kosicki, R. (2021) ‘Dietary supplements based on red yeast rice—a source of citrinin?’, *Toxins*, 13(7), pp. 1-7

Velmurugan, P., Hur, H., Balachandar, V., Kamala-Kannan, S., Lee, K. J., Lee, S. M., Chae, J. C., Shea, P. J., and Oh, B. T. (2011) ‘Monascus pigment production by solid-state fermentation with corn cob substrate’, *Journal of Bioscience and Bioengineering*, 112(6), pp. 590–594

Voidarou, C., Antoniadou, M., Rozos, G., Tzora, A., Skoufos, I., Varzakas, T., Lagiou, A., and Bezirtzoglou, E. (2021) ‘Fermentative foods: Microbiology, biochemistry, potential human health benefits and public health issues’, *Foods*, 10(1), pp. 1–27

Vourakis, M., Mayer, G., and Rousseau, G. (2021) ‘The role of gut microbiota on cholesterol metabolism in atherosclerosis’, *International Journal of Molecular Sciences*, 22(15), pp. 8074

Wang, J. J., Wang, H. Y., and Shih, C. D. (2010) ‘Autonomie nervous system and nitric oxide in antihypertensive and cardiac inhibitory effects induced by red mold rice in spontaneously hypertensive rats’, *Journal of Agricultural and Food Chemistry*, 58(13), pp. 7940–7948

Wei, Y., and Popovich, D. G. (2012) ‘Pleiotropic effects of red yeast rice (Monascus Purpureus)’, *Bioactive Compounds: Types, Biological Activities and Health Effects*, 1, pp. 307–318

Wen, Q., Cao, X., Chen, Z., Xiong, Z., Liu, J., Cheng, Z., Zheng, Z., Long, C., Zheng, B., and Huang, Z. (2020) ‘An overview of Monascus fermentation processes for monacolin K production’, *Open Chemistry*, 18(1), pp. 10–21

Xiong, X., Wang, P., Li, X., Zhang, Y., & Li, S. (2017) ‘The effects of red yeast rice dietary supplement on blood pressure, lipid profile, and C-reactive protein in hypertension: A systematic review’, *Critical Reviews in Food Science and Nutrition*, 57(9), pp. 1831–1851

Xue, Y., Tao, L., Wu, S., Wang, G., Qian, L., Li, J., Liao, L., Tang, J., and Ji, K. (2017) ‘Red yeast rice induces less muscle fatigue symptom than simvastatin in dyslipidemic patients: A single center randomized pilot trial', *BMC Cardiovascular Disorders*, 17(1), pp. 1–7

Yang, Y., Liu, B., Du, X., Li, P., Liang, B., Cheng, X., Du, L., Huang, D., Wang, L., and Wang, S. (2015) 'Complete genome sequence and transcriptomics analyses reveal pigment biosynthesis and regulatory mechanisms in an industrial strain, Monascus purpureus YY-1', *Scientific Reports*, *5*, pp. 8331

Yanli, F., and Xiang, Y. (2020) 'Perspectives on functional red mold rice: functional ingredients, production, and application', *Frontiers in Microbiology*, 11, pp. 1–10

Younes, M., Aggett, P., Aguilar, F., Crebelli, R., Dusemund, B., Filipič, M., Frutos, M. J., Galtier, P., Gott, D., Gundert-Remy, U., Kuhnle, G. G., Lambré, C., Leblanc, J. C., Lillegaard, I. T., Moldeus, P., Mortensen, A., Oskarsson, A., Stankovic, I., Waalkens-Berendsen, I., and Wright, M. (2018) 'Scientific opinion on the safety of monacolins in red yeast rice', *EFSA Journal*, 16(8), pp. 1-7

Yu, L. J., Zhang, H. X., Xie, Y. H., Ma, S. M., Liu, H., and Luo, Y. B. (2013) 'Optimization of fermentation conditions for higher monacolin K production by monascus purpureus', *Advanced Materials Research*, 781–784, pp. 1397–1402

Yuliana, A., Rahmiyani, I., Amin, S., Fathurohman, M., and Meri. (2019) 'Isolation and determination antibacterial citrinin from various fungal monascus purpureus using rice as a fermentation substrate', *Journal of Physics: Conference Series*, 1179(1), pp. 1-8

Zhang, B. B., Xing, H. B., Jiang, B. J., Chen, L., Xu, G. R., Jiang, Y., and Zhang, D. Y. (2018) 'Using millet as substrate for efficient production of monacolin K by solid-state fermentation of Monascus ruber'. *Journal of Bioscience and Bioengineering*, 125(3), pp. 333–338

Zhang, C., Chai, S., Hao, S., Zhang, A., Zhu, Q., Zhang, H., and Wang, C. (2019) 'Effects of glutamic acid on the production of monacolin K in four high-yield monacolin K strains in Monascus', *Applied Microbiology and Biotechnology*, 103(13), pp. 5301–5310

Zhu, B., Qi, F., Wu, J., Yin, G., Hua, J., Zhang, Q., and Qin, L. (2019) 'Red yeast rice: A systematic review of the traditional uses, chemistry, pharmacology, and quality control of an important Chinese folk medicine', *Frontiers in Pharmacology*, 10(12), pp. 1-7

Zubaidah, E., and Dewi, A. P. (2014) 'Effect addition of rice bran on fermentation process to increasing lovastatin and intensity of red pigment Angkak', *Advance Journal of Food Science and Technology*, 6(1), pp. 56–59

Zubaidah, E., Nadzira, and Sriherfyna, F. H. (2015) 'Formulasi laru angkak (pengaruh jenis bahan pengisi terhadap viabilitas monascus purpureus dan kadar lovastatin angkak hasil fermentasi (Formulation of laru angkak (effect of filler type on viability of monascus purpureus and levels of fermented lovastatin angkak)', *Jurnal Teknologi Pertanian*, 16(2), pp. 107–116