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

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**KEYWORDS**

GABA
Hypercholesterolemia
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**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

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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).

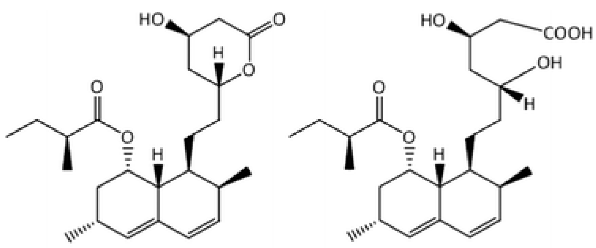


**Figure 1.** Monacolin K configuration. (a). The lactone (inactive); (b). The acid (active) (Song et al., 2019)

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).

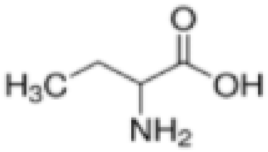


**Figure 2.** Chemical configuration of GABA (Pereira et al., 2021)

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 9$^{th}$ 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; $FeSO_4$ .7$H_2O$ 0,01 | 6,1085 mg/ml | Significant in incubation time | (Fadillah et al., 2020) |

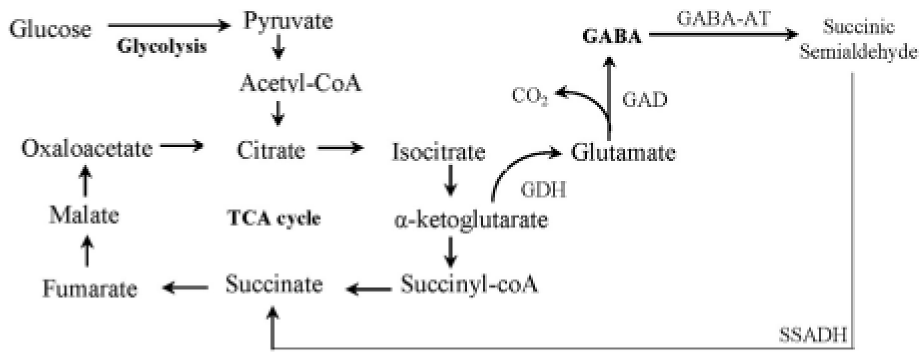


**Figure 3.** Pathway of GABA (Sahab et al., 2020)

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<br>Lifestyle intervention | (Cicero et al., 2021; Cicero & Colletti, 2015) |
| | ↓ TC, LDL (can cause muscle pain)<br>vasodilation and endothelial improvement<br>↓ oxidation of LDLC (↑ Blood glucose)<br>Stabilize atherosclerotic plaque (risk of neuropathy)<br>↑ NO, ↓ aldosteron (Risk of hepar disfunction)<br>↓ Vascular inflammation | (Ivanovic & Tadic, 2015; Wen et al., 2020) | ↓ significant 27% LDLC | (Moriarty et al., 2014) |
| | | | ↓ 10-15 % Apolipoprotein B<br>↓ TG 5-10%,<br>↑ HDL C (5-10%) | (Cicero et al., 2021) |
| | | | ↓ intracellular ROS | (Bule et al., 2018) |
| Hypertension | ↓ RAAS activity<br>↓ Angiotensin II synthesis, ↓ ATRs1 expression, ↓ aldosteron<br>↓ Stress oxidative, ↓ inflammation, ↓ artery blood pressure | (Drapala et al., 2014) | ↓ inflammation, ↓ lipid peroxidation<br>↑ endothelial function (↓ adhesion of monocytes and endothelial cells)<br>↓ Artery rigidity, adjust systemic arterial compliance. | (Xiong et al., 2017) |
| Conclusion | ↓ Significant: hypercholesterolemia, hypertension | (Ivanovic & Tadic, 2015; Murphy et al., 2020) | ↓ significant: TC, LDLC.<br>insignificant change in systolic, diastolic blood pressure, TG, HDLC<br>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<br>ITB: 70,48 ng/mL<br>IPBB: 790,17 ng/ mL<br>LipiF01: 0,85 ng/ mL<br>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.



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