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Chapter VIII

Pleiotropic Effects of Red Yeast Rice (*Monascus Purpureus*)

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Abstract

Red yeast rice (*Monascus purpureus* fermented rice) has traditionally been used as a natural food colorant and food preservative of meat and fish for centuries in Asia. It has become a popular dietary supplement due to monacolins, some of which can lower serum cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA). Monacolin K, the major monacolin found in red yeast rice is structurally identical to lovastatin; however monacolin K possess other pleiotropic effects which include and ability to induce cell apoptosis and decrease cellular triglyceride, cholesterol, and free fatty acid production by down-regulation of fatty acid synthase that is linked to decreased Akt activation and relation of peroxisome proliferator-activated receptor (PPAR)-γ. Beyond the effect of monacolin K on cholesterol metabolism, red yeast rice has anti-oxidant and anti-inflammatory properties that may convey additional bioactive effects. Red yeast rice extracts were shown to inhibit proliferation and induce apoptosis in various cancer cells. Pigments extracted from red yeast rice have also been shown to possess potential chemo-preventative properties. The red pigments rubropunctamine and monascorubramine displayed strong cytotoxicity. The dehydrogenated derivatives of the red rice pigments rubropunctamine and monascorubramine also have been reported to have cytotoxic properties. Ankaflavin, a yellow pigment from red yeast rice exhibited antitumor-initiating effects on cancer progression. This review will focus on reviewing the potential structure function effects of red yeast rice extracts in cancer cell models as well as detailing the chemical structures of the potential bioactive components.

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Keywords: *Monascus purpureus;* red yeast rice; rubropunctamine; monascorubramine; ankaflavin.

Red yeast rice (RYR) is produced by fermenting polished round-grained rice with a mold (*Monascus purpureus)* which produces a bright reddish purple color on the surface rice. Several synonyms are used for RYR, including Hong Qu, Hon-Chi, Anka or Ang-kak in China, Koji, Beni Koji or red Koji in Japan, red fermented rice, red mold rice or red Chinese rice in the United States and Europe. RYR has traditionally been used as a natural food colorant and food preservative of meat and fish for over 1000 years in China, and it has also been used in traditional Chinese medicine [1-3]. In addition to use as a food colorant, food preservative and medicine, RYR has been used for brewing red rice wine [4, 5] (Hong Qu Jiu in Chinese) in many Asian countries such as China, Japan, Philippines and Indonesia. It has also been widely used in the fermentation of industry for production of sufu (fermented bean curd, Dou Fu Ru in Chinese), fish sauce, fish paste, and red soybean curd.

Biological Active Components in RYR

Interest into RYR has grown in recent years in part due to a class of phytochemicals known as monacolins, some of which can lower serum cholesterol levels by inhibiting HMG-CoA reductase, the key enzyme responsible for cholesterol synthesis in liver [6, 7]. Monacolin K, the major monacolin found in RYR, is also known as mevinolin and lovastatin, was first isolated from *Monascus ruber* in 1979 [8] and *Aspergillus terreus* in 1980 [9]. RYR has been reported to decrease total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein (LDL) cholesterol levels, TC/high-density lipoprotein (HDL) cholesterol, LDL cholesterol/HDL cholesterol and apolipoprotein B/apolipoprotein A-I ratios [6, 10-17] without increasing creatine phosphokinase (CPK) or pain levels [18]. Even though the RYR contains a statin, RYR seems to be better tolerated by dyslipidemia patients who cannot tolerate the pharmaceutical therapy [18-23].

Besides being a HMG-CoA reductase inhibitor, RYR also has other pleiotropic effects which include being an antioxidant [24], anti-inflammatory [25], anti-hypertensive [26], anti-hyperglycemic activity [12], anti-proliferative activity [25, 27, 28], suppresses adipogenesis [29], antimicrobial activity [30] and anti-diabetic activity [24, 31]. A majority of these reported effects are due to structural related class of compounds known as monacolins or the pigments that were created during the fermentation.

Monacolins

The main biologically active components of RYR contributing to the pharmacology effects involve monacolin-type compounds [1, 8, 32]. Monacolin K (also referred to as Mevastatin, 6-demethylmevinolin, ML 236B, CS500) was the first to be isolated followed by a series of additional monacolin compounds which are structurally similar. Monacolin J and monacolin L [33], dehydromonacolin L and monacolin X [34] and monacolin M have been

characterized [35]. There are at least total 17 monacolins and their derivatives which have been isolated and purified from RYR (Figure 1). Monacolin L, J, X, M can inhibit HMG-CoA reductase mainly due to their structural similarities to monacolin K [33-36] but their relative affinity is not yet known. Monacolin K, L, J, X, M are found in their lactone form while adding 0.1 M NaOH in RYR solution transforms these monacolins from the lactone from to the corresponding hydroxy acid active form [37, 38] (Figure 2). Monacolin K and monacolin K hydroxy acid are the two main components which contributed up to 90% of the total quantity of monacolins in the RYR [39]. The monacolins in lactone forms such as Monacolin K, L, J, X, M have been structurally characterized. Contrarily, the monacolins in hydroxy acid forms are not well studied and detailed structural data is lacking which is likely hampered by the structural instability of these molecules [39]. For example, 3α-Hydroxy-3,5-dihydromonacolin L was reported to be very unstable and converted quantitatively to monacolin L when kept at pH 2 and 25°C for 10 hours [40].

Monacolins Bioactivity

RYR possesses anti-oxidant and anti-inflammatory properties [41, 42] and extracts were shown to inhibit the proliferation and induce apoptosis in various cancer cells including liver cancer cells [14], promyelocytic leukemic cells [14], lung cancer [43], colorectal cancer [2, 27, 44], prostate cancer [45]. Several reports on bioactivities of RYR have been attributed to the monacolins which are present in crude alcoholic extracts derived from RYR dry powder. Crude extracts from RYR are typically complex mixtures, with monacolin K usually present. Many studies have shown that mixtures of monacolins have measurable bioactivity in cell culture experiments. Specifically, monacolin K possesses an ability to induce cell apoptosis and decrease cellular triglyceride, cholesterol [6], and free fatty acid production by down-regulation of fatty acid synthase [46]. This down-regulation is linked to decreased Akt activation [14], down-regulating CCAAT/enhancer-binding protein (C/EBP) α [46] which is the key adipogenic transcription factor, up-regulating the transcription levels of PPAR-γ. Monacolin K also has been found to inhibit sterol response element binding protein-1(SREBP-1) and SREBP-2 mRNA expression, SREBP-1 and SREBP-2 [14, 27, 45]. Other monacolins in RYR may also have similar bioactivities to monacolin K as they are structural analogs of monacolin K [27]. However, these are not well characterized at present.

Recent studies have shown that RYR crude extract can inhibit cell proliferation and induce apoptosis in a variety of tumor cells [14]. However, the mechanism(s) responsible for monacolin K anti-proliferation and apoptosis induction is still not clear. Hepatocarcinoma cells (HepG2) were subcultured to 80% confluence and with supplemented media to induce cholesterologenesis and treated with monacolin K showed an up-regulation of PPAR-γ and inhibition of SREBP-1 mRNA expression. Suppression of fatty acid synthase (FAS) was detected in a concentration dependent manner after 24 h treatment. In HL-60 (human promyelocytic leukemic) cells treated with monacolin K (50 μM) showed five folds increase in sub-G1cells compared to untreated control [14]. Sub-G1 cell accumulation is indicative of apoptosis.

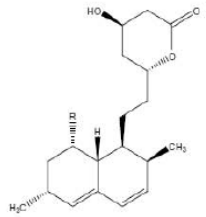
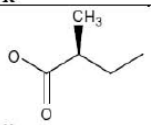
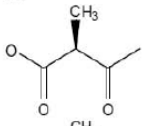
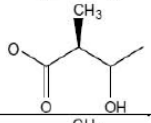
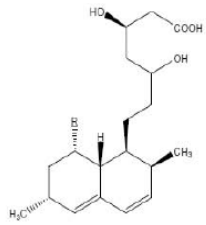
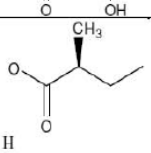
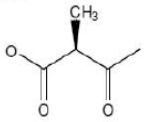
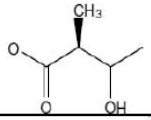
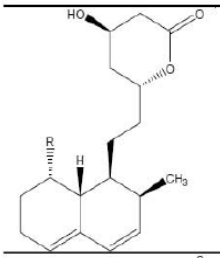
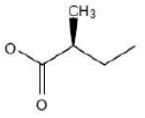
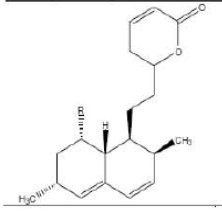
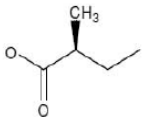
Structure	Name	R	MW	UV(λ_{max})	Formula	Refs
	1.Monacolin K		404	230, 237, 246	$C_{24}H_{36}O_5$	[8, 9, 33, 56]
	2.Monacolin L	H	304	230, 237, 247	$C_{19}H_{28}O_3$	[33]
	3.Monacolin J	OH	320	230, 237, 247	$C_{19}H_{28}O_4$	[33]
	4.Monacolin X		418	230, 237, 247	$C_{24}H_{34}O_6$	[34]
	5.Monacolin M		406		$C_{24}H_{36}O_6$	[35]
	6.MK acid form		422		$C_{24}H_{38}O_6$	[39, 57, 58]
	7.ML acid form	H	322		$C_{19}H_{30}O_4$	[39, 57, 58]
	8.MJ acid form	OH	338		$C_{19}H_{30}O_5$	[39, 57, 58]
	9.MX acid form		436		$C_{24}H_{36}O_7$	[39, 57, 58]
	10.MM acid form		424		$C_{24}H_{38}O_7$	[39, 57, 58]
	11.Compactin		390	230, 237, 247	$C_{23}H_{34}O_5$	[36]
	12.Dehydromonacolin K		386	230,237,247	$C_{24}H_{34}O_4$	[1]

Figure 1. Structural data of monacolins and their derivatives in RYR.

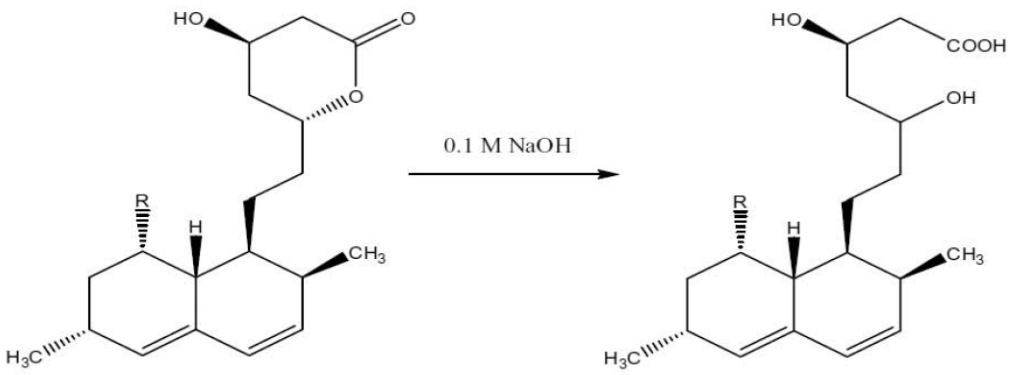


Figure 2. Transformation of a hydroxy acid form of monacolin K from the corresponding lactone form upon alkalization (0.1 M NaOH).

Monacolin K has been shown to have anti-metastatic and anti-angiogenesis effects by down-regulating vascular endothelial growth factor (VEGF)-stimulated invasive activity in murine Lewis lung carcinoma cells [43]. VEGF is an important component of the process by promoting tumor angiogenesis and vasculogenesis [43, 44]. In human colorectal adenocarcinoma cells (Caco-2), 20 proteins were identified with altered expression (treated with 50 μM monacolin K). These down-regulated proteins that were identified included heat shock protein 70, protein kinase C ε type, clusterin-associated protein 1, and two tumor suppressors (N-chimaerin and calponin-2) [2] among others.

RYR extracts inhibited cell growth and enhanced apoptosis in HCT-116 cells and this was compared to the effects of lovastatin [27]. When mevalonate was added to combat the inhibited cholesterol synthesis caused by lovastatin, the effects of lovastatin were predictably reversed. However, when mevalonate was added to RYR the effects persisted. Components in RYR, such as other monacolins, pigments acting alone or synergistically have been suggested to be responsible for these effects [27]. RYR was separated into two extracts one containing higher monacolins and one containing higher pigments content and test in human prostate cancer cells (LNCaP, LNCaP-AR cells) all extracts showed more cytotoxicity compared to lovastatin [45]. Further studies are needed on the individual monacolins that are responsible for the reported effects of RYR extracts.

Bioactive Pigments in Red Yeast Rice

There are at least 18 identified pigments detected in *Monascus* (Figure 3). These compounds are classified as azaphilone pigments which are structurally diverse family with an oxygenated bicyclic core and quaternary center [47]. In RYR six main pigments have been isolated and purified and classified according to color. The orange pigments include rubropunctatin and monascorubrin, the yellow pigments are monascin and ankaflavin are their respective reduced forms rubropunctamine and monascorubramine [48, 49]. The orange pigments have high affinity for primary amino groups, and the reaction with amino acids

yields water-soluble red pigments [50]. Various water-soluble *Monascus* coloring agents have been used as natural food coloring agents [50].

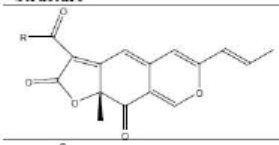
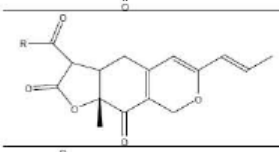
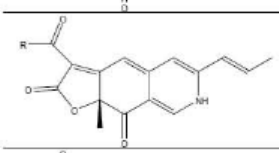
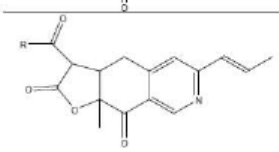
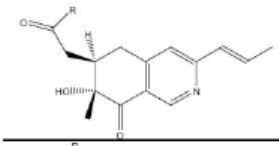
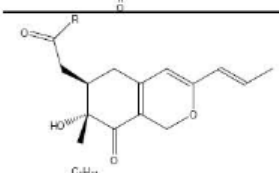
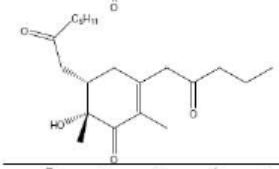
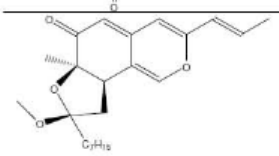
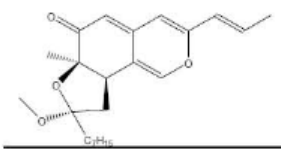
Structure	Name	R	MW	UV(λ_{max})	Formula	Refs
	1. Rubropunctatin	n-C_5H_{11}	354	300, 410, 530	$C_{21}H_{22}O_5$	[61, 62]
	2. Monascorubrin	n-C_7H_{15}	382	300, 410, 530	$C_{23}H_{26}O_5$	[61, 62]
	3. Monascin	n-C_5H_{11}	358	382, 460	$C_{21}H_{26}O_5$	[61, 62]
	4. Ankaflavin	n-C_7H_{15}	386	382, 460	$C_{23}H_{30}O_5$	[61, 62]
	5. Rubropunctamine	n-C_5H_{11}	353	250, 280, 480	$C_{21}H_{23}NO_4$	[61, 62]
	6. Monascorubramine	n-C_7H_{15}	381	250, 280, 480	$C_{23}H_{27}NO_4$	[61, 62]
	7. Monascopyridine A	n-C_5H_{11}	355		$C_{21}H_{25}NO_4$	[54]
	8. Monascopyridine B	n-C_7H_{15}	383		$C_{23}H_{29}NO_4$	[54]
	9. Monascopyridine C	n-C_5H_{11}	329		$C_{20}H_{27}NO_3$	[54]
	10. Monascopyridine D	n-C_7H_{15}	357		$C_{22}H_{31}NO_3$	[54]
	11. Monaphilone A	n-C_7H_{15}	360		$C_{22}H_{32}O_4$	[55]
	12. Monaphilone B	n-C_5H_{11}	332		$C_{20}H_{28}O_4$	[55]
	13. Monaphilone C		336		$C_{20}H_{32}O_4$	[55]
	14. Monapurfluore A		372	284, 368	$C_{23}H_{32}O_4$	[25]
	15. Monapurfluore B		372	284, 367	$C_{23}H_{32}O_4$	[25]

Figure 3. Structural data of six main pigments and other azaphilones in RYR.

Azaphilone pigments found in RYR exhibit a wide range of biological activities, including antifungal, antiviral, antioxidant, cytotoxic, nematicidal, anti-inflammatory, and anti-cancer activities [51]. Ankaflavin and its analog monascin were tested to compare their relative cytotoxicity. Ankaflavin reduced HepG2 cell growth (LC50 15 μg/mL) and induced apoptosis while showing low toxicity in normal fibroblasts, whereas monascin did not have any notable effects [52]. A likely structure-function relationships exist as monascin and ankaflavin differ by the length of the side chain possess different cytotoxic response [52].

Rubropunctatin, an orange pigment extracted and purified from RYR also showed selective cytotoxicity to BGC-823 (human gastric adenocarcinoma) cells with a concentration and time-dependent effect with an LC50 value of 12.57μM. Rubropunctatin induced apoptosis and increased sub-G1while showing low toxicity in normal gastric epithelial cell [47]. Tumor necrosis factor (TNF) was considered as a major mediator of apoptosis induced by rubropunctatin [47].

Six main pigments of RYR were isolated and purified and cytotoxic response were measured in various human cancer cells, including SH-SY5Y (human gastric cancer) cells, HepG2, HT-29, BGC-823, AGS, and MKN45 (human gastric cancer) cells [53]. Rubropunctatin showed the greatest ability to reduce cell growth which was greater than the positive control taxol [53]. The LC50 values of rubropunctatin against the human gastric adenocarcinoma cells (BGC-823, AGS, and MKN45) were below 15 μM and those against the other three cells (HepG2, SH-SY5Y, and HT-29) ranged from 30 to 45 μM [53]. However, rubropunctatin's cytotoxicity to normal human gastric epithelial cell was greater than that of taxol [53]. Activity seems to be related to chemical structure and that the 6-internal ether, 4-carbonyl, and conjugated double bonds in the tricyclic structure of rubropunctatin were necessary for an effect [53].

Besides the six main pigments found in RYR, their various derivatives bioactivities have been characterized. The monascopyridines A and B, which are dehydrogenated derivatives of rubropunctamine and monascorubramine, showed toxicological effects mainly due to their structural similarity [54]. Both showed anti-proliferative effect against HEp-2 (human laryngeal carcinoma cell line) and WiDr (human colon adenocarcinoma cell line) with relatively low toxicity to normal human lung cells [55]. Monapurfluores A and B, monascopyridines C and D, azaphilonoid derivatives, isolated from RYR also showed moderate effect on HEp-2 cell growth with LC50 values from 14.81 to 20.06 μg/mL and 12.89 to 21.14 μg/mL in WiDr cells [25]. Monapurones A-C, isolated from RYR showed selective cytotoxicity to A549 cells with LC50 values of 3.8, 2.8 and 2.4 μM respectively, with low toxicity to normal lung cells.

Conclusion

Red yeast rice has a long history of use as food, medicine and more recently as a source of food colorant. The main active constituent is an established HMG-CoA reductase inhibitor monacolin K which is identical to lovastatin. However RYR has been recently associated with other pleiotropic bioactive effects apart from the reduction in cholesterol synthesis. Other structurally related compounds to monacolin K have been reported to induce apoptosis

in a variety of cancer cell models. RYR pigments and some of their derivatives have also been shown to possess effects on reducing cancer cell growth and these effects may be dependent on the chemical structure of the pigments. However, current research has focused on RYR extracts and definitive determinations of bioactivities of individual monacolins and pigments warrants further research.

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