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Literature Review - Monacolin K in the treatment of hypercholesterolemia - chance or threat?

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Abstract

Introduction

Hypercholesterolemia is a primary element leading to the occurrence of cardiovascular diseases, which are the most common cause of death worldwide. One of the most effective drugs used in the treatment of hypercholesterolemia are statins. Monacolin K is a naturally derived substance that exhibits similar effects.

Materials and methods

The review of studies that follows is based on peer-reviewed scientific publications that may be found on PubMed, Google Scholar and CrossRef. The terms "monacolin K,"

"hypercholesterolemia," and "monacolin K in the treatment of hypercholesterolemia" were among the most searched.

Results

Review of the literature shows that Monacolin K is a promising substance that exhibits similar effects to statins and like them contributes to improving lipid profile. Unfortunately, fermented wild rice preparations lack clear information on the exact content of Monacolin K. Additionally, it is almost exclusively available in the form of dietary supplements on the Polish market, which have not been subjected to rigorous studies, so their therapeutic effects have not been scientifically proven.

Conclusion

The result of the cited studies indicates that It is necessary to regulate the market of preparations containing fermented wild rice. The package should specify the exact content of the active substance and effectiveness should be confirmed by appropriate studies. It would be promising for preparations to be developed at the level of medication rather than dietary supplements.

Key words: ”Monacolin K”; ”Hypercholesterolemia”; ”Monacolin K in the treatment of hypercholesterolemia”; ”Dietary supplements”; ”Cardiovascular risk”.

Introduction

Hypercholesterolemia is defined as increase levels of cholesterol in the blood. It is considered one of the most significant factors leading to cardiovascular diseases, which are the leading cause of death in Europe.

How serious this problem is, is demonstrated by the largest Polish study WOBASZ II (Multi-center Nationwide Study of Population Health) - it showed that 70.3% in males and 64.3% in women suffer from hypercholesterolemia. Nearly two third of adult Poles with hypercholesterolemia are uninformed that they have the illness [1]. This highlights that hypercholesterolemia is a very common phenomenon in Poland.

I. Evaluation of goal cholesterol levels and cardiovascular risk.

It has therefore become necessary to develop tools that allow for the proper classification of patients into the appropriate risk groups, enabling the adjustment of therapy and the determination of target values for lipid management parameters. At the outset, it is worth mentioning that the following scales are intended for asymptomatic, "healthy" individuals. The patient is automatically classified as high-risk if they have diabetes, chronic renal disease, or atherosclerotic illnesses.

Previously, SCORE (Systematic COronary Risk Evaluation) scales were used for this purpose [2]. As well as Pol-SCORE, which is intended for the Polish population [3]. Both of these scales allowed for the estimation of a patient's cardiovascular risk group based on factors such as age, gender, smoking status, systolic blood pressure values, and total cholesterol levels. They were used to estimate the risk of death from cardiovascular causes within 10 years.
The current recommendations include the SCORE2 system for people 40-69 years old and the SCORE2-OP system for people 70-89 years old [4]. The scales are based on the risk of not only fatal cardiovascular events, but also non-fatal cardiovascular events. Another difference from previous versions is that in the SCORE2 system and SCORE2-OP we use non-HDL cholesterol concentration (instead of total cholesterol, as in the previous version), which correlates better with risk.

Three risk categories have been identified along with their corresponding target values for laboratory parameters: Low/Moderate [LDL-C <100mg/dl, Non-HDL-C <130mg/dl, ApoB <100mg/dl]; High [LDL-C <70mg/dl and a 50% reduction from baseline, Non-HDL-C <100mg/dl, ApoB <80mg/dl]; Very high [LDL-C <55mg/dl and a 50% reduction from baseline, Non-HDL-C <85mg/dl, ApoB <65mg/dl] [4].

II. Methods of treating hypercholesterolemia.

1.Non-Pharmacological Treatment

Given that plasma cholesterol levels are largely dependent on lifestyle, initial management should start with its modification in every risk group. For individuals with low cardiovascular risk, this may prove to be the only necessary form of therapy. Methods that reduce plasma lipid concentrations and simultaneously impact cardiovascular risk factors include: Restricting the consumption of isomers of trans fats; consuming less saturated fat and more mono- and polyunsaturated fatty acids in their place; restricting calories consumed and losing weight (a BMI of 20–25 kg/m² is optimal and a woman's waist circumference should be

less than 80 cm and a man's less than 94 cm); stepping up daily exercise to 30 minutes or more, seven days a week; raising daily fiber consumption to 30-45g; restricting the amount of mono- and disaccharides, or simple carbs, that are consumed.; consuming nutritional supplements containing long-chain omega-3 polyunsaturated fatty acids and eating fish at least twice a week; consuming no more than 5 grams of salt a day and giving up smoking[5,6,7,8].

2. Pharmacological Treatment

The primary group of drugs used to lower blood cholesterol levels are statins. Their mechanism of action involves inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), which leads to diminish the liver's production of cholesterol and reduced cholesterol synthesis in the liver and increased expression of LDL receptors on the surface of hepatocytes. This results in decreased levels of LDL cholesterol, total cholesterol, and triglycerides, as well as increased levels of HDL cholesterol [9].

In the Polish pharmaceutical market, the two most effective statins are atorvastatin and rosuvastatin. In most cases, these medications can help achieve the recommended LDL cholesterol levels [10]. Besides their lipid-lowering effect, statins exhibit pleiotropic effects such as plaque stabilization, improvement of endothelial function, increased nitric oxide synthesis, anticoagulant action, and reduction of inflammatory responses [10].

Alternative forms of treatment are necessary for those who are intolerant to statins. Evolocumab, a human monoclonal antibody that binds to proprotein convertase subtilisin/kexin type 9 (PCSK9), is utilized in these situations. The Goal Achievement After Utilizing an anti-PCSK9 Antibody in Statin-intolerant Subjects (GAUSS) trial assessed its effectiveness. Patients' LDL levels decreased by 40–60% during the study's initial 12-week phase; this impact was dose-dependent. A 52-week extension of evolocumab medication was associated with an observed 52% reduction in LDL over the course of a year. Patients reported this therapy to be both safe and well-tolerated [11].

At the intersection of pharmacological and non-pharmacological treatment are preparations containing fermented wild rice, which are gaining increasing popularity in the Polish market. The main substance responsible for their therapeutic properties is Monacolin K. The rest of the article focuses on this substance.

The new nutraceutical - Monacolin K

Monacolins are substances produced during the fermentation of red rice using yeast (e.g., M. pilosus, M. purpureus, M. ruber, M. floridanus, and P. ostreatus). Depending on the

fermentation conditions and the types of yeast used, different monacolins are formed – among them, the most desired is Monacolin K. It was first isolated by Professor Akira Endo using Monascus ruber [12]. Despite the recent publicity surrounding wild, fermented rice preparations, the first documented evidence of their use dates back to 800 AD during the Tang Dynasty. At that time, red yeast rice was used as a spice, preservative, dye, and even for wine production [13]. Of course, beyond its culinary applications, it was already used in medicine – this is detailed in the Chinese pharmacopeia from the Ming Dynasty (1368–1644), which recognized this substance as beneficial for the circulatory system [14].

I. How Monacolin K works?

Monacolin K has the same structure as lovastatin, but their pharmacokinetics, bioavailability, and efficacy are different. Inhibition of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase is the primary mechanism contributing to the reduction of blood total cholesterol levels [15]. It also reduces the level of LDL-C cholesterol and TG, while leading to an increase in HDL-C cholesterol [16].

In addition to its effect on lipid profile, Monacolin K also exhibits other actions. It improves endothelial function by reducing serum high-sensitivity C-reactive protein (hs-CRP), which is considered a marker of vascular inflammation and a risk factor for cardiovascular disease, and it lowers the levels of matrix metalloproteinase (MMP) 2 and 9, recognized as markers of vascular remodeling in the serum [17]. Additionally, if fermented red yeast rice is consumed for an extended period of time, there may also be a minor improvement in arterial stiffness as indicated by a decrease in carotid-femoral pulse wave velocity. Once too, a considerable decrease in the risk of cardiovascular events (-12%) is linked to a minor improvement in pulse wave velocity (-1 m/s) [18].

II. Effectiveness of using wild rice preparations in studies.

The substance known as Monacolin K is of great interest to scientists. Numerous controlled clinical trials have been conducted to demonstrate its effectiveness. One of them is a study conducted by Gerard and co-workers. It includes 20 investigations using red yeast rice extract at doses ranging from 1200 mg to 4800 mg/day, which included 4.8 mg to 24 mg of moneclalin K. After 2 to 24 months of treatment, compared to placebo, there was an average drop in LDL-C of 1.02 mmol/l (39.4 mg/dl), according to a meta-analysis. This LDL-lowering impact was identical to those of statins with a moderate intensity (0.03 mmol/l), as lovastatin

(20 mg) and pravastatin (40 mg). In comparison to the placebo, there was also a minor rise in HDL-C levels (0.07 mmol/l) and a drop in triglyceride (TG) levels of 0.26 mmol/l [19].

Lin and associates carried out another research. The participants in the study ranged in age from 23 to 65. At the beginning of the research, the LDL content was 203.9 mg/dl. A 600 mg dose of fermented wild rice mixture (containing 5.7 mg of Monacolin K) was given to the patients twice a day. Following eight weeks, the study group showed a significant decrease in LDL-C concentration of 27.7%, TC of 21.5%, TG of 15.8%, and apoB of 26%. Meanwhile, there was a statistically insignificant rise in apolipoprotein A (by 3.4%), and HDL-C (by 0.9%). When evaluated at 4 weeks and study completion, the medication was not linked to any side effects that were characterized as an elevation in creatine kinase (CPK) and aminotransferase activity higher than or equal to 3 times the upper limit of normal [20].

Halbert et al. also conducted studies using Monacolin K in patients with indications for lipid-lowering treatment, who had discontinued statin therapy due to adverse effects—mainly myalgia. They assessed Monacolin K's safety and efficacy in a cohort of forty-three hypercholesterolemia patients. Patients were randomly assigned to two groups. One group received 20 mg of pravastatin, while the other received 2400 mg of a red yeast rice preparation. The two drugs were given twice a Day. Twelve weeks later, the results were evaluated. 30% lower LDL-C values were seen in the group taking Monacolin K, compared to 27% in the pravastatin-treated patients. The frequency of recurrence of muscle pain symptoms was minimal, with rates of 5% and 9%, respectively, in the group using red yeast rice and pravastatin [21].

The studies I mentioned are just a glimpse of the research conducted to prove the effective action of wild rice preparations.

III. Availability of fermented wild rice preparations in the Polish market.

The availability of red yeast rice preparations in the Polish market is extensive. They can be purchased in pharmacies, herbal stores, or online. Their price range is wide, but they are not generally affordable products. These preparations are produced by various pharmaceutical companies, from well-known brands to those that are less familiar. They are often supplemented with vitamins, herbal extracts, fatty acids, or macro- and microelements. However, all these products share a common feature: they almost exclusively appear in the form of dietary supplements.

According to European law, "Dietary Supplements" are defined as products that are a concentrated source of vitamins, minerals, or other substances with a nutritional or

physiological effect, intended to supplement the daily diet [22]. They look like drugs, but they are categorized as food items. They provide nutrients that lower the chance of developing some illnesses. It's crucial to keep in mind, nevertheless, that neither presentation nor advertising should suggest that they have the ability to prevent or treat disease [23].

In Poland, dietary supplements are approved for the market by the Chief Sanitary Inspector. The only things needed to be done to comply with the Act on the Health Conditions of Food and Nutrition are to submit a draft label and inform the authorities when a dietary supplement is introduced to the market [24]. Presenting the results of a stability study is not required, nor is quality control. Furthermore, supplements are not subject to pharmaceutical oversight or adverse effect monitoring, nor are they examined for possible drug interactions. The registration process is relatively easy and affordable, and it takes around a year.

IV. Potential dangers of using products contain red yeast rice.

In the above sections, I have mainly presented the advantages of fermented wild rice preparations. In contrast to these, I will now describe several aspects worth considering that cast this substance in a somewhat darker light.

1. Monacolin K as a Dietary Supplement.

The first problem was already mentioned in the previous section. It arises from the fact that Monacolin K is almost exclusively available as a dietary supplement, whose registration is simple, quick, and does not require stability study results or quality control. They are also not subject to pharmaceutical supervision, monitoring for adverse effects, or testing for possible drug interactions [24]. As a result, it is impossible to know for sure whether a particular supplement will be safe and effective, and the customer essentially consumes the prepared product at their own risk.

Ram Y. Gordon and colleagues conducted a study in which they assessed the content of Monacolin K in 12 commercially available products and checked them for citrinin content. They found striking variability in the content of monacolin in the 12 tested wild fermented rice products and the presence of citrinin in one-third of the tested preparations [25]. It is important to note that citrinin is a byproduct of the fermentation-derived mycotoxin [Monascus]. Numerous investigations on animals have demonstrated the nephrotoxic consequences of long-term citrinin consumption. Citrinin also causes developmental abnormalities, reproductive damage, and certain toxic effects on embryos (even in vitro) [26].

2. Self-medication in Poland and lack of trust in doctors.

Due to wide availability in recent years, there has been a rapid increase in the sales of dietary supplements. In Poland, between 30 and 78% of adults and adolescents report supplementing [27]. More over 40% of Polish respondents think that taking vitamin and mineral supplements keeps healthy people from getting sick, while almost 70% say that taking antioxidants keeps tumors from growing [28]. The great majority of people who use dietary supplements do so on their own initiative, with only 25% taking supplements on a doctor's recommendation [29].

Poles are third from the bottom in the EU when it comes to healthcare system trust, according to research by Eurofound. On a seven-point rating system, the average is 4.1, while the EU average is 6.411. This indicates that patients are avoiding expert knowledge in favor of reliable information from people closest to them. Furthermore, they don't think medical professionals will be able to offer trustworthy information [30]. This contributes to the occurrence of various drug interactions because often they do not inform doctors about the supplements they are taking, as they consider them herbal, natural, and therefore safe ingredients. They are not aware that natural extracts can also have a strong effect.

3. Negative effects resulting from the presence of Monacolin K itself

It cannot be forgotten that Monacolin K has side effects resulting from the presence of the substance itself, like any dietary supplement or medication.

The most frequently reported adverse effects were musculoskeletal and connective tissue disorders (myalgia being the most commonly reported) (36%), gastrointestinal disorders (e.g., diarrhea, nausea, and abdominal pain) (22%), liver and biliary system disorders (18%), and skin and subcutaneous tissue disorders (16%) [31]. These are usually mild in nature, but there are case reports illustrating the possibility of myopathy [32]. However, it happens that by taking other medications or food products, we increase the likelihood of serious side effects, including rhabdomyolysis. Particularly dangerous is taking Monacolin K with CYP450 inducers or inhibitors, which can alter the concentration of Monacolin K in the bloodstream. Examples of such products include grapefruit juice, cyclosporine, HIV protease inhibitors, fibrates, niacin, coumarin, nefazodone, macrolides, and antifungal drugs [33, 34].

Conclusion

So is Monacolin K a breakthrough in the treatment of hypercholesterolemia, or does it pose a threat? Based on the review of the studies and scientific papers presented above, it can

be concluded that Monacolin K is a promising substance for improving lipid profile similar to statins. In addition to its effect on laboratory test values, it also shows an impact on improving endothelial function and counteracts vessel remodeling.

However, the problem arises from the fact that it mainly occurs in the form of dietary supplements, which are increasingly being abused in an era of distrust towards doctors and self-medication. Patients predominantly do not inform their doctors about the supplements they are taking because they believe it does not affect their other treatments and medications. This can lead to serious interactions posing health risks and even life-threatening situations. Patients also forget that fermented red yeast preparations exhibit strong effects and can themselves cause side effects such as rhabdomyolysis, especially when combined with other drugs.

It is essential to closely examine preparations containing fermented red yeast, meticulously control the content of Monacolin K, and check for contamination with citrinin, which can occur during production. Furthermore, the fundamental issue is the lack of trust patients have in doctors and their failure to adhere to recommendations, instead seeking medical knowledge on the Internet or from acquaintances.

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Conflict of Interest Statement

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