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Original scientific paper

GC-MS analysis of cholesterol lowering dietary supplements

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Abstract

Controlling cholesterol levels and reducing the risk of cardiovascular disease requires the development of effective therapeutic strategies. In recent decades, dietary supplements (DSs) have gained attention as potential additions to conventional cholesterol management therapies, but their efficacy and safety are questionable. Accurate methods are required to evaluate the efficacy and safety of DSs. In the current study gas chromatography mass spectrometry was performed to analyze ten cholesterol-reducing DSs. The results showed that monacolin K/lovastatin was present in four samples. Moreover, using effective doses generally has minimal risks and lower incidence of adverse reactions and drug interactions. However, it must be taken into account the potential interaction of statins to induce myopathy and rhabdomyolizis. In order to prevent adverse effects, it is necessary to thoroughly evaluate and be careful when using DSs containing monacolin K.

Key words: cholesterol, antihyperlipidemic, dietary supplements, GC-MS

Introduction

Cardiovascular diseases including atherosclerosis, high blood pressure, and coronary artery disease are still the major health concerns worldwide. According to the World Health Organization (WHO), about one-third of heart disease is due to high levels of cholesterol. This highlights the significant problem that an increase in cholesterol levels, especially low-density lipoprotein cholesterol (LDL-C), is a major risk factor for such diseases (WHO, n.d.).

Lipoprotein disorders possess a crucial role in atherogenesis and the atherosclerotic cardiovascular disease. In such disease, cholesterol-lowering treatments have consistently shown a reduction in cardiovascular mortality. High cholesterol is typically defined as LDL-C greater than 190 mg/dL, greater than 160 mg/dL with one major risk factor, or greater than 130 mg/dL with two cardiovascular risk factors. These risk factors include age (male 45 years or older, female 55 years or older), positive family of premature atherosclerotic cardiovascular disease, hypertension, diabetes, and smoking (Ibrahim et al., 2023).

In order to control cholesterol levels and reduce the risk of cardiovascular diseases, it is important to develop effective therapeutic strategies. The main approach to treating high cholesterol levels is to maintain a healthy lifestyle, optimize weight, avoid smoking, exercise regularly, and eat fibers, fruits, vegetables and fish. Statins are a preferred class of drugs that reduces LDL-C by 22–50% and prevent serious cardiovascular incidents. However, their intake is associated with serious side effects such as increased transaminase levels, diabetes, myopathy and rhabdomyolysis. The alternative cholesterol reduction therapies such as biliary acid sequestration, fibrates, nicotine, PCSK9 inhibitors and others could be

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also considered (Abdul-Rahman et al., 2022; Abourbih et al., 2009; Ibrahim et al., 2023; Okopień et al., 2018).

Monacolin K (MK) is a major active component of red yeast rice (RYR). Over the years, extensive research has been conducted into the effects of MK on lipid profile, as a result, it is an appropriate supplement therapy or potential substitute for statins (Xiong et al., 2019).

Fibrates may be an appropriate treatment for patients who have not achieved the desired LDL level of statins or are resistant to them. The usual side effects of fibrates include mild increase in creatinine levels, rhabdomyolysis, muscle damage, and liver damage (Abdul-Rahman et al., 2022; Abourbih et al., 2009; Ibrahim et al., 2023; Okopień et al., 2018).

While a healthy lifestyle remains essential, the use of dietary supplements (DSs) has increased recently. These supplements contain bioactive compounds like plant steroids, omega-3 fatty acids, vitamins, soluble fibers, and plant extracts, known for their cholesterol-reducing properties. However, the composition and quality of DSs vary, emphasizing the importance of accurate and reliable analytical methods to assess their effectiveness and safety. Additionally, antioxidants like vitamin C, vitamin E, β-carotene and selenium have shown promise in cholesterol management (Maki et al., 2013; Miyazaki et al., 2008; Rodríguez-Huamán et al., 2017).

Nowadays there are many concerns about the quality of DSs. In contrast to pharmaceuticals the DSs are not obligatory tested for quality. At the same time the legalization about DSs is quite liberal in the most part of the world. For example, in the European Union and the United States of America, no premarket safety requirements exist and these products are regarded as food. The lack of obligatory quality and quantity tests of the active compounds, the lack of obligatory screening for impurities led to the introduction of many DSs with poor quality and products containing undeclared compounds. Recently many researchers reported about DSs containing undeclared compounds with serious pharmacological activity (Kozhuharov et al., 2022). Such products could cause serious side effects to consumers. It is especially important novel regulations about DSs to be introduces worldwide to provide their safety. The quality of DSs should be monitored just as the quality of pharmaceuticals.

Gas chromatography-mass spectrometry (GC-MS) is a widely used analytical technique for qualitative and quantitative analysis of complex mixtures. It offers high sensitivity, selectivity, and the ability to identify and quantify several compounds. In the specific context of DSs targeting cholesterol reduction, GC-MS proves invaluable in examining the chemical composition of these products (Sirén et al., 2014).

This study presented a comprehensive GC-MS analysis of cholesterol-lowering dietary supplements available in the market.

Material and methods

Chemicals

Standard of lovastatin was purchased from (Merck KGaA, Darmstadt, Germany). Gas chromatography grade methanol was obtained from Merck KGaA (Darmstadt, Germany). For determination of the retention indices (RIs), the following hydrocarbons were used: decane (≥99%), undecane (≥99%), dodecane (99%), tridecane (≥99%), tetradecane (≥99%), hexadecane (≥99%), heptadecane (99%), octadecane (99%), nonadecane (99%), eicosane (99%), heneicosane (≥99.5%), docosane (99%), tricosane (99%), tetracosane (99%), pentacosane (99%), hexacosane (99%), octacosane (99%) and triacontane (99%) purchased from Merck KGaA (Darmstadt, Germany).

Samples

Ten DSs used in the study were randomly selected and purchased from pharmacies and online.

GC-MS analysis

The GC-MS analyses were carried out using a Bruker Scion 436-GC SQ MS, Bremen, Germany. The mass spectra were collected over the range of m/z 50–450 in full scan mode and the ionization energy for the mass was 70 eV. The column was Bruker BR-5ms fused silica capillary (0.25 μm film thickness and 15 m × 0.25 mm i.d.). The oven temperature was initially kept at 90 °C for 1 min and then increased to 190 °C at 15 °C/min and after that increased to 300 °C at 5 °C/min and then kept for 1 min. Helium was the carrier gas with a flow rate of 1 mL/min. The temperatures of the detector and injector were 300 and 250 °C, respectively. The injection volume was 1 μL and a split ratio 1:20 was used. The MS spectra of lovastatin was compared with its spectral data from Wiley NIST11 Mass Spectral Library (NIST11/2011/EPA/NIH) and retention index obtained from the standard of lovastatin. The RI value was calculated for a C10-C35 series of n-alkane standards analysed under the same GC conditions as described above.

Results and discussion

For the study, standard of lovastatin was dissolved in methanol, which was subsequently subjected to the above GC-MS conditions. The retention time of MK/lovastatin was 21.05 min. Ten DSs, labeled to contain vitamins, plant extracts, and minerals, etc. were randomly selected from pharmacies and online stores. Each of them was dissolved in 10 mL of methanol, subjected to ultrasound treatment, and subsequently analysed. After the analysis, we found that four of the DSs contained MK/lovastatin, as present on Figure 1 and Table 1.

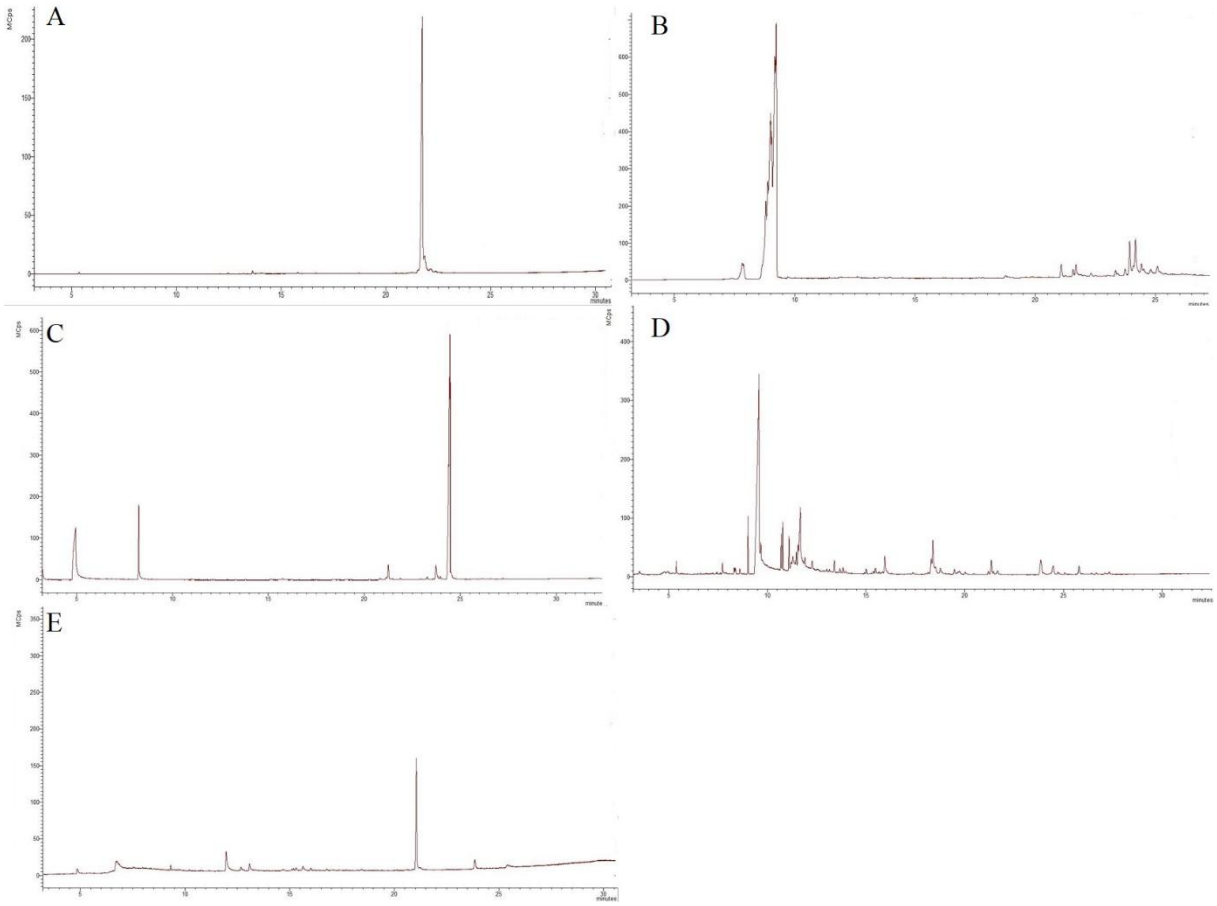

Fig.1. Chromatogram of: A) standard lovastatin; B) Sample 1; C) Sample 4; D) Sample 5 and E) Sample 8.

Table 1. Description of DSs with identified statins

Sample No.	Country of Origin of the Manufacturer	Product description	Sample Type	Identified statin
1	Italy	Caigua extract, gamma orizanol, monacolin K – 2.2 mg, co-enzyme Q, policosanol, Cr	capsule	Monakolin K (Lovastatin)
4	Italy	*Monascus purpureus* extract, octacosanol, niacin (Monacolin K – 1.5%), folic acid, piridoxin, cyancobalamin, tocoferol, *Camellia sinensis* extract	capsule	Monakolin K (Lovastatin)
	Bulgaria	*Monascus purpureus* extract (Monacolin K – 2.4 mg)	tablet	Monakolin K (Lovastatin)
8	Belgium	*Monascus purpureus* extract (Monacolin K – 10 mg), *Olea europea* extract	capsule	Monakolin K (Lovastatin)

Traces of MK were detected in sample No.1, 4, and 5 while a higher quantity was found in sample No. 8. Through qualitative analysis of sample No. 1, 4, 5, and 8 it was identified that these samples not only contained lovastatin but also the substances specified on the label. For example, sample No. 4 was explicitly labeled as containing *Monascus purpureus* extract, octacosanol, niacin (MK – 1.5%), folic acid, piridoxin, cyancobalamin, tocoferol, *Camellia sinensis* extract, we identified not only traces from MK, but also nicinamide, caffeine and vitamin E. Sample No. 5 is labeled to contained *Monascus purpureus* extract (MK – 2.4 mg), but we also identified olein and fatty acids. However, in the remaining tested samples, no unlisted substances were observed. Despite all the tested samples containing substances that were indicated on the labels, the question of their concentration remains. To further investigate this matter, it would be beneficial to validate the quantitative method for qualification purposes. Monacolin K is approved for use in food supplements, but caution should be exercised due to the potential risk of adverse reactions and drug interactions.

Monacolin K is the primary active compound in RYR and shares similarities with lovastatin (lactone form of MK is identical to lovastatin). Both compounds rapidly convert from their lactone forms to the β-hydroxy acid (HA) forms. Moreover, they are structurally similar to the β-Hydroxy β-methylglutaryl-CoA (HMG-CoA), allowing it to bind and inhibit the enzyme. Lovastatin is administered as a prodrug (*A Review on Lovastatin and Its Production - ProQuest*, n.d.; EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al., 2018). The HA form inhibits the HMG-CoA reductase enzyme. Lovastatin requires conversion from the lactone form (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al., 2018; Monu et al., 2022).

The therapeutic dose of lovastatin ranges from 10 to 80 mg/day. The minimum effective intake of MK, which achieved reductions in total cholesterol and LDL-cholesterol, was found to be between 2 and 48 mg/day (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al., 2018). The bioavailability of lovastatin increases when taken with a standard meal, typically by 30-50%. Metabolism of lovastatin involves the CYP3A4 isoform, and interactions with drugs or food ingredients that inhibit this enzyme can increase plasma levels of statins, potentially leading to higher risks of toxic effects (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al., 2018). The use of effective doses of statins is generally safe and rarely associated with significant adverse effects and drug interactions (Alsheikh-Ali & Karas, 2005; Bottorff, 2006).

However, adverse effects are associated with MK intake, even at a daily dosage of 3 mg, for periods ranging from 2 weeks to 1 year. Hospitalization was required in cases of rhabdomyolysis, other adverse effects related to hepatitis, and skin disorders, highlighting potential risks and side effects associated with its use (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al., 2018).

There are a number of side effects with lovastatin and these include: signs of liver damage, such as yellow eyes or skin, upper right abdominal pain, dark urine, and elevated liver enzymes, muscle pain, tenderness, or weakness, especially if you also have a fever or feel ill, since these may be signs of serious breakdown of muscle, known as rhabdomyolysis. Significant, unexplained changes in the amount of urine you produce. Severe allergic reactions, chest pain, dark urine, muscle pain, weakness, pale stools, red, swollen, blistered, or peeling skin; severe stomach pain, yellowing of the skin or eyes (Goswami S. et al., 2012, n.d.).

Statins undergo a complex process involving absorption, hepatic uptake, metabolism and elimination. Cytochrome P450 enzymes may metabolize statins before absorption. Hepatic uptake is facilitated by transporters like OATP1B1, which leads to phase I and phase II metabolism. Statins are metabolized from CYP3A4 and CYP2C9. Biliary excretion occurs through efflux transporters on hepatocyte membranes. However, statin drug interactions can pose a risk of myopathy and rhabdomyolysis, which are concentration-dependent and can be life-threatening. Significant interactions with statins usually involve changes in pharmacokinetics, particularly metabolism, as statins selectively inhibit HMG-CoA reductase without affecting other receptors, making pharmacodynamic interactions less common. Inhibition of intestinal CYP3A4 and OATP1B1-mediated uptake can lead to significant increases in statin concentration. Cyclosporine, telithromycin and posaconazole are likely to cause such interactions. Ritonavir (in combination with nirmatrelvir), daptomycin, tacrolimus and amiodarone have varying degrees of interactions with statins. A critical evaluation of the evidence can provide insights into managing these interactions effectively. Other drugs including sacubitril, dabigatran, and canagliflozin have limited evidence of potential statin interactions, but further research is needed before clear clinical management recommendations can be made. Moreover, elevated interleukin-6 levels in rheumatoid arthritis can lead to decreased activity of cytochrome P450 enzymes and increased drug exposure. However, tocilizumab, a medication targeting IL-6, may reverse this suppression and restore CYP3A4 activity (Schmitt et al., 2011; Williams & Feely, 2002).

However, the combination of fibrates or niacin with statins may increase the risk of myopathy. Grapefruit juice, containing a 6,7-dihydroxybergamottin, can inhibit CYP3A4, leading to increased oral bioavailability of drugs like statins that are metabolized by this enzyme in the intestinal wall. Consumption of grapefruit juice has been reported to cause statin-associated rhabdomyolysis. This is due to grapefruit juice inhibiting the first-pass metabolism of statins in the small intestine, which is mediated by the CYP3A4 enzyme. If their co-administration is necessary, the dosage of statins should be appropriately reduced. In

specific cases, such as the combination of simvastatin and amiodarone or verapamil, the incidence of myopathy was found to be higher (Alsheikh-Ali & Karas, 2005; Bottorff, 2006; Kantola et al., 1998; Lamprecht et al., 2022).

The co-administration of diltiazem significantly increased the plasma concentration of lovastatin. This suggests that the interaction between diltiazem and lovastatin occurs during the first-pass metabolism in the liver. Given the magnitude of this effect and the frequency of co-administration, caution should be exercised when administering diltiazem and lovastatin together (Azie et al., 1998).

Oral consumption of CoQ10 led to increased CoQ10 levels in the blood, often leading to improved cardiac function (Folkers et al., 1990). Overall, understanding the pharmacokinetics and potential interactions of statins is crucial for safe and effective use in clinical practice (Williams & Feely, 2002).

The investigated DSs comprised a combination of plant substances, vitamins, and other compounds, with some specifically targeting cholesterol reduction. In the case of RYR consumption, it is commonly supplemented with other plant products (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al., 2018). Green tea has been identified as having the ability to lower total cholesterol and LDL-C concentrations (Hasani-Ranjbar et al., 2010; Huang et al., 2022). Policosanol, a natural product, has demonstrated both safety and effectiveness in combating all the components of metabolic syndrome (Olatunji et al., 2022). Among the water-soluble vitamins, niacin has been scientifically proven to effectively decrease levels of total cholesterol, triglycerides, very-low-density lipoprotein, and low-density lipoprotein, while simultaneously increasing levels of high-density lipoprotein (Hamoud et al., 2013). Vitamin E has also shown potential in mitigating hyperlipidaemia (Okon et al., 2022). Additionally, various plant extracts, such as *Olea europaea* L., *Juglans regia* L. and *Camellia sinensis*, have been studied for their impact on lipid levels (Ben Saad et al., 2021; Maksoud et al., 2012; Sangi et al., 2022). Combination therapy is increasingly recommended for patients presenting with multiple lipid disorders, particularly those at a risk of experiencing coronary events. In our investigation, we focused on evaluating the long-term safety and efficacy of a novel drug formulation containing once-daily extended-release niacin and lovastatin (Kashyap et al., 2002).

In recent years, global DSs consumption has increased significantly. However, due to uncertainty about its rules, it is recommended to monitor and control its use. Furthermore, the accuracy of the labelling and the actual content of DSs is concerned. Therefore, new methods for analyzing and controlling DSs are required. The precise determination of the concentration of MK in DSs requires validated quantitative analysis using the appropriate techniques. Quality analysis of samples provides evidence of specific substances that are indicated on the label, highlighting the need for comprehensive testing and regulation in the industry. While MK is frequently present in dietary supplements, it is crucial to approach their usage with caution due to the structural resemblance between monacolin K and lovastatin, a type of statin. It is essential to be aware of the potential for adverse reactions and drug interactions when consuming these supplements, particularly in conjunction with other medications. Statins, including are effective in reducing cholesterol levels, but their inherent risks and potential side effects are particularly high in doses or in combination with certain medications. Combination therapy with statin, vitamins and natural products is a promising approach to the treatment of lipid disorders, but careful assessment of their safety, efficacy and potential interaction are of the greatest importance.

Conclusion

Cardiovascular disease continues to cause serious diseases, with high cholesterol levels as a risk factor. Statins are traditional approaches to reducing cholesterol, but the interest in alternative therapies such as red yeast rice with MK is increasing. To investigate cholesterol-lowering DSs, a gas chromatography mass spectrometry analysis of ten food supplements revealed the presence of lovastatin in four samples. Although the use of MK as food supplement is permitted, caution is needed due to the potential risks and side effects. Reports of adverse reactions associated with the intake of MK, even at low doses, emphasize the importance of taking into account potential risks and side effects. Understanding the chemical properties and potential interactions of statins are essential to their safe and effective use. Moreover, the use of accurate analytical methods to evaluate the effectiveness and safety of these supplements, especially in the presence of active ingredients such as MK. Additional research is required to fully understand the potential risks and benefits of these supplements.

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Резиме

GC-MS анализа на додатоци на исхрана за намалување на нивоата на холестерол

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Клучни зборови: холестерол, антихиперлипидемик, додатоци за исхрана, гасна хроматографија-масена спектрометрија (GC-MS)

Контролирањето на нивоата на холестерол и намалувањето на ризикот од кардиоваскуларни заболувања бара развој на ефикасни терапевтски стратегии. Во последните децении, додатоците на исхрана се сметаат како потенцијални додатоци кон конвенционалните терапии за регулирање на нивоата на холестеролот, но нивната ефикасност и безбедност се под знак прашалник. Имено, потребни се точни методи за да се оцени ефикасноста и безбедноста на овие додатоци. Во ова истражување беше изведена гасна хроматографија со масена спектрометрија со цел да се анализираат десет различни додатоци на исхрана за намалување на нивоата на холестерол. Резултатите покажаа дека монаколин К/ловастатин беше присутен во четири примероци. Притоа, користењето на ефективни дози генерално има минимален ризик и пониска појава на несакани реакции и интеракции со други лекови. Сепак, треба да се земе предвид потенцијалната интеракција со статините за индукција на миопатија и рабдомиолиза. Па оттука, за да се спречат несаканите реакции, потребно е да се внимава и да се направи детална евалуација при користење на додатоците на исхрана кои содржат монаколин К.