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# Effects of Statins on Gut Microbiota (Microbiome)

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**ABSTRACT**

Statins are the inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A, which are extensively used to decrease the concentration of cholesterol in patients with hyperlipidemia. Statins are divided into two categories based on their own unique properties. Considering the pleiotropic effects of statins, they are applied as antioxidant, anti-inflammatory, anti-thrombotic, immunomodulatory, and plaque-stabilizing agents. In addition, statins affect the diversity and population of gut microbiota, which is a complicated microbial community remarkably involved in the regulation of metabolic responses, immune system, and human health. This community is also associated with age-related health problems, allergy, asthma, and inflammatory intestinal diseases. Therefore, evaluation of the interactions between statins and gut microbiota is essential to predicting the outcomes of these agents. The present study aimed to review the properties and pleiotropic effects of statins. Furthermore, the role of gut microbiota in health was discussed, and the significant effects of statins on gut microbiota and their interactions were described based on clinical and animal studies.

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## Introduction

Recently, special attention has been paid to the use of natural compounds owing to their few side-effects and cost-efficiency, as well as their beneficial biological and therapeutic effects. According to statistics, statins have a wide range of applications, especially in patients with cardiovascular diseases.

Gut microbiota is considered to be an important determinant of health status, which is affected by various agents. Although some beneficial compounds could be used for the treatment or attenuation of a specific disorder, the compounds may adversely affect the microbiome of the gut. Therefore, it is essential to determine the association between the consumption of a specific therapeutic compound and gut microbiota in order to prevent further adverse health effects.

The present study aimed to review the interactions between statins and gut microbiota to provide a platform for further research in this regard (1-14).

Relevant articles were retrieved via searching in databases such as Google Scholar, PubMed, and ScienceDirect using keywords such as statins, gut microbiota, and statins + gut microbiota so as to browse the articles published until 2019.

## Literature Review

### *The Beneficial Cardiovascular Effects of Statins*

Statins are pharmacological inhabitants of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This enzyme is essential to mevalonate synthesis, and disturbances in this pathway lead to the decreased synthesis of downstream agents,

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such as cholesterol. In case of decreased cholesterol and serum cholesterol, statins are considered to be potential agents for reducing the risk of cardiovascular diseases (CVDs) (15).

Statins are classified into two categories based on their chemical structure (16). The first type of statins contains a hexahydro-naphthalene nucleus bound to methylbutyrate, and the second type contains a luorophenyl nucleus. While statins could decrease extracellular serum cholesterol in the form of low-density lipoprotein (LDL), they are also able to decrease cholesterol in the plasma membrane of cells. Furthermore, reduced cholesterol levels of the erythrocyte membrane have been reported as a result of statin therapy (17,18). In this regard, randomized clinical trials have provided data on the beneficial effects of statins on reducing the concentrations of LDL and total cholesterol, as well as the risk of vascular events and death (17,19,20). Moreover, reports have suggested that intensive statin therapy is more effective compared to moderate-intensity statin therapy (21).

The prevalent of CVD has been reported to be higher in patients with HIV infection (persons with hemophilia [PWH]), and statins could effectively decrease or prevent atherosclerotic CVD in the PWH (22). Atorvastatin is a potential member of statins, which could reduce atherosclerotic plaque in HIV-infected patients, while rosuvastatin could decrease the development of carotid intima-media thickness (22, 23). An observational study in this regard was conducted on the general population of adult Italians aged 40-79 years, and the results demonstrated that the proportion of the Italians with hypercholesterolemia was 55.6% (24). In addition, the mentioned research indicated that statins could effectively decrease lipid levels and CVD events. Other studies have confirmed that statins are safe drugs with proper tolerance in patients (25-27).

### *The Pleiotropic Effects of Statins*

Seemingly, statins have superior effects over reducing the levels of blood lipids. These cholesterol-independent effects are referred to as pleiotropic effects, which directly influence the kidneys, bones, glucose metabolism, and cardiovascular system. In this regard, Egashira et al. investigated the anti-inflammatory properties of pravastatin (28) using a rat model with the chronic inhibition of nitric oxide synthesis. The obtained results indicated the protective effects of pravastatin against cardiovascular inflammation, which is consistent with the findings of Jialal et al. (29).

In another research, Wagner et al. examined the antioxidant properties of statins (30), and the obtained results demonstrated that statins could remarkably decrease the capability of endothelium to synthesize $O_2$ via inhibiting p21 Rac-mediated assembly of nicotinamide adenine dinucleotide phosphate oxidase. In general, the pleiotropic effects of statins are exhibited through the antioxidant, anti-inflammatory, anti-thrombotic, immunomodulatory, and atherosclerotic plaque-stabilizing properties of these agents (31-39).

Inhibition of the synthesis of various isoprenoid intermediates (e.g., farnesyl pyrophosphate [FPP] and geranylgeranyl pyrophosphate [GGPP]) is essential to the pleiotropic effects of statins. In this regard, the findings of Chow indicated that as lipid attachments (isoprenylation), GGPP and FPP are significant intermediates for the post-translational processes of multiple cell-transducing proteins containing the small members of the GTPase family (40). The activation and intracellular transport of these G proteins are positively influenced by isoprenylation. Moreover, cell shape integrity, motility, growth, differentiation, proliferation, survival, and apoptosis inhibition, as well as intracellular and extracellular pathways, are regulated by these G proteins (41-43) (Fgure 1).

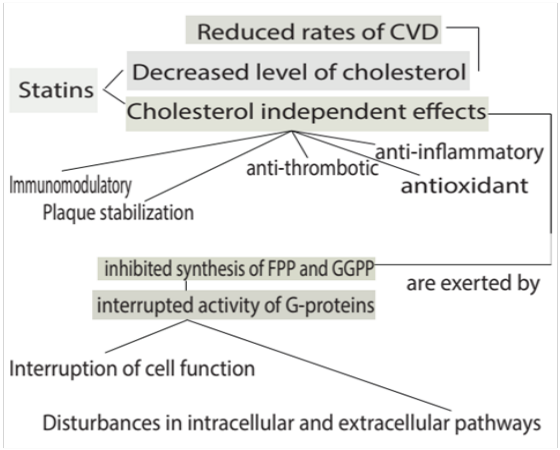


**Figure 1.** Schematic of Various Effects of Statins (CVD: cardiovascular disease; FPP: farnesyl pyrophosphate; GGPP: geranylgeranyl pyrophosphate)

### *The Role of Gut Microbiota in Health*

The sophisticated microbial communities found in the gastrointestinal tract (GIT) play a pivotal role in the regulation of metabolic responses, immune system, and human health (44). The microbial community (microbiota) of some animals contains bacteria, archaea, viruses, protozoa, and fungi. Furthermore, evidence confirms the association between the GIT microbiota and human health, while the mechanism of action in this regard remains unclear (44,45). Several studies have demonstrated that GIT microbial communities play a key role in energy homeostasis and may control weight loss or weight gain and obesity-as-

sociated disorders (46).

According to the literature, the regulation of blood pressure is correlated with gut microbiota and bacterial metabolites (47). Furthermore, chronic kidney disease (48) and the vital factors associated with CVD are regulated by the gut microbiota. The factors that cause changes in the combination or function of the gut microbiota may give rise to age-related health problems (49,50), alterations in the immune function of the host (51), inflammatory intestinal disease, allergy, and asthma (52). By exerting regulatory effects on the intestinal and systemic immune responses (53), gut microbes play a pivotal role in the appearance and/or preservation of CD4+ T cell subsets. Furthermore, irregularities in the gut microbial diversity may exacerbate the intestinal pathologies associated with the immune system (e.g., inflammatory bowel disease) (54). In this regard, Jones et al. examined the effects of the gut microbiota on bones (55), demonstrating that gut microbes are essential to the prevention of age- and menopause-related bone loss and increasing of the bone mass.

Although liver is the main organ of xenobiotic metabolism, orally administered xenobiotics may be metabolized by gut microbial enzymes, which results in their absorption from the GIT into the blood. Several studies have confirmed the role of the gut microbiota in the metabolism of orally administered compounds or phytochemicals (56,57). For instance, Yoo et al. evaluated the effects of the gut microbiota on lovastatin (58), reporting that gut microbes are significantly involved in the metabolism of lovastatin to its bioactive metabolites, so that four various chemical structures of lovastatin could be found in the fecal samples of humans and rats. Therefore, it could be concluded that the gut microbiota play a key role in metabolism and alterations in the population and diversity of the gut microbiota affect the health of the host.

### *Effects of Statins on Microbiome in Basic and Animal Studies and Its Biological Effects*

A short-term study reported no significant difference in the intestinal microbiota after statin therapy, and only a slight increase was observed in the number of Lactobacillus spp. (59). On the other hand, Martin et al. investigated the diversity of the gut microbiota after statin therapy (60), reporting that statin therapy leads to gut dysbiosis, so that the diversity would reduce based on the Shannon and Simpson indices, and Bacteroidales S24-7 group prevailed in the gut of the mice administered with statin.

According to the literature, statins could effectively inhibit the growth and virulence of bacterial pathogens (61-63). The members of genus Lactobacillus are essentially involved in cholesterol metabolism, and their reduced population in the GIT leads to the decreased synthesis of cholesterol. It is notable that the co-administration of ezetimibe (a hypolipidemic drug) with simvastatin could significantly decrease the population of Lactobacillus animalis and Lactobacillus murinus (59). Findings have also indicated that lovastatin mediates the interruptions in the synthesis of isoprenyl, as well as the cell wall of human-associated methanogens, in order to inhibit their development (64).

According to a study in this regard, atorvastatin therapy is associated with alterations in the diversity and abundance of some of the bacteria in the GIT of hypercholesterolemic rats toward to normal conditions (65). Other observations have also denoted the reactions between statins and the gut microbiota (66-69). In general, it is not completely evident whether statins directly affect the gut microbiota or the changes in the gut microbiota are as a result of the host responses affecting the gut microbiota. In a study, Miller and Wolin examined the impact of statins on the methanogens of ruminant forestomach (70), reporting that statins could reduce the generation of methane by ruminants, while elevating the efficacy of food utilization by domestic ruminants.

### *Effects of Statins on Microbiome in Clinical Studies and Its Biological Effects*

Due to the minimal side-effects of statins, a minimum of 20 milligrams per day of lovastatin, as an example, could be prescribed for human usage, which seems to be unproblematic as a component of the human diet (71). However, clinical studies investigating the effects of statins on the microbiome are scarce. Recently, Abdelmaksoud et al. examined the effects of statins on vaginal microbiome (72). In the mentioned study, the participants were selected from 4,306 women, who were candidates for the vaginal Human Microbiome project at VCU (VaMP). Samples were obtained from the mid-vaginal wall during speculum examination. According to the obtained results, the frequency of G. vaginalis was lower in the women using statins compared to those not using statins. Moreover, the women administered with statins had remarkably lower counts of Lactobacillus crispatus compared to those with normal and high levels of cholesterol using no statins. Therefore, it was concluded that the decreased number of G. vaginalis may be associated with the inhibited vaginolysin function.

Another study in this regard was focused on the effects of lovastatin on microbiota (73). In the mentioned research, 20 male goats were randomly divided into four groups and received treatment

for 12 weeks. The total bacterial diversity was determined based on the Shannon and Simpson indices, and no significant difference was observed in the species using lovastatin compared to the other species. On the other hand, the number of protozoa, Ruminococcus flavefaciens, methanogens, and methanobacteriales was observed to decrease in the species receiving statins.

## Conclusion

As potential cholesterol-lowering agents, statins are extensively used in the treatment of CVDs. Their application is not only due to their effects on cholesterol since these agents exert significant pleiotropic effects, including antioxidant, anti-inflammatory, anti-thrombotic, immunomodulatory, and plaque-stabilizing effects. Evidently, statins are used in large doses due to their remarkable properties and potential effects on the population and diversity of the gut microbiome.

The present study provided a comprehensive review regarding the effects of statins on the gut microbiota based on the in-vitro and in-vivo experiments and clinical trials. According to the in-vitro and in-vivo studies, there is a mutual interaction between statins and the gut microbiota, so that the consumption of statins is associated with the decreased population of bacteria, which plays a pivotal role in lipid synthesis. Furthermore, statins have been reported to diminish the population of lactobacillus, resulting in the reduced synthesis of cholesterol. Statins are also able to enhance food utilization in domestic animals and decrease the production level of methane. Moreover, the results of the clinical trials were consistent with the in-vitro and in-vivo experiments, demonstrating that statins could alter the population of microbiota. However, further investigations are required to assess the impact of statins on the gut microbiota (microbiome).

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## Conflict of Interest

The authors declare no conflict of interest.

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