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A Critical Review on Antibacterial Profile of Statins

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Abstract: *Statins are widely known for their lipid-lowering properties and cardiovascular benefits, have recently garnered attention for their potential antimicrobial effects. Emerging evidence suggests that certain statins, particularly simvastatin, atorvastatin, and lovastatin, exhibit antibacterial activity against a range of Gram-positive and Gram-negative bacteria. The proposed mechanisms include disruption of bacterial cell membranes, inhibition of isoprenoid biosynthesis, and modulation of host immune responses. Several in vitro and in vivo studies have demonstrated enhanced bacterial clearance and synergistic effects when statins are combined with conventional antibiotics. These findings open new avenues for repurposing statins as adjunct therapies in the treatment of bacterial infections, especially in an era of rising antibiotic resistance. However, further clinical investigations are required to fully elucidate their efficacy, optimal dosing, and safety in antimicrobial applications*

Keywords: Minimum inhibitory concentration, Statins, Antimicrobial resistance, Antibacterial mechanism, Drug repurposing

I. INTRODUCTION

The swift increase in bacterial resistance to conventional antibiotics, alongside a decrease in the discovery of new antibacterial drugs, has led to a significant global public health issue.(1) One potential solution is to repurpose existing medications to speed up the development of new antimicrobial treatments. This study reveals that simvastatin, a drug used to lower cholesterol, shows broad-spectrum antibacterial effects against crucial Gram-positive (including methicillin-resistant Staphylococcus aureus, or MRSA) and Gram-negative bacteria (after breaking through the outer membrane barrier)(2). Proteomic and macromolecular synthesis studies indicate that simvastatin disrupts various bacterial biosynthetic pathways and cellular processes, specifically targeting bacterial protein synthesis(3).This mechanism seems to aid in reducing the production of vital MRSA toxins (such as α -hemolysin and Panton-Valentine leucocidin),(4)which hinder the healing of infected skin wounds. In experiments with mice infected with MRSA, simvastatin significantly lowered the bacterial load and inflammatory cytokines in the afflicted wounds. Furthermore, simvastatin demonstrates strong anti-biofilm properties against established staphylococcal biofilms and can be effectively combined with topical antimicrobials traditionally used to treat MRSA skin infections.(5,6).Repurposing non- antibiotic medications as adjuncts to antibiotics could be instrumental in combating antimicrobial resistance (AMR). Statins, widely prescribed for cholesterol reduction, exhibit traits that could help in overcoming AMR, such as direct antibacterial effects, enhancing the efficacy of antibiotics, and boosting the host's immune response Nevertheless, the effectiveness of statins in this role may be constrained(7).

pressures that inadvertently promote resistance, turning statins into contributors to AMR instead(8).This review explores the potential of statins as AMR disruptors and their possible roles as AMR facilitators, while also highlighting gaps in our understanding of the interactions among statins, bacteria, humans, and the surrounding environment. It identifies the most promising statin for repurposing and suggests a possible mechanism for its antibacterial action based on an analysis of its structure-activity relationships(9).

Platelets have been shown to play a significant role in anti-infectious immunity, primarily through the secretion of molecules from their alpha granules. Previous research indicated that Staphylococcus aureus is susceptible to the antibacterial properties of platelets(10). Statins have been found to influence platelet activation, and several studies

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have suggested a protective role for statins in staphylococcal endocarditis. This study aimed to examine how statins affect the antibacterial capabilities of washed platelets. Blood samples were obtained from 35 healthy donors, and platelet-rich plasma (PRP) was prepared following ISTH guidelines. Bacteria were incubated for four hours with either untreated washed platelets or those treated with statins and/or GPIIbIIIa antagonists(11).To assess the antibacterial effect, the mixture of platelets and bacteria was spread on blood agar, and colony counts were taken after 18 hours. Flow cytometry measured the expression of CD41 and CD62P to evaluate the impact of statins on platelet activation induced by bacteria. The results indicated that statins enhanced the antibacterial effectiveness of washed platelets ($p < .01$ for Atorvastatin and Rosuvastatin, and $p < .001$ for Fluvastatin compared to untreated washed platelets).(12) This effect was dose-dependent, with the most significant results observed at a concentration of 20 µ M. The addition of Fluvastatin significantly elevated the expression of CD41 and CD62P on platelets ($p < .05$ and $p < .01$, respectively, compared to resting washed platelets). However, Tirofiban, a GPIIbIIIa antagonist, negated the antibacterial effect of washed platelets and diminished the enhancing effect of statins.(13) Our findings indicate that statins boost the anti- staphylococcal action of washed platelets, which could account for their beneficial effects against Staphylococcus aureus-induced infective endocarditis. Further research is needed to explore the underlying molecular mechanisms and evaluate the implications in vivo(14). The blockbuster statin drugs have revolutionized the treatment of cardiovascular disease, primarily by reducing low-density lipoprotein cholesterol (LDL-C) levels, leading to a decline in the morbidity and mortality associated with coronary artery diseases1. All statins drugs exert their effect by inhibiting the enzyme class I 3-hydroxy-3-methyl- glutaryl-CoenzymeA reductase (HMG-CoA) leading to decreased synthesis of cholesterol and increased removal of low-density lipoprotein (LDL) circulating in the body (15).These drugs possess a good safety profile with limited side effects thus permitting their frequent use in reducing lipid levels in patients with high cholesterol levels(16). In addition to their lipid-lowering effect, statins have been found to have potential use for other applications including influencing the host immune response via the drugs' anti-inflammatory and immune-modulatory properties4. Furthermore, multiple reports have investigated the potential role of statins in preventing and treating various infectious diseases and have demonstrated that statins can pre-vent the establishment of infections (by decreasing host cholesterol synthesis5,6 limiting certain bacterial species' ability to invade host cells) and potentially decrease the mortality rate attributed to bacterialdirectly inhibiting growth of Staphylococcus, Streptococcus, Enterococcus and Moraxella spp9–11. In addi-tion, simvastatin and atorvastatin are capable of increasing the mycobactericidal effect of rifampicin12bHowever, limited information is available regarding the mechanism by which statins exert their anti-bacterial effect, statins antimicrobial effect on Gram- negative pathogens, and potential applications for statins as novel antibacterial agents. Given the tremendous pressure bacterial resistance to currently available antibiotics has placed on the healthcare system (with certain bacterial strains of Staphylococcus aureus and Pseudomonas aerug-inosa exhibiting resistance to nearly every class of antibiotics), new antimicrobials are urgently needed to counter this significant public health challenge(17).Repurposing existing drugs (initially approved for treatment of one clinical indication such as lowering cholesterol levels) that also possess antibacterial activity has the potential to expedite the process to discovering new antibacterial agents (given much of the rigorous safety, pharmacokinetic, and pharmacodynamic studies have already been conducted)(18,19). Based upon preliminary studies performed to date, statins, in particular simvastatin, have potential to be repurposed as novel antibacterial agents. However additional research is required to understand statins ' antibacterial spectrum of activity, their antibacterial mechanism of action, an^{1}d^{0} to elucidate potential clinical applications in the management of bacterial infections(20). In this study, we aim to lay the foundation for utilizing statins as topical antibacterial agents by investigating the antibacterial activity of statins and their spectrum of activity on clinically-relevant Gram-positive and Gram- negative pathogens, elucidating the antibacterial mode of action of the most active statin (simvastatin), examining the effect of simvasta-tin on specific virulence factors (such as bacterial toxins and disruption of staphylococcal biofilms) and finally to validate the therapeutic efficacy of simvastatin in an appropriate animal model of S. aureus infection. Our study reveals that simvastatin has considerable promise for use as a therapeutic agent to treat MRSA skin infections and does warrant further investigation as a novel topical antibacterial agent.(21,22).

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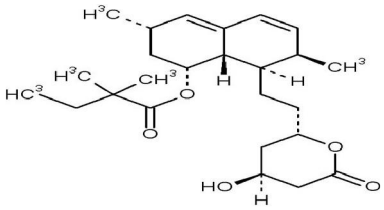
Bacteria (no. of strains screened)	Simvastatin (μg/ml)	
	MIC_{50}	MIC_{90}
Methicillin-resistant *S. aureus* (18)	32	32
Vancomycin-resistant *S. aureus* (15)	32	32
Methicillin-sensitive *S. aureus* (6)	32	32
Vancomycin-intermediate *S. aureus* (3)	32	32
Vancomycin-sensitive *Enterococcus* (9)	32	32
Vancomycin-resistant *Enterococcus* (7)	32	32
Listeria monocytogenes (6)	32	32
Streptococcus pneumoniae (2)	64	64
Bacillus anthracis (3)	16	16

Table 1. MIC of simvastatin against a panel of Gram-positive bacteria.

Structure



Antimicrobial Activity

Statins are a class of cholesterol-lowering medications that have been shown to have antimicrobial properties. The mechanism of action of statins as antimicrobial agents is complex and multifaceted.

Inhibition of HMG-CoA Reductase

Statins inhibit the enzyme HMG-CoA reductase, which is involved in the biosynthesis of cholesterol (1). This inhibition also affects the production of isoprenoids, which are essential for the synthesis of bacterial cell membranes (23).

Disruption of Bacterial Cell Membrane

The inhibition of isoprenoid synthesis disrupts the bacterial cell membrane, leading to changes in its structure and function (24). This disruption can ultimately lead to the death of the bacterial cell.

Inhibition of Bacterial Virulence Factors

Statins have been shown to inhibit the production of bacterial virulence factors, such as toxins and adhesins (25). This inhibition can reduce the ability of bacteria to cause disease.

Modulation of Host Immune Response

Statins have been shown to modulate the host immune response, enhancing the production of pro-inflammatory cytokines and activating immune cells (26). This modulation can help to eliminate bacterial infections.

Antimicrobial activities of statins were checked by agar -gel diffusion method. The cultures were grown in nutrient broth and incubated at 37°C for 24 hr. After incubation time, a suspension of bacteria was made up to turbidity equal to that of a 0.5 McFarland

standard with sterile nutrient broth. One-hundred microliters from bacterial suspension were poured into sterile Mueller-Hinton agar petri plate. The wells were bored in seeded agar. A stock solution of each statin with concentration equal to 1 mg/ml was prepared by dissolving the statin in absolute methanol(27,28). Fifty micro litters of statin solution were poured into each well. In another set of experiments, each statin was used (1 mg/ml) in combination with cholesterol, final concentration of 5 mg/ml. Standard disk diffusion method was used for assessing the antibiotic

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susceptibility of all the isolates using standard antibiotic disks; amikacin, cephalexin, gentamicin and ciprofloxacin. A growth control (well filled with distilled water) and a methanol control (well filled with absolute methanol) to determine whether methanol inhibits bacteria growth was included in each set. Plates were incubated at 37°C for 24 hr. After the incubation period the zone of inhibition was measured and recorded (13). Each set of experiments were performed at least three times. The results were taken to statistical analysis (t test) and expressed as Mean±SE. P-value <0.05 was considered to be statistically significant, comparing treatments with growth controlThe organisms, including Staphylococcus aureus, Escherichia coli, Enterococcus faecalis, and Pseudomonas aeruginosa were isolated from patients, who visited the clinical laboratory(29).The standard method for isolation and identification was followed. The samples were collected carefully, enriched in selective media and subjected to microscopic and biochemical identification and characterization (data can be obtained from the corresponding author)It was revealed that statins are able to induce variable degrees of antibacterial activity with atorvastatin, and simvastatin being the more potent than rosuvastatin. Methicillin-sensitive staphylococcus aureus (MSSA), methicillin-resistant staphylococcus aureus (MRSA), vancomycin-susceptible enterococci (VSE), vancomycin-resistant enterococcus (VRE), acinetobacter baumannii, staphylococcus epidermidis, and enterobacter aerogenes, were more sensitive to both atorvastatin, and simvastatin compared to rosuvastatin. On the other hand, escherichia coli, proteus mirabilis, and enterobacter cloacae were more sensitive to atorvastatin compared to both simvastatin and rosuvastatin. Furthermore, most clinical isolates were less sensitive to statins compared to their corresponding standard strains(30).

Mechanism of Action

Atorvastatin

Atorvastatin competitively inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase[31]. Statin medications decrease cholesterol production in the liver by preventing HMG-CoA conversion to mevalonate. Atorvastatin also increases the number of LDL receptors on the surface of hepatic cells.

In patients with homozygous or heterozygous familial hypercholesterolemia, mixed dyslipidemia, isolated hypertriglyceridemia, or nonfamilial hypercholesterolemia, atorvastatin has been shown to reduce total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), very-low-density lipoprotein (VLDL-C) and triglycerides (TGs) while increasing high-density lipoprotein cholesterol (HDL-C).

In patients with dysbetalipoproteinemia, atorvastatin has been shown to decrease intermediate-density lipoprotein (IDL-C).

Pharmacokinetics

The pharmacokinetic attributes of atorvastatin are covered below(32).

Absorption

Atorvastatin is rapidly absorbed after oral administration with a peak plasma concentration at 1 to 2 hours. The bioavailability is low at 14% due to extensive first-pass metabolism.

Distribution

Atorvastatin is highly plasma protein bound (over 98%) and has a volume of distribution of about 380 liters.

Metabolism

Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) to active ortho- and para- hydroxylated metabolites.

Excretion

Atorvastatin and its metabolites get eliminated in bile. Atorvastatin is not known to go through enterohepatic recirculation. The half-life of atorvastatin is about 14 hours, while its active metabolites have a half-life of about 20 to 30 hour

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Fluvastatin

Fluvastatin is a member of the HMG-CoA reductase inhibitor drug class. HMG-CoA reductase, the first committed enzyme of the mevalonate pathway, plays a role in the rate- limiting step of cholesterol synthesis in the liver. Statins competitively inhibit HMG-CoA reductase. Because they are molecularly similar in structure to HMG-CoA, they fit into the enzyme's active site. This binding creates competition with the native substrate, HMG- CoA. Consequently, there is a reduction in the rate by which HMG-CoA reductase can produce mevalonate. Mevalonate is the next molecule in the cascade that eventually produces cholesterol. Moreover, the lowering of blood cholesterol concentrations by fluvastatin causes an increase in the expression of LDL receptors on the liver hepatocytes and enhanced stimulation of LDL breakdown(33).

Pharmacokinetics Absorption:

The bioavailability of the fluvastatin capsule is 24%, and the extended-release tablet is 29%. Administration of a high-fat meal delays the absorption and increases the bioavailability of the ER tablet by approximately 50%. Distribution: Fluvastatin is 98% bound to plasma proteins. The volume of distribution (Vd) is estimated at 0.35 L/kg. At therapeutic concentrations, the plasma protein binding of fluvastatin is not affected by warfarin, aspirin, and glyburide(34).

Metabolism:

Fluvastatin is metabolized via hydroxylation in the liver. In addition, fluvastatin is metabolized by multiple cytochrome P450 (CYP) isozymes, including CYP2C9 (75%), followed by CYP3A4 (20%) and CYP2C8 (5%).[3]

Excretion:

Ninety-five percent of the drug is excreted in feces, with the remaining 5% excreted in the urine.[4]

Lovastatin

Lovastatin is metabolized into its active form, beta-hydroxy acid, in the stomach and functions to competitively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme is involved in the rate-limiting step of cholesterol synthesis. HMG- CoA inhibitors also decrease high-sensitivity C-reactive protein (hsCRP) levels, improve endothelial function, reduce inflammation at coronary plaque sites, inhibit platelet aggregation, and have anticoagulant effects(35). Also, a decrease in serum cholesterol stimulates LDL receptor expression on hepatocytes, further increasing LDL catabolism.

Pharmacokinetics

Lovastatin has a 30% bioavailability with an extensive first-pass effect; less than 5% reaches the systemic circulation. When administered without food, its bioavailability is reduced by 50%. It has a half-life of 1.1 to 1.7 hours and greater than 95% protein binding. It is metabolized to beta-hydroxy acid (active form) by CYP3A4, with 80 to 85% excretion in feces and 10% in urine. Therapeutic response is apparent by 2 weeks, and maximal response occurs within 4 to 6 weeks(36).

Pitavastatin

Pitavastatin competitively inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway. Inhibiting this enzyme decreases the production of mevalonic acid from HMG-CoA. This enzymatic inhibition, in turn, increases the number of LDL receptors expressed on hepatocytes to compensate for the loss of mevalonic acid and results in greater LDL catabolism(36,37). Pharmacokinetics

Absorption

Peak plasma concentrations of pitavastatin are reached within approximately 1 hour after oral administration. It has a bioavailability greater than 60%. It has some absorption in the colon; however, its absorption mainly occurs in the small intestine. In comparison to all other statins, pitavastatin reaches peak plasma concentrations the fastest and has the

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highest bioavailability. 10

Distribution

Pitavastatin is largely bound to protein (>99%), primarily to albumin and alpha-1 acid glycoprotein, with a mean volume of distribution of 148L.

Metabolism

Pitavastatin is mainly metabolized in the liver by UGT1A3 and UGT2B7 and minimally by CYP2C9 and CYP2C8.

Excretion

The half-life of pitavastatin is approximately 12 hours. The majority of pitavastatin (79%) is excreted in the feces, whereas approximately 15% is excreted in the urine.[6]

Results.

Against Gram-positive bacteria, simvastatin generally exerted the greatest antibacterial activity (lowest MIC) compared to atorvastatin, rosuvastatin, and fluvastatin.

Against Gram-negative bacteria, atorvastatin generally exhibited similar or slightly better activity compared to simvastatin, but both were more potent than rosuvastatin and fluvastatin.

Discussion.

Statins may serve as AMR breakers by working synergistically with existing topical antibiotics, attenuating virulence factors, boosting human immunity, or aiding in wound healing. It is probable that statins mechanism of antibacterial activity involves interference of bacterial cell regulatory functions via binding and disrupting cell surface structures such as wall teichoic acids, lipoteichoic acids, lipopolysaccharides, and/or surface proteins. The widespread use of statins for cardiovascular protection may favor selective pressures or co- selection for resistance, including dysbiosis of the human gut microbiota, sublethal plasma concentrations in bacteremic patients, and statin persistence in the environment, all possibly culminating in AMR(38).

II. CONCLUSION

Simvastatin appears to be the most suitable statin for repurposing as a novel adjuvant antibiotic. Current evidence better supports statins as potential AMR breakers, but their role as plausible AMR makers cannot be excluded. Elucidating the Subjects Microbiology, Drugs and Devices, Global Health, Infectious Diseases, Pharmacology

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