

Synthesis of Statin Drug from Fungal Sources and their Preclinical Studies

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Abstract

Statins are a type of medication that helps to lower high cholesterol (Hypercholesterolemia). Statins generally fall into three groups: natural statins that come straight from the fungi, semi-synthetic statins, which are the modified version of natural statins, and fully synthetic statins, which are fully made in labs. Some statins come from natural sources. They are made from the fermentation of certain fungi they are, *Monascus* species, *Penicillium* species, and *Aspergillus* species. Lovastatin and Pravastatin are naturally obtained Statins. Hydroxymethyl glutaryl-coenzyme A reductase is the enzyme that is used in cholesterol biosynthesis. For lowering of cholesterol and triglyceride levels, nicotinic acid and fibrates were the options before the discovery of statins. Not only do statins reduce the cholesterol level, but they also treat various types of disorders such as cancer and neurodegenerative diseases. The studies of statins in animals take place before the clinical trials.

Keywords: Statins, Fungal source, Cholesterol, Animal studies.

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Received: 11-08-2026

Revised: 28-08-2026

Accepted: 16-09-2026

Published: 30-09-2026

Introduction

Statins are a group of medications widely used to lower cholesterol levels, particularly in the management of dyslipidemia and to reduce the risk of atherosclerotic cardiovascular disease (ASCVD).^[1]

Due to their proven ability to reduce both morbidity and mortality in individuals at elevated ASCVD risk, statins are often considered the first-line treatment. Their comprehensive impact on lipid profiles and strong cardioprotective properties have made them some of the most commonly prescribed drugs globally.^[2]

Their origin as secondary metabolites from fungal polyketide pathways and their evolution into synthetic and semi-synthetic derivatives highlight both their biological and pharmaceutical significance.

In animal models, statins have shown consistent cholesterol-lowering effects, with varying degrees of efficacy across species and diets.

However, their impact on other physiological parameters such as blood pressure, infarct volume, and survival remains inconsistent, reflecting the complexity of their pharmacodynamics. It can be classified into naturally occurring compounds, their derivatives and fully synthetic

forms.

During a large-scale screening of over 6,000 fungal strains for their potential to block cholesterol synthesis using a method involving rat liver membranes that convert radioactive acetate into cholesterol a blue-green mold named *Penicillium citrinum*, isolated from rice, demonstrated notable inhibitory activity against HMG-CoA reductase.^[3] The cholesterol biosynthetic pathway, starting from acetyl-CoA units, involves more than 25 enzymes, rate-limiting step is the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate HMG-CoA reductase. Early Triparanol, one of the developed compounds that blocks the penultimate biosynthetic step, produces accumulation of sterols in tissues with serious side effects the inhibition of HMG-CoA reductase, at an earlier stage of cholesterol biosynthesis, results in accumulation of HMG-CoA, without any buildup of lipophilic ring simpler compounds can be metabolized.^[4]

Statins are molecules formed by secondary fungal metabolism, which can inhibit HMG-CoA reductase activity. Thus the mechanism involved in the control of endogenous cholesterol levels by statins makes these molecules suitable for therapeutic use.^[1]

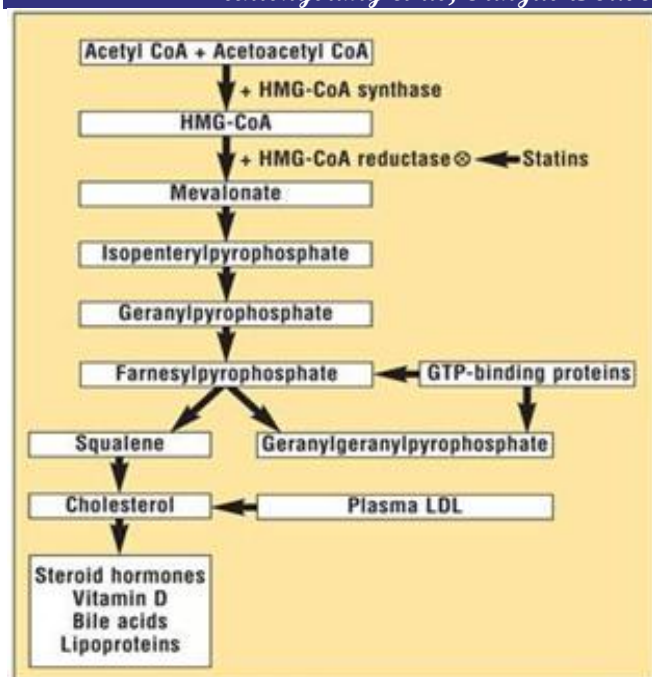


Figure 1: Cholesterol biosynthesis pathway

[CoA: coenzyme; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; GTP: guanosine tri phosphate; LDL: low-density lipoprotein]

STATINS FROM FUNGAL FERMENTATION

Statins are produced as secondary metabolites through the polyketide biosynthetic pathway. This pathway is inhibited by polyketide synthase genes similar as LovB, LovF, and LovD, which play pivotal places in regulating recap and the product of these composites. The product of statins generally occurs in fungi under stress conditions. Acetyl- CoA serves as a precursor, acting as a crucial link between primary and secondary metabolism, and contributes to the conformation of various secondary metabolites, including terpenes and polyketides like statins.^[5] Lovastatin is commercially attained through the fermentation of *Aspergillus terreus*, while simvastatin is produced by chemically modifying lovastatin, generally through direct alkylation. Although compactin is less effective at inhibiting HMG- CoA reductase compared to lovastatin, its semi-synthetic outgrowth, pravastatin, is significantly more potent in lowering cholesterol. Statin product can be carried out using different fermentation styles, including solid- state fermentation (SSF) and submerged fermentation(SMF), with artificial- scale product generally counting on submerged batch fermentation.^[6]

PRE CLINICAL STUDIES

From the studies and clinical trials, the effectiveness of statins in lowering cholesterol situations and reducing cardiovascular complaint threat. In this study, we conducted a methodical review and meta- analysis of exploration involving beast models specifically mice, rats, and rabbits to examine differences in statin efficacy across species. Through the magnitude of the effect varied statins reduce total cholesterol in all the three models such as 30% in

rabbits, 20 in mice, and 10 in rats. The cholesterol-lowering effect was more pronounced in creatures fed a high-cholesterol diet.^[7] While statins were shown to reduce infarct volume, they didn't constantly impact blood pressure or overall survival rates. Also, only a limited number of studies concentrated on beast strains with a high threat of cardiovascular complaint or assessed clinically applicable issues. Many preclinical studies replicated conditions that nearly act the mortal conditions statins are intended to treat. The finding states that statins are more effective at lowering cholesterol deduced from identical sources challenges the understanding of their primary medium of action.^[8]

TREATING SEPSIS IN MURINE MODEL

Sepsis, as defined as systemic seditious response touched off by infection, frequently aggravated by a vulnerable response in the host. Accordingly, both introductory exploration and clinical trials have concentrated on remedial strategies aimed at interposing crucial way.^[9]

In experimental models, sepsis was introduced in murine via cecal ligation and puncture (CLP). Six hours post-induction the stage marked by significant hemodynamic concession interventions were initiated with atorvastatin, fluvastatin, pravastatin, simvastatin, or placebo. Statin treatment, with the exception of fluvastatin, significantly prolonged survival compared to the control group. This marked improvement in outcomes was associated with preserved cardiac function and stabilized hemodynamic parameters, both of which were severely disrupted in untreated septic murine.^[10]

The statin remedy appeared to enhance responsiveness to endothelial nitric oxide synthase (eNOS) activation and reduce leukocyte adhesion to the endothelium, indicating bettered endothelial function following treatment. These findings suggest that beyond their well- established use in managing lipid diseases and coronary complaint, statins may offer a new remedy for managing sepsis.^[11] Further confirmation was in fresh trials where simvastatin treated mice demonstrated a pronounced survival benefit compared to placebo- treated counterparts. None of the operated murine anyhow of treatment succumbed. still, among CLP- convinced creatures, simvastatin extended median survival from 28 hours in the control group to 108 hours in the treated group, emphasizing its eventuality as a defensive agent in septic conditions.^[12]

EFFECT OF STATINS ON THE FERTILITY OF MICE "IMPACT OF ROSUVASTATIN AND ATORVASTATIN ON FERTILITY PARAMETERS IN MICE ACROSS TWO GENERATION"

The study aimed to estimate the goods of rosuvastatin and atorvastatin on specific fertility- related parameters in male and female mice, as well as their influence on the first and alternate generations of seed. For the first- generation analysis, an aggregate of 30 male and 60 female mice were aimlessly assigned to four groups, each conforming of age-matched individualities (3-4 males and 6-8 females per group). Rosuvastatin (3.5mg/kg) and atorvastatin (10.6mg/kg) was administered orally formerly daily over a 21- day period, with the dosage delivered in 0.1 ml per 20 g of body weight. The crucial reproductive and experimental parameters were assessed, including the number of live and stillborn pups, gestation success rate, doggy birth weight,

gravidity duration, manly- to- womanish seed rate, presence of natural anomalies, serum testosterone situations in males, testicular weight and confines, and testicular histopathology. For the alternate- generation analysis, seed from the original groups were allowed to copulate, and posterior reproductive issues similar as fertility, gestation success, and onset of sexual maturity were covered.

The findings suggest that atorvastatin exerts more effects on reproductive function than rosuvastatin, particularly in terms of reduced serum testosterone situations and dropped testicular weight in male mice.^[13]

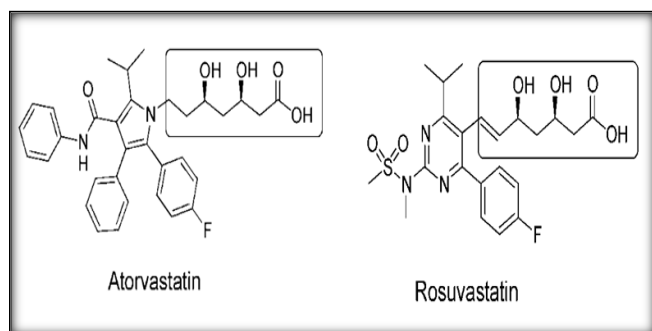


Figure 2: Chemical structures of Atorvastatin and Rosuvastatin

FLAWS IN ANIMAL STUDIES

In total 161 studies were examined to assess the characteristics of experimental design, models, and methodologies. Over half of these studies (55%) didn't report the use of randomization, and a significant maturity (88%) demanded descriptions of procedures. While all studies provided some information about the experimental protocols, numerous failed to specify crucial characteristics similar as coitus, age, or weight. Furthermore, some studies did not report the number of animals used, and none provided information on the sample size. Meta -logical comparisons using fixed- and arbitrary- goods models yielded markedly divergent issues, with effect size estimates varying by as important as fivefold. Substantial diversity was observed across models, and conforming for implicit covariates had minimum influence on reducing this variability.^[14] Although statins were found to be effective in animal models, the preclinical studies identified major problems in study design, data reporting, and analysis. These flaws significantly hamper the interpretability and reproducibility of results. The inconsistency among meta- logical styles further underscores the difficulty of directly estimating effect sizes. To improve the quality, transparency, and ethical norms of animal study, there's a pressing need for comprehensive policy interventions involving experimenters, journal editors.^[15]

The above mentioned study of treating sepsis in murines shows that the trial with simvastatin shows increased survival rates. The study also shows that the use of simvastatin in sepsis it reduced the effect of septic hearts and increased blood pressure.

The other study which is based on the effect of statins in fertility of the mice shows that the statins increase the fertility when there is use of atorvastatin rather than rosuvastatin.^[13]

Similarly, investigations into the reproductive toxicity of statins reveal differential effects, where atorvastatin appears

to have a more detrimental impact on male fertility compared to rosuvastatin. Despite their demonstrated efficacy, significant methodological short comings undermine the reliability of preclinical statin research. Inadequate reporting on randomization, blinding, sample size, and animal characteristics contributes to high heterogeneity and suspected publication bias. The lack of standardized protocols and inconsistencies in meta-analytic approaches further complicate the interpretation and translation of findings.^[10]

Conclusion

Statins, widely known for their lipid-lowering and cardio protective properties, have demonstrated a broader spectrum of effects across various experimental settings. The use of statins in experimental models of sepsis has results, with certain statins improving survival and preserving cardiovascular function. Overall, while statins show clear therapeutic potential beyond lipid regulation, these benefits must be interpreted cautiously due to the limitations in study design and reporting. To advance the field, there is an urgent need for stricter adherence to research quality standards, transparent reporting practices, and institutional accountability in preclinical animal studies.

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How to cite this article: Antony A, Rajan RR, Anandan H, Dhanisha JL, Babuselman V. Synthesis of Statin Drug from Fungal Sources and Their Preclinical Studies. Asian J. Med. Res. 2026;15(3): 20-23.

Source of Support: Nil, **Conflict of Interest:** None declared.

