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Potential of Natural Compounds and Biological Products as HMG-CoA Reductase Enzyme Inhibitors: a Literature Study

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ABSTRACT
HMG-CoA Reductase is a primary target in hypercholesterolemia therapy due to its role in cholesterol biosynthesis in the liver. This study aims to review the potential of natural substances, microbes, and in silico approaches in identifying HMG-CoA Reductase inhibitor compounds. The review was conducted on 10 national and international journals using methods such as molecular docking, enzymatic activity analysis, in silico toxicity validation, and epidemiological studies. The results show various compounds from plants such as Piper crocatum, Allium sativum, Syzygium polyanthum, as well as fermented products like Lactobacillus acidophilus have high potential as inhibitors of this enzyme. Combination therapy, modification of statin compounds, and educational approaches for patients also contribute to the effectiveness of cholesterol therapy.

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INTRODUCTION

Hypercholesterolemia is a metabolic disorder characterized by high blood cholesterol levels, a major risk factor for cardiovascular diseases such as atherosclerosis, stroke, and coronary heart disease. One of the primary targets of hypercholesterolemia therapy is the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA Reductase), a key enzyme in cholesterol biosynthesis in the liver (Dewi & Merry, 2017).

Commonly used drugs to inhibit this enzyme are statins, such as simvastatin, atorvastatin, and lovastatin. While effective, long-term statin use can cause side effects such as myopathy, liver damage, and drug intolerance (Purnama & Merry, 2017). Therefore, safer and more natural alternative therapies with similar mechanisms of action are needed.

Natural ingredients such as medicinal plants, fermented microbial products, and flavonoid compounds from local herbs have been widely reported to have the potential to lower cholesterol levels by inhibiting the HMG-CoA Reductase enzyme (Yonas & Harjo, 2023; Hartanti et al., 2019; Normaidah & Nurmansyah, 2021). These natural compounds work through a competitive mechanism at the active site of the HMGCR enzyme, as evidenced by various in silico and in vitro studies (Suatowijaya et al., 2019; Nugraha et al., 2022). Furthermore, computational technology approaches such as molecular docking have become important methods in the exploration and validation of potential inhibitor compounds due to

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their efficiency and accuracy in predicting ligand affinity for protein targets (Widya & Amin, 2025; Faturohman et al., 2024).

This process allows for rapid and cost-effective initial screening of candidate compounds before proceeding to the experimental stage. Not only plant-derived compounds, microorganisms such as Lactobacillus acidophilus and Lactobacillus delbrueckii have also been reported to produce natural lovastatin, which has inhibitory activity against HMGCR (Kusuma et al., 2025). This opens up significant opportunities for the development of probiotic-based functional foods for cholesterol therapy.

On the other hand, therapeutic success depends not only on the effectiveness of the compound but also on patient compliance. Observational studies have shown that patient knowledge about statin drugs significantly influences adherence and long-term treatment effectiveness (Lawuningtyas et al., 2020). Therefore, a multidisciplinary approach encompassing the exploration of bioactive compounds, molecular technology, and patient educational interventions is a highly promising strategy for developing safer, more effective, and sustainable hypercholesterolemia therapies.

The aim of this study is to conduct a literature review of various research findings related to the potential of natural compounds and biological products as HMG-CoA reductase inhibitors, using experimental, in silico, and clinical approaches. This study is expected to provide a comprehensive overview and direction for further development of scientifically based and holistic hypercholesterolemia therapy.

METHOD

This study uses a descriptive qualitative approach through a literature study of various relevant scientific journals. The literature was collected from databases such as Google Scholar, PubMed, and ScienceDirect. Inclusion criteria include: (1) Journals published between 2015–2025, (2) Topics discussing HMG-CoA Reductase inhibitors from natural, synthetic, or microorganism materials, (3) Using molecular docking methods, spectrophotometric tests, HPLC, in silico, or observational studies related to cholesterol therapy. Exclusion criteria included articles that did not contain outcome data or did not focus on the HMG-CoA reductase enzyme. A total of 10 journals were reviewed, comprising experimental, in silico, and clinical observational studies.

RESULTS AND DISCCUSION

Table 1. Results of literature study analysis

No	Author Name	Research Title	Research methods	Research Object	Research result
1	Suatowijaya et al. (2019)	Virtual Screening of Simvastatin Modified Structure on HMG-CoA Reductase Enzyme	Molecular docking, Lipinski Rule	Three modified ligands of simvastatin	Ligand 3 has an affinity of -9.1 kcal/mol, stronger than native simvastatin. Reacting amino

No	Author Name	Research Title	Research methods	Research Object	Research result
					acid residues: L ys735, Glu559, Ser684.
2	Nugraha et al. (2022)	Internal Validation of the HMG-CoA Reductase–Atorvastatin Receptor Complex	Re-docking (YASARA), 1000 simulations	Atorvastatin complex with HMGCR	RMSD = 0.3181 Å indicates the validity and stability of the docking method.
3	Widya & Amin (2025)	Natural Compounds as Cholesterol Therapy Candidates	Molecular docking, in silico review	Trifolin, phloretin, trigonelline compounds	Capable of inhibiting NPC1L1 and HMGCR synergistically.
4	Faturohman et al. (2024)	In Silico Toxicity Testing of Herbal Compounds	In silico (ProTox II)	10 herbal compounds from the Coconut database	Two compounds with LD50 > 3750 mg/kg, very low toxicity.
5	Hartanti et al. (2019)	Effect of Bay Leaf Extraction on Antioxidant Activity & HMGCR	DPPH and FRAP spectrophotometry	Bay leaf extract	The Soxhlet method produced IC50 = 15.5 µg/mL, more effective than the percolation method.
6	Lawuningtyas et al. (2020)	The Relationship Between Knowledge and Use of Simvastatin in Hypercholesterolemia Patients	Observational (cross-sectional) study	Patients using simvastatin at a pharmacy in Malang City	High knowledge correlates significantly (p=0.000) with appropriate medication use.
7	Yonas & Harjo (2023)	Exploration of Flavonoid Compounds from Piper crocatum	Molecular docking	Compound CHEMBL216163 from *Piper crocatum*	Affinity value -8.3 kcal/mol, competitive with atorvastatin.
8	Kusuma et al. (2025)	Isolation of Lovastatin-Producing Lactic Acid Bacteria from Bekasi	Microbial isolation, HPLC, enzyme activity test	*Lactobacillus acidophilus* and *L. delbrueckii*	Produces natural lovastatin, HMGCR enzyme inhibition power

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					up to 66.67%.
9	Normaidah & Nurmansyah (2021)	In Silico Study of H. polyrhizus & A. sativum Compounds	Molecular docking, RMSD validation	Vicenin, γ-glutamyl-phenylalanine	Valid interaction with HMGCR, RMSD < 2Å.
10	Dewi & Merry (2017)	The Role of Statins in Preventing Recurrent Ischemic Stroke	Retrospective cohort study	Ischemic stroke patients	Statins reduce the incidence of recurrent stroke and improve clinical outcomes.

Results from ten scientific articles indicate that the HMG-CoA Reductase (HMGCR) enzyme remains a key focus in hypercholesterolemia therapeutic strategies. This enzyme plays a role in the initial and limiting steps of the cholesterol biosynthesis pathway, so its inhibition can significantly lower blood cholesterol levels. Various approaches have been used in recent studies to evaluate the potential of HMGCR inhibitors, including molecular docking, enzyme activity assays, in silico validation, and observational studies of patient behavior.

Research by Suatowijaya, Riza, and Fajriaty (2019) showed that structural modification of simvastatin produced a new ligand with a binding energy affinity of -9.1 kcal/mol, higher than native simvastatin (-7.9 kcal/mol). This ligand fulfills Lipinski's rule, making it potentially suitable for development as an active cholesterol-lowering compound. Further validation by Nugraha, Suprayetno, and Pangestu (2022) using the atorvastatin re-docking method against HMGCR yielded an RMSD value of 0.3181 Å. This value indicates that the docking method used is valid and the binding model is quite stable.

The potential of natural compounds has also been extensively studied. Yonas and Harjo (2023) explored flavonoid compounds from Piper crocatum using molecular docking and found that the compound CHEMBL216163 had an affinity of -8.3 kcal/mol, close to the value of atorvastatin as a positive control. These results indicate that the compound has the potential to be a competitive inhibitor of HMGCR. Meanwhile, Hartanti et al. (2019) compared the extraction method of bay leaves (Syzygium polyanthum) and showed that the Soxhlet method produced an IC_{50} of 15.5 µg/mL with high phenol and flavonoid content, as well as strong antioxidant activity that supports HMGCR inhibition.

A study by Normaidah and Nurmansyah (2021) showed that vicenin and γ-glutamyl-phenylalanine compounds from Allium sativum and Hylocereus polyrhizus can interact with the active site of the HMGCR enzyme with valid RMSD values (<2 Å), indicating that these ligands occupy a conformation suitable for the binding site. A multi-target approach was also described by Widya and Amin (2025), who showed that the compounds trifolin, phloretin, and trigonelline not only inhibit HMGCR but also the cholesterol transporter NPC1L1. The synergistic effect of inhibiting these two targets has the potential to increase the effectiveness of hypercholesterolemia therapy.

On the other hand, microbial biotechnology approaches have yielded interesting results. Kusuma et al. (2025) successfully isolated Lactobacillus acidophilus and L. delbrueckii from

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bekasam and found that both bacteria were capable of naturally producing lovastatin. HPLC analysis results showed a lovastatin content of 9.49 ppm, and activity tests showed an HMGCR inhibition rate of 66.67%. This suggests that traditional Indonesian fermented foods can be utilized as a source of natural cholesterol inhibitors.

Compound safety is also a focus of research. Faturohman, Fakih, and Yuniarta (2024) performed in silico toxicity predictions on ten herbal compounds from the Coconut database. Two of them, CNP0202071 and CNP0187364.1, had high LD_{50} values (5000 and 3750 mg/kg) and were classified as low-toxicity compounds (GHS class 5). This indicates that these compounds are predictively safe for further development.

In addition to molecular and biological aspects, research also highlights the importance of patient understanding of statin medication use. Lawuningtyas et al. (2020) conducted an observational study of hypercholesterolemic patients at a pharmacy in Malang City and found that patient knowledge was positively correlated with adherence to simvastatin use ($p = 0.000$; coefficient = 0.287). This suggests that educational interventions from pharmacists are crucial for improving treatment effectiveness.

A clinical study by Dewi and Merry (2017) in patients with recurrent ischemic stroke demonstrated that statin use can improve functional outcomes and reduce the incidence of subsequent strokes. This reaffirms that HMGCR inhibition has therapeutic effects not only on lipid profiles but also on long-term clinical prognosis.

Based on all the reviewed studies, it can be concluded that the combination of in silico approaches, exploration of natural compounds, microbial products, biological validation, and enhanced patient education constitutes a comprehensive approach to developing future cholesterol-lowering therapies. This integrative strategy holds promise not only for effectiveness but also for safety, availability, and sustainability in clinical practice.

CONCLUSION

Based on the literature reviewed, it can be concluded that the HMG-CoA Reductase enzyme is a primary therapeutic target in the treatment of hypercholesterolemia. Various approaches have been used to effectively and safely inhibit the activity of this enzyme. Natural compounds such as flavonoids from Piper crocatum, compounds from Allium sativum, and fermentation compounds such as natural lovastatin produced by Lactobacillus have shown strong potential as inhibitors. Molecular docking and in silico validation methods have proven effective as initial steps in identifying candidate compounds, while toxicity testing strengthens the prediction of compound safety for further development. Multi-target approaches such as inhibition of the HMGCR enzyme and the cholesterol transporter NPC1L1 offer broader therapeutic prospects. Furthermore, patient education and knowledge have been shown to influence the effectiveness of statin therapy. The combination of biological approaches, molecular technology, and educational approaches could provide new directions in the development of more effective, safe, and sustainable hypercholesterolemia therapies.

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