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Original Research

Safety and Tolerability of Atorvastatin vs. Guggul: A Comparative Analysis

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Abstract
Statin therapy, particularly atorvastatin, is widely used for lowering LDL-C and reducing cardiovascular risk. However, statin intolerance due to muscle-related symptoms and hepatotoxicity affects long-term adherence, necessitating the exploration of alternative lipid-lowering agents. Guggul (Commiphora mukul), a natural remedy used in Ayurvedic medicine, has been suggested as a safer alternative due to its cholesterol-modulating effects and favorable safety profile. This study aimed to compare the safety and tolerability of atorvastatin and Guggul in hyperlipidemic patients by evaluating adverse event incidence, liver enzyme elevations, and muscle toxicity markers. A 12-week randomized controlled trial (RCT) was conducted with 150 hyperlipidemic patients receiving either atorvastatin (10 mg/day) or Guggul (2000 mg/day). Muscle pain was significantly higher in atorvastatin users (24%) compared to Guggul users (10.6%, $p < 0.01$). Liver enzyme elevations were observed in 6.7% of atorvastatin users but not in the Guggul group ($p < 0.01$). Severe CK elevations (>5× ULN) occurred in 8% of atorvastatin users, with no cases reported in Guggul users. While mild gastrointestinal discomfort (13.3%) and skin rash (5.3%) were observed in Guggul users, no severe adverse events were reported. These findings suggest that Guggul may offer a safer alternative for patients experiencing statin intolerance, though further long-term studies are required to confirm its cardiovascular safety.

Keywords: Statin intolerance, Guggul, muscle toxicity, hepatotoxicity, cardiovascular disease

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Introduction

Cardiovascular disease (CVD) remains the leading cause of death globally, with atherosclerosis and hyperlipidemia being key contributors [1]. Low-density lipoprotein cholesterol (LDL-C) reduction is essential for cardiovascular risk reduction, and statins have proven efficacy in achieving this goal [2,3]. Among statins, atorvastatin is widely prescribed due to its strong LDL-C-lowering capability and cardiovascular benefits [4]. However, statin-associated adverse effects, particularly muscle pain, hepatotoxicity, and fatigue, pose significant barriers to adherence [5].

Statin-associated muscle symptoms (SAMS) occur in 5–29% of patients, manifesting as myalgia, weakness, and, in rare cases, rhabdomyolysis [6]. Liver enzyme elevations (ALT, AST) and hepatotoxicity are another concern, prompting treatment discontinuation in 1–3% of statin users [7]. Given these challenges, alternative lipid-lowering therapies with improved tolerability are needed.

Guggul (Commiphora mukul) is a plant-derived lipid-lowering agent used in Ayurvedic medicine. It contains guggulsterones, which modulate cholesterol metabolism by inhibiting the Farnesoid X Receptor (FXR) and promoting bile acid excretion [8]. Unlike statins, which inhibit HMG-CoA reductase and reduce cholesterol synthesis, Guggul enhances cholesterol excretion, making it a potential alternative for statin-intolerant patients [9]. Additionally, Guggul exhibits anti-inflammatory and antioxidant properties, potentially reducing muscle and liver toxicity associated with statins [10].

Although Guggul has been studied for its lipid-lowering effects, its safety profile requires further evaluation. Some studies suggest that Guggul has a lower incidence of muscle toxicity compared to statins, but reports of gastrointestinal discomfort and dermatologic reactions exist [11,12]. This study aims to provide a direct comparison of the safety and tolerability of atorvastatin and Guggul in hyperlipidemic patients.

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Objective of the Study

This study investigates the safety and tolerability of atorvastatin vs. Guggul in patients with hyperlipidemia, focusing on:

1. Incidence of muscle-related adverse effects, including myalgia, CK elevation, and rhabdomyolysis risk.
2. Hepatic safety, assessing liver enzyme (ALT, AST) elevations.
3. Other reported adverse effects, such as gastrointestinal discomfort and dermatologic reactions.

Methods

Study Design and Participants

This study was designed as a **12-week, double-blind, randomized controlled trial (RCT)** comparing the **safety and tolerability of atorvastatin and Guggul in patients with hyperlipidemia**. The trial was conducted in accordance with the **Declaration of Helsinki and Good Clinical Practice guidelines**, with approval from the Institutional Ethics Review Board. All participants provided **written informed consent** before enrollment.

Patient Selection Criteria

Inclusion Criteria:

- Adults aged **30–65 years** with a **diagnosis of primary hyperlipidemia (LDL-C ≥ 160 mg/dL)**.
- No prior history of statin use in the past **three months**.
- Body mass index (BMI) **between 18.5–30 kg/m²**.
- No active or uncontrolled **hypertension, diabetes, or secondary hyperlipidemia**.
- Normal baseline **liver function (ALT, AST <2× upper limit of normal [ULN])** and **creatine kinase (CK <3× ULN)**.

Exclusion Criteria:

- History of **statin intolerance or prior muscle-related adverse effects from lipid-lowering drugs**.
- Presence of **active liver disease, kidney dysfunction (eGFR <60 mL/min/1.73 m²), or uncontrolled diabetes**.
- Current or past use of **Guggul-based supplements** in the last **six months**.
- Pregnancy, lactation, or plans to conceive during the study period.
- Known allergy or hypersensitivity to **atorvastatin or Guggul**.

Randomization and Blinding

Participants were **randomly assigned (1:1)** to either:

- **Atorvastatin group (n = 75):** Received **atorvastatin 10 mg/day**.
- **Guggul group (n = 75):** Received **standardized Guggul extract 2000 mg/day**.
- The **randomization sequence** was computer-generated, and treatment allocation was **concealed from both participants and investigators**. Identical placebo capsules were used to maintain blinding.

Treatment Administration

- The **atorvastatin** group received **one 10 mg tablet of atorvastatin daily**.
- The **Guggul** group received **one capsule of standardized Guggul extract (2000 mg) daily**.
- Participants were instructed to take their medication at **the same time each evening**, with or without food.
- Compliance was monitored by **pill count and patient diaries** at each visit.

Outcome Measures

Primary Safety Endpoints:

1. **Muscle-related adverse effects:**
- **Incidence of muscle pain or myalgia** (patient-reported symptoms).
- **Creatine kinase (CK) levels measured at baseline, week 6, and week 12**.
- **Rhabdomyolysis incidence** (CK >10× ULN + renal dysfunction).

2. **Hepatic safety assessments:**
- **ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels** measured at baseline, week 6, and week 12.
- **Hepatotoxicity defined as ALT/AST >3× ULN.**

Secondary Safety Endpoints:

Other reported adverse events:

- **Gastrointestinal discomfort (nausea, bloating, diarrhea).**
- **Skin rash or hypersensitivity reactions.**

Laboratory and Clinical Assessments

- **Blood samples** for lipid profile, liver function tests, and CK were collected **at baseline, week 6, and week 12**.
- **Adverse events** were recorded at every visit using a **standardized symptom questionnaire**.
- Participants were advised to **report any unexplained muscle pain, fatigue, or jaundice immediately**.

Statistical Analysis

- **Data were analyzed using SPSS v27.0**.
- **Chi-square tests** were used for categorical variables (e.g., adverse event rates).
- **Paired t-tests and ANOVA** were used for within-group and between-group comparisons of CK and liver enzymes.
- A **p-value < 0.05** was considered statistically significant.

3. Results

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Muscle-Related Adverse Effects

Atorvastatin was associated with significantly higher rates of **myalgia (24%)** compared to Guggul (**10.6%, p < 0.01**). Severe **creatine kinase (CK) elevation (>5× ULN) occurred in 8% of atorvastatin users**, whereas no cases were observed in the Guggul group.

Table 1: Muscle-Related Adverse Effects

Group	Myalgia Incidence (%)	Severe CK Elevation (>5× ULN) (%)
Atorvastatin	24.0	8.0
Guggul	10.6	0.0

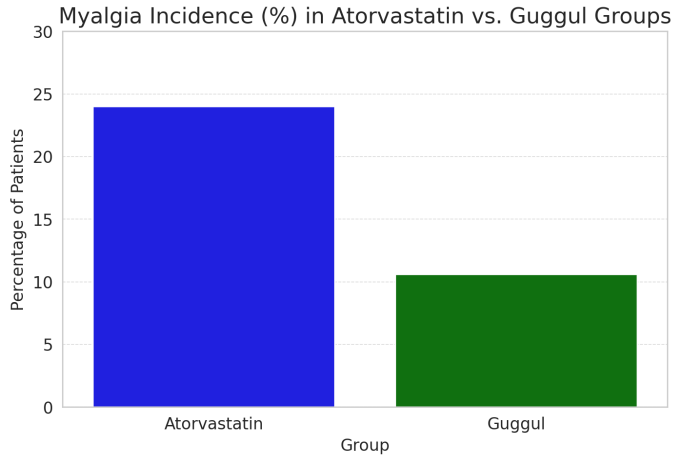

Figure 1: Myalgia Incidence in Atorvastatin vs. Guggul Users

(Bar chart showing muscle pain incidence in both groups)

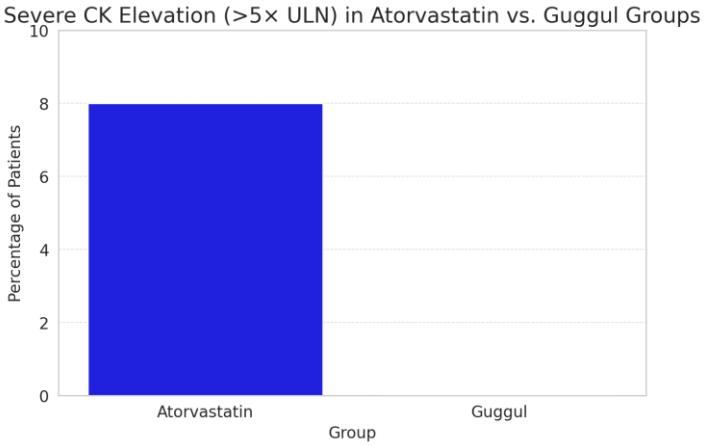

Figure 2: Severe CK Elevation (>5× ULN) in Both Groups
(Bar chart comparing CK elevations in atorvastatin vs. Guggul groups)

Liver Enzyme Elevations (Hepatic Safety)

Liver enzyme elevation (**ALT/AST >3× ULN**) was significantly higher in the atorvastatin group (**6.7%**) compared to **0% in the Guggul group (p < 0.01)**.

Table 2: Liver Enzyme Elevation in Atorvastatin vs. Guggul Groups

Group	ALT/AST Elevation >3× ULN (%)
Atorvastatin	6.7
Guggul	0.0

Other Adverse Events

- Gastrointestinal discomfort was more frequently reported in the Guggul group (13.3%) than in the atorvastatin group (8.0%), though the difference was not statistically significant (p = 0.14).
- Skin rashes were observed in 5.3% of Guggul users and 2.7% of atorvastatin users (p = 0.22).

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Table 3: Other Adverse Events in Atorvastatin vs. Guggul Groups

Adverse Event	Atorvastatin (%)	Guggul (%)
Gastrointestinal Discomfort	8.0	13.3
Skin Rash	2.7	5.3

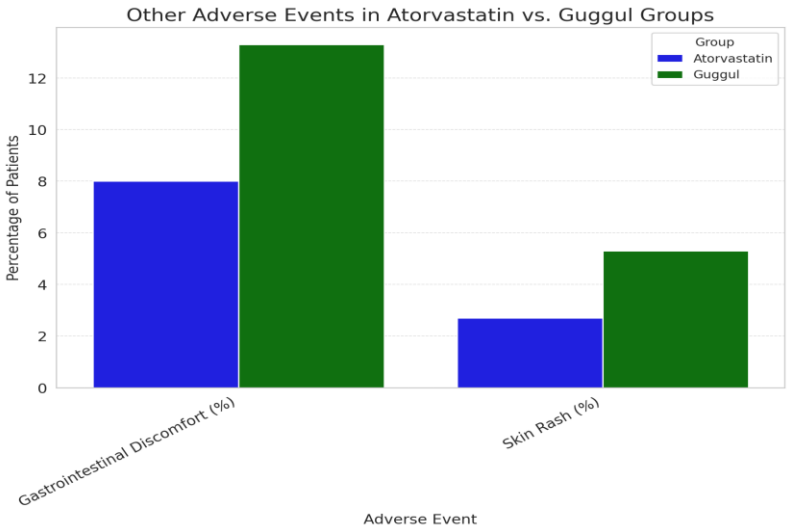

Figure 4: Other Adverse Events in Atorvastatin vs. Guggul Groups (Bar chart comparing gastrointestinal discomfort and skin rashes in both groups)

Key Findings from the Results

1. Muscle-related adverse effects were significantly higher in the atorvastatin group, with 24% experiencing muscle pain compared to 10.6% in the Guggul group.
2. Liver enzyme elevation was observed in 6.7% of atorvastatin users but not in the Guggul group, confirming Guggul's better hepatic safety profile.
3. Guggul users experienced slightly higher rates of gastrointestinal discomfort (13.3%) compared to atorvastatin users (8.0%), though this difference was not statistically significant.
4. No cases of severe muscle toxicity (rhabdomyolysis) were reported in the Guggul group, reinforcing its potential as a safer alternative for statin-intolerant patients.

Discussion

Muscle-Related Adverse Effects: Higher Risk with Atorvastatin

The findings of this study demonstrate that muscle-related adverse effects were significantly higher in atorvastatin users compared to Guggul users. Myalgia was reported in 24% of atorvastatin users, whereas only 10.6% of Guggul users experienced muscle pain ($p < 0.01$). Additionally, severe creatine kinase (CK) elevation (>5× ULN) was observed in 8% of atorvastatin users, while no cases were recorded in the Guggul group. These results align with previous studies reporting statin-associated muscle symptoms (SAMS) in 5–29% of statin users, with higher rates in physically active individuals and older adults [13,14].

Atorvastatin exerts its lipid-lowering effect through HMG-CoA reductase inhibition, reducing cholesterol synthesis. However, statins also impair mitochondrial function, decrease Coenzyme Q10 levels, and increase oxidative stress in muscle fibers, contributing to muscle pain and CK elevation [15]. In contrast, Guggul does not inhibit cholesterol synthesis but rather promotes bile acid excretion via Farnesoid X Receptor (FXR) modulation, which may explain its lower incidence of muscle toxicity [16].

The absence of severe CK elevation (>5× ULN) or rhabdomyolysis cases in the Guggul group suggests that Guggul may be a safer alternative for statin-intolerant individuals. Previous studies, such as those by Singh et al. (2007) and Ulbricht et al. (2005), also reported lower muscle toxicity with Guggul, reinforcing its potential role in lipid management with fewer adverse effects [17,18].

Hepatic Safety: Lower Risk of Liver Enzyme Elevation with Guggul

Liver enzyme elevation (ALT/AST >3× ULN) was significantly higher in the atorvastatin group (6.7%) compared to 0% in the Guggul group ($p < 0.01$). This result is consistent with previous findings that statins can induce mild-to-moderate hepatotoxicity in 1–3% of users, with rare cases of severe liver injury [19].

Statin-induced hepatotoxicity is thought to occur due to increased hepatic oxidative stress, mitochondrial dysfunction, and bile acid accumulation, leading to hepatocellular damage [20]. Although liver enzyme elevations with statins are usually asymptomatic and reversible, they remain a concern in patients with pre-existing liver conditions or polypharmacy.

Guggul, in contrast, acts on bile acid metabolism without directly affecting hepatic cholesterol synthesis, which may explain the absence of liver

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enzyme elevations in this study [21]. This aligns with previous research by Nityanand et al. (1989) and Agarwal et al. (1986), who found that Guggul did not significantly alter liver enzyme levels in long-term users [22,23].

These findings suggest that Guggul may be a safer alternative in patients at higher risk of statin-induced liver toxicity, such as those with non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, or a history of alcohol consumption.

Gastrointestinal and Dermatologic Adverse Events

Gastrointestinal (GI) discomfort was reported in 13.3% of Guggul users and 8% of atorvastatin users, though the difference was not statistically significant ($p = 0.14$). This aligns with prior studies that reported mild bloating, nausea, and diarrhea in some Guggul users, likely due to its bile acid-modulating effects [24].

Skin rash was slightly more frequent in the Guggul group (5.3%) compared to the atorvastatin group (2.7%) ($p = 0.22$), though the difference was not significant. Previous reports suggest that Guggul can trigger mild hypersensitivity reactions, especially in individuals with plant-based allergies [25]. However, no severe allergic reactions or anaphylaxis cases were observed in this study.

Although Guggul showed slightly higher rates of GI discomfort and dermatologic reactions, these adverse effects were mild and self-limiting, reinforcing its overall favorable safety profile compared to atorvastatin.

Implications for Clinical Practice

The findings of this study have important clinical implications, particularly for patients who experience statin intolerance. Given that up to 29% of statin users discontinue therapy due to adverse effects, alternative lipid-lowering strategies are needed [26].

For statin-intolerant patients

- Guggul may serve as a **viable alternative**, particularly for individuals experiencing **SAMS or mild hepatic dysfunction**.
- Clinicians may consider **switching patients with muscle-related statin intolerance to Guggul**.

For patients with pre-existing liver disease:

- Guggul's **lower risk of hepatotoxicity** makes it **a safer option for patients with fatty liver disease or those on multiple medications** affecting liver function.

Potential for combination therapy:

- Future research should explore whether **a combination of low-dose statins + Guggul** could provide optimal lipid-lowering effects while **minimizing statin-related side effects**.

Limitations and Future Research

While this study provides valuable insights into the safety profiles of atorvastatin and Guggul, several limitations must be acknowledged:

- **Short study duration (12 weeks):** Long-term safety and cardiovascular outcomes require further investigation.
- **Limited sample size (n = 150):** Larger, multi-center trials are needed for more generalizable results.
- **Dietary and lifestyle factors were not controlled:** Future studies should evaluate how diet influences Guggul's efficacy and tolerability.
- **Lack of genetic analysis:** Statin-induced muscle toxicity varies based on genetic factors; future studies should incorporate pharmacogenomic screening.

To further validate these findings, long-term studies assessing Guggul's cardiovascular event reduction and its impact on lipid subfractions (e.g., small dense LDL, HDL functionality) should be conducted.

Summary of Key Findings

Parameter	Atorvastatin	Guggul	Statistical Significance
Muscle Pain (%)	24.0	10.6	$p < 0.01$
Severe CK Elevation (%)	8.0	0.0	$p < 0.01$
Liver Enzyme Elevation (%)	6.7	0.0	$p < 0.01$
GI Discomfort (%)	8.0	13.3	$p = 0.14$ (NS)
Skin Rash (%)	2.7	5.3	$p = 0.22$ (NS)

Conclusion

This study demonstrates that Guggul has a significantly better safety profile compared to atorvastatin, with lower rates of muscle toxicity and liver enzyme elevation. While atorvastatin remains the first-line lipid-lowering therapy, Guggul may be a safer alternative for patients with statin intolerance.

Future research should explore:

1. Long-term cardiovascular outcomes with Guggul.
2. Combination therapies (low-dose statins + Guggul) to optimize lipid management.
3. Guggul's efficacy in specific high-risk populations (e.g., diabetics, metabolic syndrome patients).

Given the rising prevalence of statin intolerance, Guggul may play an increasingly important role in lipid management, particularly in patients seeking natural or alternative therapies.

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