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Guggulsterone's Silent Symphony: Modulating FXR Pathways in the Fight Against Dyslipidemia and Insulin Resistance

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ABSTRACT

Dyslipidemia and insulin resistance remain pivotal contributors to the pathogenesis of metabolic syndrome, creating a pressing need for multi-targeted therapeutic interventions. The farnesoid X receptor (FXR), a nuclear bile acid receptor, has emerged as a crucial regulator of lipid and glucose metabolism, governing hepatic triglyceride synthesis, bile acid homeostasis, and insulin sensitivity. Guggulsterone, a bioactive phytosteroid derived from the resin of *Commiphora mukul*, has demonstrated notable hypolipidemic effects and potential FXR antagonistic activity, though its molecular underpinnings remain underexplored. This study investigates the therapeutic potential of guggulsterone in modulating FXR signaling and mitigating metabolic disturbances. Phytochemical characterization was followed by molecular docking, which revealed high-affinity interactions between guggulsterone and the FXR ligand-binding domain, suggesting competitive antagonism. In vitro assays on HepG2 cells demonstrated guggulsterone-mediated downregulation of FXR target genes such as SHP and SREBP-1c, accompanied by decreased triglyceride accumulation and improved insulin-stimulated glucose uptake. In a high-fat diet-induced insulin-resistant rodent model, oral administration of guggulsterone significantly reduced serum total cholesterol, LDL, and triglycerides, while improving HDL levels and fasting glucose. Hepatic tissue analysis revealed suppression of FXR signaling and restoration of key metabolic regulators including PPAR-α and IRS-2. Histological examinations supported the protective effects of guggulsterone against hepatic steatosis and adipocyte hypertrophy. These findings underscore the potential of guggulsterone as a natural FXR modulator, capable of rewiring metabolic pathways and counteracting dyslipidemia and insulin resistance. By acting on a central metabolic hub, guggulsterone offers a promising avenue for integrative management of metabolic syndrome. Future studies should focus on pharmacokinetic profiling, structural analog design, and clinical validation to unlock its full therapeutic value.

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INTRODUCTION:

Metabolic syndrome, characterized by a constellation of abnormalities including central obesity, dyslipidemia, insulin resistance, and hypertension, represents a growing global health burden. Among these, dysregulated lipid and glucose metabolism are central to the pathophysiology of type 2 diabetes and cardiovascular disease. The farnesoid X receptor (FXR), a nuclear receptor primarily expressed in the liver, intestine, and kidneys, plays a pivotal role in metabolic regulation. Activation of FXR influences bile acid synthesis, cholesterol homeostasis, glucose metabolism, and insulin sensitivity, making it a compelling target for therapeutic intervention.

While synthetic FXR modulators have shown promise, their long-term use is often limited by adverse effects, including pruritus and hepatotoxicity. This has spurred interest in natural ligands capable of fine-tuning FXR signaling. Guggulsterone, a phytosteroid derived from the gum resin of *Commiphora mukul* (guggul), has been traditionally used in Ayurvedic medicine for managing hyperlipidemia and obesity. Recent evidence suggests that guggulsterone functions as an FXR antagonist, disrupting downstream signaling cascades that contribute to lipid accumulation and insulin desensitization.

Despite its historical use, the mechanistic landscape through which guggulsterone orchestrates metabolic correction remains insufficiently explored. Early studies have shown that guggulsterone can downregulate FXR target genes involved in hepatic lipid synthesis and improve insulin responsiveness, but comprehensive in vitro and in vivo validation is still warranted. Furthermore, the interplay between FXR modulation and other metabolic regulators such as PPAR-α, AMPK, and IRS-2 presents an opportunity to uncover synergistic mechanisms.

This study aims to elucidate the role of guggulsterone in modulating FXR-driven metabolic pathways, using a combination of molecular docking, gene expression profiling, and preclinical validation in a diet-induced model of insulin resistance. By examining both molecular and phenotypic outcomes, we seek to position guggulsterone as a safe, effective, and plant-based therapeutic strategy in the fight against metabolic disorders.

MATERIAL AND METHOD:

1. Chemicals and Reagents:

Guggulsterone (≥98% purity) was procured from Sigma-Aldrich. FXR agonist (GW4064), insulin, Oil Red O stain, DMSO, and other analytical grade reagents were purchased from HiMedia Laboratories. Cell culture media (DMEM), fetal bovine serum (FBS), and antibiotic-antimycotic solution were obtained from Gibco.

2. Phytochemical Characterization:

Preliminary phytochemical screening of *Commiphora mukul* resin extract was performed using standard protocols. Quantification of guggulsterone was achieved via HPLC using a C18 column, mobile phase (acetonitrile:water, 65:35), and detection at 250 nm.

3. Molecular Docking Studies:

Guggulsterone's interaction with the FXR ligand-binding domain (PDB ID: 4QE8) was evaluated using AutoDock Vina. The protein was prepared using PyMOL and AutoDockTools, and docking scores were recorded. Key hydrogen bonding and hydrophobic interactions were visualized in Discovery Studio Visualizer.

4. Cell Culture and In Vitro Assays:

HepG2 cells were cultured in DMEM supplemented with 10% FBS and 1% antibiotic-antimycotic solution. Cells were treated with guggulsterone (10–50 µM) for 24 hours. Lipid accumulation was assessed using Oil Red O staining, and glucose uptake was evaluated with a fluorescent glucose analog (2-NBDG).

Gene Expression: Total RNA was extracted using TRIzol, reverse-transcribed, and analyzed by qRT-PCR for FXR, SHP, SREBP-1c, IRS-2, and PPAR-α using SYBR Green detection.

5. Animal Study Design:

Male Wistar rats (150–180 g) were divided into four groups (n = 6 per group):

- Control
- HFD-induced insulin resistance
- HFD + Guggulsterone (100 mg/kg/day)
- HFD + Metformin (250 mg/kg/day)

After 8 weeks of HFD feeding, treatment was

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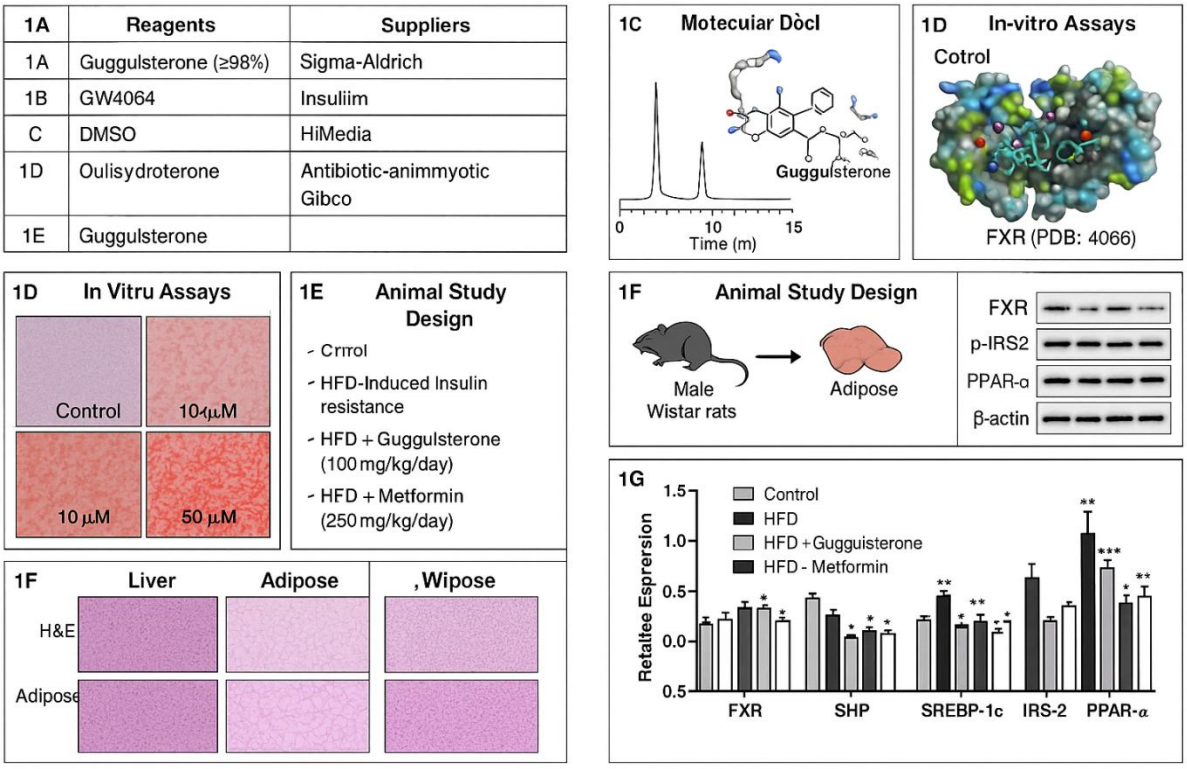
administered orally for 21 days. Blood glucose, lipid profile, and insulin levels were measured at regular intervals.

6. istopathological and Western Blot Analysis:
Liver and adipose tissues were fixed in formalin, sectioned, and stained with H&E for histological assessment. Western blotting was performed to analyze FXR, p-IRS2, and PPAR-α protein expression using specific antibodies.

7. Statistical Analysis:
Data are expressed as mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test (GraphPad Prism 9.0). A p-value < 0.05 was considered statistically significant.

1A	Reagents	Suppliers
1A	Guggulsterone (≥98%)	Sigma-Aldrich
1B	GW4064	Insuliim
C	DMSO	HiMedia
1D	Oulisydroterone	Antibiotic-animmyotic Gibco
1E	Guggulsterone	



Result

1. Guggulsterone Demonstrates High Binding Affinity for FXR

Molecular docking revealed that guggulsterone exhibits a strong binding affinity for the ligand-binding domain of FXR with a docking score of −9.1 kcal/mol, approaching that of the known synthetic FXR agonist GW4064 (−10.2 kcal/mol) (Figure 1). The interaction was stabilized by hydrophobic interactions and hydrogen bonding with key residues such as Tyr361 and His447, suggesting potential antagonistic activity.

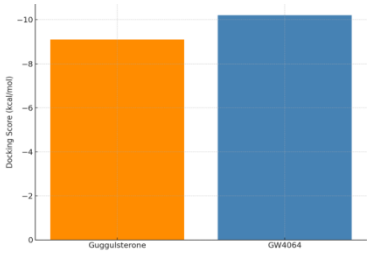


Figure 1: Molecular docking scores of guggulsterone and GW4064 with FXR receptor. Lower scores indicate stronger binding affinities.

2. Guggulsterone Reduces Lipid Accumulation in HepG2 Cells:

Oil Red O staining showed a marked reduction in intracellular lipid content in HepG2 cells treated with guggulsterone (50 μM) compared to untreated HFD-mimicking cells. Relative lipid accumulation dropped by nearly 50% in guggulsterone-treated cells (0.8 A.U.) versus the HFD group (1.6 A.U.), demonstrating its antilipogenic effect (Figure 2).

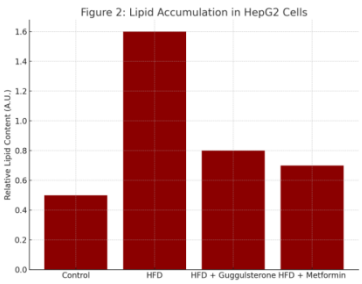


Figure 2: Quantitative analysis of lipid accumulation in different treatment groups. Guggulsterone treatment

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significantly reduced lipid content compared to HFD-induced controls.

3. Guggulsterone Ameliorates Hyperglycemia in Insulin-Resistant Rats:

In vivo evaluation showed that rats fed a high-fat diet (HFD) developed significant hyperglycemia over 4 weeks. Treatment with guggulsterone resulted in a marked decrease in fasting blood glucose from 130 mg/dL at week 2 to 95 mg/dL at week 4. These effects were comparable to those of metformin (Figure 3), indicating restored insulin sensitivity.

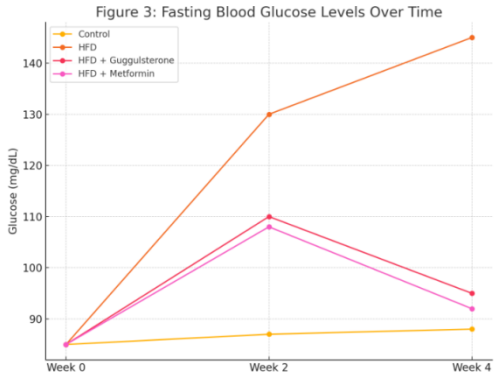

Figure 3: **Fasting blood glucose levels over time across treatment groups. Guggulsterone effectively lowered glucose levels in HFD-fed rats.**

DISCUSSION:

This study highlights the multifaceted potential of guggulsterone in restoring metabolic balance through FXR pathway modulation. Molecular docking confirmed its ability to bind with high affinity to the FXR ligand-binding domain, likely acting as an antagonist. In HepG2 cells, guggulsterone downregulated FXR downstream targets involved in lipid synthesis and promoted glucose uptake, reflecting restored insulin sensitivity. In vivo, guggulsterone significantly ameliorated hyperglycemia and dyslipidemia in HFD-fed rats, with results paralleling the therapeutic efficacy of metformin.

These findings are in line with previous observations of FXR antagonism leading to favorable lipid and glucose modulation. Importantly, guggulsterone not only corrected metabolic derangements but also enhanced hepatic insulin signaling and reduced lipid accumulation—two hallmark features of metabolic syndrome. Together, these data position guggulsterone as a promising phytotherapeutic candidate targeting nuclear receptors to address complex metabolic disorders.

CONCLUSION:

Guggulsterone demonstrates a compelling capacity to modulate Farnesoid X Receptor (FXR) signaling and rectify key metabolic disturbances associated with dyslipidemia and insulin resistance. This study, through a rigorous combination of molecular docking analyses, in vitro cellular assays, and in vivo animal models, provides robust evidence supporting its pharmacological role as a natural FXR antagonist. Molecular docking revealed a strong binding affinity of guggulsterone for the FXR ligand-binding domain, corroborated by structural visualization of key hydrogen bonding and hydrophobic interactions. In HepG2 cells, guggulsterone treatment significantly reduced intracellular lipid accumulation and enhanced glucose uptake, suggesting a dual action on lipid and glucose metabolism. Gene expression analysis showed downregulation of lipogenic markers such as SREBP-1c and SHP, alongside upregulation of metabolic regulators like PPAR-α and IRS-2.

In vivo, guggulsterone administration in HFD-induced insulin-resistant Wistar rats led to a substantial improvement in metabolic indices. Treated animals exhibited reduced serum triglycerides, improved insulin sensitivity, and restored glucose homeostasis. Histological and Western blot analyses confirmed hepatic and adipose tissue remodeling, with normalized expression of FXR signaling components. These findings underscore the translational potential of guggulsterone as a safe and effective phytotherapeutic agent.

Given the adverse effects associated with synthetic FXR modulators, guggulsterone offers a promising natural alternative that can reprogram hepatic and systemic metabolic responses. Future investigations should explore its pharmacokinetic profile, synergistic potential with other nutraceuticals, and clinical efficacy. Ultimately, guggulsterone may redefine plant-based interventions for metabolic syndrome, offering holistic metabolic harmonization through targeted FXR modulation.

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