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RESEARCH

Aegeline from *Aegle marmelos* as a dual-target agonist for managing type II diabetes mellitus

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Type II Diabetes Mellitus (T2DM) is a multifactorial metabolic disorder requiring therapeutics that act on multiple pathways. A prominent therapeutic target is the Peroxisome Proliferator-Activated Receptor (PPAR) family, specifically the PPARγ and PPARα subtypes. The mechanism of action of Aegeline, a natural compound extracted from *Aegle marmelos* leaves, is examined in a computational study and it is evaluated against synthetic PPAR agonists Pioglitazone, Rosiglitazone, and Fenofibrate. Full agonistic activity requires binding within the Ligand Binding Domain (LBD) and forming specific hydrogen bond interactions, which was found to be crucial through molecular docking analysis. The binding pose of Aegeline in the PPARγ LBD was unique, as it did not have the conserved hydrogen bonds with His323 and Tyr473, which are characteristic of full agonists, suggesting that it acts as a partial agonist. In contrast, Aegeline showed a binding mode that was comparable to Fenofibrate, as it bonds with Tyr334 and Ala333. Based on these findings, Aegeline is believed to act as a PPARα agonist and a partial PPARγ agonist, providing both antihyperglycemic and antilipidemic benefits.By using Aegeline, a natural compound that offers a promising lead, dual-target therapies that may have fewer side effects may be possible. In the future, the aim of research should be to verify these findings in vivo and explore their effect on diabetic complications.

Keywords: PPARs, Aegeline, molecular docking, dual agonist, partial agonism, type II diabetes, *Aegle marmelos*

Introduction

Cardiovascular diseases, such as myocardial infarction, coronary artery disease, hypertension, and dyslipidemia, are significantly impacted by diabetes mellitus, which is an important independent risk factor. The majority of patients with type 2 diabetes experience elevated blood glucose levels and hyperlipidemia. Non-insulin-dependent diabetes mellitus (NIDDM) is a rapidly growing global public health concern that affects about 80–90% of all cases of diabetes (1). It involves insulin resistance, impaired glucose-stimulated insulin secretion, abnormally elevated glucagon levels, and chronic hyperglycemia.

The current pharmaceutical strategies for managing type 2 diabetes concentrate on a variety of molecular targets, such as PPARs, Sur1-Kir6.2, several kinases, DPP-IV, and others. The NR1 subfamily of nuclear receptors comprises PPARs, which function as transcription factors activated by ligands and play a crucial role in regulating fat and carbohydrate metabolism. In clinical settings, synthetic agonists aimed at specific PPAR isoforms are utilized to lower serum triglycerides and improve insulin sensitivity. The identification of PPAR targets, including normoglycemic thiazolidinediones (TZDs) and lipid-lowering fibrates, has created new avenues for developing cutting-edge treatments for type 2 diabetes.

Pioglitazone and rosiglitazone, two of the most effective TZDs, are associated with side effects such as weight gain, edema, cardiac hypertrophy, and an increased risk of heart failure. The search for new PPAR ligands, like pan-agonists, PPAR partial agonists, and PPAR/dual agonists, with better safety profiles has been prompted (2). Recent data suggests that partial agonists may present therapeutic benefits despite having fewer adverse effects than full agonists.

Consequently, a single drug possessing dual hypolipidemic and hypoglycemic actions is highly desirable.

Aegle marmelos (L.) Correa (Rutaceae), commonly known as bael, is a medicinal plant traditionally used in India. Numerous studies across South Asia have confirmed the hypoglycemic properties of its extracts (3, 4). Recent work by Narender et al. identified potent antihyperglycemic and antidyslipidemic activities in the alcoholic leaf extract and its chloroform fraction (5, 6). The plant contains various bioactive compounds, including the alkaloid aegeline, which is of particular interest.

While A. marmelos has been investigated for various pharmacological effects [e.g., anti-ulcer, antimicrobial, anti-inflammatory (7, 8)], its precise mechanisms of action remain incompletely elucidated. This study employs insilico methods to hypothesize the mechanism of the natural compound Aegeline against type II diabetes mellitus (T2DM). We aimed to identify its mode of action and compare its efficacy to synthetic reference agonists (Pioglitazone, Rosiglitazone, Fenofibrate) at the PPARγ and PPARα receptors (**Figure 1**).

Background

The development of synthetic dual and pan-PPAR agonists has reached advanced clinical stages. However, the progression of several candidates has been halted due to long-term safety concerns, including the induction of malignancies in murine models (9). Consequently, the safety and therapeutic benefit of these synthetic agonists necessitate further rigorous investigation before regulatory approval (10).

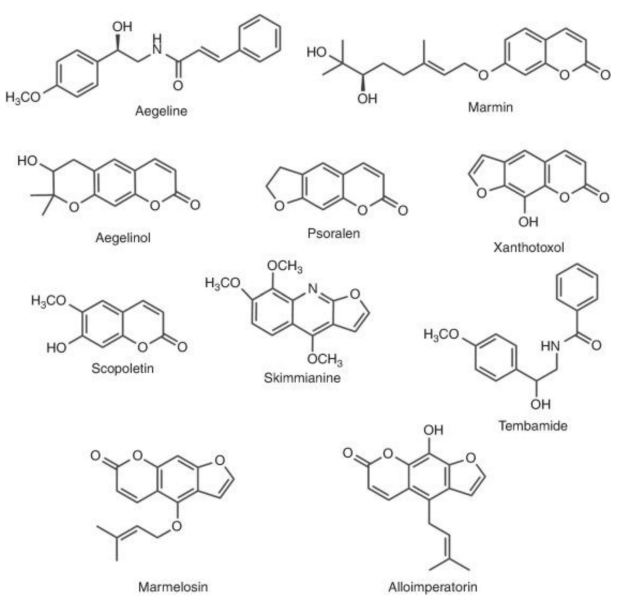

FIGURE 1 | Structure of the chemical components in Bael.

This underscores the value of exploring natural product-derived leads, which may offer the combined benefits of glitazones and fibrates within a single molecule while minimizing adverse effects. The design of dual PPARα/γ agonists remains a major objective in medicinal chemistry (11), and partial agonists are considered to offer a distinct and potentially safer clinical profile compared to full agonists.

Results and discussion

Structural overview of PPAR receptors peroxisome proliferator-activated receptors (PPARs)

These are ligand-inducible transcription factors part of the nuclear hormone receptor superfamily. Three mammalian isoforms exist: PPARα, PPARγ, and PPARδ. All are implicated in treating metabolic syndrome, a cluster of conditions that elevate the risk for cardiovascular disease and diabetes (12). PPARα is the molecular target for fibrate drugs (13), while PPARγ, highly expressed in adipose tissue, mediates adipocyte differentiation and is the target for TZDs (14). Their functions are summarized in **Table 1**.

Ligand binding domain (LBD) of PPARγ

The PPARγ ligand binding domain (LBD) features a large, T-shaped hydrophobic cavity situated in the lower half of the domain. This cavity extends between helix H3 and a β-sheet, running parallel to H3, and another section stretches orthogonally toward the C-terminal AF-2 helix (15). The apo-PPARγ structure has a pocket volume of approximately 1,300 $Å^3$. A proposed ligand entry site exists between H3 and the β-sheet, lined with hydrophilic residues (D243, E290, R288, E295) (15). The domain consists of 13 α-helices and a small 4-stranded β-sheet. The region between helix 1 and helix 3, known as the Ω-loop, displays significant structural

TABLE 1 | Human peroxisome proliferator-activated receptors (PPARs) as targets in the metabolic syndrome.

Receptor	Functions	Conditions targeted by agonists
PPARα	Regulation of lipid metabolism, fatty acid oxidation.	Atherogenic dyslipidemia [high triglycerides, low HDL (high-density lipoprotein)]. Target of fibrates.
PPARγ	Control of glucose metabolism, adipocyte differentiation, insulin sensitization.	Insulin resistance in type II diabetes mellitus (T2DM). Target of thiazolidinediones (TZDs).
PPARδ	Influences multiple facets of metabolic syndrome.	Metabolic syndrome, obesity, atherosclerosis.

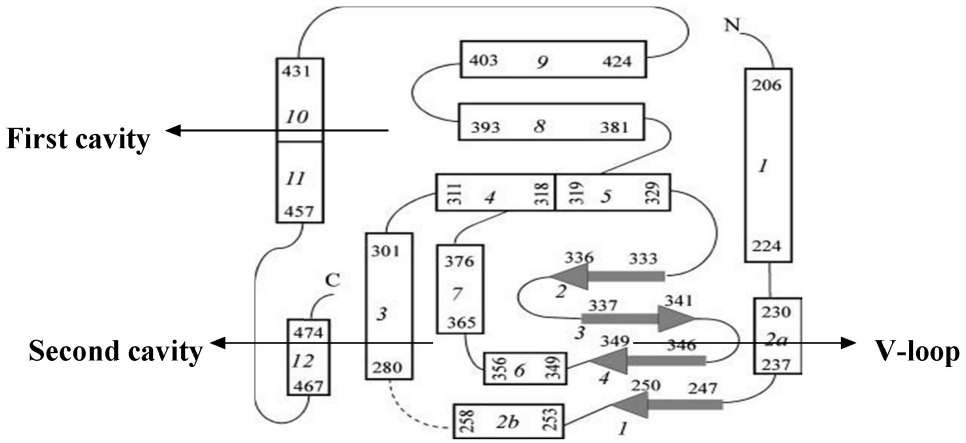

FIGURE 2 | Structural features (19) of the ligand binding domain (LBD) of PPAR γ.

variability and is highly flexible (15). In the crystallized apo-form, helix 12 covers the ligand-binding pocket. Its stabilization via a salt bridge (e.g., between Lys319 and Asp475) is critical for transcriptional activation (16).

The canonical ligand-binding pocket is formed by helices H3, H5, H7, H11, and H12. It is characterized by a polar surface created by residues His323, Tyr327, Lys367, His449, and Tyr473. A second cavity extends toward helix 1 and the β-sheet. The overall hydrophobic nature of these pockets is suitable for binding natural ligands like fatty acids and prostaglandin metabolites (17, 18) (**Figure 2**).

Ligand binding domain (LBD) of PPARα

PPARα possesses a ligand-binding pocket that is larger than that of many other nuclear receptors but similar in overall size and T-shape to PPARγ and PPARδ (20, 21). However, the PPARα pocket is more hydrophobic and less solvent-exposed. A key structural difference is the substitution of Tyr334 in PPARα for His323 in PPARγ; the bulkier tyrosine sidechain induces a conformational shift in the bound ligand, a major determinant of subtype selectivity (22). The ligand entry channel in PPARα is partially obstructed by Tyr334, which forms a hydrogen bond with Glu282, and a flexible loop (residues 254–264), requiring ligand flexibility for binding (23) (**Figure 3**).

Molecular basis of PPAR agonism

Full agonism is characterized by a conserved pattern of hydrogen bond formation. TZDs typically form H-bonds with His323 on helix 5 and Tyr473 on the AF2 helix in PPARγ. Similarly, fibrates like Fenofibrate form critical H-bonds with Tyr334 in PPARα. The absence of these conserved interactions often underpins partial agonistic activity, as most full agonists stabilize the receptor complex through these specific bonds (24) (**Figure 4**).

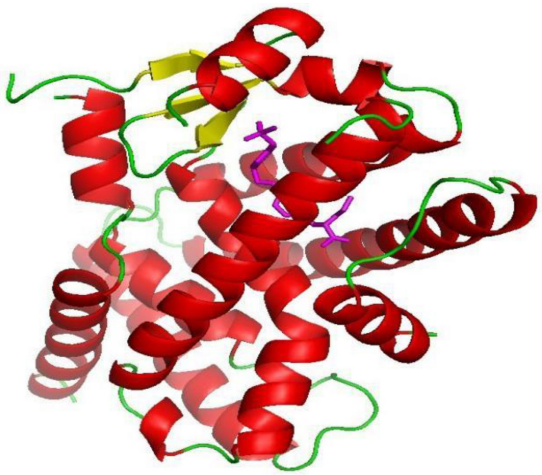

FIGURE 3 | Structure of PPARα with the ligand.

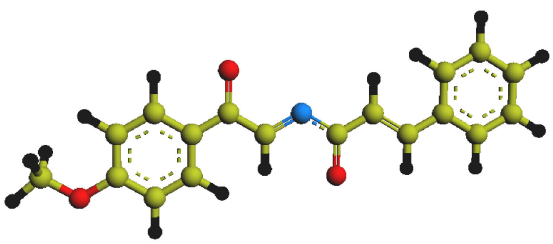

FIGURE 4 | Structure of the natural lead Aegeline.

Docking analysis: Aegeline vs. synthetic agonists on PPARγ

The molecular structure of Aegeline(C18H19O3N) was constructed computationally. Synthetic drug structures were sourced from DrugBank (**Figure 5**).

Aegeline docked into the PPARγ LBD (PDB: 3PRG) with a high affinity score of −11.3282 kcal/mol. It was positioned in the characteristic T-shaped cavity. Notably, it formed a single hydrogen bond with SER289 (distance: 2.671780 Å)

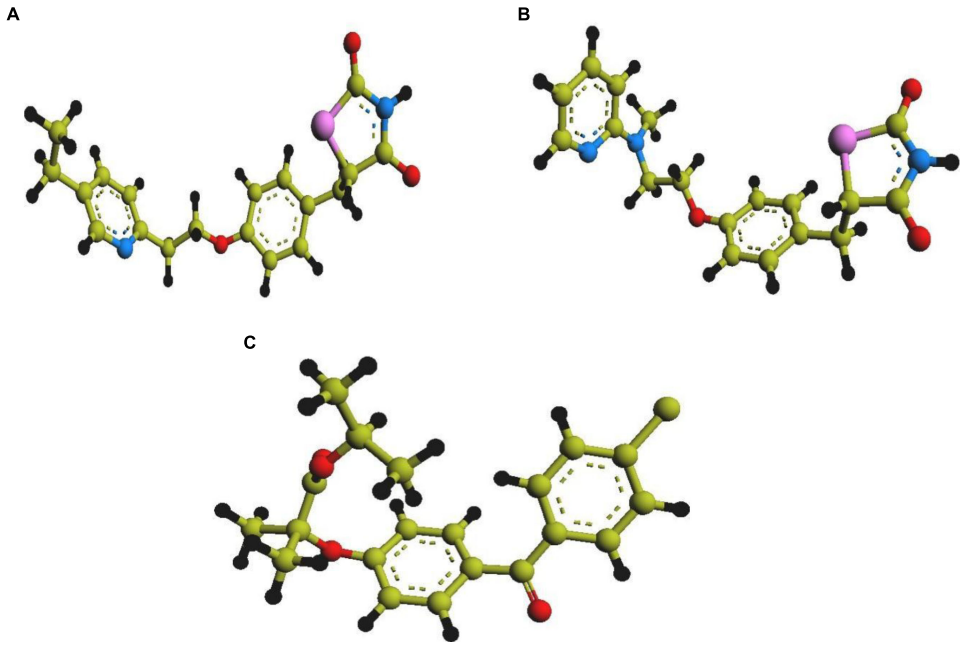

FIGURE 5 | (A) Structure of Pioglitazone. **(B)** Structure of Rosiglitazone. **(C)** Structure of Fenofibrate.

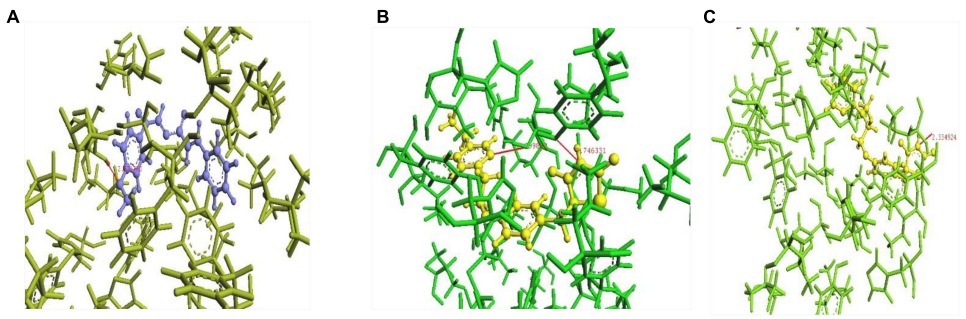

FIGURE 6 | (A) H-bonding between the lead Aegeline and the LBD of PPARγ. **(B)** H-bonding pattern between the drug Pioglitazone and the LBD of PPARγ. **(C)** H-bonding between the drug Rosiglitazone and the LBD of PPARγ.

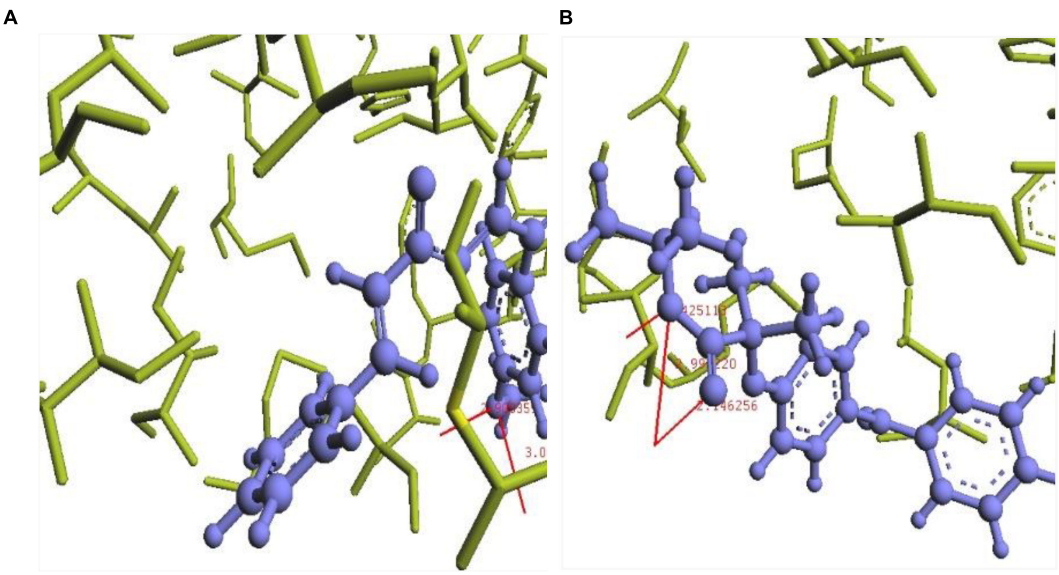

FIGURE 7 | (A) H-bonding between the lead and LBD of PPARα. **(B)** H-bonding between the drug Fenofinrate and LBD of PPARα.

TABLE 2 | Docking scores and hydrogen bond interactions.

Receptor	Ligand	Docking score (kcal/mol)	Hydrogen bond	
			Residue	Distance(A)
3PRG (PPAR-gamma)	Pioglitazone	−10.48	SER 289	2.999832
			TYR473	2.746331
	Rosiglitazone	−9.3712	MET329	2.334924
	Aegeline	−11.3282	SER 289	2.671780
1I7G (PPAR-alpha)	Fenofibrate	−9.95199	TYR334	2.146256
			TYR334	2.997220
			ALA333	2.425113
	Aegeline	−9.94966	ALA333	2.908359
			TYR334	3.000147

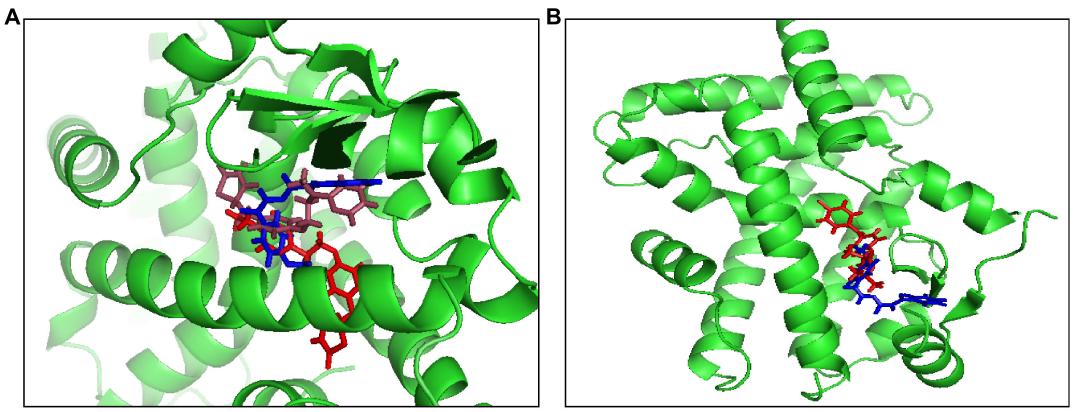

FIGURE 8 | (a) Superimposition of the ligand binding domain of PPAR-γ along with the synthetic drugs pioglitazone and rosiglitazone and the natural lead aegeline. **(b)** Superimposition of the ligand binding domain of PPAR-α along with the synthetic drug fenofibrate and the natural lead aegeline.

but lacked the conserved interactions with His323 and Tyr473 (**Figure 6a**).

Pioglitazone scored −10.48 kcal/mol, forming H-bonds with TYR473 (2.746331 Å) and SER289 (2.999832 Å) (**Figure 6b**).

Rosiglitazone scored −9.3712 kcal/mol, forming an H-bond with MET329 (2.334924 Å) (**Figure 6c**).

The failure of Aegeline to form the canonical H-bonds with His323 and Tyr473 suggests it acts as a partial agonist of PPARγ.

Docking analysis: Aegeline vs. Fenofibrate on PPARα

Aegeline docked into the PPARα LBD (PDB: 1ITT) with a score of −9.94966 kcal/mol. It formed two hydrogen bonds: one with ALA333 (2.908359 Å) and one with TYR334 (3.000147 Å) on the β2-sheet (**Figure 7a**).

Fenofibrate scored −9.95199 kcal/mol and formed three H-bonds: two with TYR334 (2.146256 Å, 2.997220 Å) and one with ALA333 (2.425113 Å) (**Figure 7b** and **Table 2**).

Superimposition of the docked complexes confirmed that Aegeline occupies the same general cavity in PPARγ as synthetic drugs (though in a distinct pose) and binds in a nearly identical position and orientation to Fenofibrate within the PPARα binding site (**Figures 8a** and **b**).

Conclusion

Type II diabetes mellitus (T2DM) poses a severe health burden in India and worldwide. Despite advances with synthetic drugs, their side effects have renewed interest in medicinal plants. Discovering dual-acting agents from traditional medicine is a significant pursuit. This in silico study elucidates the mechanism of Aegeline, a bioactive compound from *Aegle marmelos*.

Our findings indicate that Aegeline functions as a PPARα agonist and a PPARγ partial agonist. Its ability to activate PPARα, like Fenofibrate, suggests antilipidemic effects. Its partial agonism of PPARγ, due to a lack of conserved H-bonding, suggests it may confer insulin-sensitizing benefits with a potentially reduced risk of the

adverse effects associated with full agonists. The hydrogen bond distances formed were comparable to those of synthetic drugs. As a natural product, Aegeline represents a promising lead compound for developing a dual-target therapeutic for T2DM with an improved safety profile. Future work should include in vitro and in vivo validation of these effects and exploration of its potential to mitigate cardiovascular complications linked to diabetes.

The translational potential of dual PPAR agonists is supported by recent developments, such as the approval of saroglitazar in India (25) and the progression of pan-agonists like lanifibranor for NASH (26). Novel synthetic and natural dual-target compounds continue to emerge, highlighting the relevance and promise of this approach and positioning Aegeline as a compelling candidate for further investigation.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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