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Uncovering Anti-Obesity Candidates from Robusta Green Coffee: In Silico Evaluation of Bioactive Compounds Targeting PPAR-α

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Abstract

Obesity arises from a chronic imbalance between energy intake and expenditure, leading to excessive accumulation of body fat. Peroxisome proliferator-activated receptor-alpha (PPARα) plays a key regulatory role in lipid metabolism, particularly in reducing the de novo synthesis of fatty acids. Robusta coffee has been widely consumed as part of the lifestyle, yet scientific evidence for its pharmacological effects is limited. This study aimed to evaluate the molecular interactions between secondary metabolites from Green Bean Coffee Robusta (*Coffea canephora* P.) and PPARα using *in silico* approaches. The workflow included screening compounds from *C. canephora* based on Lipinski's Rule of Five (RO5) and ADMET predictions, followed by molecular docking simulations using AutoDock against PPARα (PDB ID: 2P54). All the bioactive constituents in *C. canephora* met the requirements of RO5, and several metabolites were assessed based on their pharmacokinetic profile and toxicology prediction. Further molecular docking analysis identified 4-ethyl-2-methoxyphenol as the most promising anti-obesity candidate, demonstrating the lowest binding energy (-4.58 kcal/mol) and an inhibition constant of 440.47 μM. The compound formed key hydrogen bonds with amino acid residues ALA333, THR279, CYS276, and CYS275. These findings suggest that 4-ethyl-2-methoxyphenol from Green Bean Coffee Robusta exhibits potential as an anti-obesity agent through its interaction with the PPARα receptor. Further in vitro and in vivo studies are required to validate its pharmacological effects.

Keywords: Obesity; PPAR-α; *Coffea canephora*; Molecular Docking

1. INTRODUCTION

Obesity is defined as a chronic condition characterized by an imbalance between energy intake and expenditure, resulting in excessive fat accumulation [1]. Its increasing prevalence worldwide has made it a major public health concern. In Indonesia, the prevalence of obesity among adults rose from 21.8% in 2018 to 23% in 2023 [1-2]. Factors contributing to obesity include unhealthy dietary patterns, physical inactivity, genetic predispositions, and certain medical conditions. Modern lifestyle changes, such as frequent consumption of fast food, increased reliance on motorized transportation, and reduced physical activity due to sedentary occupations, have further accelerated obesity rates [3]. Obesity is strongly associated with numerous non-communicable diseases, including type 2 diabetes mellitus, cardiovascular disease, hypertension, and certain cancers, as well as mental health disorders such as depression and anxiety [4-6]. Although lifestyle modifications remain the foundation of obesity management, many individuals do not achieve or maintain sufficient weight loss through diet and exercise alone [7]. Consequently, pharmacological interventions play an important role in comprehensive obesity treatment [8].

Currently available anti-obesity drugs, such as orlistat, naltrexone–bupropion, and phentermine–topiramate, demonstrate clinical benefits but are often associated with gastrointestinal, neurological, and psychological side effects [9,10]. These limitations have driven growing interest in natural compounds with potential anti-obesity effects but fewer adverse reactions. One promising therapeutic target for managing obesity is the peroxisome proliferator-activated receptor-alpha (PPARα), a key regulator of lipid metabolism. PPARα modulates the expression of proteins involved in fatty acid transport and β-oxidation (e.g., CPT1 and ACC), helping reduce triglyceride accumulation and improve lipid homeostasis. Activation of PPARα can also suppress enzymes such as ACC and FAS, decrease de novo fatty acid synthesis, and improve plasma lipid profiles [11]. Robusta coffee (*Coffea canephora* P.) contains several bioactive compounds, notably chlorogenic acid and caffeine- that have demonstrated lipid-lowering, anti-obesity, and antidiabetic effects [12-14]. Beyond these well-known constituents, green coffee beans also contain a diverse range of secondary metabolites, including phenols, benzenediol derivatives, methoxyphenols, fatty acids, sterols, and others, which may contribute to metabolic benefits [15,16].

Despite growing evidence supporting the anti-obesity potential of coffee-derived compounds, there is a lack of systematic computational studies exploring the binding affinity and interaction profiles of diverse secondary metabolites from green robusta coffee with PPARα. In particular, the contribution of non-major constituents beyond chlorogenic acid and caffeine has not been adequately investigated at the molecular level. Recent computational studies have demonstrated the utility of in silico approaches, such as molecular docking and molecular dynamics simulations, in identifying natural ligands capable of modulating PPARα activity. Several plant-derived polyphenols, flavonoids, and fatty acid derivatives have been computationally predicted to bind favorably to the PPARα ligand-binding domain, suggesting their potential as PPARα agonists or modulators. Nonetheless, most existing in silico investigations have focused on isolated compounds from well-characterized medicinal plants, while comprehensive computational screening of secondary metabolites from green robusta coffee against PPARα is still limited. Thus, the present study aims to evaluate the molecular interactions between secondary metabolites from green bean robusta coffee and PPARα using an in silico approach. By employing molecular docking and interaction analysis, this study seeks to identify promising coffee-derived compounds that may act as PPARα modulators, thereby providing a rational basis for further in vitro and in vivo investigations toward the development of natural anti-obesity agents.

2. MATERIALS AND METHODS

2.1. Materials and Instruments

The materials used in this study included a laptop (Windows 11, 64-bit) with an AMD Ryzen 5 5600H processor (12 CPUs) ~3.3 GHz and 8 GB RAM, as well as supporting software such as Chrome Browser (version 125.0.6422.113), LigandScout 4.4.9 (licensed by Laboratory of Medicinal Chemistry, Faculty of Pharmacy Unpad), and AutoDock 4.2.6.

2.2. Method

2.2.1. Lipinski Rule of Five (RO5)

The physicochemical properties of the bioactive constituents of *C. canephora* P. were assessed using the Lipinski Rule of Five prediction, which was performed through 2D modeling for the test compound, downloaded directly from PubChem. Physicochemical analysis was then performed using the mcule web (http://mcule.com/apps/property-calculator). Molecular weight, log P value, and hydrogen-bond donor and acceptor counts were the Lipinski RO5 parameters. A compound was considered suitable for oral administration if it did not violate more than one of these criteria.

2.2.2. ADME/Tox Determination

Determination of ADME/Tox, which includes absorption, distribution, metabolism, excretion, and toxicity profiles, was done by drawing the structure of the compound that was to be determined and calculating it on the website https://preadmet.webservice.bmdrc.org/.

2.2.3. Molecular Docking

In the receptor preparation, the PPAR-α (PDB ID: 2P54) was downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank website (https://www.rcsb.org/) and the receptor structure was improved by adding polar hydrogen atoms and Kollman charges to the receptor separated from its native ligands using the AutoDock, further this tool was also used to combine compounds into non-polar and give Gasteiger charge to the ligand, then input torque into them. Validation was performed to determine the optimal position and size of the grid box (60×60×60) for stimulating molecular docking. The native ligands were reintroduced to the receptor during the validation process using the AutoDock. The size of the grid box was adjusted so that the genetic algorithm obtains a value of 10 during the running process. The validation results were only accepted if the reference RMSD value was ≤ 2 Å and the binding energy was negative or less than zero. The molecular docking process of the test ligand to the receptor or target protein was performed using the same stages as in the validation process, but with the Lamarckian Genetic Algorithm (LGA) and a population size of 100. The molecular docking results were analyzed using the Autodock 4.2.6. The analysis results were then visualized using the BIOVIA Discovery Studio 2020 application to obtain 2D and 3D visualization of the test ligand docked to the receptor.

3. RESULT AND DISCUSSION

3.1. Lipinski's Rule of Five (RO5) Prediction

Lipinski's Rule of Five evaluates drug-likeness based on molecular weight, LogP, hydrogen bond donors, and hydrogen bond acceptors. According to the MCule property calculator (http://mcule.com/apps/property-calculator), all compounds being assessed met RO5 criteria, indicating good potential for oral bioavailability (Table 1).

Table 1. Lipinski Rule of Five Prediction Results from the Phytoconstituents of Green Bean Robusta Coffee

Compound	Molecular Weight (<500Da)	Log P (<5)	Hidrogen Bond		Conclusion
			Donor (<5)	Acceptor (<10)	
Phenol	94.11	1.39	1	1	Suitable
1,2-Benzenediol	110.11	1.10	2	2	Suitable
2-Methoxy-4-Vinylphenol	150.17	2.04	2	1	Suitable
Hydroquinone	110.11	1.10	2	2	Suitable
Acetic acid	60.05	0.09	1	2	Suitable
n- Hexadekanoic acid	256.42	5.55	1	2	Suitable
Caffeine	194.19	-1.03	0	6	Suitable
Pyridine	79.10	1.08	0	1	Suitable

Quinic acid	192.63	-2.32	5	6	Suitable
Beta-sitosterol	414.71	8.03	1	1	Suitable
4-Ethyl-2-methoxyphenol	152.20	1.96	1	2	Suitable
Furaneol	128.13	0.76	3	1	Suitable
9,12-Octadecadienoic acid	280.45	5.89	1	2	Suitable
Ergost-5-en-3-ol	40.68	7.64	1	1	Suitable
2-Furanmethanol	98.01	0.77	1	2	Suitable

3.2. ADMET Profile Prediction

ADME/Tox evaluations were conducted using key pharmacokinetic parameters, including human intestinal absorption (HIA), Caco-2 permeability, Plasma Protein Binding (PPB), blood-brain barrier (BBB) penetration, and mutagenicity and carcinogenicity predictions. Most compounds exhibited HIA values above 70%, suggesting favorable oral absorption; notable examples include β-sitosterol and 9,12-octadecanoic acid, which demonstrated particularly strong absorption potential. Several compounds, including phenolic derivatives, n-hexadecanoic acid, 4-ethyl-2-methoxyphenol, and furaneol, showed high PPB (>90%) and substantial BBB permeability (>0.9) (Table 2). High PPB suggests strong affinity to plasma proteins, which may reduce the freely available active fraction but can prolong systemic exposure and half-life [17]. Meanwhile, high BBB permeability indicates the ability of these compounds to enter the central nervous system, which may be advantageous or undesirable depending on therapeutic intent [18]. In terms of toxicity prediction, only n-hexadecanoic acid was identified as non-mutagenic and non-carcinogenic, whereas other compounds displayed potential mutagenicity or carcinogenicity alerts. Incorporating ADME/Tox screening at this stage is crucial for reducing late-stage compound failure and guiding early optimization efforts [19].

Table 2. ADME/Tox Prediction Results from the Phytoconstituents of Green Bean Robusta Coffee

Compound	Absorption		Distribution			Toxicity	
	HIA (%)	Caco-2 (nm/sec)	PB (%)	BBB	Mutagen	Carcinogen	
						Mouse	Rat
Phenol	100.00	21.69	89.71	1.67	Mutagen	Negative	Negative
1,2-Benzenediol	87.41	16.55	97.32	1.56	Mutagen	Negative	Positive
2-Methoxy-4 Vinylphenol	96.73	41.06	57.70	1.48	Mutagen	Negative	Positive
Hydroquinone	87.42	16.55	96.28	1.56	Mutagen	Negative	Positive
Acetic acid	78.72	20.76	64.82	0.62	Non-mutagen	Negative	Positive
n-Hexadekanoic acid	100.00	21.91	100.00	20.61	Non-mutagen	Negative	Negative
Caffeine	93.82	21.26	14.08	0.33	Mutagen	Negative	Positive
Pyridine	100.00	54.48	70.23	1.53	Mutagen	Negative	Negative
Quinic acid	20.29	8.27	6.60	0.43	Mutagen	Negative	Positive
Beta-sitosterol	100.00	52.37	100.00	19.89	Non-Mutagen	Positive	Negative
4-Ethyl-2-methoxyphenol	96.55	41.59	100.00	2.12	Mutagen	Positive	Positive
Furaneol	88.80	1.11	96.32	0.37	Mutagen	Positive	Positive
9,12-Octadecadienoic acid	98.37	28.08	100.00	7.32	Mutagen	Positive	Positive
Ergost-5-en-3-ol	100.00	51.40	100.00	19.70	Non-Mutagen	Positive	Negative
2-Furanmethanol	93.82	11.92	82.06	0.47	Mutagen	Positive	Positive

All compounds complied with Lipinski's Ro5, indicating acceptable drug-likeness and potential oral bioavailability. ADME/Tox predictions further showed that several compounds—particularly phenolic derivatives, n-hexadecanoic acid, β-sitosterol, 4-ethyl-2-methoxyphenol, furaneol, 9,12-octadecanoic acid, and ergost-5-en-3-ol—exhibited high intestinal absorption and strong plasma protein binding. While high PPB may reduce the free fraction of a compound, it

may also prolong systemic circulation [17]. BBB permeability was also noted for several compounds, which could be relevant for metabolic pathways involving central regulation [18]. Toxicity screening revealed that only n-hexadecanoic acid was predicted to be non-mutagenic and non-carcinogenic, while the others presented potential alerts, highlighting the importance of early ADME/Tox filtering in compound prioritization. Although ADMET prediction indicated that most compounds were classified as potentially mutagenic, this outcome may be influenced by limitations of in silico models, including structural alerts, model bias, or overestimation by rule-based algorithms. Therefore, these findings should be interpreted cautiously and require confirmation through appropriate experimental mutagenicity assays.

3.3. Molecular Docking Analysis

The validation results presented in Table 3 show that the reference ligand achieved an RMSD value of 0.77 Å and a binding energy of −10.44 kcal/mol. This RMSD value falls well within the acceptable threshold (<2 Å), confirming that the docking protocol used in this study was reliable [20]. Docking of the test compounds using the same grid parameters revealed that β-sitosterol, 4-ethyl-2-methoxyphenol, furaneol, and ergost-5-en-3-ol demonstrated strong binding affinities, with binding energies ranging from −9.80 to −11.20 kcal/mol and inhibition constants (Ki) between 0.014 and 0.035 μM. As shown in Figure 1, these ligands formed hydrogen bonds, π–π interactions, and hydrophobic contacts with key residues within the PPAR-α active site. The presence of these multiple non-covalent interactions supports the stability of the ligand–receptor complexes and reflects favorable binding characteristics [21]. Overall, the docking results suggest that the evaluated compounds may interact effectively with PPAR-α and have the potential to modulate its biological activity.

Docking protocol validation yielded an RMSD of 0.77 Å, confirming the reliability of the docking method. Among the tested compounds, ergost-5-en-3-ol demonstrated the strongest binding affinity (ΔG = −10.71 kcal/mol; Ki = 0.014 μM). Several other compounds, including β-sitosterol, furaneol, 4-ethyl-2-methoxyphenol, and 9,12-octadecanoic acid also formed stable interactions with PPARα, including hydrogen bonds and hydrophobic contacts with key residues.

These interactions align with the regulatory role of PPARα in lipid oxidation and energy homeostasis [22,23]. Notably, 4-ethyl-2-methoxyphenol showed consistently favorable binding characteristics, supporting its potential as a PPARα modulator.

The interaction profiles further strengthen this interpretation. The presence of hydrogen bonds, π–π stacking, and hydrophobic interactions reflects a multifaceted stabilization pattern that is commonly associated with active PPAR-α ligands. Such non-covalent interactions are known to facilitate conformational changes in the receptor that promote coactivator recruitment and subsequent transcriptional activation. Thus, the ability of the test compounds to engage multiple key residues highlights their potential to influence receptor activity in a biologically meaningful way.

Moreover, the low predicted inhibition constants (Ki) support the notion of strong ligand–receptor engagement, suggesting that these compounds may exert modulatory effects at relatively low concentrations. This aligns with previous reports indicating that phytochemicals with comparable structural features, particularly sterol- and phenolic-based molecules, can interact with nuclear receptors and modulate metabolic or anti-inflammatory pathways.

The use of multiple computational approaches strengthens this study by providing complementary insights into ligand–target interactions, thereby improving the reliability and robustness of the predictions. Integrating several in silico methods also reduces methodological bias and enhances confidence in the identification of promising PPARα modulators. Collectively, the docking results point to a plausible molecular basis for the biological activities associated with these compounds and provide a foundation for future *in vitro* or *in vivo* validation studies.

Table 3. The Molecular Docking Analysis Result from the Phytoconstituents of Green Bean Robusta Coffee

No.	Compound	Binding Energy (Kcal/ mol)	KI (μM)	Amino Acid Interactions	
				Hydrogen Bonds	Other interactions
Native ligand	2-Methyl-2-(4-{[({4-Methyl-2-[4-(Trifluoromethyl)Phenyl]-1,3-Thiazol-5-il}Carbonyl)Amino]Methyl}Phenoxy)Propanoic Acid	-10.44	22.33 nM	CYS275, TYR464, SER280, MET330, CYS276	LEU247, ILE272, ILE339, LEU344, MET355, TYR464, HIS440, PHE273, VAL444, VAL255, VAl332
1.	Phenol	-4.30	704.96	TYR464, HIS440	LEU460
2.	1,2-Benzenediol	-4.14	917.84	TYR314, HIS440	CYS276
3.	2-Methoxy-4 Vinylphenol	-4.70	361.38	ALA333, THR279, CYS376	ILE272, LEU247, CYS275, MET330, VAL382
4.	Hydroquinone	-4.56	455.60	PHE273, HIS440, TYR464, SER280	CYS276
5.	Acetic acid	-2.88	7790	TYR334, ALA333,THR279	
6.	n-Hexadekanoic acid	-5.11	180.06	GLN277, SER280	CYS276, MET355, PHE318, HIS440, VAL332, MET330
7.	Caffeine	-4.71	351.52	CYS276, ALA333	VAL332, ILE339, LEU247, ILE272, CYS275
8.	Pyridine	-3.63	2180	TYR464, HIS440	VAL444, LEU460
9.	Quinic acid	-3.48	2.82	SER280, CYS276	HIS440
10.	Beta-sitosterol	-10.55	0.01853		MET330, ILE339 VAL332, LEU344, CYS275, ILE272, LEU247, CYS276, MET355, LEU321
11.	4-Ethyl-2-methoxyphenol	4.58	440.47	ALA333, THR279, CYS276	ILE272, ILE339, CYS275, MET330, VAL :332
12.	Furaneol	-4.27	738.56	SER280, TYR314, TYR464	VAL444, HIS440, ILE354, PHE273, CYS276
13.	9,12-Octadecadienoic acid	-5.83	53.24		ALA333, VAL332, CYS278, CYS275, VAL255LEU:254, ILE272, ILE339, LEU247
14.	Ergost-5-en-3-ol	-10.71	0.01419		MET355, LEU344, MET330, CYS276, VAL332, ALA250.
15.	2-Furanmethanol	-4.70	361.38	ALA333, THR279	VAL255, ALA333, ILE339, CYS275, ILE272, LEU321 CYS276, VAL332, CYS275

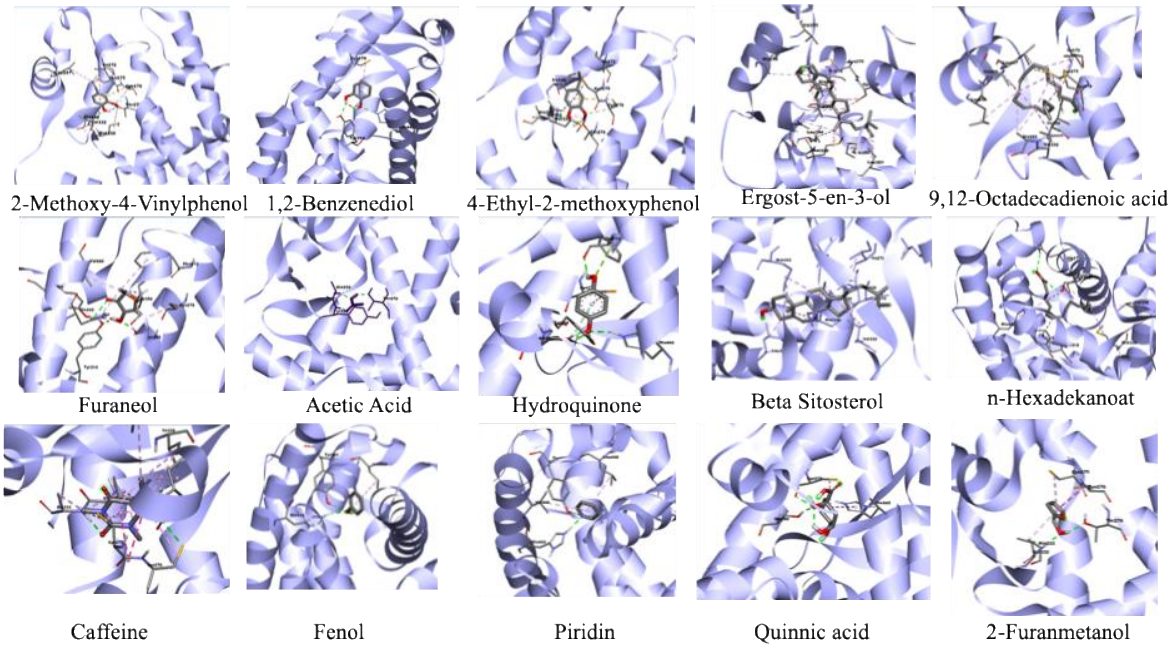

Figure 1. The 3D visualization of the molecular interaction between the phytoconstituents of Green Bean Robusta Coffee against PPAR-α docking site

4. CONCLUSION

Based on the in silico analysis conducted in the current study, Ergost-5-en-3-ol, a secondary metabolite identified in green bean Robusta coffee (*Coffea canephora*), demonstrated the strongest potential as an anti-obesity candidate. This compound exhibited the most favorable binding affinity and inhibition constant, with a binding energy of -10.71 kcal/mol and a Ki of 0.01419 μM, indicating a stable interaction with the PPARα receptor. These findings suggest that ergost-5-en-3-ol may contribute to the modulation of lipid metabolism and warrant further investigation through comprehensive in vitro and in vivo studies to confirm its pharmacological potential.

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