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Original Research Article

In Silico Discovery of Green Tea and Green Coffee Bioactive Compounds Against IGF-1R, PPAR-*α*, and TLR4 as a Therapeutic Candidate for Metabolic Disorder

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ABSTRACT

Metabolic syndrome (MetS) affects millions of people globally since it is linked to multiple risk factors, including obesity, dyslipidemia, high blood pressure, and type 2 diabetes mellitus (T2DM). Several molecular factors are contributing to MetS developments, including insulin-like growth factor-1 receptor (IGF-1R), peroxisome proliferator-activated receptor *α* (PPAR-*α*), and Toll-like receptor-4 (TLR4). Green tea (GT) and green coffee (GC) have unique flavors due to their bioactive compounds, which act as antioxidants, anti-inflammatories, and antihypertension. This work aimed to examine the pathways implicated in the development of MetS and discover bioactive chemicals contained in GT and GC that have promising as inhibitors of IGF-1R, PPAR-*α*, and TLR4. The protein-protein interaction was explored using STRING, and the roles of bioactive compounds were evaluated in STITCH. The interaction between (-)-epigallocatechin (EC), catechin gallate (CG), epicatechin (EC), epigallocatechin gallate (EGCG), theobromine, trigonelline, chlorogenic acid, and caffeic acid against IGF-1R, PPAR-*α*, and TLR4 was measured by molecular docking. The present result demonstrated that eight protein interactions are involved in Mets development. The molecular docking result demonstrated that EGCG from GT has the best binding affinity (kcal/mol) to IGF-1R (-9.1), PPAR-*α* (-9.5), and TLR4 (-6.5). In conclusion, bioactive compounds from GT were superior to GT through computational study. Both might be promising as anti-inflammatories and regulate the metabolism under MetS conditions.

***Keywords*:** anti-inflammatory, catechin, flavonoids, *in silico*, metabolic syndrome

Introduction

Metabolic syndrome (MetS) is a constellation of interrelated risk factors, including abdominal obesity, hypertension, dyslipidemia, and elevated fasting blood glucose, collectively amplifying cardiovascular disease risk and T2DM.[1] T2DM is a chronic metabolic disorder with high blood sugar (glucose) levels.[2] MetS and T2DM are potentially life-altering medical conditions affecting millions worldwide and substantially burdening healthcare systems due to their profound implications for public health.[3,4] The condition often develops slowly and may go undiagnosed for years, leading to severe complications, such as cardiovascular disease, kidney problems, nerve damage, and vision impairment.[2]

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Insulin-like growth factor-1 (IGF-1) is a hormone that plays in the pathophysiology of metabolic syndrome due to its implication on lipid and carbohydrate metabolism. Dysregulation of IGF-1 increases the risk of T2DM, insulin resistance, and non-alcoholic fatty liver disease (NAFLD).[5] Moreover, peroxisome proliferator-activated receptor *α* (PPAR-*α*) is also involved in lipid metabolism and inhibition of inflammation. PPAR-*α* has been reported as a potential target for metabolic syndrome therapy, including insulin resistance and dyslipidemia.[6]

The innate immune system, Toll-like receptor-4 (TLR4), contributes to T2DM and metabolic syndrome.[7] TLR4 is well recognized for identifying pathogen-associated molecular patterns (PAMPs) [8] and beginning the immune response to infectious pathogens, but it has also been linked to chronic inflammatory processes in T2DM and metabolic syndrome. Inflammatory cytokines disrupt insulin signaling, causing insulin resistance, a key component in T2DM. MetS and T2DM are often managed with lifestyle changes such as dietary alterations, physical activity levels, and medication.[9,10]

Nowadays, researchers have turned their attention to natural compounds in various dietary sources due to low toxicity, generally regarded as safe (GRAS) by the United States Food and Drug Administration (FDA). Green tea (GT), derived from the leaves of *Camellia sinensis*, and green coffee (GC), made from unroasted coffee beans enjoyed by millions worldwide for their unique flavors, have gained substantial scientific interest due to their potential health benefits. Recent studies have revealed that they contain bioactive compounds, such as catechins in GT and chlorogenic acids in GC, which exhibit antioxidant, anti-

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inflammatory, and metabolic-regulating properties.[11] A previous study demonstrated that GT and GC extract suppressed cardiotrophin-1 (CT-1), signal transducer and activator of transcription *3* (STAT3), GATA binding protein 4 (GATA4), and B-type natriuretic peptide (BNP) expression.[12] Therefore, GT and GC might be promising for chronic disease prevention and management.

In modern pharmaceutical and natural medicine research, discovering herbal compounds and their potential therapeutic applications through computational modeling represents a promising and innovative trend. This trend represents a shift towards a more systematic and data-driven approach to herbal medicine research. Using computational modeling in science has raised efficiency, reduced mistakes, and saved resources.[13] Moreover, the computational approach accelerates the drug discovery process and encourages the integration of traditional herbal knowledge with modern scientific methodologies. Therefore, molecular docking was carried out in the current study to investigate the potential interaction between bioactive compounds from GT and GC and IGF-1R, PPAR-*α*, and TLR4.

Materials and Methods

Protein interaction and networking analysis

Protein-protein interactions (PPI) between IGF-1R, PPAR-*α,* and TLR4 were analyzed using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://string-db.org/).[14] STITCH (http://stitch.embl.de/) was also used to analyze the ligand's interaction with PPI.

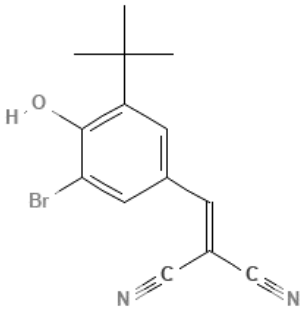
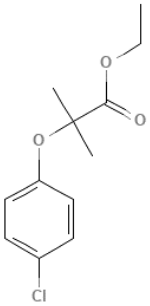
Ligand Preparation

Five selected bioactive compounds of GT ((-)-epigallocatechin, catechin gallate, epicatechin, epigallocatechin gallate, theobromine) and three selected bioactive compounds from GC (trigonelline, chlorogenic acid, and caffeic acid) were selected for molecular docking. The selection was based on the phytochemical screening result by liquid chromatography high-resolution mass spectroscopy (LCHRMS) (data not shown). The chemical structure of selected bioactive compounds is illustrated in Table 1. The .sdf file format retrieved all 3D structures of specified molecules from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The .sdf file format of ligands was then converted into a PDB file using PyMOL (Schrödinger Inc., LLC). Open Babel in PyRx 0.8 (The Scripps Research Institute, California) was used to reduce the energy of the downloaded molecules after they were converted to.pdb format with PyMOL (Schrödinger Inc., LLC). Minimized energy is generally undertaken before molecular docking to achieve a stable conformation near the original state in the biological system.[15]

Docking simulation

The target proteins for this research were IGF-1R, PPAR-*α*, and TLR4. The proteins were downloaded from the Protein Data Bank (PDB) (https//rcsb.org/). Autodock Vina with PyRx v.0.8 was utilized to analyze ligand-protein interactions. Reverse docking was used in this study to determine the location of each protein's active site by starting with a control drug inhibitor. Reverse docking utilizes a pharmacological inhibitor like the native ligand to find a different therapeutic candidate for a protein implicated in a specific disease pathway. Reverse docking is used to find possible targets among the many proteins and receptors by looking at their crystal structures or known ligands.[16] The three-dimensional structures in the bound site might provide essential information about ligand-protein interaction.[17] The active site of each target protein is presented in Table 2. The binding affinity value in kcal/mol determined the bonding strength between protein and ligands. Amino acid residues were analyzed using BIOVIA Discovery Studio.[18] The molecular docking was performed on computer using Intel® Celeron® N4500 processor with 8gb DDR4-2933 MHz RAM.

Table 1: The structures of bioactive compound and inhibitor drug for molecular docking

Ligand	CID	Structure
Tryphostin (IGFR1 inhibitor)	2044	
Clofibrate (PPAR-*α* inhibitor)	2796	

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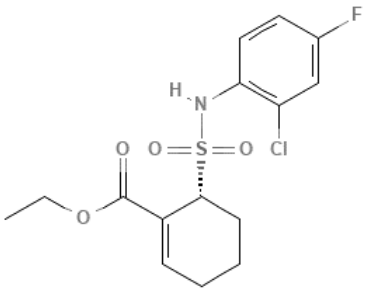
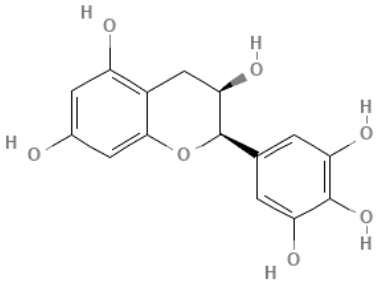
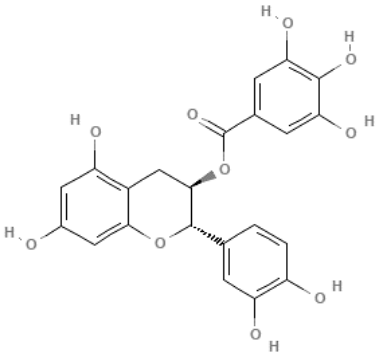
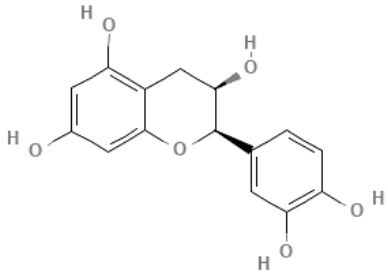
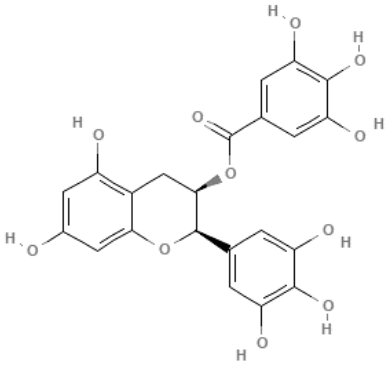
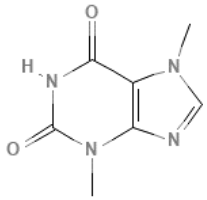
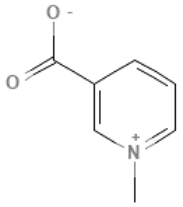
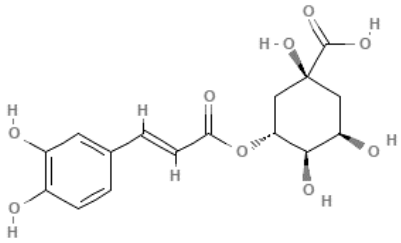
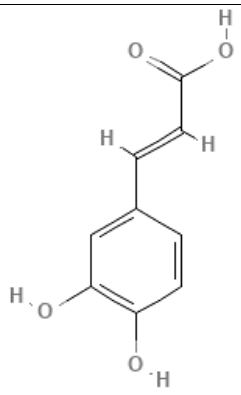
Resatorvid (TLR4 inhibitor)	11703255	
Epigallocatechin	72277	
Catechin gallate	6419835	
Epicatechin	72276	
Epigallocatechin gallate	65064	

Theobromine	5429	
Trigonelline	5570	
Chlorogenic acid	1794427	
Caffeic acid	689043	

Result and Discussion

Protein network analysis (Figure 1) showed metabolic disorders such as insulin resistance, T2DM, and NAFLD have various involved proteins including PPAR-α, IGF1, AMP-activated protein kinase (PRKAA1), insulin receptor (INSR), insulin (INS), interleukin 6 (IL6), IL1B, tumor necroses factor (TNF), TNF receptor superfamily member 1A (TNFFRS1A), and dipeptidyl peptidase 4 (DPP4). The insulin resistance pathway with false discovery 6.82 x 10^{-12} has eight protein interactions, the T2DM pathway with false discovery rat 4.88 x 10^{-15} also has eight protein interactions, while NAFLD with false discovery rat 1.00 x 10^{-14} has ten protein interactions. The pathogenesis of such pathways relates to how they contribute to metabolic syndrome, characterized by lifestyle changes, a lack of physical activity, an unhealthy diet, and obesity.[19]

Insulin-like growth factor-1 receptor (IGF-1R) is a critical cell surface receptor that plays a key role in growth, development, and cell survival. IGF-1R signalling has metabolic effects as well. It can influence glucose uptake and utilization in various tissues, similar to the actions of insulin.[20] This interaction between IGF-1R and insulin signalling can affect energy metabolism. IGF-1R is associated with metabolic syndrome in the context of insulin resistance and dysregulated glucose metabolism.[5] Dysregulation of IGF-1R signalling can lead to insulin resistance, a central feature of metabolic syndrome. Tyrphostin is part of a broader class of tyrosine kinase inhibitors, including IGF-1R.[21]

Based on stitch analysis, they indicated caffeic acid, chlorogenic acid, and trigonelline. Epigallocatechin, epicatechin gallate, and EGCG correlate due to their structure from polyphenolic constituent (Figure 2).[22] EGCG also showed direct bonding with TLR4, signal transducer and activator of transcription 3 (STAT3), IL6, epidermal growth factor receptor (EGFR), protein tyrosine phosphatase non-receptor type 1 (PTPN1), and IGF-1. This analysis suggested that EGCG could treat diseases related to those proteins.

The molecular docking study (Table 3) revealed that tryphostin as an IGF-1R inhibitor only has a binding affinity value of -6.2 kcal/mol, while GT and GC active compounds have higher binding affinity values. EGCG can reach up to -9.1 kcal/mol and become the highest binding affinity value for IGF-1R ligand docking. Green tea and its components are known for their potential health benefits, particularly in cancer prevention, metabolic health, and antioxidant properties. EGCG is one of the most abundant and well-studied catechins in green tea.[23] It has been shown to have various health benefits, including potential effects on IGF-1R signalling. EGCG can modulate the expression and activity of IGF-1R and its downstream signalling components, such as the phosphatidylinositol 3-kinase/protein kinase B (PI3K-AKT) and mitogen-activated protein kinases (MAPK) pathways.[24] The ligands mostly binding with amino acid residue of Met1082, Lys1033, and Val1063 (Table 4). Met1082 was the amide nitrogen in the active site of IGF-1R. Meanwhile, Lys1033 is a conserved residue in IGF-1R.[25]

Furthermore, molecular docking on PPAR-α with an inhibitor drug only reached a binding affinity value at -6.3 kcal/mol. The active compounds from GT and GC, such as ECG, CG, EGCG, chlorogenic acid, and caffeic acid, have higher binding affinity values.

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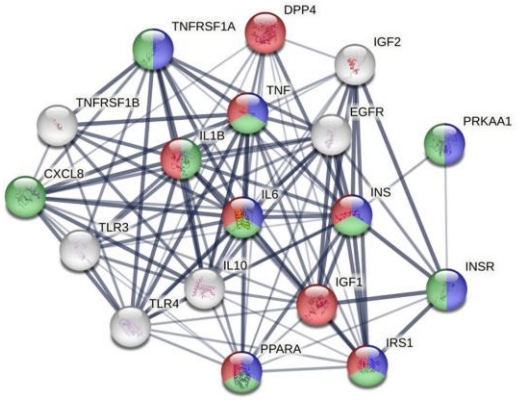

Pathway description	False discovery rate	Proteins
Insulin resistance	6.82×10^{-12}	PRKAA1, PPARA, INSR, IRS1, INS, IL6, TNF, TNFRSF1A
Type 2 Diabetes Mellitus (T2DM)	4.88×10^{-15}	PPARA, IRS1, IGF1, INS, IL6, IL1B, TNF, DPP4
Non-alcoholic fatty liver disease (NAFLD)	1.00×10^{-14}	PRKAA1, PPARA, INSR, IRS1, INS, IL6, IL1B, TNF, CXCL8, TNFRSF1A

Figure 1: STRING analysis for protein-protein interaction at certain pathway.

Table 2: Active site of each protein for molecular docking

	x	y	Z
IGF-1R (PDB ID: 3LVP)			
Grid center	2.2967	55.5627	15.8598
Dimension (Angstrom)	13.4872	12.9361	13.0692
PPAR-α (PDB ID: 3VI8)			
Grid center	4.121	7.7287	-3.4122
Dimension (Angstrom	12.9600	12.6943	14.6663
TLR4 (PDB ID: 3FXI)			
Grid center	-6.5342	38.4789	-2.9021
Dimension (Angstrom)	14.1868	15.3485	17.6384

EGCG also still has the highest binding affinity value among other ligands that bond to PPAR-α. The binding model demonstrated that Thr283 and Glu286 were found in every complex except the chlorogenic acid-PPAR-α complex (Table 4). The previous study reported that bonding with Glu286 in PPAR-α might induce a conformational change in PPAR-α.[26] Interestingly, only EGCG and caffeic acid binds with Ser280, known as essential AA residues, due to facilitating the binding to the nuclear receptor.[27] PPAR-α is a master regulator of lipid metabolism. It promotes the catabolism (breakdown) of fatty acids in the liver, producing ketone bodies, which are used as an alternative energy source, especially during fasting or prolonged exercise.[28] PPAR-α activates the expression of genes involved in fatty acid oxidation, which includes the breakdown of long-chain fatty acids to generate energy, which is particularly important for maintaining energy balance in the body. PPAR-α activation has been associated with improved insulin sensitivity, a central issue in metabolic syndrome and T2DM.[29] By increasing the efficiency of fatty acid oxidation, PPAR-α can reduce lipid accumulation in tissues like the liver and muscles, contributing to insulin resistance. Both green tea and green coffee are known for their potential health benefits. EGCG is one of the major polyphenols in green tea and has been extensively studied for its potential health benefits. EGCG can activate PPAR-α, promoting fatty acid oxidation and the breakdown of stored fat for energy.[30] This may help improve lipid metabolism, making it relevant for individuals with metabolic syndrome. Green coffee beans are a source of chlorogenic acids as potent antioxidants. Chlorogenic acids have the potential to improve lipid metabolism and insulin sensitivity. Chlorogenic acid enhances lipid metabolism in the liver by increasing fatty acid oxidation and TG lipolysis while decreasing TG synthesis and fatty acid transport.[31]

On the other hand, protein TLR4-ligand docking resulted in the binding affinity of resatorvid as TLR4 inhibitory drug was -6.3 kcal/mol, while CG and EGCG have binding affinity values -7.1 and -6.5 kcal/mol, respectively. Chlorogenic acid also has a binding affinity value similar to drug inhibitors -6.3 kcal/mol. Asp596, Ser589, and Gln562 were frequently found in the molecular docking result (Table 4). These interactions were suggested to inhibit TLR4 activation[32]. The results showed that GT and GC active compounds could be used as drug candidates for replacing tryphostin, clofibrate, and resatorvid. TLR4 is a key component of the innate immune system, and it plays a role in the development and progression of type 2 diabetes mellitus (T2DM) and metabolic syndrome.[7] TLR4 is primarily known for recognizing pathogen-associated molecular patterns (PAMPs) [33] and initiating the immune response to infectious agents, but it has also been implicated in non-infectious, chronic inflammatory processes associated with T2DM and metabolic syndrome. Inflammatory cytokines can interfere with normal insulin signaling, leading to insulin resistance, which is a central factor in the development of T2DM. TLR4 can be activated by endogenous ligands, including fatty acids and products of cellular stress, which are present in obese and metabolically dysfunctional individuals. When TLR4 is activated, it can trigger an inflammatory response that contributes to insulin resistance.[34]

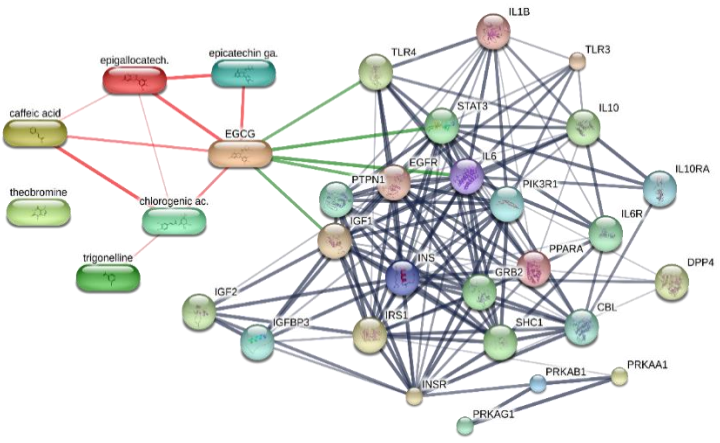

Figure 2: STITCH analysis between target protein and bioactive compounds from GT and GC.

Table 3: Binding affinity value between protein-ligand docking

Ligand	Binding affinity value (kcal/mol)		
	IGF-1R	**PPAR-*α***	**TLR4**
Tryphostin (IGFR1 inhibitor)	-6.2	-	-
Clofibrate (PPAR-*α* inhibitor)	-	-6.3	-
Resatorvid (TLR4 inhibitor)	-	-	-6.3
Green tea (GT)			
Epigallocatechin	-7.5	-7.4	-6.2
Catechin gallate	-9.0	-8.6	-7.1
Epicatechin	-7.5	-8.0	-6.2
Epigallocatechin gallate	-9.1	-9.5	-6.5
Theobromine	-5.7	-6.1	-4.9
Green coffee (GC)			
Trigonelline	-4.7	-5.3	-4.2
Chlorogenic acid	-7.7	-8.6	-6.3
Caffeic acid	-5.8	-6.4	-5.2

Table 4: Amino acid residues from molecular docking study

Compounds	IGF-1R		PPAR-*α*		TLR4	
	Van der Waals	**Hydrogen Bond**	**Van der Waals**	**Hydrogen Bond**	**Van der Waals**	**Hydrogen Bond**
Tryphostin (IGF-1R inhibitor)	Leu1005 Gly1006 Lys1033 Val1063 Met1079 Met1082 Gly1152 Asp1153 Asn1140		-	-	-	-
Clofibrate (PPAR-*α* inhibitor)	-	-	Asn219 Thr279 Thr283 Glu286 Leu321 Gly335	Ala333 Tyr334	-	-
Resatorvid (TLR4 inhibitor)	-	-	-	-	Gln562 Glu563 Ser589 Asp596	Leu564 Gln565
Epigallocatechin	Gln1007 Lys1033 Val1063 Leu1081 Thr1083 Gly1085	Leu1005 Met1079 Glu1080 Met1082	Phe218 Asn219 Met220 Met320 Ser323 Leu331	Thr283 Glu286	Gln562 Glu563 Gln565 Gln592 Gln597	Ser589 Asp596

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	Gly1152		Val332			
			Ala333			
			Tyr334			
			Gly335			
Catechin gallate	Gly1006	Gln1007			Gln562	Leu564
	Glu1080	Ser1009			Glu563	Asn565
	Leu1081	Met1082			Phe590	Ser589
	Arg1084	Thr1083			Gln592	
	Gly1085				Asp596	
	Asp1153					
Epicatechin	Gly1006	Met1080	Tyr214	Thr279	Gln562	Ser589
	Gln1007	Met1082	Phe218	Met320	Glu563	Asp596
	Lys1033		Asn219		Gln565	
	Val1063		Asn221		Gln597	
	Leu1081		Cys276			
	Thr1083		Glu282			
	Gly1085		Thr283			
			Glu286			
			Leu321			
			Ser323			
			Val324			
			Met330			
			Leu331			
			Val332			
			Ala333			
			Tyr334			
Epigallocatechin gallate	Gly1006	Ser1009	Tyr214	Asn219	Gln562	Leu564
	Phe1010	Lys1033	Phe218	Met220	Glu563	Gln565
	Asp1036	Met1079	Asn221	Cys276	Phe590	Ser589
	Glu1050	Arg1139	Ser280	Thr283	Gln592	Trp593
	Glu1060	Asn1140	Ile317		Asp596	
	Leu1061	Asp1153	Phe318		Gln597	
	Val1063		Ser323			
	Gly1152		Met330			
	Gly1155		Leu331			
			Gly335			
Theobromine	Lys1033	Met1082	Phe218	Thr283	Glu563	Gln562
	Met1079		Thr279	Glu286	Gln565	Ser589
	Glu1080		Glu282		Gln592	Asp596
	Leu1081		Leu321			
	Thr1083		Val324			
	Gly1085		Tyr334			
Trigonelline	Leu1005	Met1082	Phe218	Met220	Glu563	Gln562
	Glu1080		Asn219		Ser589	Gln565
	Leu1081		Thr279			
	Gly1085		Thr283			
			Glu286			

			Met320			
			Leu321			
Chlorogenic acid	Phe1010	Glu1050	Phe218	Tyr214	Phe1010	Glu1050
	Ala1031	Met1082	Asn221	Asn219	Ala1031	Met1082
	Lys1033	Gly1152	Lys222	Met220	Lys1033	Gly1152
	Phe1047	Asp1153	Thr279	Thr283	Phe1047	Asp1153
	Met1079		Glu282	Leu331	Met1079	
	Leu1081		Ile317	Tyr334	Leu1081	
	Thr1083		Leu321	Gly335	Thr1083	
	Arg1084		Ser323		Arg1084	
	Gly1085		Val324		Gly1085	
	Met1142		Met330		Met1142	
	Ohe1154		Val332		Phe1154	
	Gly1155		Asp372		Gly1155	
Caffeic acid	Leu1005	Gln1007	Met220	Thr283	Leu1005	Gln1007
	Gly1006		Ser280	Ile317	Gly1006	
	Gly1008		Thr279	Leu321	Gly1008	
	Ala1031		Met320	Tyr334	Lys1033	
	Lys1033		Leu331		Val1063	
	Val1063		Val332		Met1079	
	Glu1080		Ala333		Glu1080	
	Leu1081		Asn336		Leu1081	
	Met1082				Met1082	

EGCG can inhibit the TLR4 signalling pathway by reducing its expression of TLR4 and downstream inflammatory molecules.[35,36] Furthermore, EGCG may help mitigate the inflammatory response mediated by TLR4. EGCG is a potent antioxidant. Jain et al. reported that chlorogenic acid inhibits TLR4 activation by downstream pathway, thus decreasing proinflammatory cytokine.[37] This inhibition can help reduce the inflammatory response mediated by TLR4. EGCG and chlorogenic acid as potential treatments for conditions involving TLR4-mediated inflammation should be considered in the context of a broader therapeutic strategy.

Conclusion

The molecular docking pathway indicated that bioactive compounds from GT and GC potentially act as therapeutic agents for metabolic syndrome disease. Bioactive compounds from GT and GC also have higher binding affinity values than drug inhibitors. Utilization of GT and GC could be as promising alternative drug candidates, especially to treat T2DM and insulin resistance as a part of metabolic syndrome. Further studies about GT and GC bioactive compounds are required to determine the detailed mechanism in the IGFR-1, PPAR-*α*, and TLR4 signalling pathway through in vitro and in vivo studies.

Conflict of Interest

Authors declare no conflict of interest

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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