Effectivity of Black Tea Polyphenol in Adipogenesis Related IGF-1 and Its Receptor Pathway Through In Silico Based Study

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Abstract. Obesity has been established as an emerging metabolic disease worldwide. The change of global lifestyle does not only become a significant health issue in the developed countries but also in the most deprived area around the world. The administration of obesity addressed to inhibit adipogenesis by using several potential herbal drugs. Recently, black tea treatment showed an essential result whereas it can decrease cell proliferation, differentiation, and induced apoptosis. The aim of this in Silico study was to provide a comprehensive data as the confirmation to in vitro and in vivo model. We compared the potential anti-obesity properties among black tea polyphenol on the activation of insulin-like growth factor 1 receptor (IGF-1R). The molecular interaction prediction between black tea polyphenol and IGF-1R was analyzed by docking model. Our in Silico data showed that theaflavin 3,3' -digallate (TF3) had the primary function to trigger cell apoptosis, differentiation inhibition, and improved global energy-linked binding affinity between TF3 and IGF-1R. The higher value of repulsive Van der Waals energy of TF3 enhanced the alteration of stability of IGF-1 and its receptor. As a result, the binding site dynamic of molecular complex between IGF-1 and IGF-1R significantly was changed by the molecular modification on autophosphorylation domain of IGF-1R. In conclusion, black tea polyphenol, TF3 tends to become a promising future candidate for herbal therapy combating obesity and metabolic syndrome. This preliminary bioinformatics data provides a hallmark for TF3 molecular activity during adipogenesis.

Keywords: Theaflavin, adipogenesis, obesity, IGF-1R, In Silico
1. Introduction
Obesity is a metabolic perturbation disease resulting from the imbalance between energy intake and energy dissipation [1]. The vast majority of obesity incidence was observed in the developed countries [2]. In contrary, the recent report showed that obesity is an emerging disease in the several developing countries particularly in the Asia Pacific [3]. Indeed, Indonesia and some Southeast Asia countries facing a global burden of obesity among different age-groups within their population. The gradual changes in obesity prevalence are closely and significantly associated with the common alteration of daily intake in the Asian community [4]. Modernization and westernization related to unhealthy food have strongly stimulated the progression of obesity in five Asian countries, including Indonesia [5].

The emerging problem of obesity in Indonesian urban area has suggested an origin from low socioeconomic groups with different dietary pattern [6]. It was reported that high caloric or fast food consumption, lack of physical activities, sedentary lifestyle, and less fiber diet induce overweight and accelerate obesity development in the low-income and low-middle income (LMC) countries, especially in South and South East Asia region [7]. As a consequence, increased obesity prevalence showed a crucial contribution to several gastrointestinal and metabolic diseases development especially non-alcoholic fatty liver disease, gastrointestinal cancer and type 2 diabetes mellitus [8-10].

Several programs were developed to reduce the higher prevalence of obesity, including the regular monitoring of community health services through eating and daily activities [11]. Moreover, the exploration of novel and potential drug candidates from natural resources against obesity and its complication has been widely reported in the last two decades [12, 13]. The future goal of herbal medicine treatment will address to inhibit or reduce adipogenesis rate linked to adipocyte number and size. Previous studies in both animal and human trial have shown that herbal therapy including green tea and black tea administrations decreased adipogenesis. The metabolic intervention by using green tea reduced adipogenesis through angiogenesis and adipose tissue growth inhibition [14], lowering total cholesterol and LDL (low-density lipoprotein) concentration [15]. Moreover, it also induced endopeptidase neprilysin and AMPK (Adenosine Monophosphate-activated Protein Kinase) pathway activation [16, 17], regulate feeding behavior, energy homeostasis related to a circadian gene, and fat browning [18, 19]. In addition, this treatment was able to reduce fat deposition and inflammation [20], insulin resistance and blood pressure [21], and changing the serum level of ghrelin and leptin in the circulation [22].

Importantly, theaflavin (black tea polyphenol) has been suggested that it provides an opportunity to become a novel candidate for clinical obesity therapy. The polyphenol of black tea has been able to regulate lipid metabolism through upregulation of AMPK (Adenosine Monophosphate-activated Protein Kinase), inhibit pancreatic lipase by in silico modeling, protein phosphatase PTP1B (Tyrosine-protein phosphatase non-receptor type 1) inhibition, stimulate lipolysis via mitochondrial uncoupling activity, and inactivate PEPCK (phosphoenolpyruvate carboxykinase) promoter as the primary enzyme of gluconeogenesis through FOXO1a (Forkhead box protein O1a) phosphorylation [23-27]. Such data proved that theaflavin could control adipogenesis rate and indirectly could regulate lipid metabolism, glucose homeostasis, and adipocyte mass. Hence, a specific target molecule in adipogenesis and insulin signaling pathway combined with black tea polyphenol long-term treatment may offer as an alternative clinical target in the patient against obesity via down/up-regulation of the specific molecular pathway.

The primary pathway of preadipocyte differentiation into mature adipocyte and insulin signaling activity involve several growth factors, cytokines, kinase protein and critical transcription factors. Among those potential growth factors, it was well established that insulin-like growth factor-1 (IGF-1) and its receptor (IGF-1R) play an essential role during the adipogenesis program [28-30]. Interestingly, the expression of IGF-1 and IGF-1R were significantly increased in obese children [31]. Also, the activation of IGF-1R has a significant correlation with cancer-linked energy balance and obesity [32, 33]. This data imply that the activation of IGF-1R by insulin and mimics of insulin (IGF-1) is the critical target for combating obesity, metabolic syndrome and cancer-related obesity. Even though previous studies have been done to explore the potential role of herbal treatment model by using green and black tea polyphenol, however, there is a lack of information on how black tea polyphenol directly regulates
IGF-1R activity. Here, our In Silico-based study will provide the preliminary and comprehensive data related to the molecular interaction modeling between the black tea polyphenol and IGF-1R activity. We suggest that the potential polyphenol within black tea can regulate adipogenesis through the IGF-1R to control lipid deposition, pre-adipocyte differentiation, glucose and lipid metabolism, and indirectly decreased obesogenic program.

2. Experimental Methods

2.1. The preparation of target protein sample database, ligand chemical structure, and the prediction of potential molecular pathway
PassOnline web server (www.pharmaexpert.ru/passonline/), Swiss Target Prediction database (www.swisstargetprediction.ch) and STRING database (www.string-db.org) were used as the primary online dataset to predict the essential function of black tea polyphenol (theaflavin) on the target protein in the intracellular signaling pathway. The three-dimensional structure of black tea polyphenol and target protein were obtained from the molecular database (www.pubchem.ncbi.nlm.nih.gov). The detail of target protein sequence information for insulin-like growth factor 1 (IGF-1) P05019 and insulin-like growth factor 1 receptor (IGF-1R) P08069IGF-1 were collected from UniProt database (www.uniprot.org). Furthermore, PassOnline web server also was utilized to predict the biological function of the ligand by submitting the SMILE query molecule to obtain the probability activity value (Pa) and probability inhibitor score (Pi). The probability activity value was expected > 0.7 (Pa > 0.7) that illustrates the similarity of the in Silico prediction and analysis compared to laboratory test/experiment.

2.2. Target protein modeling, virtual screening, and protein-protein docking
The tertiary structure modeling of IGF-1 and IGF-1R was done on protein modeling database Swiss Model (www.swissmodel.expasy.org) by using homology modeling. The homology modeling resulted in a homolog protein structure with conserved protein sequence with more than 20% similarity value. The validation of the previous protein structure was analyzed by 3D Ramachandran plot web server (www.mordred.bioc.cam.ac.uk/~rapper/rampage). To examine the binding affinity between black tea polyphenol and IGF-1R, virtual screening for molecular docking (reverse docking method) was done using PyRx software to build the simulation of molecular interaction among ligand to the target protein. In the additional test for ligand-protein interaction, to predict and develop a rigid molecular interaction model, PatchDock webservice (www.bioinfo3d.cs.tau.ac.il/PatchDock) was chosen to provide the structural conformation of binding complex and atomic contact energy (ACE). Then, the result of this step will be sent to FireDock web server for refinement docking to provide the flexible structure of protein complex/molecules complex, final binding energy, and Van der Waals binding data. All those data were used to know the difference of chemical interaction energy for every atom within the ligand-protein complex when IGF-1R bound to the tea polyphenol or in regular binding activity (IGF-1 and IGF-1R interaction).

2.3. Ligand-Protein Interaction and Visualization
The visualization of the three-dimensional structure of ligand and primary target protein related to it secondary structure were quantified and analyzed by PyMol software (www.pymol.org). The different types of amino acid residue position and ligand-protein interaction were shown on LigPlot software. The chemical interaction of both molecules related to hydrogen bond, hydrophobic bond, and the contribution of each amino acid residue on that binding complex was analyzed entirely using LigPlot software.
Figure 1. The Prediction of IGF-1R Signaling Pathway and its Protein Interactor. The red line shell shows protein query and the black circle illustrates the potential role of IGF-1R as the initiator protein on the primary signaling pathway.

3. Results and Discussion
The prediction of the potential molecular pathway of IGF-1R activation showed in Figure 1. The preliminary result of our In Silico study found that IGF-1R phosphorylation would induce the mitogen-activated protein kinase (MAPK) signaling pathway, the inhibition of apoptosis protein, and enhanced mitotic protein on cell cycle step. The predictive score or highest confidence value of this data was about 90% which meant the validity of those results was close to the real data from in vitro and in vivo database. The number of protein that contributed to that pathway was 35 protein involved in MAPK activity (13 protein), apoptosis silencing (10 protein), differentiation inhibition (8 protein), and mitotic cell cycle (4 protein). The majority of interactor protein for IGF-1R were contributed to the MAPK signaling pathway. The blue and purple lines implied the protein-protein interaction based on the database and experimental studies respectively (Figure 1).
Figure 2. The Visualization of Protein Structure with Homology Modelling Method and Structure Validation. (A). The basic structure of *Insulin-like growth factor 1* (IGF-1), (B). *Insulin-like growth factor 1 receptor* (IGF-1R)

The majority of essential chemical molecules consist of caffeine, theaflavin, catechin, theobromine, theophylline, thearubigin, gallic acid, chlorogenic acid, pectin, and theanine. For the next data analysis, the target protein homology modeling also described the conserved characteristic of IGF-1 and its receptor with a higher similarity score. The value of the favored region for IGF-1 and IGF-1R is more than 90% which mean both molecular structures have a more elevated validity model. The visualization of IGF-1 and IGF-1R is shown in Figure 2. The cartoon model with specific staining for the secondary structure of both proteins including alpha-helix, beta-sheet, and the coil is red, yellow and green respectively within the white transparent surface model. Despite the primary data from homology modeling, the researchers also tried to visualize the autophosphorylation domain of IGF-1R. The specific domain of protein phosphorylation for IGF-1R is shown in Figure 3. The phosphorylation domain of IGF-1R consists of tyrosine residue (Tyr-1161, Tyr-1165 and Tyr-1166). This specific domain provided in spheres and stick structure within the transparent surface model.
Next, to trace the probability of black tea polyphenol binding activity to IGF-1R, reverse docking model was applied to our data. The result of this study proved that the lower binding affinity of black tea polyphenol was found in thearubigin (-10.0 kcal/mol) while another polyphenol showed a strong binding affinity to this receptor (theophylline = -7.0 kcal/mol, theaflavin 3,3’-digallate = -6.7 kcal/mol, and theaflavin = -6.7 kcal/mol). The detail information of reverse docking data analysis was shown in Table 1.

| Ligand                         | PubChem ID | Target Protein | Binding affinity (kcal/mol) |
|--------------------------------|------------|----------------|-----------------------------|
| Thearubigin                    | 100945367  | IGF-1R         | -10.0                       |
| Theophylline                   | 3055685    | IGF-1R         | -7.0                        |
| Theaflavin 3,3’-digallate      | 58252602   | IGF-1R         | -6.7                        |
| Theaflavins                    | 114777     | IGF-1R         | -6.7                        |
| (-)-Epigallocatechin gallate   | 65064      | IGF-1R         | -6.6                        |
| (-) Epicatechin gallate        | 107905     | IGF-1R         | -6.5                        |
| Chlorogenic Acid               | 1794427    | IGF-1R         | -6.5                        |
| (-) Epicatechin gallate        | 107905     | IGF-1R         | -6.5                        |
| (-)-Epigallocatechin           | 72277      | IGF-1R         | -6.3                        |
| (-) Epicatechin                | 72276      | IGF-1R         | -6.3                        |
| Theaflavin 3-gallate           | 102115506  | IGF-1R         | -6.0                        |
| Pectin                         | 441476     | IGF-1R         | -5.1                        |
| Theobromine                    | 5429       | IGF-1R         | -5.0                        |
| Gallic Acid                    | 370        | IGF-1R         | -4.8                        |
| Caffeine                       | 2519       | IGF-1R         | -4.5                        |
| Theanine                       | 228398     | IGF-1R         | -4.4                        |

Table 1. The binding affinity of query molecules in black tea (Camellia sinensis).

To classify the potential molecule with a strong binding affinity to autophosphorylation domain of IGF-1R, the computational analysis using LigPlot software was used. Interestingly, our data showed that theaflavin 3,3’-digallate (TF3) and theophylline had a significant interaction with the tyrosine residue at Tyr1611 (Table 2). However, there was no significant interaction between thearubigin and other polyphenol molecules.
Table 2. Ligand-Protein Interaction between Black tea Polyphenol and IGF-1R

| Ligand                  | Interaction                                      |
|-------------------------|--------------------------------------------------|
| Theaflavin 3,3’-digallate| Hydrogen bond: Glu1162, Asp1159, Asn1049, Arg1167, Glu1056  |
|                         | Hydrophobic: Val1053, Tyr1161, Ser1052, Arg1158, Phe1131 |
| Theophylline             | Hydrogen bond: Ile1160, Thr1190, Lys130, Tyr1161, Tyr1192, Ser1258, Asn1127, Phe1259, Ala1128 |
| Theaflavins              | Hydrogen bond: Ser1052, Glu1162, Lys130, Asp1159  |
|                         | Hydrophobic: Glu1056, Lys1055, Asn1129, Val1053, Phe1131, Asn1049, Arg1158 |
| Thearubigin              | Hydrogen bond: Glu1056, Lys1055, Asn1129, Asn1058  |
|                         | Hydrophobic: Phe1131, Tyr1125, Ser1282, Phe1279, Cys1059 |
| Autophosphorylation      | Hydrogen bond: Glu1056, Lys1055, Asn1129, Asn1058  |
| Domain                  | Hydrophobic: Phe1131, Tyr1125, Ser1282, Phe1279, Cys1059 |

Figure 4. Ligand query interaction with amino acid residues Tyr1161 on IGF-1R autophosphorylation domain. (A). Theaflavin 3,3’-digallate (TF3); (B) Theophylline; (C) RMSD comparison of TF3 and theophylline.

The interaction of TF3 and theophylline on IGF-1R phosphorylation domain is shown in Figure 4. The clarification of the affinity profile of TF-3 and theophylline was supported by the distance of atomic binding according to root square deviation value (RMSD). This score obtained from the distance interaction between atoms from the ligand and amino acid residues at autophosphorylation domain. In the final analysis, we also tried to investigate the rigid model of ligand-protein interaction through refinement docking method. The binding energy resulting from atomic contact energy, repulsive and attractive Van der Waals bond, global energy and a hydrogen bond is shown in Figure 5. In the natural condition (green color), the absence of black tea polyphenols on IGF-1R autophosphorylation domain resulted in global energy about -46.16 kcal/mol, attractive and repulsive Van der Waals bond -42.86 and 17.30 kcal/mol respectively, and hydrogen bond -5.87 kcal/mol. However, the present of TF3 (blue color) caused the significant changes in global energy into -27.23 kcal/mol and -40.15 kcal/mol for theophylline (red color). Importantly, the repulsive Van der Waals energy of TF3 also showed more significantly compared to theophylline. Also, the binding energy from hydrogen bond formation in TF3
was more favorable (-2.46 kcal/mol) and more positive than theophylline (-4.44 kcal/mol). Due to the potential chemical properties of Theaflavin 3,3'-digallate (TF3) and theophylline on IGF-1R signaling, to complete our in silico based study the researcher finished with a biological function analysis using PassOnline database. The probability activity (Pa) score of TF3 was higher and significantly different in lipid peroxidation than apoptosis and phosphatase inhibition (Figure 6). TF3 was predicted to work as lipid peroxidase inhibitor, apoptosis agonist, and phosphatase inhibitor. Overall, the probability activity value (Pa) of TF3 was ranging from 70-92% while the probability score for phosphatase inhibitor (Pi) was in the lower range (2-13%).

Figure 5. The comparison of binding energy between IGF-1, TF3, and Theophylline on IGF-1R

The primary function of IGF-1 and insulin was closely related to several aspects, including leading to protein synthesis (gene expression), cell proliferation or death, and lipid-glucose metabolism [34]. It was proven that the binding activity of IGF-1 to its receptor (IGF-1R) strongly associated with the up-regulation of pro-obesogenic gene expression. The differentiation of preadipocytes linked IGF-1 signaling correlated to MEK/ERK (mitogen-activated protein kinase family) activation to enhance the up-regulation of transcription factor PPARγ (peroxisome proliferator-activated receptor gamma) and C/EBPα (CCAAT/enhancer-binding protein alpha) gene expression [35]. The disruption of IGF-1 signaling suggested that the results in impaired adipogenic program and thermogenesis [36]. Moreover, the higher expression of IGF-1R was able to induce adipocyte differentiation from immature adipocytes or preadipocytes [37]. The recruitment of IGF-1R was reported to play a significant role in adipogenesis through regulating primary cilium elongation on preadipocytes during the differentiation process [38]. The IGF-1R was abundantly expressed in preadipocytes while IR predominantly found in mature adipocytes. Therefore, the primary treatment against obesogenic program was developed to inhibit IGF-1 and IGF-1R during preadipocyte differentiation.
Some studies have proven that green tea and black tea polyphenol have a potential activity to reduce growth factor receptors and transcription factor activation. In silico study suggested that green tea polyphenol can inhibit the adipogenesis by blocking the primary transcription factor PPARγ (peroxisome proliferator-activated receptor gamma) activity [39]. Furthermore, theaflavin 3, 3’-digallate (TF3) showed an ability to downregulate EGFR (epidermal growth factor receptor) improved that anti-proliferative effect of black tea on cell proliferation [40]. TF3 was able to inhibit NIH3T3 cell proliferation more effectively than epigallocatechin-3-gallate (EGCG) corroborate, the likely impact of this black tea polyphenol against adipogenesis [41]. Also, theaflavins within black tea exhibited apoptosis and reduced inflammation through in vivo and in vitro experiments [42]. Thus, the essential polyphenol in black and green tea could be proposed as the future treatment against adipogenesis.

Importantly, the primary question that might have risen in our preliminary study was whether TF3 potentially decreased adipogenesis through the IGF-1R pathway. Linear to previous findings, in our both preliminary laboratory work through animal and cell culture experiment it was proven that black tea and its potential polyphenol could decrease adipogenesis significantly through downregulating the expression of IGF-1, ERK1/2 (extracellular signal-regulated kinases), and PPARγ (data not shown). Black tea polyphenol was suggested to suppress obesity, hyperglycemia, visceral fat mass, fatty acid synthesis related gene attenuation, and insulin resistance [20, 43, 44]. We hypothesized that the treatment of black tea extract on the animal model and TF3 on preadipocytes culture were disrupted IGF-1 expression and its receptor activation/phosphorylation. However, to elucidate our preliminary speculation the prediction of this biological pathways by using in silico model is required. Here, we tried to build a first molecular forecast on how black tea polyphenol can reduce obesogenic activity by using molecular docking the query component within black tea. The baseline data showed that IGF-1 phosphorylation modulates MAPK (mitogen-activated protein kinase family) signaling while the inhibition of this growth factor expression will decreasing the number of cell amount-induced apoptosis. It was supported by the highest confident score from in silico data on STRING database. The computational analysis has shown that black tea polyphenol may bind to IGF-1R binding domain particularly on tyrosine residue (Tyr-1161, Tyr-1165, and Tyr-1166). IGF-1R phosphorylation domain could be potential to become the primary target for some inhibitors including the query molecule of black tea (theaflavin).

Our study also delineated the binding performance by bioinformatics way through molecular docking of potential black tea polyphenol, theaflavin 3,3’ digallate (TF3) with IGF-1R. In the drug development model, the general computational study suggested by reverse docking approach [45]. The results of our study showed that among potential black tea polyphenols, TF3 inhibit markedly IGF-1R activity. The binding affinity of TF3 was similar to theophylline with hydrophobic interaction on Tyrosin residue (Tyr1611). Molecular reverse docking model indicates that TF3 has a strong binding activity with IGF-1R compared to theophylline. The interaction of TF3 on autophosphorylation domain of IGF-1R results
in significant positive global energy (-27.23 kcal/mol) than theophylline (-40.15 kcal/mol). This data imply the instability of IGF-1R phosphorylation domain due to TF3 binding activity induced the alteration of molecular interaction on IGF-1 and IGF-1R complex. The amount of energy for binding affinity can indicate some ability for active compound binding on the target protein, to form a protein-ligand complex stabilized and it requires the negative value of binding affinity. Even though the attractive Van der Waals of theophylline was much stronger than TF3, however, based on the global energy, repulsive Van der Waals, and hydrogen bond profile of TF3 improved that this black tea polyphenol has a more significant inhibitory effect than other polyphenols. The global energy value illustrates the total binding energy between the ligand and its receptor to form a complex during molecular interaction [46]. Also, the Van der Waals force is strongly associated with protein-protein interaction among ligand-receptor interaction [47] while thermodynamics protein association determine to contribute to complex binding stability [48]. As a consequence, it may stimulate the down-regulation of IGF-1 signaling pathway activation especially during adipogenesis program within adipose tissue.

Another additional data also showed that TF3 might act as the anti-obesity agent through inhibit cell proliferation (apoptosis agonist) and phosphatase inhibitor based on probability activity score (Pa score) analyzed by PassOnline measurement [49]. The higher score of TF3 probability activity (> 0.7 or 70%) emphasizes our theory which is the black tea polyphenol attenuate adipogenesis to induce apoptosis of immature adipocyte cells. We suggest that TF3 alleviated anti-apoptosis protein and enhanced cell death program. Nevertheless, the limitation of our study is that we cannot fully elucidate the blocking effect of TF3 to transcriptional molecules that play a pivotal role in the adipogenesis. Hence, the future pre-clinical investigation is crucial to recommend the administration of black tea polyphenol for a patient with metabolic syndrome symptom particularly overweight and obesity.

4. Conclusion
In summary, the black tea polyphenol Theaflavin 3,3′-digallate (TF3) is a promising and potential candidate as a herbal therapeutic agent for obesity prevention. TF3 may directly regulate adipose tissue growth via down regulate IGF-1 expression and IGF-1R activation. While our study employed fundamental data for further clinical applications, the extensive and comprehensive research are required to emphasize and clarify our findings. Importantly, the data presented here provide a foundation or hallmark for the molecular mechanism of black tea polyphenol in the translational investigation.

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