

Computational Investigation of Ajwa-Derived Quercetin as a Potential EGFR-Targeting Scaffold for Oral Squamous Cell Carcinoma

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Abstract

Phoenix dactylifera L. (Ajwa date) has a variety of bioactive phytoconstituents and has demonstrated impressive anticancer properties. Quercetin was found to be a major component of an Ajwa-based formulation using LC-MS analysis. The present study aimed to explore the possibility of molecular basis for quercetin activity against oral squamous cell carcinoma (OSCC) through computer-aided drug design approach with epidermal growth factor receptor (EGFR) kinase domain as the target.

Molecular docking was carried out using the target protein: EGFR (PDB ID: 7AED); a reference ligand: Osimertinib. The docking protocol was tested with the re-docking of the native ligand that yielded an RMSD of 0.6786 Å. The docking score for Osimertinib was -9.980 kcal/mol while the docking score for quercetin was -8.501 kcal/mol. The hydrogen-bond interactions of quercetin were with ASN842, MET793, LYS745 and ASP855, and the hydrophobic interactions were with ALA743, VAL726, LEU792, MET793, PRO794, LEU718, CYS797 and LEU844. Quercetin and Osimertinib displayed similar binding site properties in SiteMap analysis: SiteScore/Dscore = 1.043/1.063 and 1.027/1.037, respectively.

The molecular weight of quercetin was 302.24 Da, LogP was 0.386, it contained 4 hydrogen-bond donors, 5 hydrogen-bond acceptors and no violations of Lipinski Rules of Five were found by in-silico ADME analysis. Overall, the results indicate that Ajwa-derived quercetin may interact with the EGFR kinase domain and suggest a molecular basis for studying quercetin as a scaffold for cancer treatment in OSCC.

Keywords: *Phoenix dactylifera*; Quercetin; Oral squamous cell carcinoma; Molecular docking; Binding Mode Analysis; In-silico ADME calculation

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1. Introduction

Oral squamous cell carcinoma (OSCC) is the most prevalent histological type of oral cancer and a significant health problem in the world. Surgery, radiotherapy, chemotherapy, targeted therapy or a combination of these is the usual treatment [1, 2]. Therapeutic resistance, recurrence, toxicity of treatment, however, and molecular heterogeneity remain as obstacles to treatment. These challenges underscore the importance of the discovery of new compounds and molecular targets that could lead to the development of a novel and effective anti-cancer approach [3].

Phoenix dactylifera L. Date palm (Arecaceae), also referred to as fruit palm, is one of the plants which has a long history of being used for food and traditional medicine. The fruits have a variety of phytoconstituents such as phenolic acids, flavonoids, carotenoids, and other bioactive compounds [4, 5]. The reported phytochemical constituents and biological activities of *P. dactylifera* have attracted greater interest in its potential therapeutic applications. Ajwa date is one of the cultivars of the dates, and is particularly

interesting scientifically due to its unique phytochemical composition and its reported biological properties and is traditionally grown in Madinah, Saudi Arabia [6, 7].

We had started our research on the Ajwa date (*P. dactylifera*) because of its reported phytochemical and pharmacological significance. A comprehensive literature search was carried out to gain insight into its phytochemical composition and reported biological activities. It was of special interest in this investigation that the plant had possible anticancer importance. A formulation was then prepared based on ajwa dates for its anticancer activity and the formulation was investigated. The formulation showed good anti-cancer activity, and can serve as an experimental foundation for continuing studies of the phytoconstituents that may be linked to this biological activity [8].

For the investigation of the chemical components of the plant material, liquid chromatography-mass spectrometry (LC-MS) profiling was conducted (manuscript is under communication). A series of phytoconstituents were identified, of which

quercetin appeared to be a key compound. This finding served as a rational basis to select quercetin as a drug for further computational studies. Quercetin is a naturally occurring flavonol with multiple hydroxyl groups and aromatic conjugated system. These structural properties allow for a variety of protein–ligand interactions. Besides, quercetin has been explored in cancer related models, such as oral cancer, and effects have been reported related to cellular proliferation, oxidative stress, apoptosis and cell-cycle regulation. Hence, the identification of Quercetin in the investigated Ajwa sample, and considering its reported anticancer relevance, it was considered to be the candidate phytoconstituent for the present study [8]. Computer-aided drug discovery (CADD) offers effective methods to explore protein-ligand recognition and to select meaningful bioactive compounds. Using molecular docking, the orientation of the binding site of a ligand can be predicted and docking scores and relationships between the residues and the ligand can be obtained, such as hydrogen bonding and hydrophobic interactions [9, 10]. Docking scores are however, not real experimental values of binding affinity or biological efficacy, but rather computational predictions. An additional information about the structural and physicochemical properties of possible ligand binding regions can be obtained with complementary binding site analysis. Parameters such as site score, size and volume can be used to characterize the binding site properties using SiteMap analysis. Absorption, distribution, metabolism, and excretion (ADME) analysis can be performed in-silico and can give an early estimation of the pharmacokinetic properties and drug-likeness of the compound [11-15].

Following this concept, the present study aimed to examine the EGFR kinase domain of *P. dactylifera* (Ajwa date) against OSCC. The computational workflow comprised protein target analysis, molecular docking of quercetin and Osimertinib, residue level analysis of the predicted protein-ligand interactions, SiteMap-based binding-site characterization and in-silico ADME evaluation. The aim was to explore the potential of establishing favourable interaction within the EGFR kinase domain binding region, and to determine the structural and pharmacokinetic properties relevant to the continued process of drug discovery and development from the Ajwa derived quercetin. This study aimed to hypothesize at the molecular level how the phytochemical profile of Ajwa date is correlated with its observed anticancer activity and to validate the activity of quercetin in biochemical and cell-based models of OSCC.

2. Materials and Methods:

Structural and stereochemical studies were performed to determine the suitability of the protein target for further molecular docking studies. The

three-dimensional structure of the target protein was downloaded from the Protein Data Bank (PDB) [16] and analyzed in terms of overall structure, surface topology and the presence of a ligand binding site. Molecular surface representation of the protein and the predicted active/binding site were used to find out the cavity which is suitable for the ligand to be accommodated in the site. Quality of the protein model was also assessed using a Ramachandran plot, in which the number of amino acid residues falling in the allowed or disallowed regions was plotted. The three-dimensional surface representation of the protein, identification of the binding site, and Ramachandran plot are shown in Figure 1A, 1B and 1C respectively. The validated protein structure was then used to prepare the protein and for molecular docking with quercetin and reference ligand Osimertinib.

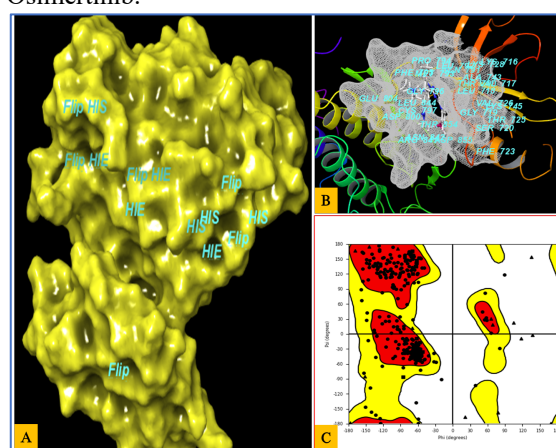


Figure 1. Structural and stereochemical analysis of the selected protein target. (A) Three-dimensional surface representation of the protein structure showing the overall molecular surface; (B) predicted active/binding site of the protein showing the ligand-accommodating region; and (C) Ramachandran plot showing the stereochemical distribution of amino acid residues.

2.1 Molecular docking studies:

2.1.1. Protein Preparation

The crystal structure of the epidermal growth factor receptor (EGFR) kinase domain was obtained from the Protein Data Bank (PDB ID: 7AEI) [17]. The protein structure was prepared with the Protein Preparation Wizard found in Maestro molecular modelling suite. The preparation protocol was used to determine appropriate bond orders and formal charges as well as adding hydrogen atoms to the protein structure [18]. Other crystallographic components and non-essential solvent molecules were removed, if applicable. The assignment of hydrogen bond was then optimized to get a structurally suitable receptor for molecular docking. Finally, the prepared protein was energy minimized to remove the unfavorable contacts and achieve a stable conformation of the receptor for docking using the OPLS2005 force field [19].

2.1.2. Receptor Grid Generation

The receptor grid was created in the Glide docking workflow with the help of the module Receptor Grid Generation [20]. The grid was generated by considering the EGFR binding site in the crystallographic structure and known protein-ligand interactions in the EGFR kinase domain. The ATP-binding region with functionally important residues for the recognition of the ligand, such as Lys745, Met793 and Cys797, were specially highlighted. This receptor grid was then utilized for docking of quercetin and reference ligand, Osimertinib, under similar computational conditions.

2.1.3. Ligand Preparation and molecular docking.

LigPrep was used to prepare the 3D structures of quercetin and Osimertinib with Maestro suite. Protonation states, stereochemical configurations and low energy conformations were generated and then energy minimized using the OPLS2005 force field. Molecular docking of the prepared ligand structures with the EGFR receptor was then performed using the prepared EGFR receptor.

The docking module used for molecular docking was the Glide docking module. Quercetin and Osimertinib were separately docked to the pre-determined binding site of EGFR, with the same docking conditions. The extra-precision (XP) mode was used in the docking protocol for obtaining reliable predictions of the ligand-binding poses and protein-ligand interactions. After docking, post-docking minimization was carried out and the docked ligand structures were ranked based on the docking score. The top five poses were selected for further analysis of interactions. The possibility of hydrogen-bonding, hydrophobic, polar and other non-covalent interactions among the ligands and EGFR were explored by using Maestro Pose Viewer and XP Visualizer software.

2.1.4. Docking Protocol Validation:

The validated docking protocol was used to re-dock the co-crystallized ligand into its relative EGFR binding site. The calculated position was compared to the crystallographic orientation position obtained by experiment, by the root-mean-square deviation (RMSD). The RMSD of the generated mode was ≤ 2.0 Å was considered a reasonable representation of the experimental binding mode. The obtained RMSD value of 0.6786 Å validated the docking protocol and served as evidence for comparative analysis of quercetin and Osimertinib in order to demonstrate the efficacy of the docking approach. The RMSD value obtained with this docking protocol was found to be 0.6786 Å, which was considered suitable for further comparative analysis of quercetin and Osimertinib to show the efficacy of the docking approach.

2.2 Binding Mode analysis:

The binding mode of quercetin was also investigated using the SiteMap module of the Schrödinger suite [21]. The binding-site environment of quercetin and

the reference drug in the EGFR binding region was characterized and compared by using SiteMap analysis. The spatial distribution of hydrophobic and hydrophilic regions, the hydrogen-bond donor and acceptor features, the site points, the exposure, the enclosure, the contact properties, the site volume, the SiteScore and the Druggability Score (Dscore) were analyzed. The physicochemical parameters were used as a basis to evaluate the druggability of the binding region of the respective ligands.

The SiteMap derived from the quercetin and the reference drug were comparatively analyzed. The binding-site environment and binding mode of the ligands appear to be similar if the same values were found and the spatial properties are comparable for the parameters analyzed. This analysis was then employed in conjunction with the molecular docking analysis and the protein-ligand interaction profile in order to ascertain if quercetin could assume a mode similar to that of the drug used as a reference in the binding site of EGFR.

2.3: In-silico ADME calculations:

QikProp (version 3.0) (Schrödinger, LLC, New York, 2005) was used to predict the pharmacokinetic properties of quercetin and the reference drug. The selected compounds have undergone analysis to evaluate their drug-likeness and preliminary pharmacokinetic properties. The predicted properties were molecular weight, hydrogen-bond donors, hydrogen-bond acceptors and octanol/water partition coefficient (LogP) as per Lipinski Rule of five. The Jorgensen Rule of Three was also taken into account to evaluate overall drug-like property of the compounds. Furthermore, polar surface area, predicted aqueous solubility, human oral absorption and Caco-2 permeability were considered to provide a preliminary understanding of absorption and physicochemical properties of the compounds studied.

3. Results and Discussion:

A computational analysis was carried out to examine the possible binding interaction and drug likeness of quercetin towards the selected EGFR target involved in oral squamous cell carcinoma. Protein structure analysis, protein binding-site analysis, molecular docking, docking validation, docking binding-site site mapping, and in-silico ADME prediction were conducted as part of the study. Quercetin was compared with Osimertinib drug, a clinically approved drug targeting the EGFR [22, 23]. Docking score, key protein-ligand interaction, binding site properties and predicted pharmacokinetic properties were used to evaluate possible potential of quercetin to be further investigated for OSCC. Before the start of computational studies, the software was validated by extracting and redocking of internal ligand without change in its heterostate and RMSD value was calculated. The figure 2 showing the superimposed structure of before and after docking of internal ligand

with the RMSD value 0.6786 Å, indicating that the software is ready to use for further computational studies.

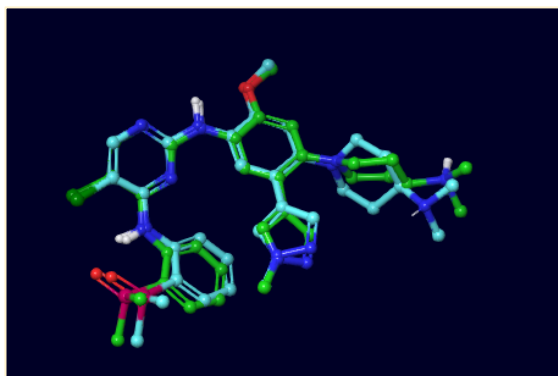


Figure 2: Software validation and RMSD calculation of before and after docked internal ligand

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3.1. Molecular Docking Studies

To gain insight into the possible binding mode of quercetin in the EGFR kinase domain and to elucidate the possible molecular mechanism of quercetin against OSCC, molecular docking was carried out. A popular CADD method used to predict the preferred orientation of the ligand in the protein binding pocket and a gain of binding favourability is called docking [24]. The kinase domain of EGFR (PDB ID: 7AEI) was chosen in the present study because EGFR mediated signalling is crucial to the proliferation and survival of cancer cells. The obtained results are summarized in table 1 and the interactive diagrams are given in figure 3 and different types of interactions are summarized in table 1. The docking results revealed that Osimertinib had a docking score of -9.980 kcal/mol while quercetin had a score of -8.501 kcal/mol when used as the reference compound. The score value for quercetin was not as good as Osimertinib but suggested good predicted interaction with the EGFR binding region.

Osimertinib had hydrogen-bond interactions at the residue level with Met793, Cys797 and Asp800. In contrast, quercetin was found to form hydrogen bonds with the residues of Asn842, Met793, Lys745

and Asp855. In addition, hydrophilic contacts were observed with the following residues: Val726, Ala743, Met793, Pro794, Leu718, Cys797, and LEU844, and further with Gly796, Thr854, Arg841. While some of these residues are partially shared with the predicted binding regions, such as Met793, Cys797, Leu792, Leu718, Val726, Ala743, Leu844 and Gly796 the majority are distinct.

The results obtained are in accord with the previous computational studies reporting the binding of quercetin to the EGFR, with residues Lys745 and Met793 showing favourable interaction. A recent study with the crystal structure of EGFR PDB 7AEI shows the interaction of quercetin with Lys745 and Met793. However, with the use of a different approach to docking, the score was less negative (-6.73 kcal/mol). A second computational study found the EGFR-quercetin docking score to be -8.7 kcal/mol and that Met793 and Asp855 were important interacting residues. Therefore, the present results support the hypothesis that quercetin may interact with the EGFR kinase domain region, thereby offering further computational support. Important, the lower docking score compared to Osimertinib does not constitute a proof of equivalent inhibitory potency. Instead, it seems that the overlap of the residues interactions indicates that the quercetin binds a biologically relevant part of EGFR and offers a structural background for the future studies of its anticancer mechanism. Docked complexes were then subjected to further advanced binding-mode and drug-design analysis, such as SiteMap and in-silico ADME evaluation to further explore the potential of quercetin as a lead compound for drug discovery in the context of OSCC.

Table 1. Different binding interactions of selected compounds with the EGFR kinase domain

Compound	Docking Score Kcal/mole	H-bond interactions	Other predicted interactions	Key active-site residues
Osimertinib	- 9.980	Met793, Cys797, Asp800	Hydrophobic, polar, glycine and charged-residue contacts	Met793, Cys797, Asp800, Phe795, Pro794, Leu792, Leu718, Phe723, Val7

				26, Ala7 43, Leu8 44, Gln7 91, Thr7 90, Thr8 54, Ser7 20, Gly7 19, Gly7 96, Lys7 45, Lys7 28, Asp8 55, Glu8 04
Querce tin	-8.501	Asn842 , Met793 , Lys745, Asp855	Hydroph obic, polar, glycine and charged- residue contacts	Asn8 42, Met7 93, Lys7 45, Asp8 55, Ala7 43, Val7 26, Leu7 92, Pro7 94, Leu7 18, Cys7 97, Leu8 44, Gly7 96, Thr8 54, Arg8 41

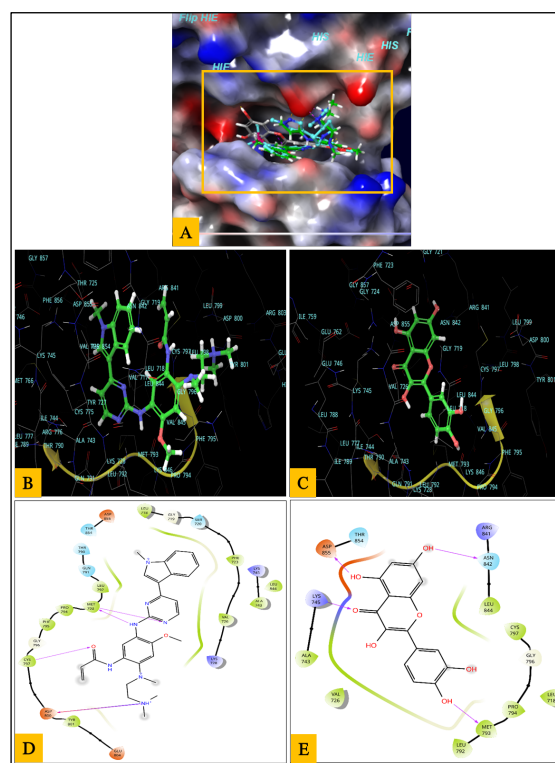


Figure 3: Molecular docking results of Quercetin and Osimertinib molecules against the kinase domain of EGFR (PDB ID: 7AEI). Where A) Molecular surface diagram of protein with selected molecules. While later represent the 3D and 2D interactive diagrams showing the different types of interactions with active site residues. B & D) Osimertinib and C & E) Quercetin

3.2. Binding Mode Analysis using SiteMap.

To explore the binding environment of quercetin and Osimertinib in the EGFR kinase domain, SiteMap analysis was carried out the data are summarized in table 2 while different paraments with active site are displayed in figure 4. SiteMap also offers quantitative data about the physicochemical properties and druggability of protein binding sites, which can be combined with molecular docking for the interpretation of ligand binding. The present study found that the SiteMap profiles of the complexes between quercetin and EGFR, and between Osimertinib and EGFR exhibited similar values for most of the parameters of the binding site. The SiteScore for quercetin and Osimertinib were 1.043 and 1.027, respectively, and their Dscore values were 1.063 and 1.037, respectively. The site size predicted was 138 site points for quercetin and 120 site points for Osimertinib with site volumes of 446.243 Å³ and 341.628 Å³, respectively. The SiteScore and Dscore values are similar, suggesting that both ligands are in a favourable binding-site environment in the EGFR kinase domain. The slightly higher SiteScore and Dscore values indicated for quercetin indicate that binding environment is not poorer than the reference ligand with regards to the site characteristics derived from

the SiteMap. The larger site size and volume may be associated with the different molecular geometry of quercetin which is the space that it occupies in the binding pocket. Importantly, these results must be interpreted in conjunction with the docking interaction profile and not as a direct comparison of binding affinities.

Quercetin interacted with Met793, Lys745, Cys797, Asp855, Ala743, Val726, Leu792, Pro794, Leu718, Leu844, Gly796, Thr854 and Arg841, with some residues overlapping the Osimertinib interaction network. The results of the combined docking and SiteMap thus support the hypothesis that the binding region of the EGFR for quercetin can be accessed and interacts with a structurally relevant region in a binding environment similar to that of the reference drug. The results will serve as a molecular basis for further investigation of quercetin as a scaffold for targeted anti-cancer agents directed against the EGFR, and will assist with moving the compound to later stages of computational drug design and experimental testing.

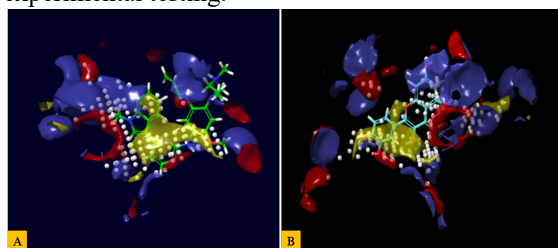


Figure 4: The figure showing the different types of contour map where; blue colour shows the H-bond donor; red colour H Bond acceptor; Yellow displayed the hydrophobic cavity; white dots represent the site points.

Table 2: SiteMap analysis data of Osimertinib and Quercetin used for binding mode analysis

Sr No.	Compounds	SiteScore	Size	DScore	Volume
	Osimertinib	1.027	120	1.037	341.628
	Quercetin	1.043	138	1.063	446.243

3.3 In-silico ADME calculations:

The preliminary drug like and absorption properties of quercetin and Osimertinib have been evaluated and results are summarized in table 3. The results revealed that quercetin had a molecular weight of 302.24 Da, while Osimertinib had a molecular weight of 499.61 Da, with 4 hydrogen-bond donors and 5 hydrogen-bond acceptors, and 8 hydrogen-bond donors and acceptors, respectively.

The LogP value for quercetin and Osimertinib were predicted as 0.386 and 4.526, respectively, which showed a significantly lower lipophilic nature for quercetin. Table 3 indicates that the QikProp output for OSI-929 (quercetin) was 20.528, whereas the output for Osimertinib was 576.001. The human oral absorption values were predicted to be 52.692% for

quercetin and 76.482% for Osimertinib, with a BBB value of 5 reported for both compounds. Importantly, no violations of Lipinski Rule of Five and one violation of Jorgensen Rule of Three were observed for quercetin, while there were no violations for either of the rules for Osimertinib.

The results indicate that quercetin has some desirable physiochemical properties for medicinal applications, such as moderate molecular weight, and reduced lipophilicity. But its estimated oral absorption was less than Osimertinib, suggesting that absorption and bioavailability must be taken into account during lead optimization. In conclusion, the ADME profile promotes the further exploration of quercetin as a scaffold for new anticancer drugs, and indicates that experimental pharmacokinetic studies and the optimization of structural changes or formulation are necessary to explore the drug delivery properties of quercetin. Therefore, the predicted ADME characteristics, along with the good EGFR binding interactions, offer further encouragement to proceed with quercetin in further stages of computational and experimental drug discovery.

Table 3: In-silico ADME calculation results of Quercetin and Osimertinib molecules

Molecule	Molecular Weight	H Bond Donors	H Bond Acceptors	LogP	LogS	LogB	Molar Weight	% Absorption	PSA	Ro5 Violations	Ro3 Violations
Quercetin	302.24	4	5	0.386	-2.528	5	5	52.692	14.0251	0	1
Osimertinib	499.61	8	8	4.526	-0.62	5	5	76.482	7.64	0	0

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3. Summary and Conclusion:

Molecular docking results indicated that quercetin had a favorable docking score of -8.501 kcal/mol with the EGFR kinase domain and interacted with several residues of the enzyme via hydrogen bond interactions, including Asp855, Lys745, Met793 and Asn842, as well as multiple hydrophobic contacts with key EGFR residues. The SiteMap analysis also revealed similar binding-site properties for quercetin and Osimertinib, indicating that the binding cavity of the kinase domain of EGFR is similar. The in-silico ADME analysis showed good drug-like physicochemical properties for quercetin, but its predicted OAC was less compared to Osimertinib. Overall, these results offer a molecular level hypothesis for the possible anti-EGFR-mediated OSCC activity of Ajwa quercetin and its potential as an anticancer scaffold. But the results of the present work are computational predictions and not biological efficacy or EGFR inhibition. Further biochemical, cellular, pharmacokinetic and in vivo experiments are recommended to confirm the proposed mechanism and the therapeutic potential of quercetin in OSCC.

Conflicts of Interest: Authors declare no conflict of interest

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