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The potency of lempuyang wangi (*Zingiber zerumbet*) as aldose reductase inhibitor: an alternative of anti-diabetes drugs

E B Minarno*, V S Belina, D Rimadhani, A A Pramudja, T N Punjungsari, A Jannah, and M Imamudin

Biology Department, Faculty of Science and Technology, State Islamic University of Maulana Malik Ibrahim Malang, Jl. Gajayana No.50, Kota Malang, Jawa Timur 65144, Indonesia

*Email: budi_minarno@bio.uin-malang.ac.id

Abstract. Aldose reductase is an enzyme that plays a role in glucose metabolism. An increase in aldose reductase will trigger an increase in blood sugar concentration by converting glucose to sorbitol. Increased sorbitol conditions will result in diabetes complications such as diabetic cataracts. So we need an inhibitor that can inhibit the working system of the aldose reductase enzyme. One of the medicinal plants that has anti-diabetic properties is lempuyang wangi. Lempuyang wangi has a secondary metabolite compound which has the potential as an anti-diabetic. The purpose of this study was to examine the anti-diabetic properties of lempuyang wangi using the in silico method. In this research, docking was carried out with Pymol and Pyrx software, and visualization using Biovia Discovery Studio to see the interaction between zerumbone compounds and aldose reductase and compared with zopolrestat compounds. The docking result of zopolrestat as a comparison compound is -9 kcal/mol, while xanthorrhizol has a binding affinity value of -8,7 kcal/mol and has the same amino acid bonds with zopolrestat, making it a potential candidate as an antidiabetic herbal drug in inhibiting the working system of the aldose reductase enzyme

1. Introduction

Aldose reductase plays a role in glucose metabolism polyol pathway which is responsible for forming fructose and glucose [1]. An increase in aldose reductase will trigger an increase of blood sugar concentration. The AR protein can bind to antidiabetic drugs so that it can inhibit the enzyme's action to change it glucose into sorbitol fructose and hyperglycemia by sorbitol dehydrogenase [2]. The aldose reductase enzyme is an enzyme whose role is to catalyze the reduction of glucose into sorbitol. During hyperglycemia conditions, blood glucose increases which causes enzymes to convert glucose into sorbitol and then sorbitol will be oxidized to fructose by sorbitol dehydrogenase (SDH) which results in the oxidation of NADPH to NADP+ in the polyol pathway (intracellular hyperglycemia) [3-5]. Increase sorbitol conditions will disrupt cell osmoregulation resulting in cell damage and diabetes complications such as neuropathy, retinopathy and diabetic cataracts [6-9].

Lempuyang wangi (*Zingiber zerumbet*) is a pseudo-stemmed plant that has single alternate leaves, green in color with tapered tips and flat leaf edges. The rhizomes are widely used as traditional medicinal plants, such as stomach aches, intestinal inflammation and so on. Lempuyang contains saponins, flavonoids and tannins. Zerumbon is the main compound that can be found in lempuyang wangi (*Zingiber zerumbet*). Zerumbone has potential as an antidiabetic, anticancer, antioxidant, anti-inflammatory, antipyretic, antimalarial, antiviral [2], and antibacterial [7]. Other compounds contained

in lempuyang wangi are also linalool, beta-selinene, 3-Octadecyne, xanthorrhizol, cyclohexanol, humulene oxide [12]. So the aim of this research is to see the potential of secondary metabolite compounds of lempuyang wangi (*Zingiber zerumbet)* as aldose reductase protein inhibitors by looking at the binding affinity.

2. Methods

2.1. Receptor and bioactive compound preparation

3D structure of aldose reductase dowloades from the RSCB (Research Collaboratory for Structural Bioinformatics) protein data bank (https://www.rcsb.org/structure/2HV5). Ligands of bioactive compound secondary metabolite (3-octadecyne, xanthorrhizol, beta-selinene, linalool, cyclohexanol, zerumbone, humulene) and zopolporestat are downloaded in Pub Chem (https://pubchem.ncbi.nlm.nih.gov/). BIOAVIA software was used to separate aldose reductase (2hv5) from water and protein thereby obtaining a clean enzyme file. The enzyme was saved in a pdb extension file. Proteins and ligands were prepared into ready-to-use files using the AutoDock and Openbabel conversion facilities in PyRx.

2.2. Docking simulations and pharmacophore analysis

Docking of the native ligand is carried out to look for the 3D conformation of the native ligand to the receptor by paying attention to the coordinates of the center of mass of the structure and the gridbox size of the binding site pocket in angstrom units (Vina) or number of points (AutoDock). The conformation of the docking results obtained is aligned with the native ligand conformation. The result that is used as a reference is the binding activity value, the greater the minus value. Docking of the test ligands was carried out to produce binding energy values in units of kcal/mol. The binding energy value used is the one that gets the value the greater the minus value the higher the better the bond.the program showes us the 2D and 3D stucture position and interaction of ligand in the biding pocket of the receptor. The 2D figure identified by color and symbol. Interactions conventional hydrogen bond, halogen (fluorine), hidrogen bond donor (HBD), alkyl/pi-alkyl,pi-pi shaped, pi-sulfur, pi-sigma were labeled as green, light blue, white, pink, fuschia yellow and purple.

3. Result and discussion

3.1. Interaction between aldose reductase protein with secondary metabolite and zopolrestat

The best binding affinity value was xanthorrhizol (-8,7 kcal/mol) then beta-selinene (-7,6 kcal/mol) and humulene (-7,6 kcal/mol), after that 3-octadecyne (-7,4 kcal/mol). This result is better than zerumbone (-5,5 kcal/mol) and cyclohexanol compounds (-5,3 kcal/mol). However, it is still not good when compared to Zopolrestat (-9,2 kcal/mol). but indicates that the secondary metabolite compounds of lempuyang wangi could be candidates for aldose reductase protein inhibitors (Table 1).

Table 1. Binding affinity value of secondary metabolites from lempuyang wangi *(Zingiber zerumbet)*.

Ligand	Binding affinity (kcal/mol)
Zopolrestat (control)	-9,2
3-octadecyne	-7,4
Xanthorrhizol	-8,7
Beta-selinene	-7,6
Linalool	-6,6
Cyclohexanol	-5,3
Zerumbone	-5,5
Humulene	-7,6

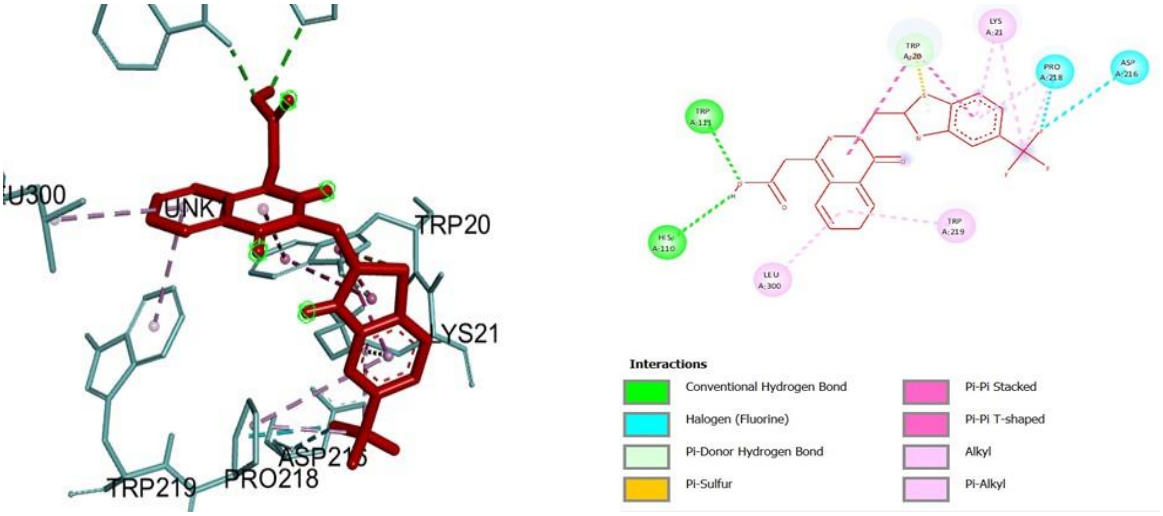

Figure 1. Structure docking of AR protein interactions with zolpolrestat (control).

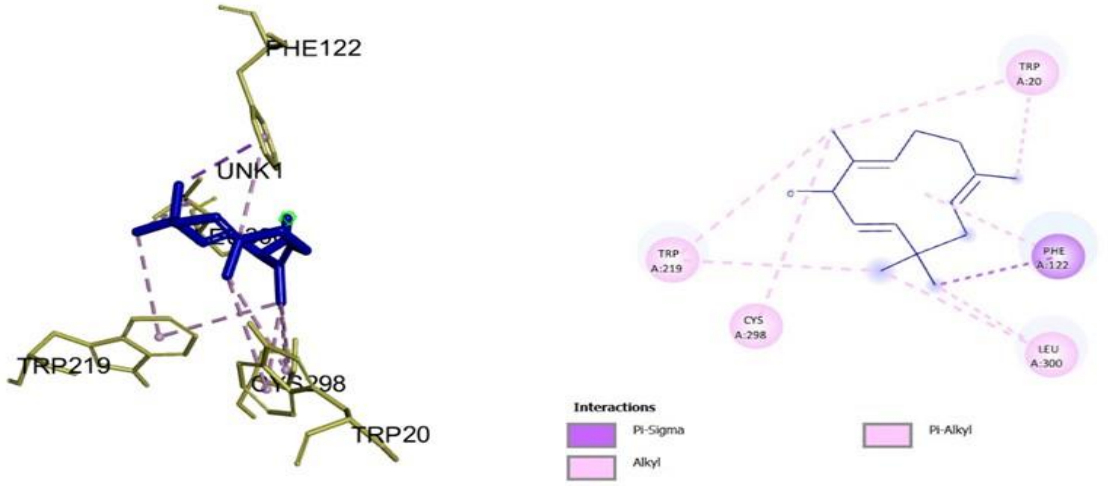

Figure 2. Structure docking of AR protein interactions with zerumbone.

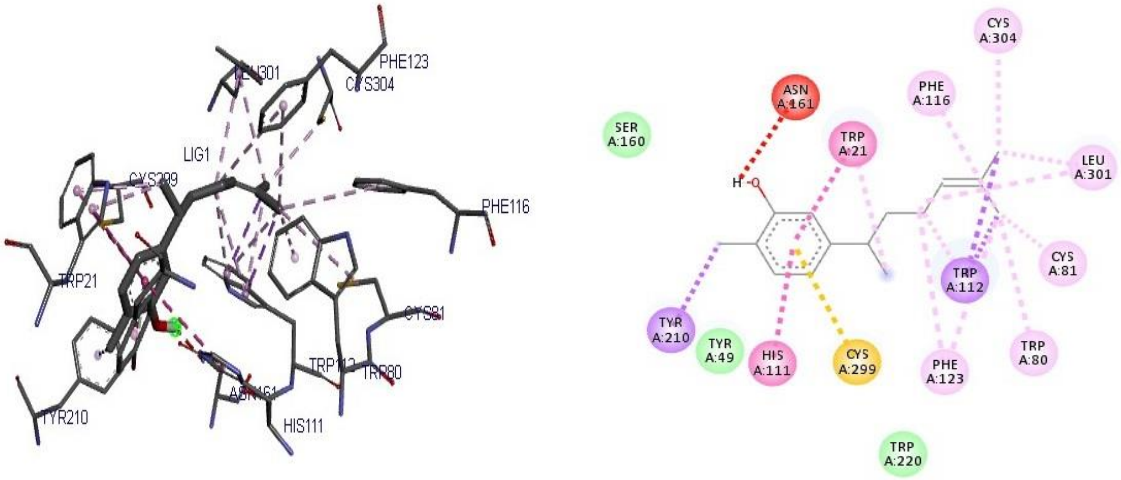

Figure 3. Structure with xanthorrhizol. docking of AR protein interactions

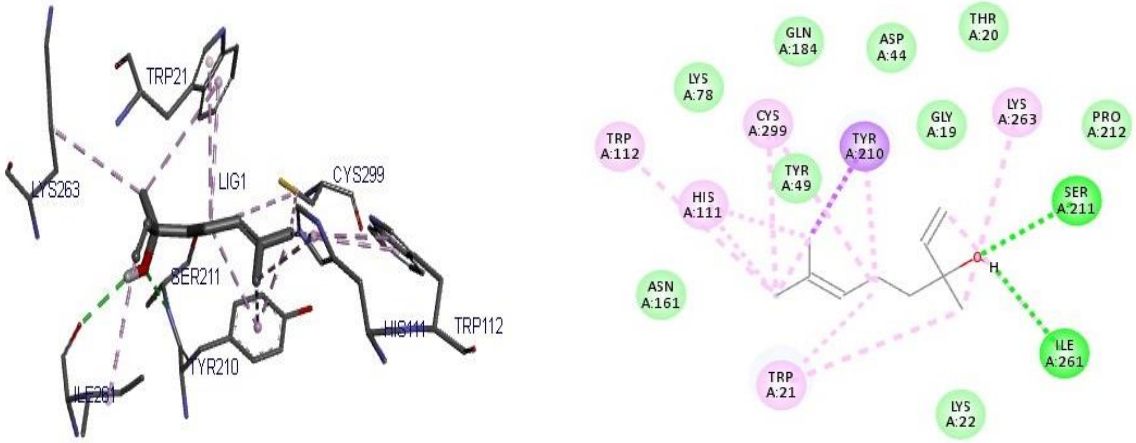

Figure 4. Structure the docking of AR protein interactions with linalool.

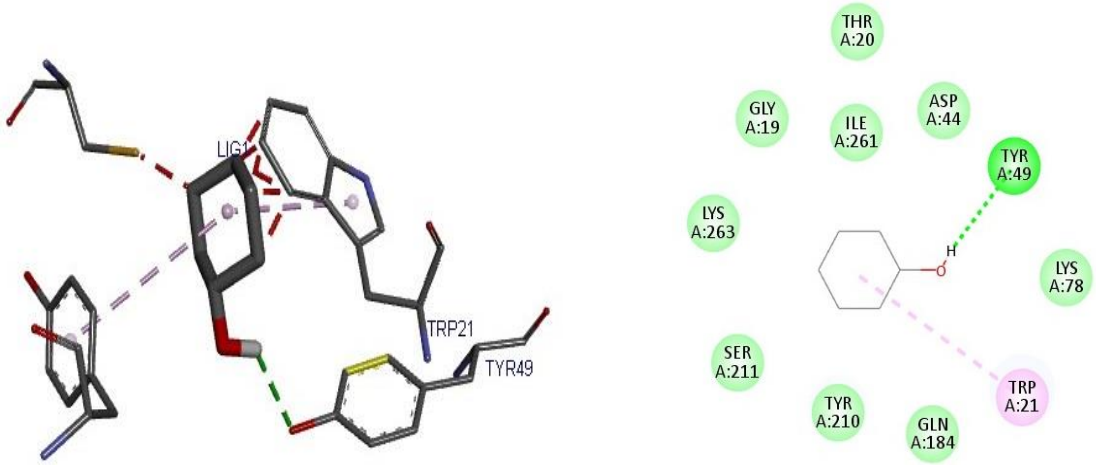

Figure 5. Structure docking of AR protein interactions with cyclohexanol.

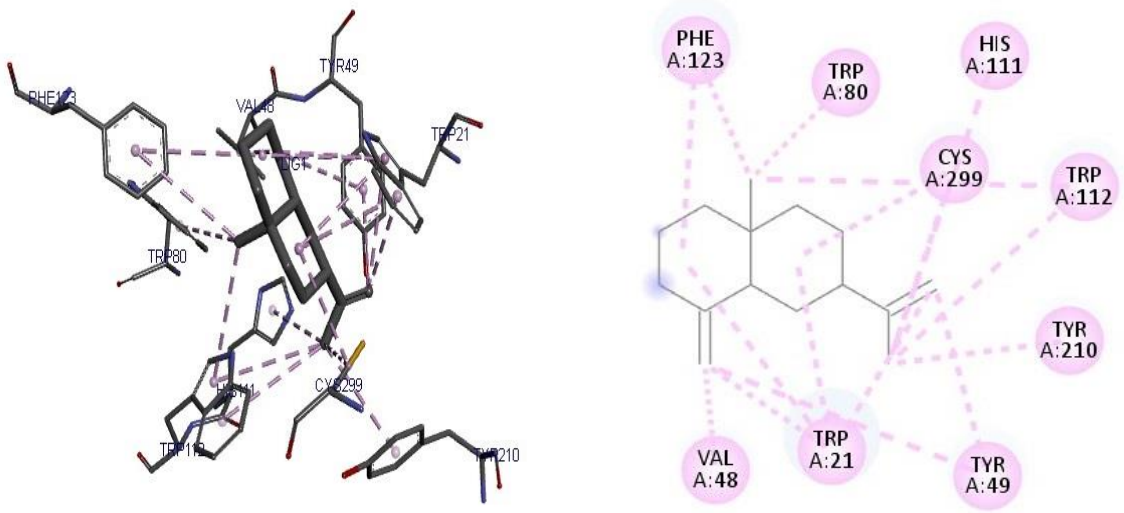

Figure 6. Structure docking of AR protein interactions with beta-selinene.

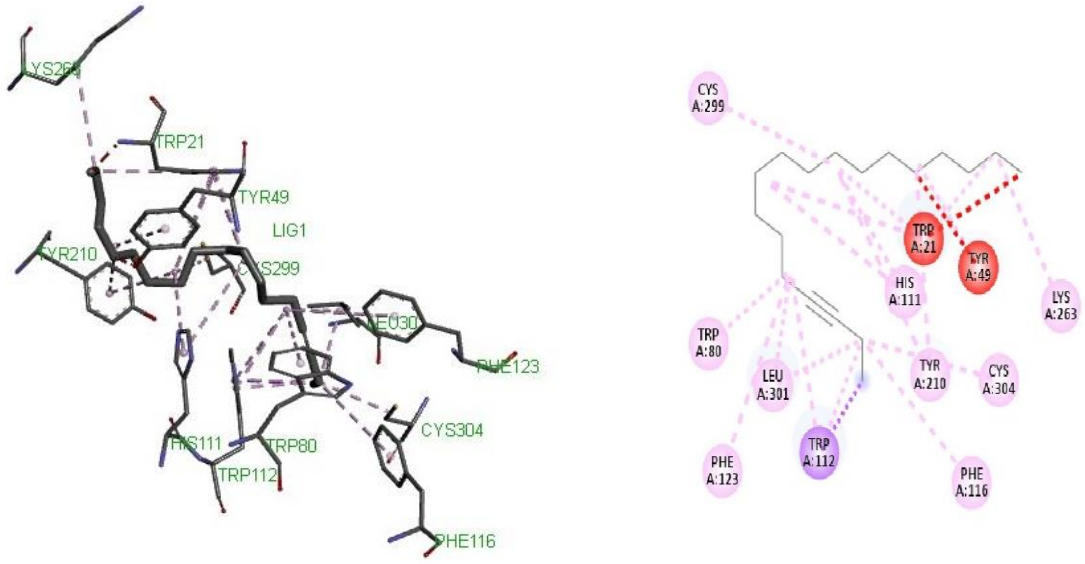

Figure 7. Structure docking of AR protein interactions with 3-octadecyne.

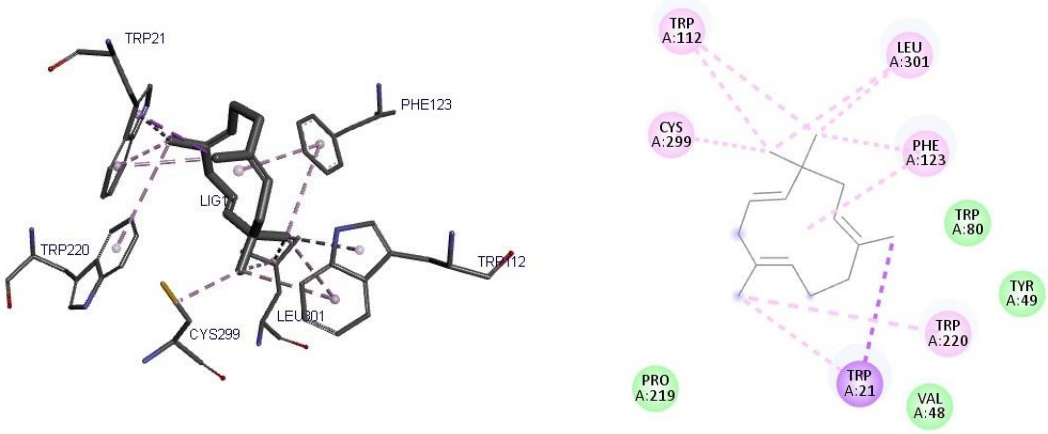

Figure 8. Structure docking of AR protein interactions with humulene.

The amino acids that actively inhibit aldose reductase are TRP 20, LEU 300, TRP 219, LYS 21, TRP 111, ASP 216, PRO 218, HIS 110. When compared with the active components of secondary metabolites of lempuyang wangi *(Zingiber zerumbet)* have shown that xanthorrizol has the same amino HIS 111, TRP 220, LEU 301, TRP 112, TRP 21 that there are alkyl/pi-alkyl, pi sigma, pi-sulfur, van der waals bonds formed on the amino acid residues (Figure 3). TRP 111 and TRP 112 provide increase in binding affinity towards the ligand [11]. Zerumbone molecular docking visualization show that there are alkyl/pi-alkyl bonds formed on the same amino acid residues TRP 219, TRP 20, LEU300 (Figure 2). Mainwhile 3-Octadecyne show that there are alkyl, pi-alkyl, pi-sigma bond formed on the same amino acid residues LEU 301, TRP 20, TRP 111 etc (Figure 7), in Beta-selinene show that there are alkyl, pi-alkyl bonds formed on the same amino acid residues TRP 21, HIS 111, TRP 112 (Figure 6). Cyclohexanol show that there are alkyl/pi-alkyl on the same amino acid residues TRP 21 (Figure 5). Humulene compound show that there are alkyl/pi-alkyl, pi-sigma, van der waals bonds formed on the same amino acid residues TRP 112, LEU 301, TRP 21, TRP 220 (Figure 8). In Linalool show that there are alkyl/pi-alkyl bonds formed on the amino acid residues TRP 21, HIS 111, TRP 220 (Figure 4). The results of docking zopolrestat contain hydrogen and hydrophobic bonds, which means that the bonds are very strong (Figure 1).

The compound zopolrestat has been shown to be able to treat diabetic neuropathy. In addition, this compound is also able to reduce ischemia in the liver and help the proliferation of carcinoma cells in the colon [10]. However, you need to pay attention to the use of the active chemical compound zopolrestat, especially regarding the dosage used and the side effects it causes. Doses of drug use, especially chemical compounds, if excessive, can damage organs and systems in the human body. Chemical compounds that are used continuously can affect the natural performance of the human body, thereby making systems in the human body dependent on these compounds [12].

The use of herbal compounds is an alternative solution to reducing side effects on the body, natural ingredients provide effects that are more usable in the long term by minimizing the side effects that occur. Zerumbon is the main isolate compound found in the rhizomes of the Zingiber plant family and is known to have antidiabetic activity either in extract form or through virtual studies [3]. Also Xanthorrhizol compounds on lempuyang wangi (*Zingiber zerumbet*) is isolate compound that indicated that it can be used as medicine because the active compound zerumbone can inhibit protein aldose reductase. Xanthorrhizol has been well established to possess a variety of biological activities such as anticancer, antimicrobial, anti-inflammatory, antioxidant, antihyperglycemic, antihypertensive, antiplatelet, nephroprotective, hepatoprotective, estrogenic and anti-estrogenic effects [13].

Even though the docking results show that zopolestat works better in inhibiting the AR protein with a binding activity value of -9,2 kcal/mol, it cannot be denied that the xanthorrhizol compound is also capable of inhibiting the AR protein with a binding activity value of -8,7 kcal/mol, so it is indicated that it could potentially be used as a drug development compound. The results of analysis of lempuyang rhizome extract using GCMS showed that around 50 components were detected. Zerumbone and xanthorrhizol is the main component of lempuyang with a value of 36–49% in almost all accessions which acts as an anti-diabetic, anti-cancer drug and so on [12].

In conclusion, the secondary metabolite compound in lempuyang wangi is indicated to be used as a drug to inhibit the aldose reductase protein working system. The comparison of the binding activity of Zopolrestat is -9,2 kcal/mol and the binding activity of the secondary metabolite compounds lempuyang wangi there in -5,3 until -8,7 kcal/mol. Even though the results of the docking moleculer for Zopolrestat are better, this does not rule out the possibility of developing the secondary metabolite compound lempuyang wangi as a drug with the advantage of being a herbal medicine with low side effects even if consumed long term.

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