ORIGINAL PAPER

Virtual Prediction of the Delphinidin-3-O-glucoside and Peonidin-3-O-glucoside as Anti-inflammatory of TNF-α Signaling

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ABSTRACT

Introduction: Anthocyanin is the bioactive compound in black rice, which promotes some health benefits for human body. Present study revealed that black rice anthocyanins improve the biomarker of the metabolic syndrome, such as tumor necrosis factor alpha (TNF-α). However, the mechanism of anthocyanin in preventing metabolic syndrome has not been elucidated. **Aim**: This study was performed to identify the interaction of six types of black rice anthocyanin towards TNF-α protein and TNF-α receptor through *in silico* studies, to assess the molecular properties and bioactivity of black rice anthocyanin. **Methods**: We retrieved the black rice anthocyanin compounds from the PubChem database and the proteins (TNF-α protein and TNF-α receptor) from Protein Data Bank (PDB) database. Protein and ligands were docked using Hex 8.0 software and visualized by Discovery Studio 4.1 program. **Results**: This study found the possibility that black rice anthocyanins interacted with TNF-α have no influence into TNF-α and TNF-α receptor interaction. The binding of delphinidin-3-O-glucoside & peonidin-3-O-glucoside to TNF-α receptor inhibited the TNF-α and TNF-α receptor signaling. The black rice anthocyanins had low activity as a drug. Interestingly, black rice anthocyanins had a potency as an antioxidant due to the hydrogen donor or acceptor in their structure, as protein kinase inhibitor, nuclear receptor ligand, and enzyme kinase inhibitor. **Conclusion**: This study suggests that delphinidin-3-O-glucoside and peonidin-3-O-glucoside might have function as anti-inflammatory factor related with TNF-α signaling.

Keywords: anthocyanin, anti-inflammatory, black rice, in-silico, TNF-α.

1. INTRODUCTION

Anthocyanins are flavonoid compounds with structures consisting of two aromatic rings, which are separated by a heterocyclic ring with an oxygen cation. Naturally, anthocyanins have been found in glycosides form (1, 2). More than 500 types of anthocyanins have been identified in plants, but only six of them are primary anthocyanins. They are cyanidin, delphinidin, malvidin, pelargonidin, petunidin, and peonidin (2-4). High amounts of anthocyanins are found in colored grains, such as black rice (6-8), purple maize (4, 9) which may be used as a replacement of synthetic food dyes. Ingestion of polyphenolic compounds is also associated with potential health benefits. Proanthocyanidins (PA, and blue wheat (10). Anthocyanins have been detected in the pericarp and aleurone layer of black rice (11-14) Japan, and Korea for a long time. It has been used for strengthening kidney function, treating anemia, promoting blood circulation, removing blood stasis, treating diabetes, and ameliorating sight in traditional Chinese medicine. The extracts from pigmented rice are used as natural food colorants in bread, ice cream, and liquor as well as functional food. The pigmented rice is mainly black, red, and dark purple rice, and contains a variety of flavones, tannin, phenolics, sterols, tocols, γ-oryzanols, amino acids, and essential oils. Anthocyanins are thought as major functional components of pigmented rice. Several anthocyanins have been isolated and identified from the pigmented rice, including cyanidin 3-glucoside, cyanidin 3-galactoside, cyanidin 3-rutinoside, cyanidin 3,5-diglucoside, malvidin 3-galactoside, peonidin 3-glucoside, and pelargonidin 3,5-diglucoside. This review provides up-to-date coverage of pigmented rice in regard to bioactive constituents, extraction and analytical methods, and bioactivities. Special attention is paid to the bioactivities including antioxidant and free radical scavenging, antitumor, antiatherosclerosis, hypoglycemic, and antiallergic activities. The profiles of bioactive compounds (including phenolics and flavonoids in free and bound fractions, anthocyanins, proanthocyanidins, vitamin E, and γ-oryzanol. Most of them are cyanidin-3-O-glucoside and peonidin-3-O-glucoside (4, 15-17) there has been little research on the 'Cempo Ireng' cultivar from Sleman, Yogyakarta. The aim of this present study was to determine the anthocyanin, antioxidant activity, and macro- and micronutrients contents of black rice bran from this local cultivar. The anthocyanin in the black rice bran was extracted using the maceration method with methanol as a solvent. The extract obtained was separated through a preparative thin layer chromatography (TLC, delphinidin (16), malvidin and pelargonidin-3-O-glucoside (17, 18). Petunidin-3-O-glucoside was discovered in the black rice variety Chinakuromai (18).

Previous studies revealed that anthocyanins demonstrate various biological effects such as antioxidant activity (6, 19-21), anti-inflammatory (2, 22-24) a by-product derived from processing rice, is a rich source of bioactive compounds. Recent studies have suggested that the fermentation can improve their biological activities. This study aimed to determined the level of γ-oryzanol, β-glucan and total phenol contents of fermented rice bran from 21 Korean varieties, as well as to evaluate their antioxidant activities. We also assessed the validation of the analytical method for determining γ-oryzanol content in fermented rice brans. Among the fermented rice brans, the Haedam rice bran contained the highest level of total phenol content (156.08 mg gallic acid equivalents/g, anti-hyperglycemia (2, 25-27) muscles and adipose tissues. The loss of insulin sensitivity is generally associated with persistent hyperglycemia (diabetes, and anti-hyperlipidemia effects (28-30). Anti obesity mechanisms of black rice anthocyanin are scavenging ROS, increasing SOD activity, and reducing adipose tissue size and pro-inflammatory cytokines production via inhibition MAPK pathway (30). Black rice anthocyanins also increase HDL in plasma, inhibit cyclooxygenase activity and down-regulate the expression of pro-inflammatory cytokines, such as IL-8, IL-6, IL-1β, and TNF-α (22, 24) a by-product derived from processing rice, is a rich source of bioactive compounds. Recent studies have suggested that the fermentation can improve their biological activities. This study aimed to determined the level of γ-oryzanol, β-glucan and total phenol contents of fermented rice bran from 21 Korean varieties, as well as to evaluate their antioxidant activities. We also assessed the validation of the analytical method for determining γ-oryzanol content in fermented rice brans. Among the fermented rice brans, the Haedam rice bran contained the highest level of total phenol content (156.08 mg gallic acid equivalents/g.

The TNF-α is an inflammatory cytokine that overexpressed in metabolic syndrome (31). In human obesity, TNF-α levels are higher in adipose tissue than other tissues. Therefore, TNF-α is an important target for treating obesity-related metabolic diseases (32). In the last decade, several drugs, including adalimumab, golimumab, certolizumab pegol, etanercept, infliximab, and CDP-870, have been developed as TNF-α inhibitor (33-37){"id":"ITEM-2","itemData":{"DOI":"10.3390/antib4010048","abstract": "Deregulation of the tumor necrosis factor (TNF. *In-silico* studies showed infliximab and etanercept have a high affinity for binding to TNF-α. Infliximab attached to TNF-α, while etanercept interacted with TNF-α receptor (38, 39). However, recent studies reported infliximab and etanercept increase mortality in some patients (40-42).

Natural compounds become a promising breakthrough to inhibit TNF-α (43, 44). Anthocyanins, along with rutin, gallic acid and genestein, are predicted to have anti-inflammatory activities via TNF-α signaling (43, 45, 46). However, the mechanism of anthocyanin anti-inflammatory activity via TNF-α signaling is still unknown. Virtual screening and modeling can be used as a preliminary analysis preceding to functional anthocyanin assay.

2. AIM

We investigated the six black rice anthocyanins (cyanidin-3-O-glucoside, malvidin-3-O-glucoside, petunidin-3-O-glucoside, delphinidin-3-O-glucoside, pelargonidin-3-O-glucoside, and peonidin-3-O-glucoside) as an anti-inflammatory through interaction with TNF-α/TNF-α receptor using computational docking. The physicochemical properties and the biological activity of black rice anthocyanins were also presented.

3. METHODS

Protein and ligands preparation

The three-dimensional protein structure of TNF-α protein (PDB ID: 2az5) and TNF-α-receptor (PDB ID: 1ncf) were taken from the RCSB Protein Data Bank. Protein preparation was conducted by Discovery Studio 4.1 (http://3dsbiovia.com/products/). The structure of ligands was obtained from the PubChem NCBI database. The ligands were cyanidin-3-O-glucoside (CID 12303221), malvidin-3-glucoside (CID 443652), peonidin-3-glucoside (CID 443654), petunidin-3-O-glucoside (CID 443651), pelargonidin-3-O-glucoside (CID 3080714), and delphinidin-3-O-glucoside (CID 443650). The three-dimensional structures of ligands were prepared by minimizing the binding energy using PyRx software (47).

Molecular docking, drug likeness, and biological activity prediction

The molecular docking between anthocyanin-TNF-α protein, anthocyanin-TNF-α receptor, anthocyanin-TNF-α protein-TNF-α receptor, and among anthocyanin-TNF-α receptor-TNF-α protein were carried out by Hex 8.0 (48) and were analyzed by Discovery studio 4.1 (http://3dsbiovia.com/products/). The drug-likeness and biological activity of anthocyanin compounds were predicted using molinspiration software (https://www.molinspiration.com/).

Compound	miLogPa	TPSAb	n- ONc	n- OHNHd	n- violations	GPCR ligand	Ion channel modulator	Nuclear receptor ligand	Inhibitor		
									Kinase	Protease	Enzyme
Cyanidin 3-O-glucoside	-2.79	191.46	11	8	2	0.04	-0.02	0.11	0.02	-0.05	0.26
Delphinidin 3-O-glucoside	-3.08	211.69	12	9	2	0.02	-0.02	0.07	0.03	-0.05	0.28
Malvidin-3-glucoside	-2.47	189.7	12	7	2	-0.02	-0.08	0.01	0.00	-0.09	0.22
Pelargonidin 3-O-glucoside	-2.30	171.23	10	7	1	0.03	-0.03	0.10	-0.01	-0.04	0.25
Peonidin-3-glucoside	-2.49	180.47	11	7	2	0.00	-0.06	0.05	0.01	-0.10	0.22
Petunidin 3-O-glucoside	-2.78	200.70	12	8	2	-0.01	-0.06	0.02	0.01	-0.10	0.24

Table 1. The physicochemical properties and Biological activity prediction of anthocyanins

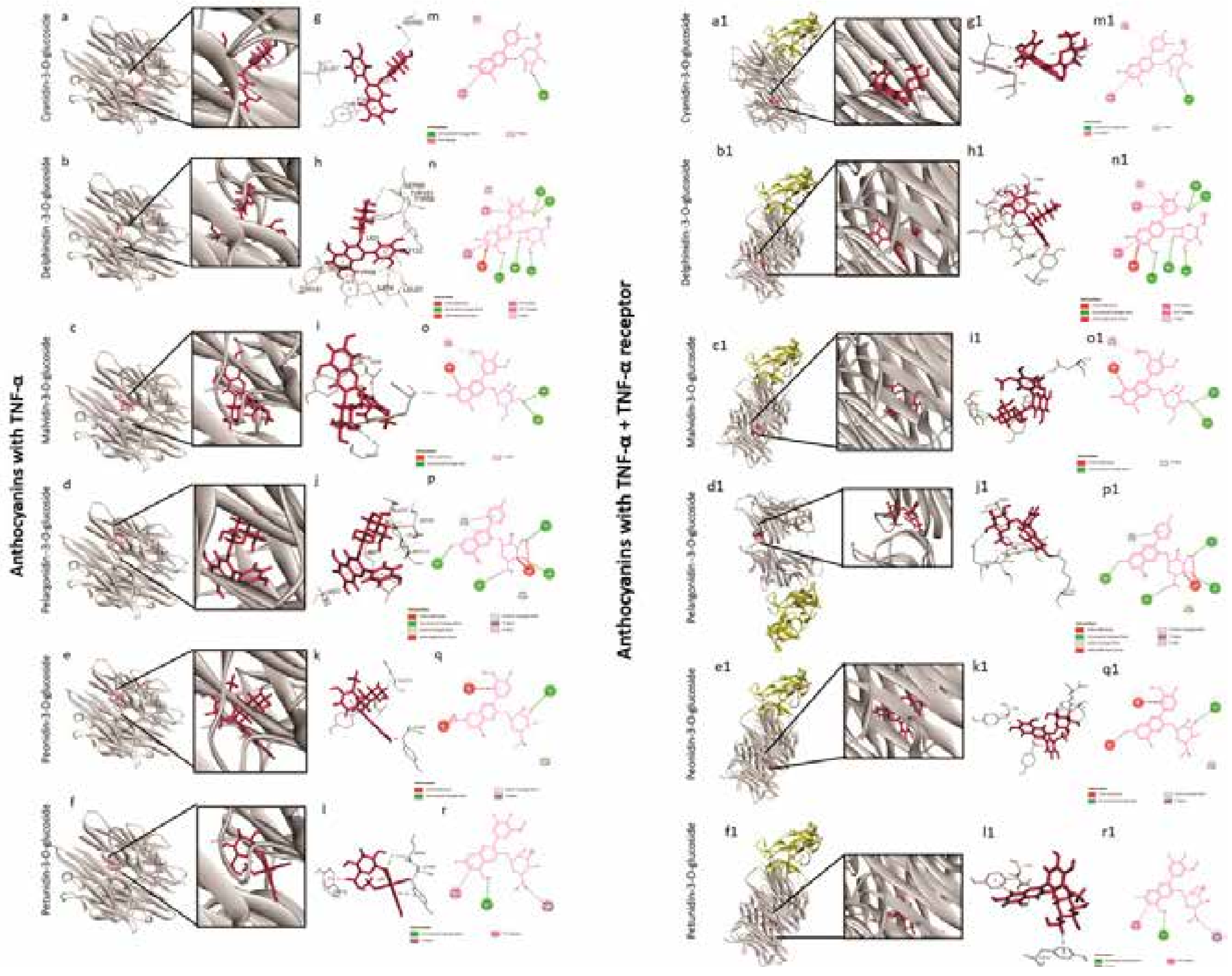

Figure 1. The interaction among anthocyanin, TNF-α protein, and TNF-α receptor. The kinds of anthocyanin showed in different rows, the 3D interaction showed in the left and the middle and the 2D interaction showed on the right side. The grey color showed TNF-α protein and yellow color showed TNF-α receptor protein. Alphabet numbering showed the interaction between anthocyanin and TNF-α protein (a-r). The alphabet with number showed the complex of anthocyanin associated with TNF-α protein then TNF-α receptor (a1-r1).

4. RESULTS

The binding pattern of anthocyanins-TNF-α protein and anthocyanins-TNF-α protein-TNF-α receptor were illustrated in Figure 1, Table 1. The Ser60, Leu57 and Tyr59 residues of TNF-α protein were predominantly found in cyanidin-3-O-glucoside-TNF-α, delphinidin-3-O-glucoside-TNF-α, and petunidin-3-O-glucoside-TNF-α interaction. The 3D structure of anthocyanins-TNF-α-TNF-α receptor interaction revealed that anthocyanins stabilized the TNF-α and TNF-α receptor signaling.

*The physicochemical properties and biological activity of anthocyanin were predicted from molinspiration online program. a. Logarithm of partition Coefficient Between n-octanol and water (miLogP); b. Topological Polar Surface area (TPSA); c. Number of hydrogen bond acceptors (n-ON); d. Number of Hydrogen Bond Donors (n-OHNH).

The interaction between anthocyanin, TNF-α receptor

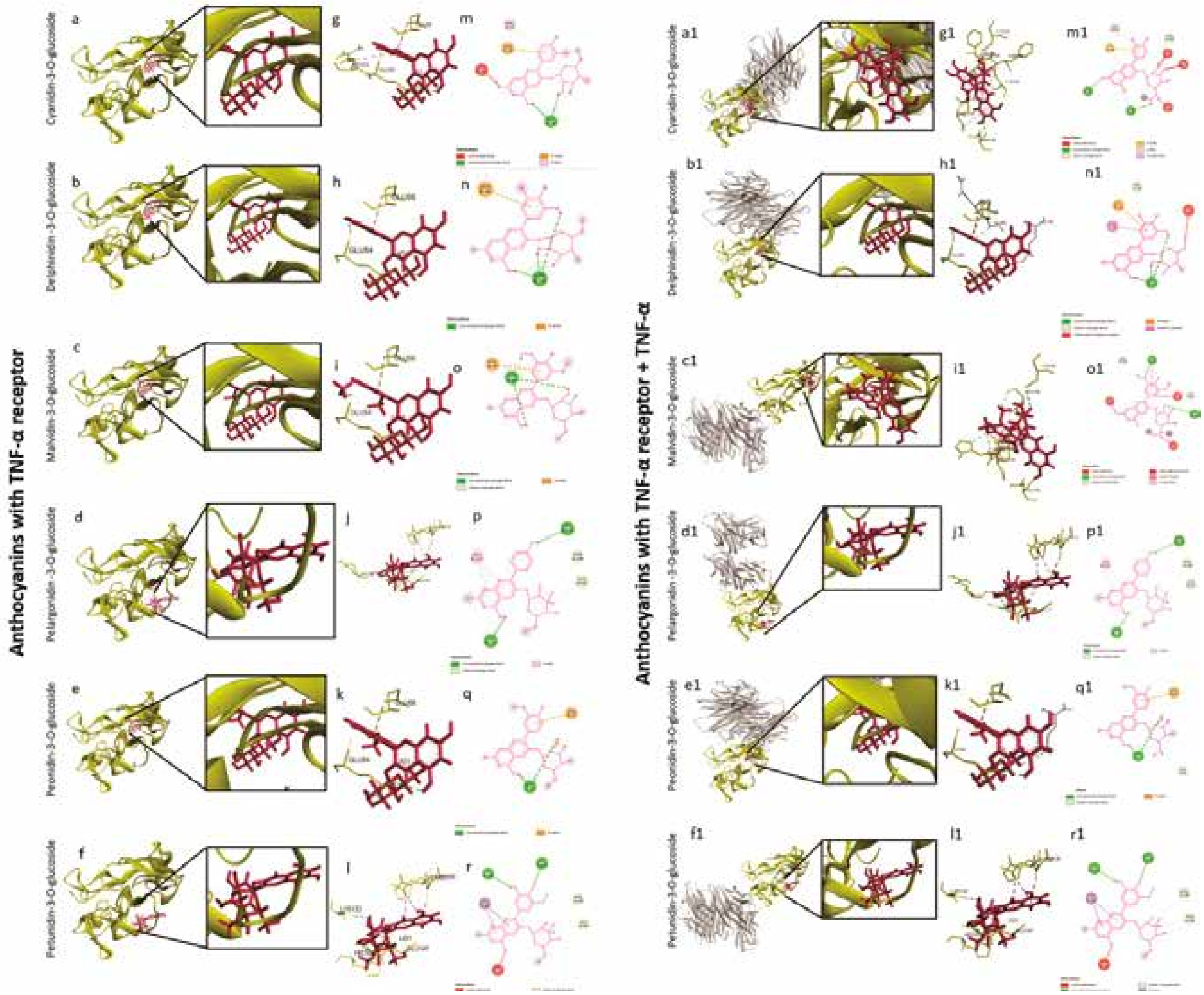

Figure 2. The interaction among anthocyanin, TNF-α receptor, and TNF-α protein. The TNF-α receptor was illustrated in yellow color, anthocyanins were demonstrated in pink color and TNF-α protein was shown in grey color. The six kinds of anthocyanin showed in different rows. The 3D models of the complex showed in the left and the middle side, while the 2D interaction showed on the right side. Alphabet numbering showed the interaction between anthocyanin and TNF-α protein (a-r). The alphabet with number showed the complex of anthocyanin associated with TNF-α protein then TNF-α receptor (a1-r1).

and TNF-α was shown in Figure 2. The interaction of cyanidin-3-O-glucoside, malvidin-3-O-glucoside, pelargonidin-3-O-glucoside, or petunidin-3-O-glucoside to TNF-α receptor did not prevent TNF-α and TNF-α receptor signaling. Interestingly, delphinidin-3-O-glucoside & peonidin-3-O-glucoside inhibited the TNF-α receptor and TNF-α signaling through binding into TNF-α receptor (Figure 2 b-n, b1-n1, e-q, e1-q1). Different residues have been detected in the delphinidin-3-O-glucoside-TNF-α receptor-TNF-α protein and peonidin-3-O-glucoside-TNF-α receptor-TNF-α protein. There were five residues in delphinidin-3-O-glucoside-TNF-α receptor-TNF-α protein interaction. Three of them (Asn39, Gly40, and Glu42) were the residues of TNF-α protein (Figure 2 h1, n1). The peonidin-3-O-glucoside-TNF-α receptor-TNF-α protein had three residues involved, the Glu54 and Glu56 from TNF-α receptor and the Glu42 from TNF-α protein (Figure 2 k1, q1). These data supported that delphinidin-3-O-glucoside and peonidin-3-O-glucoside can prevent the interaction between TNF-α receptor and TNF-α protein. The binding of anthocyanins-TNF-α protein or anthocyanins-TNF-α receptor presented higher binding energy than the complex of anthocyanins-TNF-α-TNF-α receptor or anthocyanins-TNF-α receptor-TNF-α.

The binding energy of anthocyanins-TNF-α protein-TNF-α receptor was -471.4 to -447.3 kcal/mol. The binding energy of the complex of anthocyanins-TNF-α receptor-TNF-α protein were -515.3 until -445.0 kcal/mol. The energy binding of anthocyanins-TNF-α protein and anthocyanins-TNF-α receptor were ranged from -325.5 to -307.7 kcal/mol, and -272.6 until -248.5 kcal/mol, respectively. Several kinds of interaction among anthocyanin, TNF-α protein and TNF-α receptor including electrostatic, hydrophobic bond, hydrogen bond, and π-stacked, and π-alkyl (Figure 1, 2). The physicochemical properties and the biological activity of all the anthocyanin demonstrated in Table 1. Based on Lipinski rule of five, anthocyanin is not effective as drug. Fortunately, anthocyanin has miLogp below five indicated high permeability in the cell. All anthocyanins showed two violations orally inactive, except pelargonidin-3-O-glucoside that has one violation. Based on the biological activity prediction, anthocyanins have potential activity as a nuclear receptor ligand, kinase, and enzyme inhibitors.

5. DISCUSSION

The Leu-57 and Tyr59 residues predominantly identified on the interaction between anthocyanins, TNF-α, and TNF-α receptor, which are similar binding site of rutin and TNF-α (43, 45). Our study proved that black rice anthocyanin stabilize the interaction between TNF-α-TNF-α receptor signaling. Fortunately, the delphinidin-3-O-glucoside and peonidin-3-O-glucoside interacted directly with TNF-α receptor lead to the receptor prevented from TNF-α protein interaction. Contrary with our study, cyanidin as anti-inflammatory through inhibiting TNF-α, reducing NF-kB and ERK1/2 signaling (23). Malvidin also down-regulated the expression of TNF-α (49, 50). The delphinidin effectively inhibited TNF-α and the downstream signaling (23). Li *et al.,* reported that delphinidin-3-O-glucoside reduced the level of the downstream of TNF-α cell signaling, such as transcription factors NF-kB, CCAAT/enhancer-binding protein (C/EBPα), and activator protein-1 (AP-1) (51).

Several interaction types contributed the binding energy (52, 53). Hydrogen bond promotes the binding affinity and contributes to binding energy calculation. Moreover, the position of the active ligand interaction and the types of interaction between ligand and protein also provided the binding energy calculations (53, 54). The physicochemical is an important feature for corresponding the activity of the drug (52). Three mechanism have been proposed anthocyanin as antioxidant activity, there were donating a hydrogen atom, transferring electrons to free radicals, and breaking through the structure (5, 23). Delphinidin have more hydrogen in that structure and have higher activity as an antioxidant (5). Molecules with a biological activity score more than 0.00 are recognized to be active and less than -0.50 are inactive (55).

6. CONCLUSION

This study showed that the delphinidin-3-O-glucoside and peonidin-3-O-glucoside may have biological function as inhibitor for TNF-α and TNF-α receptor signaling.

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- **Conflict of interest:** There are no conflict of interest.
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