

ORIGINAL PAPER

doi: 10.5455/medarh.2021.75.94-100

MED ARCH. 2021 APR; 75(2): 94-100

RECEIVED: MAR 19, 2021

ACCEPTED: APR 16, 2021

¹Doctoral Program of Medical Science, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

²Department of Physiology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

³Department of Surgery, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

⁴Department of Pharmacology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

⁵Department of Biology, Faculty of Mathematic and Natural Science, Universitas Brawijaya, Malang, Indonesia

⁶Research Centre of Smart Molecule of Natural Genetics Resources, Universitas Brawijaya, Malang, Indonesia

Corresponding author: Prof. Fatchiyah, Ph.D., Department of Biology, Faculty of Mathematic and Natural Science, Universitas Brawijaya, Jl. Veteran, Malang, 65145, Malang, Indonesia. Phone: +62 341-575841. E-mail address: fatchiya@ub.ac.id. ORCID ID: <https://orcid.org/0000-0001-6241-9665>.

Purple Sweet Potatoes from East Java of Indonesia Revealed the Macronutrient, Anthocyanin Compound and Antidepressant Activity Candidate

Nia Kurnianingsih^{1,2,6}, Retty Ratnawati², Tommy Alfandy Nazwar³, Mulyohadi Ali⁴, Fatchiyah Fatchiyah^{5,6}

ABSTRACT

Introduction: The development of new antidepressant is crucial to overcome the remission rate limitation. Anthocyanin on purple sweet potatoes (PSP) from East Java cultivar previously demonstrated a behavioural effect. However, the certain mechanism and the nutritional compound need further exploration. **Aim:** This study aimed to characterize macronutrient content, amino acids, anthocyanin, and revealed the potential of PSP from East Java-Indonesia as antidepressant agent through D2-dopamine receptor (D2DR). **Methods:** This study was characterized the macronutrient content using proximate analysis. The amino acids were analysed using Ultra-Performance Liquid Chromatography (UPLC) and High-Performance Liquid Chromatography (HPLC). Anthocyanin was identified using Ultra High-Performance Liquid Chromatography (UHPLC). Molecular docking was conducted to predict the interaction between anthocyanins and D2 dopamine receptor. **Results:** We were found the predominance of water on proximate analysis. Alanine was demonstrated as the highest content of amino acid. Cyanidin, cyanidin-3-O-glucoside and peonidin-3-O-glucoside were identified as major anthocyanin content. Molecular docking was showed that cyanidin bound to similar binding site with dopamine on D2DR with stronger interaction than cyanidin-3-glucoside. **Conclusion:** Current study was indicated that cyanidin as major anthocyanin from purple sweet potatoes has potential health beneficial as antidepressant potential candidate.

Keywords: purple potatoes, anthocyanin, physicochemical, in-silico, dopamine

1. INTRODUCTION

Depression is one of serious mental disorder worldwide. Approximately, more than 300 million people are living with depression. Nowadays, depression ranked as the first largest global contributor to non-fatal health loss. According to the World Health Organization (WHO) data, over 50 million depressed people live with disability. This disease burden affects more than 80% of low-middle income countries (1). The burden are originating from the declining of psychosocial function (2), suicide (3) and other associated physical illness especially various chronic diseases such as diabetes, hypertension, heart disease, arthritis, asthma, chronic obstructive pulmonary disorder (4) and chronic pain (5). Early detection and adequate treatment should be performed in order to reduce this disease burden (6).

Antidepressant is an important part of depression treatment algorithm (7). Serotonin selective reuptake inhibitors (SSRIs) drug are widely prescribed in health care setting. The efficacy and relatively benign side effects are favorable advantages of SSRI application. However, the low remission rate, i.e. 30% and long onset of SSRIs therapeutic cannot be ruled out as drug limitation (8). Considering these limitations, researcher had been developing the alternative approaches for investigate the new potential of antidepressant. Recently, intensive research that use plant bioactive compound as antidepressant are growing tremendously (9).

Flavonoid as natural products from various plants previously reported as antidepressant in animal model studies, for instance citrus maxima leaf (Sheik, *et al.*, 2014), icariin from *Epimedium brevicornum Maxim*, kaempfer-

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Interaction D2DR with dopamine			
Interaction	Distance (Å ⁰)	Category	Type
UNK1:H- ASP114:OD2	2.6	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:H- TYR416: OH	2.7	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:H-VAL115:O	2.6	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:H-THR119:OG1	1.9	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:H - THR119:OG1	3.1	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:H - SER197:O	2.5	Hydrogen Bond	Conventional Hydrogen Bond
UNK1 - TRP386	4.9	Hydrophobic	Pi-Pi T-shaped
TRP386-UNK1	5.4	Hydrophobic	Pi-Pi T-shaped
UNK1 - CYS118	4.0	Hydrophobic	Pi-Alkyl
Interaction D2DR with ligand cyanidin			
UNK0:H19 - SER193:O	2.7	Hydrogen bond	Conventional hydrogen bond
UNK0:H20 - CYS118:O	2.1	Hydrogen bond	Conventional hydrogen bond
UNK0:H18 - TYR416: OH	1.9	Hydrogen bond	Conventional hydrogen bond
A:SER197:CB:UNK0:019	3.0	Hydrogen bond	Conventional hydrogen bond
A:ASP114:OD2 -UNK0	3.4	Electrostatic	Pi-Anion
UNK0 - TRP386	4.7	Hydrophobic	Pi-Pi T-shaped
UNK0 - PHE390	5.1	Hydrophobic	Pi-Pi T-shaped
UNK0 - PHE389	4.9	Hydrophobic	Pi-Pi T-shaped
UNK0 - PHE389	4.6	Hydrophobic	Pi-Pi T-shaped
A:TRP386 -UNK0	4.9	Hydrophobic	Pi-Pi T-shaped
UNK0 - CYS118	4.1	Hydrophobic	Pi-Alkyl
Interaction D2DR with cyanidin-3-O-glucoside			
UNK0:H25 - GLU95:OE1	1.9	Hydrogen bond	Conventional hydrogen bond
UNK0:H26 - GLU95:OE1	2.8	Hydrogen bond	Conventional hydrogen bond
UNK0:O28-A:PRO405:O	2.2	Hydrogen bond	Conventional hydrogen bond
UNK0:H31-A:TYR416:OH	2.2	Hydrogen bond	Conventional hydrogen bond
A:TRP413:NE1-UNK0:26	2.9	Hydrogen bond	Conventional hydrogen bond
A:THR412:CG2-UNK0	4.0	Hydrophobic	Pi-Sigma
UNK0-A:TYR408	4.7	Hydrophobic	Pi-Pi Stacked
UNK0-A:TYR408	4.1	Hydrophobic	Pi-Pi Stacked

Table. 1. Interaction ligand of dopamine, cyanidin and cyanidin-3-O-glucoside on D2DR

itritin from Asteraceae, luteolin from *Cirsium japonicum* also quercetin in onion, apple, and broccoli. Although the mechanism remains uncertain, it suggested that flavonoid can form an interaction with monoamine receptor including dopaminergic receptors (11).

Anthocyanin is one of plant flavonoid that previously demonstrated a preventive effect in animal models of psychological stress. Anthocyanin from blueberry was showed increases the dopamine neurotransmitter in several brain area of those animal models (12). Anthocyanins are also contained in other plants including sweet purple potatoes (13). Earlier studies were revealed the neuroprotective effect of anthocyanin from purple sweet potatoes (14). Our previous work was suggested the effect of anthocyanin from East Java cultivar on behaviour of prenatal stress model mice (15). However, the nutritional value and the predictive mechanism of anthocyanin from East Java PSP as antidepressant is remain unclear and need further studies.

2. AIM

The aim of this study was to identify the nutritional value such as macronutrient, amino acids, anthocyanin profiles as well as determination the agonist function of anthocyanin on D2DR. This study would be supporting the potential use of anthocyanin from PSP as drug candidate for antidepressant.

3. METHODS

Ethics

This research was approved by Research Ethic Committee of Universitas Brawijaya No:1193-KEP-UB.

Plant and chemical materials

The East Java cultivar of PSP were harvested from Legumes and Tubers Research Institute (Malang, East Java, Indonesia) at four months planting age. The standard of peonidin-3-O-glucoside ($\geq 95\%$ purity, Cat.0929 S), cyanidin ($\geq 96\%$ purity, Cat.0909 S) and cyanidin-3-O-glucoside ($\geq 96\%$ purity, Cat.0915 S) were purchased from Extrasynthese (France).

Total anthocyanin extraction and calculation

Fresh grinded tuber roots were macerated overnight in acidified methanol at room temperature, followed by filtration and evaporation (16). Total anthocyanin content was expressed as cyanidin-3-glucose per 100g sample (C3G mg/100g) as previously described (17).

Anthocyanin identification

The Ultra-High Performance Liquid Chromatography with diode array detector (UHPLC DAD, Agilent 1100 series) was used to identify the anthocyanin compounds according to previous protocol. In brief, 2 µl of extract (0.5mg/ml) was injected into system and separated through a column of Zorbax SB-C18 2.1x150 mm 1.8-micron (Agilent, USA; Part Number:5188-5328). The 0.2% formic acid and acetonitrile were set as mobile phase with flow rate at 0.2 ml/min (18).

Amino acid and proximate analysis

The amino acids were analyzed using Ultra-Performance Liquid Chromatography (UPLC) except the tryptophan by High-Performance Liquid Chromatography (HPLC). The analysis of procedures were performed according to previous method (19). The percentage of water, ash, total fat, protein and carbohydrate were analyzed and calculated as previously described with minor modification (20).

Molecular interaction and physicochemical prediction

Ligand of cyanidin (CID: 128861) and cyanidin-3-O-glucoside (CID: 441667) were retrieved from PubChem National Centre for Biotechnology Information (NCBI) database. Protein of D2-dopamine receptor (ID: 6CM4) was imported from Protein Data Bank (<http://rcsb.org>). The PyRx 0.8 software was used to dock the ligand with D2DR to predict interaction and energy binding. The interaction was visualized using Discovery Studio Visualizer v19.1.0.18287 program (21). The physicochemical properties and bioactivity score of ligands were predicted using Molinspiration online software and classified as previously detailed (22) (23).

4. RESULTS

The total anthocyanin was calculated to be 150 mg/100g. Three anthocyanins were tentatively identified as cyanidin, cyanidin-3-O-glucoside and peoni-

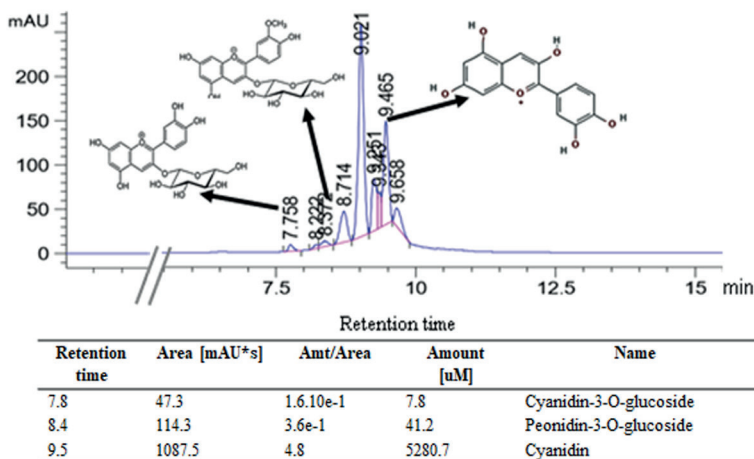


Figure 1. The identification of anthocyanin was determined using UHPLC analysis. The level of absorbance was measured at 520nm wavelengths. Three major anthocyanins were identified

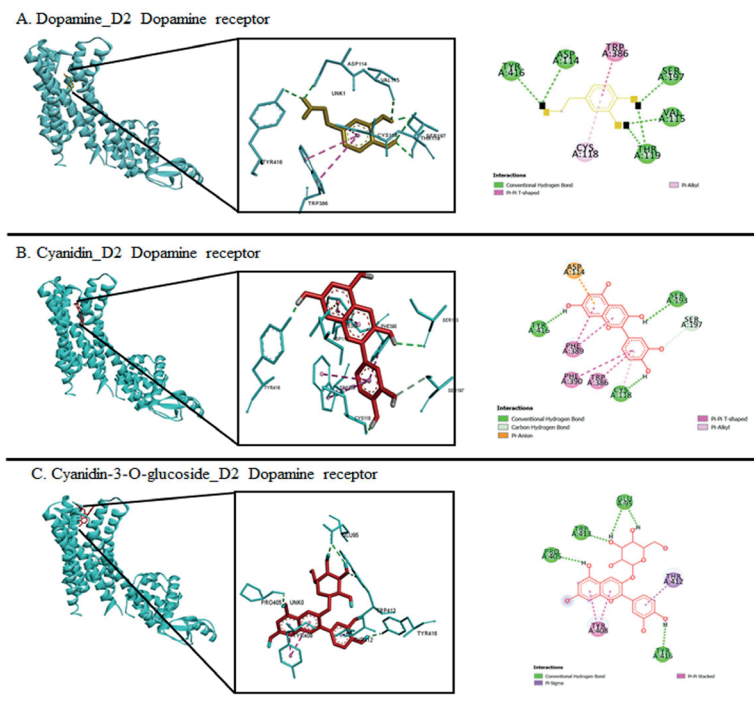


Figure 2. The molecular docking interaction visualization of dopamine (A), cyanidin (B) and cyanidin-3-O-glucoside (C) with D2DR. Dopamine is shown as yellow while anthocyanins are shown as red color. The left panel showed 3D interaction and the right panel is the 2D diagram interaction.

din-3-O-glucoside (Figure 1). We found higher component of water (77.2%) followed by carbohydrate (21.1%), protein (0.9%), ash (0.7%) and fat (<0.02%). Amino acid of alanine was the highest content (917.3 mg/kg) followed by histidine (914.9 mg/kg), serine (830.2 mg/kg), glutamic acid (823.9 mg/kg), and aspartate (803.7mg/kg). Cystine, methionine and tryptophan were not detected on our PSP.

Molecular interaction of cyanidin_D2DR was facilitated by 4 hydrogen bond, 1 electrostatic bond and six hydrophobic bonds (Table 1) at residues ASP₁₁₄, CYS₁₁₈, SER₁₉₃, SER₁₉₇, TRP₃₈₆, PHE₃₈₉, PHE₃₉₀, and TYR₄₁₆ thus resulting binding affinity -9.6 kcal/mol. These binding sites were similar with the interaction residue of dopamine_D2DR bond. Meanwhile, cyanidin-3-O-glucoside was demonstrated less binding site at residues GLU₉₅, PRO₄₀₅, TYR₄₀₈, THR₄₁₂, TRP₄₁₃, and TYR₄₁₆ with binding affinity of -8.9 kcal/mol (Figure 2).

Additionally, we were performed docking interaction between anthocyanin_D2DR complex with ligand dopamine and resulting more stable interaction with the receptor (Figure 3). In a hence, to ensure the possibility of both anthocyanins as drug candidate, we were analysed their physicochemical properties and biological activities. According to Lipinski's rule of five, cyanidin was predicted to have better absorption and permeability than cyanidin-3-O-glucoside due to cyanidin-3-glucoside has 8 hydrogen bond donors (OH and NH groups) and 11 hydrogen bond acceptors (N and O). For biological activities prediction, based on the score, both cyanidin and cyanidin-3-glucoside were predicted as enzyme and kinases inhibitors. Cyanidin was predicted as moderately active protease inhibitors contrast to cyanidin-3-glucoside, which were predicted to be inactive activity as protease inhibitors.

5. DISCUSSION

Current research was revealed the differences of amino acid concentration in compared to our previous work (19). Environmental conditions such as water, light, heat, and cold have an important regulation in plant amino acid metabolism. Drought stress, heat stress and light stress were included into abiotic stress for plants and affect the amino acids biosynthesis pathway (24).

Amino acids have important regulation for physiological function in human, for instance protein synthesis, hormone synthesis, immune response regulation, antioxidant defenses, neurotransmitter synthesis, wound healing, and cell signaling (25)(26).

Human body can synthesize amino acid that are classified into non-essential amino acid such as glutamate, proline, glycine, glutamine, cysteine, arginine, aspartate, alanine, asparagine, serine, and tyrosine. Others amino acids cannot be synthesized in human therefore dietary requirement are needed to maintenance the physiological process, i.e. histidine, leucine, tryptophan, threonine, phenylalanine, methionine, isoleucine, lysine, and valine (27).

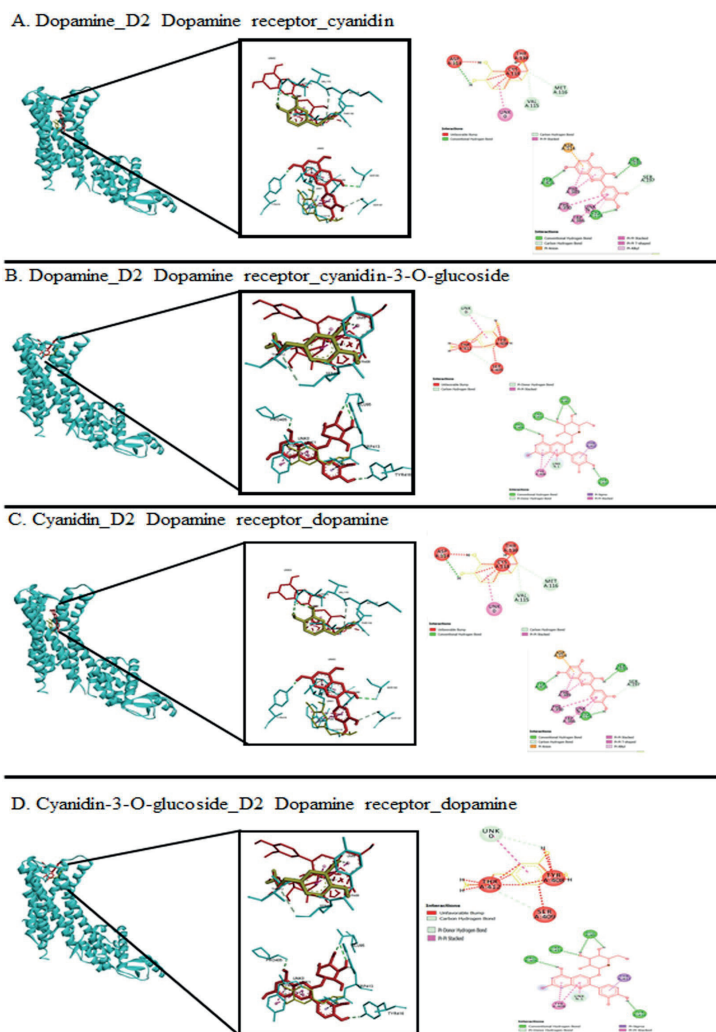


Figure 3. The Dopamine_D2DR complex was docked with anthocyanin (A-B). The Anthocyanins_D2DR complex were interacted with dopamine. Dopamine is shown as yellow while anthocyanins are shown as red color. The left panel showed 3D interaction and the right panel is the 2D diagram interaction.

Our proximate analyses were demonstrated lower carbohydrate, higher protein, higher water and lower fat compared to earlier investigation using PSP from Malaysia (28). Rodrigues, et al (29) was conducted similar analyses using fresh purple sweet potatoes from Brazil. Those study was revealed a higher protein, fat, and carbohydrate in compared to current results. The variation of proximate analysis can be determined by several factors including geographical, soil fertility and period of harvest (30). Total anthocyanin content on our PSP is slightly higher than previously reported (31). Other study was reported total anthocyanin content of 132 mg/100g from PSP at China (32). The difference of solvent can affect the yield of anthocyanin extraction. The use of acidic solvent can improve the extracted anthocyanin level (33). In addition, other factors for instance the color of tuber roots, varieties, climate, and agricultural characteristic were correlated with the anthocyanin quantities (34).

Earlier research was identified similar aglycone i.e., cyanidin and peonidin from various cultivar of PSP using Ultra-performance Liquid Chromatography Photodiode Array (UPLC-PDA), which were identified as cyanidin-3-caffeoyl-p-hydroxybenzoyl sophoroside-5-glucoside, cyanidin-3-caffeoyl-vanilloyl-sophoroside-5-glucoside, and peonidin-3-caffeoyl-vanilloyl-sophoroside-5-glucoside (35). Other study has demonstrated two major acetylated anthocyanin in PSP, the proposed compound are b-D-glucopyranoside)-5-O-(b-D-lucopyranoside) and peonidin-3-O-(6-O-(E)-caffeoyl-(2-O-(6-O-(E)-feruloyl)-b-D-glucopyranosyl)-b-D-glucopyranoside)-5-O-(b-D-glucopyranoside) (36). Current study was used three anthocyanin standards, therefore the broad anthocyanin characters on PSP has not been fully identified. Anthocyanin content in plant tissues can be influenced by nutrition during plant growth. For instance, the application of magnesium, potassium, calcium, and nitrogen as nutrient resulting a positive effect for anthocyanin in various fruits (37). Anthocyanin is secondary metabolites which are responsible to provide spectrum color blue, purple and red in various plant tissues (38). Color spectrum was influenced by the ratio of cyanidin and peonidin. Previous study well documented blue color predominance in sweet potatoes which has peonidin/cyanidin ratio < 1 so called cyanidin-type, whereas the peonidin type has ratio peonidin/cyanidin > 1 that dominance in red color (39).

Previous study correlated our finding with earlier study, which was predicted the binding site of agonist human D2 dopamine receptor. The essential amino acid residues were ASP₁₁₄ in trans membrane (TM) 3 domain and SER₁₉₇ in TM5 domain. The mostly hydrophobic pocket component for dopamine binding as agonist, were CYS₁₁₈, PHE₁₈₉, TRP₃₈₆ and PHE₃₉₀ (40). In accordance with our analyses, we predicted that cyanidin might have stronger potential to substitute dopamine at dopamine-2 receptor. D2 dopamine receptor distribution in central nervous systems is associated with emotional regulation at dopaminergic pathway i.e. striatum including nucleus accumbens and ventral tegmental area (41). Considering that depression is correlated with dopaminergic dysregulation, therefore D2-dopamine receptor are interesting to be develop as potential target for depression therapeutic (41)(42).

6. CONCLUSION

This study indicated that cyanidin as major anthocyanin from purple sweet potatoes (*Ipomoea batatas*) and has being more potential as antidepressant activity through D2- dopamine receptor interaction. Future studies are necessary to confirm this antidepressant function in preclinical approaches.

• **Author contributions:** NK, RR, TAN, MA, and FF had contribution in research design. NK, and FF were contributed for data acquisition. NK, RR, TAN, and FF was interpreted the data. The draft manuscript were prepared by NK and FF. All authors revising it critically for intellectual content.

- **Conflict of interest:** No conflict of interest
- **Acknowledgement:** We gratefully acknowledge to JRK Cairns, Ciptati, and SMONAGENES members for supporting this research.
- **Funding:** This work was financially supported by the Ministry of Research and Technology/National Research and Innovation Agency of Republic Indonesia, with grant number: 127/SP2H/LT/DRPM/2020.

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SUPPLEMENT TABLES

Interaction D2DR_dopamine with cyanidin			
Point of interaction	Distance (A°)	Category	Type
UNK0:H19 - SER197:O	2.0	Hydrogen bond	Conventional hydrogen bond
UNK0:H20 - CYS118:O	2.3	Hydrogen bond	Conventional hydrogen bond
UNK0:H18 - TYR416:OH	2.4	Hydrogen bond	Conventional hydrogen bond
THR119:OG1 -UNK0:O19	2.9	Hydrogen bond	Conventional hydrogen bond
ASP114:OD2 -UNK0	3.4	Electrostatic	Pi-Anion
UNK0 - PHE198	5.9	Hydrophobic	Pi-Pi T-shaped
UNK0 - TRP386	4.7	Hydrophobic	Pi-Pi T-shaped
UNK0 - PHE389	4.9	Hydrophobic	Pi-Pi T-shaped
UNK0 - PHE389	4.6	Hydrophobic	Pi-Pi T-shaped
TRP386 -UNK0	4.9	Hydrophobic	Pi-Pi T-shaped
UNK0 - CYS118	4.1	Hydrophobic	Pi-Alkyl
Interaction D2DR_dopamine with cyanidin-3-O-glucoside			
UNK0:H25 - GLU95:OE1	2.4	Hydrogen bond	Conventional hydrogen bond
UNK0:H31 - TYR416:OH	1.9	Hydrogen bond	Conventional hydrogen bond
SER409:OG - UNK0:O28	3.2	Hydrogen bond	Conventional hydrogen bond
THR412:CG2 - UNK0	3.6	Hydrophobic	Pi-Sigma
UNK0 - TYR408	4.7	Hydrophobic	Pi-Pi Stacked
UNK0 - TYR408	4.0	Hydrophobic	Pi-Pi Stacked
Interaction Cyanidin_ D2DR with dopamine			
UNK1:H - A:ASP114:OD1	2.2	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:H - A:ASP114:OD1	2.4	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:C - A:VAL115:O	3.5	Hydrogen Bond	Carbon Hydrogen Bond
UNK1:C - A:MET116:O	3.3	Hydrogen Bond	Carbon Hydrogen Bond
UNK1 - :UNK0	3.7	Hydrophobic	Pi - Pi Stacked
Interaction Cyanidin-3-glucoside_D2DR with dopamine			
UNK1:H - A:ASP114:OD1	2.2	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:H - A:ASP114:OD1	2.4	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:C - A:VAL115:O	3.5	Hydrogen Bond	Carbon Hydrogen Bond
UNK1:C - A:MET116:O	3.3	Hydrogen Bond	Carbon Hydrogen Bond
UNK1 - :UNK0	3.7	Hydrophobic	Pi - Pi Stacked
Interaction Cyanidin_ D2 dopamine receptor with dopamine			
UNK1:H - A:ASP114:OD1	2.2	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:H - A:ASP114:OD1	2.4	Hydrogen Bond	Conventional Hydrogen Bond
UNK1:C - A:VAL115:O	3.5	Hydrogen Bond	Carbon Hydrogen Bond
UNK1:C - A:MET116:O	3.3	Hydrogen Bond	Carbon Hydrogen Bond
UNK1 - :UNK0	3.7	Hydrophobic	Pi - Pi Stacked
Interaction Cyanidin-3-glucoside with D2 dopamine receptor			
Interaction	Distance (A0)	Category	Type
UNK0:H25 - A: GLU95:OE1	1.8	Hydrogen Bond	Conventional Hydrogen Bond
UNK0:H26 - A: GLU95:OE1	2.8	Hydrogen Bond	Conventional Hydrogen Bond
UNK0:H28 - A:PRO405:O	2.2	Hydrogen Bond	Conventional Hydrogen Bond
UNK0:H31 - A: TYR416:OH	2.2	Hydrogen Bond	Conventional Hydrogen Bond
TRP413:NE1 - :UNK0:O26	2.9	Hydrogen Bond	Conventional Hydrogen Bond
THR412:CG2 - :UNK0	3.6	Hydrophobic	Pi-Sigma
UNK0 - A: TYR408	4.7	Hydrophobic	Pi-Pi Stacked
UNK0 - A:TYR408	4.1	Hydrophobic	Pi-Pi Stacked
Interaction Cyanidin-3-glucoside_D2 dopamine receptor with ligand dopamine			
UNK1:C - A: SER409:O	3.7	Hydrogen Bond	Carbon Hydrogen Bond
UNK1:H -UNK0	2.9	Hydrogen Bond	Pi-Donor Hydrogen Bond
UNK1 -UNK0	3.8	Hydrophobic	Pi-Pi Stacked
UNK1 -UNK0	4.8	Hydrophobic	Pi-Pi Stacked