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A computational exploration into the structure, antioxidant capacity, toxicity and drug-like activity of the anthocyanidin "Petunidin"

Vijisha K. Rajan, C. Ragi, K. Muraleedharan *

Department of Chemistry, University of Calicut, Malappuram, 673635, India

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ABSTRACT

A computational investigation on the structure and antioxidant property of a natural food colorant Petunidin (PT) was performed under DFT/B3LYP/6-31+ G (d, p). PT has a drug score of +0.804 which indicates its drug-like nature. The antioxidant property of PT was well explained by HAT mechanism and it has been found that the electron releasing substituents decreases the BDE value. PT has lowest BDE value at C3 position and is confirmed by the lowest pKa value, high atomic charge and lowest bond order. PT easily donates the hydrogen atom and exists in the deprotonated form in blood as the pKa value at C3 is less than the pH value of blood. PT shows no violation to Lipinski's rule of 5 indicating its nature as an orally admissible drug. More over PT has considerable bioactivity against nuclear receptor ligand while it shows only moderate activity towards GPCR and ion channel modulator. Also it shows moderate activity as an enzyme inhibitor and protease inhibitor but shows considerable activity as a kinase inhibitor. PT is non toxic in nature and all these factors favor its use as a potential antioxidant and a drug.

1. Introduction

The imbalance produced by the so called Reactive Oxygen Species (ROS) leads to Oxidative Stress (OS) in biological system. The ROS, including peroxy, superoxy, alkoxy and hydroxyl radicals, hydrogen peroxide and organic peroxides, are highly reactive free radicals causing damages to DNA and proteins, resulting in a number of diseases. In order to neutralize these ROS, our body has normal defense mechanisms provided by the secondary metabolites called antioxidants. Sufficient amount of antioxidants in living systems, maintain normal cellular activities, good health to heart, normal blood pressure, etc. [1, 2, 3, 4, 5, 6, 7]. The electron transfer to molecular oxygen takes place at the respiratory chain and the electron transport chain is located on the mitochondria implying that the ROS are mostly produced in mitochondria. Thus chemists and pharmaceutical experts are actively involved in research to discover prominent candidates for removing the ROS in mitochondria, i.e., to act on mitochondrial membranes.

Antioxidants are widely distributed in various parts of plants like fruits, leaves, flowers, etc., and a number of antioxidants are present in cow milk and honey [2, 8, 9]. One must include these in diet to maintain the optimum level of antioxidants in the body. Studies have shown that polyphenols (both natural and synthetic) are promising antioxidants [10, 11]. But synthetic antioxidants have lots of side effects and thus, we are focused on the natural antioxidants. Polyphenols contains hydroxyl groups which make them able to scavenge free radicals and the main mechanism for radical scavenging reaction has been found to be hydrogen atom transfer (HAT) [12].

The title compound, Petunidin (PT), is an important anthocyanidin found in plants. Anthocyanidins, a class of natural polyphenols, are major constituents of vascular plants and are harmless water soluble natural color pigments [13]. The attractive color makes their wide acceptance as good natural food colorants. They also found to have the capacity to chelate metal ions in biological systems [14] and thus they can prevent the peroxidations catalyzed by metal ions like Cu. Due to the wide range of uses, there are a number of research articles available in literature about anthocyanidins. Studies have shown that they have antioxidant, anticancer and antidiabetic capacities [15]. The advantage of using anthocyanidins as food colorants is, besides their coloring ability, they also serve as radical scavengers [16]. Another important property of anthocyanidins is that they can be used as pH indicators [17] as they show different colors at different pH values.

Bilberries and blueberries contain high concentrations of PT and are an extremely good source of PT. Berries and grapes are widely used in wine making; for example, muscadine is the major source of PT used in

* Corresponding author.
E-mail address: kmuralika@gmail.com (K. Muraleedharan).

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Table 8
Pharmacokinetic properties of PT.

Properties	Values
miLogP	-0.73
TPSA	121.54
nAtoms	23
MW	317.27
nHBA	7
nHBD	5
nViolations	0
nROTB	2
Volume	260.36

Table 9
Bioactivity scores against different drug targets.

Targets	Bioactivity score
GPCR ligand	-0.15
Ion channel modulator	-0.17
Kinase inhibitor	0.03
Nuclear receptor ligand	0.01
Protease inhibitor	-0.29
Enzyme inhibitor	-0.01

Table 10
Parameters from DataWarrior.

Property	Score
Drug score	0.804
clogP	1.980
Mutagenic	None
Tumorigenic	None
Reproductive effective	None
Irritant	None
Druglikeness	1.310
Solubility	-2.338

3.8. *Toxicity analysis and drug score*

The studies regarding the toxicity of anthocyanidins were limited and were based on the extracts obtained from fruits and vegetables. PT, being a widely accepted natural food colorant, and is stable up to a pH value of 8. In present study, we have carried out a toxicological analysis by the free online software called OSIRIS Property Explorer. The results are given in Table 10.

Table 10 clearly shows that PT is nonmutagenic, nontumorigenic and nonirritant. Solubility is important in the evaluation of drug absorption and distribution characteristics. Low solubility implies low absorption. For most of the commercially available drugs, the solubility is found to be greater than -4.00 [53]. PT shows a good solubility (of -2.328). The positive value for drug score (0.804) indicate that PT can act as a potential drug. Thus PT can be used as a potential antioxidant without any side effects to biological system. Along with the coloring property, PT in food items also serves as a potential antioxidant too.

4. Conclusions

The article summarizes the computational investigation on the structure and antioxidant property of an anthocyanidin, Petunidin (PT). The work was performed under DFT/B3LYP/6-31+G (d, p) in both gases as well as in aqueous phase. The toxicological analysis by OSIRIS property explorer has shown that PT is nontoxic, nonmutagenic, nontumorigenic and nonirritant. PT has a drug score of +0.804 which indicates that it has considerable drug likeness which are comparable with the existing drugs. The antioxidant property of PT can be well explained by HAT mechanism with a BDE value of 78.72 and 77.02 kcal/mol in gaseous and aqueous phase respectively. The BDE values are greatly influenced by the nature of substituents and found that the electron releasing substituents decreases the BDE value. So one can tailor the antioxidant capacity of PT. PT has lowest BDE value at C3 position and is further supported by the pKa values, atomic charge analysis and bond order analysis from NBO. The most active site (C3) have the lowest pKa value and is found to be less than the pH value of blood so that it exists in blood as deprotonated. The study is very useful as the title compound is a widely accepted natural food colorant. PT shows no violation to Lipinski's rule of 5 indicating its nature as an orally admissible drug. Moreover PT has considerable bioactivity against nuclear receptor ligand while it shows only moderate activity towards GPCR and Ion channel modulator. Also it shows moderate activity as an enzyme inhibitor and Protease inhibitor but shows considerable activity as a kinase inhibitor. All these factors favor its use as a potential antioxidant and an orally admissible drug. Further the study can be extended to molecular docking analysis with protein like Mono Amine Oxidase B and also to study the metal chelation capacity to prevent the catalysis of peroxidation reactions by metal ions.

Declarations

Author contribution statement

Vijisha K. Rajan, Ragi C., Muraleedharan K: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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