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Drug like potential of Daidzein using SwissADME prediction: In silico Approaches

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Citation: Haseeba Sardar. Drug like potential of Daidzein using SwissADME: In silico approaches *PHYTONutrients* **2023**, *02*:02-08. https://doi.org/10.62368/pn.vi.19

Editor: Michael Aschner
Received: date: 13th January 23
Accepted: date: 25th March 23
Published: date: 16th April 23

ABSTRACT: In the early stages of drug development, predicting the drug candidates' absorption, distribution, metabolism, and elimination (ADME) profiles prior to their synthesis may help in the selection of potential candidates. Since *in-vivo* ADME assessment is proven to be expensive, time-consuming, and involved animal studies, *in-vitro* ADME analysis is preferable since it is better, less expensive, and gives accurate data more rapidly. Daidzein, also known as 7-hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, is a nonsteroidal phytoestrogen that occurs naturally. The aim of the present study is to predict the *in vitro* ADME study of Daidzein using web tool called SwissADME. The 2D structure of Daidzein was drawn on chemdraw Ultra version 12. By taking into consideration the features of flexibility, lipophilicity, saturation, size, polarity, and solubility, the bioavailability radar revealed that the colored zone is the ideal physicochemical region for oral bioavailability. According to the location of the compounds in the WLOGP-versus-TPSA referential, the pharmacokinetic features were examined using the boiled egg model, which enables straightforward evaluation of passive gastrointestinal absorption and brain penetration. The white portion has a high likelihood of being absorbed passively by the gastrointestinal tract, whereas the yolk-colored yellow section has a high likelihood of penetrating the brain. The study concluded that Daidzein did not violate the recommended ranges for Lipinski's rule of five, rotational bond count and TPSA. The compound also showed moderate lipophilicity and good water solubility. It did not act as a substrate for P-glycoprotein. Daidzein displayed a potential to inhibit CYP1A2, CYP2D6 and CYP3A4. Besides that, the compound exhibited no action against CYP2C19 and CYP2C9. It exhibited a uniform and good bioavailability score of 0.55 (55%) with high gastrointestinal (GI) absorption capabilities and the ability to permeate the blood-brain barrier. Additionally, Synthetic Accessibility score of daidzein revealed an easy step reaction of synthesis. As a result, the compound could be considered as a potential candidate for new drug discovery.

Keywords: Daidzein; SwissADME; absorption; distribution; metabolism, excretion.

1. INTRODUCTION

A rapidly expanding branch of study called computational pharmacology develops methods for creating and analyzing molecular, biological, and medical data from diverse sources using software and databases (Ekins et al., 2007; Wu et al., 2020). Since the beginning of drug development, the techniques have been used to screen and find novel lead compounds present in molecular libraries (Daina et al., 2017; Dong et al., 2018; Schyman et al., 2017), permitting simultaneous optimization of chemical efficacy and drug-like characteristics, hence contributing to the improvement in the standards of drug candidate (Al-Nour et al., 2019). Although access to physical samples is restricted, the design and development of pharmacological molecules need earlier evaluation of pharmacokinetic characteristics, absorption, distribution, metabolism, and excretion (ADME) (Arnott and Planey, 2012; Daina et al., 2017). About 11% of drugs approach the clinical development stage to reach the market due to the limited pharmacokinetics and toxicity profile of novel drug-like compounds (Dong et al., 2018; Ghose et al., 2006). The pharmaceutical industry is facing significant challenges, specifically in dealing with the high rate of attrition in drug development. This challenge has led to a heightened interest in the application of computer-aided methods for toxicity and pharmacokinetic profile predictions (Waring et al., 2015). It is widely recognized that these methods offer significant advantage in search for novel drug molecules as compared to the experimental techniques with respect to time, human and material resources (Azminah et al., 2019; Plewczynski et al., 2011). As a result, computational chemistry and computer-aided drug design have made an outstanding progress. Utilizing these techniques, novel chemical species and their chemical characteristics have been screened (Pathak et al., 2017). Several online platforms including ADMETlab, Pro Tox-II and SwissADME—have been developed to predict ADMET properties of drug candidate (Banerjee et al., 2018; Daina et al., 2017; Dong et al., 2018).

Free access to a variety of quick yet reliable predictive models for physicochemical attributes, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness is provided via the SwissADME web service, which also includes internally developed techniques like the BOILED-Egg, iLOGP, and Bioavailability Radar. Strong points of SwissADME include, but are not limited to: multiple molecule computation, several input sources, and the ability to display, save, and distribute results on a per-molecule basis or globally via intuitive and interactive graphs. The SwissDrugDesign workspace also incorporates SwissADME. A variety of CADD tools created by the Molecular Modelling Group of the SIB Swiss Institute of Bioinformatics are accessible with just one click e.g. biotarget prediction (SwissTargetPrediction), ligand-based virtual screening (SwissSimilarity), bioisosteric design (SwissBioisostere), molecular docking (SwissDock) or molecular mechanics (SwissParam) (Daina et al., 2017).

Daidzein, also known as 7-hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one, is a nonsteroidal phytoestrogen that occurs naturally (Cassidy, 2003), possessing various pharmacological properties including antioxidant, antihemolytic and anti-inflammatory potentials (Bingham et al., 1998; Dwiecki et al., 2009). Structurally, daidzein resembles mammalian hormone naming estrogens, which enables it to become a potential candidate for a dual function by substituting or inhibiting such hormones and their accompanying receptors. Therefore, daidzein could be considered a therapeutic agent in health conditions dependent on estrogen including breast (Sathyamoorthy and Wang, 1997) and prostate (Adjakly et al., 2013) cancer, osteoporosis, diabetes, and cardiovascular disease (Vitale et al., 2013). Besides that, the compound also exhibits biological potentials independent of estrogen receptors including reduction of oxidative damage, regulation of the immune reaction (Masilamani et al., 2012) and induction of apoptosis, which are directly linked to anticancer effects of the compound (Lo et al., 2007).

In the present study, *in-silico* pharmacokinetic (ADME) properties, drug-likeness and medicinal chemistry of daidzein were examined using SwissADME.

2. MATERIAL AND METHODS

The 2D structure of daidzein was drawn on Chemdraw Ultra version 12.0. The structure was imported and the structure smiley was entered. The Swiss ADME drug design study was run and the reading were noted down.

3. RESULTS

a. Analysis of physicochemical properties

Daidzein did not violate Lipinski's rule of five. Values of Molecular weight, No of H-bond

donors, Topological Polar Surface Area, Log P and number of hydrogen bond acceptors were 254.24, 2, 70.67, 2.24 and 4, respectively. The compound exhibited 1 rotatable bond. The molar refractivity of daidzein was 71.97, as shown in the **table 1**.

Table 1: The Physicochemical property of Daizein calculated with SwissADME database.

Ligands	Molecular Formula	M.W g/mol)	nHA	nAHA	F. Csp3	nRB	nHBA	nHBD	MR	TPSA (A^2)
D	C15H10O4	254.24	19	16	0.00	1	4	2	71.97	70.67

Molecular weight: M.W, No. heavy atom: nHA, No. arom. heavy atom: nAHA, No. of sp^3 hybridized carbon out of total carbon count: F. Csp^3, No. rotatable bonds: nRB, No. H-bond acceptors: nHBA, No. H-bond donors: nHBD, Molar refractivity: MR, Topological Polar Surface Area: TPSA

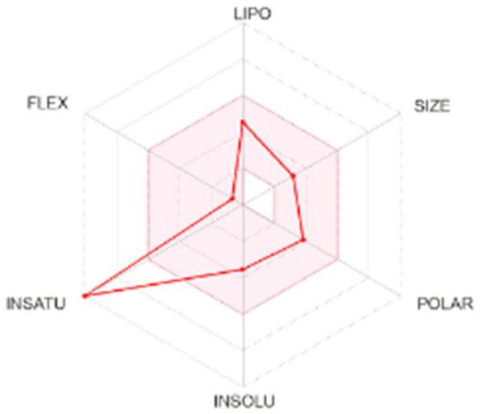

Fig 1: Schematic diagram of Bioavailability Radar for Drug likeness of a molecule (lipophilicity: XLOGP3 between-0.7 and+5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 A2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds**)**

b. Lipophilicity and water solubility of Daidzein

Log $P_{o/w}$ values of Daidzein was 2.24, which indicated its moderate lipophilicity. Concurrently, the Log S value signifies the aqueous solubility of compounds. Daidzein exhibited good water solubility, as shown in **Table 2**.

Table 2: Lipophilicity and water solubility of Daidzein

Ligands	Lipophilicity	Water Solubility					
	Consensus Log $P_{o/w}$	Log S (ESOL)	Solubility Class	Log S (Ali)	Solubility Class	Log S (SILICOS-IT)	Solubility Class
D	2.24	-3.53	Soluble	-3.60	Soluble	-4.98	Moderately Soluble

c. Pharmacokinetic Profile

The comprehensive evaluation performed via the SwissADME database unveiled noteworthy gastrointestinal (GI) absorption capabilities of a compound. The graphical representation of Daidzein in the form of a boiled-egg graph is visually depicted in **Figure 2**. Daidzein exhibited the ability to permeate the blood-brain barrier.

Additionally, it was ascertained that the compound did not function as substrate for P-glycoprotein. Daidzein displayed a potential to inhibit CYP1A2, CYP2D6 and CYP3A4. Besides that, the compound exhibited no action against

CYP2C19 and CYP2C9. Compound revealed a uniform bioavailability score of 0.55, signifying a consistent pattern in this regard, as shown in **table 3**.

Table 3: Pharmacokinetics of Daidzein calculated with SwissADME database

Ligands	GI absorption	BBB permission	P-gp substrate	CYP1A2 inhibitors	CYP2C19 inhibitors	CYP2C9 inhibitors	CYP2D6 inhibitors	CYP3A4 inhibitors	Log Kp (skin permeation) (cm/s)
D	High	Yes	No	Yes	No	No	Yes	Yes	-6.10

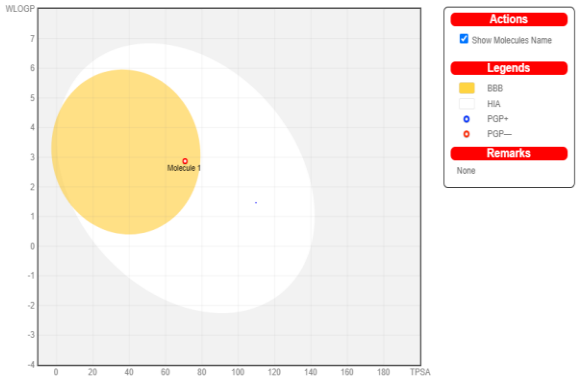

Fig 2: **Boiled graph representations of Daidzein**

d. Drug likeness

The compound did not violate any of the five drug likeness parameters including Lipinski, Muegge, Ghose, Veber and Egan rules of drug likeness, as shown in the **table 4**.

e. Medicinal chemistry

Daidzein had no PAINS alert; free from α-screen artifacts, frequent hitters, and reactive compounds. Brenk structural alert has identified no reactive groups in Daidzein. Compound can serve as Leads. The SwissADME database has assigned the Synthetic Accessibility score of 2.79 to the daidzein, which represents easy step reactions of synthesis, as shown in **table 4**.

Table 4: Drug likeness and Medicinal chemistry

Ligands	Drug likeness rules					Medicinal chemistry				
	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score	PAINS	Brenk	Lead likeness	Synthetic Accessibility
D	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55	0 alert	0 alert	Yes	2.79

4. DISCUSSION

Lipinski's rule of five is necessary for rational drug development. Any drug molecule violating even one of the rules may have low permeability or poor absorption (Pathak et al., 2017). The original Lipinski's Rule of Five (RO5)

was formulated to address compounds intended for oral activity. It established four fundamental physicochemical parameters: a molecular weight ≤500, log P ≤ 5 to signify hydrophobicity, H-bond donors ≤ 5, and H-bond acceptors ≤ 10. These attributes have demonstrated an association with 90% of orally active medications that have successfully progressed to phase II clinical trials (Lipinski, 2004). Molecular weight (MW), the count of hydrogen bond acceptors (nHBA) and the count of hydrogen bond donors (nHBD) for daidzein are within the required range.

Fsp^3 is the fraction of sp^3 carbon atoms out of the total carbon count. This reflects the carbon saturation and characterizes complexity of molecular spatial structure. A suitable value considered optimum for Fsp^3 is ≥ 0.42, as about 84 % of commercial drugs meet this criterion (Kombo et al., 2013). However, sp^3 content needs to be increased within a range; because higher Fsp^3 score is not a guarantee of higher performance and can increase the difficulty of chemical synthesis (Gerlach et al., 2019). Synthetic products usually have a lower fraction of sp^3 than natural molecules, and so natural products are rich source of drugs (Jia et al., 2020).

Rotatable bond count is employed as 'drug filter' which is correlated with reduced rat oral bioavailability if the number of rotatable bonds is greater than 10 (Veber et al., 2002). Mechanistically utilizing 'rotatable bond filter' is still unclear as its count does not correlate with *in vivo* clearance rate in rats. However, the filter is justified from in vitro screening prospect because ligand affinity decreases at an average of 0.5 kcal for each two rotatable bonds (Andrews et al., 1984). Oral drugs have fewer H-bond acceptors, donors, and rotatable bonds (Ahmad et al., 2021; Lipinski, 2004). Daizein manifests a rotational bond count of 1, fulfilling the required criteria.

The molecules with a TPSA of $\geq$140 Å^2 would be poorly absorbed with less than 10% fractional absorption, while those with a TPSA upto60 Å^2 would be well absorbed with greater than 90% fractional absorption (Clark, 1999). Daizein has TPSA values within the established limits and are predicted to have better absorption.

The Log Po/w, an essential parameter calculated utilizing SwissADME, constitutes an average of iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT values, collectively referred to as consensus Log Po/w. This Log Po/w signifies the logarithm of the octanol/water partition coefficient, a pivotal metric. Higher log $P_{o/w}$ value indicates higher lipophilicity, and it depends upon polarity, molecular size, and hydrogen bonding (Bitew et al., 2021). Log $P_{o/w}$ value of daizein is 2.24, indicated its moderate lipophilicity.

Concurrently, the Log S value signifies the aqueous solubility of compounds. In this context, the Daidzein exhibits good water solubility.

The comprehension of a drug molecule's pharmacokinetics (PK) holds paramount significance in attaining the intended pharmacological objectives, as each pharmacokinetic parameter of a compound can exert considerable influence over the drug's pharmacological profile.

P-glycoprotein interactions may ultimately affect the pharmacological profile of other drugs (Zhang et al., 2021). Daizein does not function as substrate for P-glycoprotein.

CYP3A4 is one of the most important isoform of CYP P450 system metabolizing majority of drugs and endogenous chemicals. Daidzein displays a potential to inhibit CYP1A2, CYP2D6 and CYP3A4. Besides that, the compound exhibited no action against CYP2C19 and CYP2C9.

The calculation of bioavailability and permeability is important before proceeding for synthesis or any advanced testing. Therefore, a probability-based score is given to a drug candidate to have F > 10 % in rat (Martin, 2005). Daizein exhibits a uniform and good bioavailability score of 0.55 (55%). The compound does not violate any of the five drug likeness parameters including Lipinski, Muegge, Ghose, Veber and Egan rules of drug likeness.

The yellowish region on the boiled-egg graph represents CNS penetration, the white region represents human intestinal absorption. If the drug absorption is other than oral route it will be represented in the gray area of the graph (Daina et al., 2017). Daidzein shows high gastrointestinal (GI) absorption capabilities. Also, the compound exhibits the ability to permeate the blood-brain barrier.

PAINS have an unrestrained behavior of producing false positive hits during HTS. The mechanism is poorly understood; however, they are associated with protein reactivity and non-covalent interactions (Bolz et al., 2021). Daidzein had no PAINS alert; free from α-screen artifacts, frequent hitters, and reactive compounds. Brenk structural alert has identified no reactive groups in Daidzein

In SwissADME a Structural Alert is created for 105 fragments identified by *Brenk et al*. which are chemically reactive, toxic, metabolically unstable, or likely to bear poor pharmacokinetics. This can identify a problematic fragment found in a given molecule (Brenk et al., 2008). Brenk structural alert has identified no reactive groups in Daidzein.

Lead likeness parameter represents the ability of a molecule to serve as 'lead' in the drug discovery process (Ahmad et al., 2021). Compound can serve as Leads. The SwissADME database has assigned the Synthetic Accessibility score of 2.79 to the daidzein, which represents easy step reactions of synthesis. The difficult synthetic approaches for those molecules having a score of 10 (Ahmad et al., 2021).

5. CONCLUSION

The current study presents *in vitro* ADME evaluation of Daidzein using web tool called SwissADME. Daidzein did not violate the

recommended ranges for Lipinski's rule of five, rotational bond count and TPSA. The compound also showed moderate lipophilicity and good water solubility. It did not act as a substrate for P-gp. Daidzein displayed a potential to inhibit CYP1A2, CYP2D6 and CYP3A4. Besides that, the compound exhibited no action against CYP2C19 and CYP2C9. It exhibited a uniform and good bioavailability score with high gastrointestinal (GI) absorption capabilities and the ability to permeate the blood-brain barrier. Additionally, Synthetic Accessibility score daidzein represented easy step reactions of synthesis. As a result, the compound could be considered as a "Lead".

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