Absorption, Distribution and Toxicity Prediction of Curculigoside A and its Derivatives

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Received: 8 Oktober 2014 / Accepted: 30 November 2014

Abstract:
Curculigoside A is a major bioactive phenolic glycoside of the medicinal plant of *Curculigo orchioides*. The present study was intended to obtain detail information of the pharmacokinetic properties including oral absorption, distribution, metabolism and toxicity of curculigoside A and its derivatives using *in silico* methods. Pharmacokinetic properties, absorption as well as distribution prediction using parameters of HIA (Human Intestinal Absorption), plasma protein binding, and permeability to Caco-2 cells were studied using the PreADMET and Toxtree package. The result showed that curculigoside A has absorption properties and permeability (permeability: middle) at medium level, and weakly bound to plasma proteins. Aglycone of curculigoside A was predicted to have good absorption properties and its permeability (permeability: middle) at medium level, and weakly bound to plasma proteins. Its derivatives, compounds of (2), (3), (4), (5), and (12), showed better absorption and distribution properties than that of curculigoside A. Toxicity prediction of curculigoside A and its derivatives showed no mutagenic or carcinogenic properties.

Key words: *ADMET, curculigoside A, in silico, pharmacokinetic properties*

Introduction

Curculigoside A is a phenolic glycoside compound isolated from the rhizome *Curculigo orchioide* [1]. It is the major bioactive compound present in *Curculigo orchioides*. It stimulates the secretion of estradiol by cultured primary granulosa cells and exhibits potent inhibitory activity against matrix metalloproteinase-1 in cultured human skin fibroblasts [2,3]. It also attenuates human umbilical vein endothelial cell injury induced by H_2O_2 [4], up-regulates VEGF in MC3T3-E1 cells [5], and decreases infarct volume, alleviates cerebral damage, and reduces the expression of HMGB1 and phosphorylation of IkB-α and NF-kB in ischemic brain tissue [6].

In silico approaches are being used today in drug discovery to assess the ADME (Absorption, Distribution, Metabolism, Excretion) and toxicity properties of compounds at the early stages of discovery/development. The need for early consideration of ADME properties is also increasingly urgent because of the implementation of combinatorial chemistry and high- throughput screening, since this can generate vast numbers of potential lead compounds.

In the present research, Absorption, Distribution, Metabolism, Excretion dan Toxicity (ADMET) properties of curculigoside A and its aglicone, as well as it derivatives were predicted using Pre-ADMET software, and the toxicity prediction was generated using Toxtree software.

Experimental

The Pre-ADMET program was accessed at http://preadmet.bmdrc.org/. Curculigoside A and its derivatives were used in this study. The structure of all compounds were converted into molfile (*.mol). The program automatically calculated the predictive absorption for Caco-2 cell, and HIA (Human Intestinal Absorption), and distribution for plasma protein binding [7]. Prediction of toxicity properties was performed using Toxtree by applying and using Benigni/Bossa rule-base methods (for mutagenicity and carcinogenicity) [8].

Results and Discussion

The pharmacokinetic properties including absorption, distribution, metabolism and excretion of drug has an important role on its efficacy. Prediction of HIA is a major goal in the design, optimization, and selection of candidates for development as oral drugs, where the absorption of drug compounds in intestinal depends both on complex biological processes (including passive membrane penetration, active transport mechanisms and metabolism in the gastrointestinal tract).

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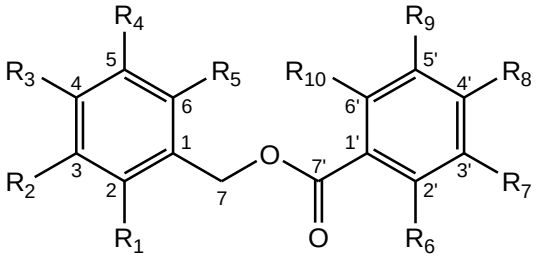
Tabel 1. Curculigoside A and its derivatives



No.	Compound	Substituens								
		R_1	R_2	R_3	R_4	R_6	R_7	R_8	R_9	R_{10}
1	Curculigoside A	OGLY	H	H	OH	OCH_3	H	H	H	OCH_3
2	Aglycone	OH	H	H	OH	OCH_3	H	H	H	OCH_3
3	2	H	OH	H	OH	OCH_3	H	H	H	OCH_3
4	3	H	OH	H	OH	H	OH	H	OH	H
5	4	OH	H	H	OH	H	OH	H	OH	H
6	5	OH	H	H	OH	OCH_3	H	Cl	H	OCH_3
7	6	OH	H	Cl	OH	OCH_3	H	Cl	H	OCH_3
8	7	OH	H	Cl	OH	OCH_3	H	H	H	OCH_3
9	8	OH	Cl	Cl	OH	OCH_3	H	Cl	H	OCH_3
10	9	OH	H	Cl	OH	OCH_3	Cl	Cl	H	OCH_3
11	10	OH	H	Cl	OH	OCH_3	H	Cl	Cl	OCH_3
12	11	OH	Cl	Cl	OH	OCH_3	H	H	H	OCH_3
13	12	OH	H	H	OH	OCH_3	Cl	Cl	H	OCH_3
14	13	OH	H	H	OH	OCH_3	H	Cl	Cl	OCH_3
15	14	OH	Cl	H	OH	OCH_3	H	Cl	H	OCH_3
16	15	OH	CF_3	Cl	OH	OCH_3	H	H	H	OCH_3
17	16	OH	H	H	OH	OCH_3	CF_3	Cl	H	OCH_3
18	17	OH	CF_3	H	OH	OCH_3	H	Cl	H	OCH_3
19	18	OH	H	Cl	OH	OCH_3	CF_3	H	H	OCH_3
20	19	OH	CF_3	Cl	OH	OCH_3	H	Cl	H	OCH_3
21	20	OH	H	Cl	OH	OCH_3	CF_3	Cl	H	OCH_3
22	21	OH	CF_3	NO_2	OH	OCH_3	H	H	H	OCH_3
23	22	OH	H	H	OH	OCH_3	CF_3	NO_2	H	OCH_3
24	23	OH	H	Cl	OH	OCH_3	CF_3	NO_2	H	OCH_3
25	24	OH	CF_3	NO_2	OH	OCH_3	H	Cl	H	OCH_3
26	25	OH	H	NO_2	OH	OCH_3	CF_3	NO_2	H	OCH_3
27	26	OH	H	NO_2	OH	H	H	NO_2	H	H
28	27	H	OH	NO_2	OH	H	OH	NO_2	OH	H
29	28	OH	H	H	OH	H	H	NO_2	H	H
30	29	OH	H	H	OH	H	OH	NO_2	OH	H

Table 2. Predictive absorption, distribution, and toxicity of curculigoside A and its derivatives.

No.	Name of Compound	Absorption		Distribution	Toxicity risk parameters	
		HIA (%)	*In Vitro* Caco-2 cell permeability (nm sec^{-1})	*In vitro* plasma protein binding (%)	Mutagenicity	carcinogenicity
1	Tamoksifen	100.00	49.54	94.74	No risk	No risk
2	Curculigoside A	52.20	11.83	59.98	No risk	No risk
3	Aglycone	92.53	20.78	85.75	No risk	No risk
4	Compound 2	92.53	15.56	86.98	No risk	No risk
5	Compound 3	75.34	11.71	81.35	No risk	No risk
6	Compound 4	75.34	11.71	88.52	No risk	No risk
7	Compound 5	93.84	20.68	89.03	No risk	No risk
8	Compound 6	94.34	21.36	93.53	No risk	No risk
9	Compound 7	93.84	21.22	92.94	No risk	No risk
10	Compound 8	94.96	21.33	95.16	No risk	No risk
11	Compound 9	94.96	20.28	89.84	No risk	No risk
12	Compound 10	94.96	21.33	90.17	No risk	No risk
13	Compound 11	94.35	20.72	94.33	No risk	No risk
14	Compound 12	94.36	20.39	89.08	No risk	No risk
15	Compound 13	94.36	20.39	89.08	No risk	No risk
16	Compound 14	94.36	20.39	91.38	No risk	No risk
17	Compound 15	93.98	22.00	88.36	No risk	No risk
18	Compound 16	93.98	21.00	88.08	No risk	No risk
19	Compound 17	93.98	21.53	87.55	No risk	No risk
20	Compound 18	93.98	21.73	87.49	No risk	No risk
21	Compound 19	94.49	22.67	90.43	No risk	No risk
22	Compound 20	94.49	22.49	89.08	No risk	No risk
23	Compound 21	74.67	19.76	86.53	No risk	No risk
24	Compound 22	74.67	17.91	87.74	No risk	No risk
25	Compound 23	86.12	16.00	86.44	No risk	No risk
26	Compound 24	86.12	15.32	86.45	No risk	No risk
27	Compound 25	27.79	17.27	91.32	No risk	No risk
28	Compound 26	33.28	10.83	84.48	No risk	No risk

Table 2. Predictive absorption, distribution, and toxicity of curculigoside A and its derivatives (continued)

No.	Name of Compound	Absorption		Distribution	Toxicity risk parameters	
		HIA (%)	*In Vitro* Caco-2 cell permeability (nm sec^{-1})	*In vitro* plasma protein binding (%)	Mutagenicity	carcinogenicity
29	Compound 27	8.02	1.88	84.37	No risk	No risk
30	Compound 28	79.72	10.78	82.52	No risk	No risk
31	Compound 29	35.38	1.96	89.59	No risk	No risk

***Classification**: % human intestinal absorption (% HIA): 70-100 % well absorbed, 20-70 % moderately absorbed, 0-20 % poorly absorbed; *In Vitro* Caco-2 cell permeability (nm sec^{-1}): less than 4 low permeability, between 4-70 medium permeability, greater than 70 higher permeability; % plasma protein binding: > 90 strongly bound, < 90% weakly bound.

In this study, the Pre-ADMET program was used to predict ADME of curculigoside A and its derivatives. The aspect prediction of absorption properties included percentage human intestinal absorption (% HIA) and Caco-2 cell permeability. Caco-2 cells are derived from a human colon carcinoma and possess multiple drug transport cycles through the intestinal epithelium. The Caco-2 cells are widely used as an *in vitro* model for predicting human drug absorption, while HIA is the sum of bioavailability and absorption evaluated from the ratio of excretion or cumulative excretion in urine, bile, and feces. The distribution properties were calculated using Pre-ADMET which will produce predictive plasma protein binding value. Those parameters is important because the degree of plasma protein binding of a drug has an important role on its disposition and the drug`s efficacy [7].

Absorption

All compound in table 1 were predicted to have good absorption properties (% human intestinal absorption, % HIA), exception for compounds (25), (26), (27), and (29). Compounds (25), (26), and (29) was predicted to have moderate absorption, while compound (27) have poor absorption proterties. Curculigoside A derivatives has a better absorption than its curculigoside A. Thus, in vitro Caco-2 cell permeability properties of these compounds were predicted to have medium permeability properties; exception for compounds (27) and (29) has low permeability properties.

Distribution

The compounds of (6), (7), (8), (10), (11), (14), (19), (25), and tamoksifen is strongly bound to plasma proteins while the other compounds are weakly bound to plasma protein. The ability of binding protein plasma affect to drug distribution process.

Toxicity

The toxicity of curculigoside A and its derivatives was predicted using Toxtree. The curculigoside A and its derivatives show a negative in mutagenicity and carcinogenicity

Conclusions

Curculigoside A has absorption properties and permeability at medium level, and is weakly bound to plasma proteins. Aglycone of curculigoside A was predicted to have good absorption properties and its permeability at medium level, and is weakly bound to plasma proteins. Its derivatives, compounds of (2), (3), (4), (5), and (12), showed better absorption and distribution properties than that of curculigoside A (lead). Toxicity Prediction of curculigoside A and its derivatives showed no mutagenic or carcinogenic properties.

Acknowledgement

This research was supported in part by Riset KK ITB 2014 and Hibah Disertasi Doktor Directorat General of Higher Education 2014.

References

[1] J. Valls, T. Richard, F. Larronde, V. Leblais, B. Muller, J.C. Delaunay, J.P. Monti, K.G Ramawati, and J.M. Mérillon, *Fitoterapia*, **77**, 2006,416-419.

[2] B.F. Dong, Z.Q. Fang, and J.R. Shi, *Zhongguo Zhong Xi Yi Jie He Za Zhi*, **26** (Suppl), 2006, 122-125.

[3] S.Y. Lee, M.R. Kim, H.S. Choi, H.I. Moon, J.H. Chung, D.G. Lee, and E.R. Woo, *Arch. Pharm. Res.*, **32**, 2009, 1433-1439.

[4] Y.K. Wang, Y.J. Hong, M. Wei, Y. Wu, Z.Q. Huang, R.Z. Chen, and H.Z. Chen, *J. Ethnopharmacol.*, **132**, 2010, 233-239.

[5] C. Ma, J. Zhang, J. Fu, L. Cheng, G. Zhao, and Y. Gu, *Phytother. Res.*, **25**, 2011,922-926.

[6] W. Jiang, F. Fu, J Tian, H. Zhu and J. Hou, *Neurosci.*, **192**, 2011, 572–579.

[7] S.K. Lee, I.H. Lee, H.J. Kim, G.S. Chang, and J.E. Chung, *Blackwell Publishing Massachusetts*, 2003, 418-420.

[8] R. Benigni, C. Bossa, N. Jeliazkova, T. Netzeva, and A. Worth, *European Commission Reports*, 2008.