Research Journal of Pharmacognosy (RJP) 5(2), 2018: 1-7
Received: 10 Dec 2017
Accepted: 17 Feb 2018
Published online: 13 Mar 2018
DOI: 10.22127/RJP.2018.58474

Original article

Starting Dose Calculation for Medicinal Plants in Animal Studies; Recommendation of a Simple and Reliable Method

Amirsaeed Hosseini[1,2], Seyed Afshin Shorofi[1,3], Ali Davoodi[4], Mohammad Azadbakht[4*]

[1]Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran.
[2]School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
[3]Adjunct Research Fellow, Flinders University, Adelaide, Australia.
[4]Department of Pharmacognosy, School of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.

Abstract

Background and purpose: Research studies indicate that almost 80% of the present day drugs are derived directly or indirectly from medicinal plants. The estimation of a safe starting dose is a concern when a new substance is to be investigated including medicinal plants, in clinical and laboratory studies. This study was intended to explore a simple and reliable method of calculating the starting dose for animal studies. Actually, the method helps to calculate the accurate animal dose based on Persian medicine. **Methods:** After the botanical names were identified, the dosages of the plants recommended in Persian medicine (PM) were converted to gram unit. Then the body surface area normalization method (BSA) was used for an allometric dose translation. **Results:** Ninety eight plants were identified and their effective parts and dosages were determined based Persian medicine. **Conclusions:** Dosing calculations for drugs could be performed based both on BSA method and experiences of ancient Persian scholars.

Keywords: animal study; calculation; medicinal plants; starting dose

Citation: Hosseini A, Shorofi SA, Davoodi A, Azadbakht M. Starting dose calculation for medicinal plants in animal studies; recommendation of a simple and reliable method. Res J Pharmacogn. 2018; 5(2): 1-7.

Introduction

In the Persian and modern medicine, many pharmaceutical products have been apparently effective in the treatment of diseases and could reduce the signs and symptoms of ailments. It is of importance to note that the long-term use of these medications can lead to detrimental effects [1]. In addition, the high cost of medications, patients' inadequate response, drug resistance, and emerging diseases such as Ebola virus disease, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) must also be taken into account [2,3]. These are grounds for claiming that the discovery and development of new drugs tends to continue to preserve public health.

Fabricant and Farnsworth (2001) have identified 122 compounds of described chemical structures, derived from only 94 plant species. It is noteworthy to report that, based on data collected by Fabricant and Farnsworth, 80% of these plant-derived compounds 'have had an ethnomedical use identical or related to the current use of the active elements of the plant' [4]. Research studies have indicated that almost 80% of the present day drugs are derived directly or indirectly from medicinal plants [5-7]. A strategy for the discovery of new drugs is, therefore, to scientifically examine the plants with medicinal use in traditional systems of medicine [8, 9]. There has been a long-standing relationship between traditional medicine and pharmacognosy as the science of drug discovery based on natural

*Corresponding author: MAzadbakht@mazums.ac.ir, Azadbakhtm@hotmail.com

products. Reverse pharmacognosy has facilitated the development of drugs from natural sources, from molecules to organisms containing them, with the use of natural products databases and computer tools. Reverse pharmacognosy is a process of transformation of Persian medicine (PM) into modern medicine [10, 11].

The estimation of a safe starting dose is a concern, when a new substance is to be investigated, including medicinal plants, in clinical and laboratory studies. A common method to estimate human starting dose is to calculate one tenth of the lethal dose (LD_{10}) [12]. In addition to conventional methods ancient medical references, used by ancient physicians for centuries, can be reliable sources to determine a safe human dose and be a basis for the initial dosage calculation in animal studies. To this end, the species of medicinal plants delineated in ancient sources have to be identified and their botanical names should be detected, followed by finding a way to convert the amounts specified in ancient sources to doses acceptable for use in human and animal studies. PM is one of the most important ancient medical systems, and builds on four elements of water, earth, fire, and air. Ancient Persian physicians are believed to have had an outstanding role in the advancement of medicine and their masterpieces can constitute a basis for relevant studies in contemporary medicine [6, 13]. This manuscript is intended to present the botanical name of some popular medicinal plants in PM and convert the amounts specified in ancient sources to doses acceptable for use in clinical and laboratory studies so as to introduce a simple and reliable method for dosage calculation in medicinal plants.

Material and Methods

Ethical considerations

The present study was approved by the Medical Research and Ethical Committee of Mazandaran University of Medical Sciences, Sari, Iran (approval no. IR.MAZUMS.REC.95-1325).

Botanical identification of plants described in PM

An important question to answer is what the botanical name of a traditional plant which some properties have been attributed in ancient Persian sources is. Any mistake in this phase can lead to very serious consequences as properties of one plant may be wrongly ascribed to another one. Steps in botanical name identification in PM have been depicted in figure 1.

Traditional name, effective parts, and recommended dosage of the plants were set based on "Makhzan-ol Advieh", a reference book in PM, written by Hakim Aghili Khorasani (18th century) [14].

Conversion of traditional units to gram

The traditional units were converted to gram amounts (table 1), and were then recorded in table 3.

Table 1. Conversion of traditional units to gram

Traditional unit	Gram
"Methghal"	4.547958
"Derham"	3.183571
"Dantraag"	0.5306
"Aoghiyeh"	34.10969
"Ghirat"	0.2653
"Ratl"	409.31627

Conversion method

In this study, the body surface area normalization method was used for an allometric dose translation, approved by U.S Food & Drug Administration (FDA) [15, 16].

Human equivalent dose (HED) (mg/kg) = Animal dose (mg/kg) multiplied by Animal km/ Human km

According to figure 1, Km is a dose conversion factor to convert dose in mg/kg to dose in mg/m^2 [17]. Table 2 has illustrated the km values for human and various animal species.

Table 2. Conversion of animal doses to HED based on BSA (Body Surface Area)*

Species	Weight (kg)	BSA	*K* factor
Human adult	60	1.6	37
Human child	20	0.8	25
Baboon	12	0.6	20
Dog	10	0.5	20
Monkey	3	0.24	12
Rabbit	1.8	0.15	12
Guinea pig	0.4	0.05	8
Rat	0.15	0.025	6
Hamster	0.08	0.02	5
Mouse	0.02	0.007	3

*Adapted from Ref [16].

Results and Discussion

Ninety eight plants were identified and their effective parts and dosages were determined (table 3). These data and conversion method can make it possible to obtain effective doses in animal studies. For instance, it is has been intended to examine the effects of *Boswellia carterii* on memory in mouse. In such a case, the

question of how to determine the starting dose of *Boswellia carterii* will become important.
Findings in the literature on PM indicate that a daily dose of *Boswellia carterii* for an adult human with the body weight of 60 kg could be 1.5917855 g (table 3) and Km factors are 37 and 3 for human and mice, respectively (table 2). In the first step, the daily dose was converted from g/60 kg to mg/ kg:

60	1.5917855
1	x

X= 1.5917855 / 60= 0.02653g/kg = 26.53mg/kg

The second step is used to normalize the dose of *Boswellia carterii* to body surface area:

(Human Equivalent Dose) (Mg/kg) = Animal dose (mg/kg) ×Animal km/ Human km

26.53(mg/kg) = Animal dose (mg/kg) × 3/37
Animal dose = 327.2 (mg/kg)
As a final result, 327.2 mg/kg is the computed dose for mice. The same approach could be used to estimate starting doses in other plants and animals.
Despite all disagreements about drug dosage conversion and calculation of effective doses, dosing calculations for drugs based on BSA, is still the most appropriate method for drug dose calculation [16]. Medical research is trying to improve health outcomes for all patients, and it therefore might be inevitable to rely on medicinal plants that have their roots in ancient medicine with a long history of use. This manuscript has tended to merge the BSA method of drug dose calculation with the knowledge of PM in order to recommend it to medical researchers.

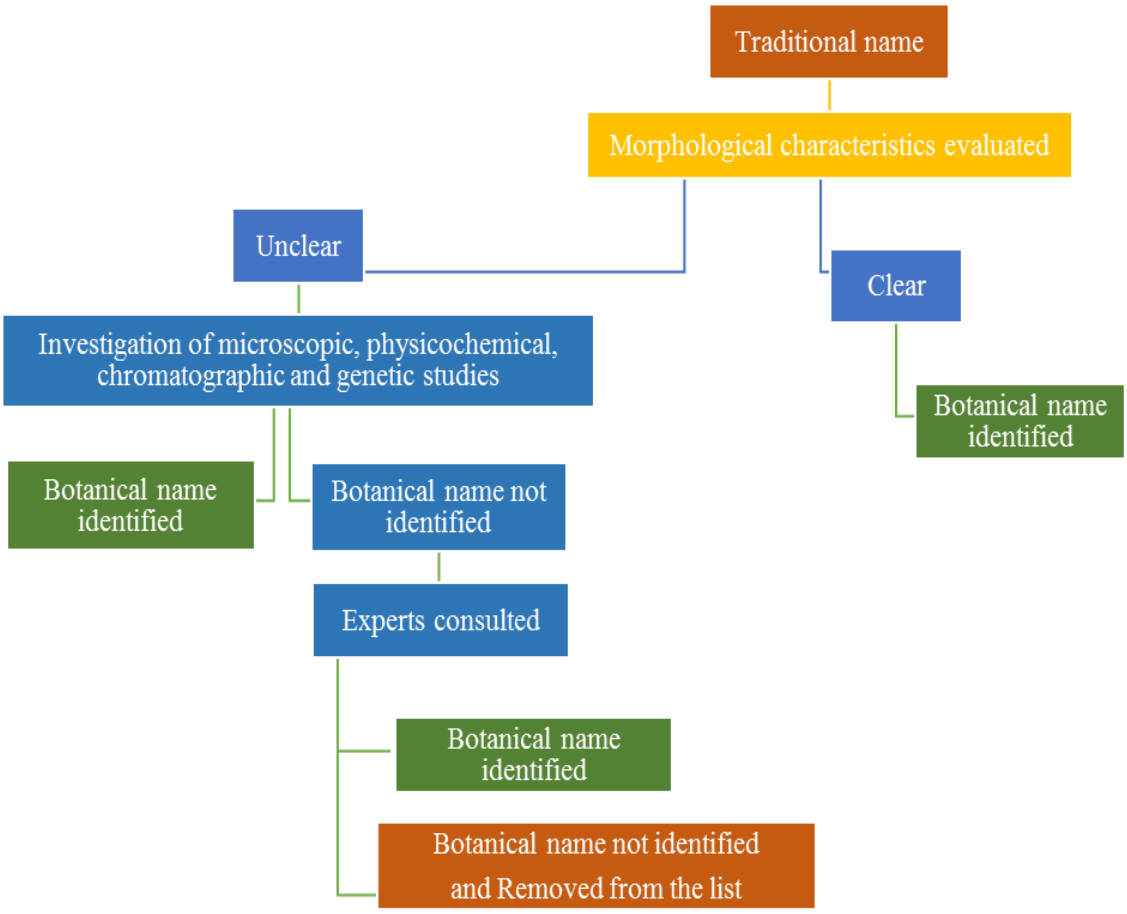

Figure 1. Steps in botanical name identification in PM

Table 3. Medicinal plants and the doses of their effective parts in PM*

No.	Botanical name	Traditional name	Effective part	Dose in PM (g/day)	
1	*Acorus calamus* L.	Vaj	Rhizome	4.547958	
2	*Adiantum capillus-veneris* L.	Baresiāvashān (ā = a:)	Aerial parts	Decoction	Up to: 63.67142
				Dried	Up to: 22.284997
3	*Agrimonia eupatoria* L.	Qāfeth	Flower	Decoction	22.284997
				Dried	9.550713
4	*Alhagi maurorum* Medik.	Taranjabin	Manna	13.643874 - 31.835706	
5	*Allium cepa* L.	Basal	Bulb	4.547958	
6	*Althaea officinalis* L.	Khatmi	Flower, seed, Root	Decoction	136.43874
				Dried	4.547958
7	*Anethum graveolens* L.	Shebat	Seed, aerial parts	25.468568	
8	*Apium graveolens* L.	Karafs	Arial parts	juice	47.753565
				Dried	9.550713
			Root (decoction)	15.917855	
			Seed	3.183571	
9	*Arnebia euchroma* (Royle) I.M.Johnst.	Abukhalsā	Root	6.367142	
10	*Artemisia absinthium* L.	Afsantin	Aerial parts	Decoction	Up to: 6.367142
				Dried	4.547958
11	*Asparagus officinalis* L.	Halion	Seed	9.550713	
12	*Asarum europaeum* L.	Asāroon	Rhizome	4.547958 - 13.643874	
13	*Astragalus gumifer* Labill.	Katirā	Gum	3.183571- 15.917855	
14	*Berberis vulgaris* L.	Ambarbāris	Fruit	Juice	90.95916
				Dried	68.21937
			Seed	13.643874	
15	*Boswellia carteri* Birdw.	Kondor	Oleo gum resin	1.5917855	
16	*Brassica napus* L.	Shaljam	Seed, root, leaf	6.367142	
17	*Brassica nigra* (L.) K.Koch	Khardal	Seed	Crushed	9.550713
				Uncrushed	15.917855
18	*Brassica oleracea* L.	Kornob/Karanb	Fresh leaves	9.550713	
19	*Cannabis sativa* L.	Ghennab	Aerial parts	Up to 3.183571	
20	*Capparis spinosa* L.	Kabar	Root	Up to 9.550713	
21	*Carthamus tinctorius* L.	Osfor	Seed	15.917855 - 31.83571	
22	*Cassia angustifolia* M.Vahl	Sanā	Leaf	Decoction	12.734284-22.284997
				Dried	9.550713
23	*Cassia fistula* L.	Khiārshanbar	Fruit	22.73979 - 90.95916	
24	*Cerasus mahaleb* (L.) Mill.	Mahlab	seed	9.550713- 15.917855	
25	*Cichorium intybus* L.	Hendebā	Leaf	juice	204.658135
			Seed	6.367142-15.917855	
			Root	3.183571-12.734284	
				Decoction	15.917855-47.753565
26	*Cinnamomum camphora* (L.) J.Presl	Kāfoor	Oleoresin	Up to 0.5306	
27	*Cinnamomum bejolghota* (Buch.-Ham.) Sweet	Salikhah	Bark	6.367142	
28	*Cinnamomum zeylanicum* Blume	Dārsini	Bark	6.367142-15.917855	
29	*Citrullus colocynthis* (L.) Schrad.	Hanzal	Fruit	1.5917855- 3.183571	
30	*Citrus medica* L.	Otroj	Fruit	Dried	15.917855
				Jam	22.73979
31	*Commiphora molmol* (Engl.) Engl. ex Tschirch	Morr	Oleogum resin	Up to 1.5917855	
32	*Balsamea mukul* Baill.	Moghl e azragh	Oleogum resin	3.183571	
33	*Convolvulus scammonia* L.	Saghmuniā	tuber	Juice	0.2653-1.0612
34	*Cordia myxa* L.	Sapestān	Fruit	Up to 45.47958	
35	*Coriandrum sativum* L.	Kozborah	Aerial parts	Juice	34.10969
				Dried	68.21938
			Seed	15.917855-34.10969	
36	*Corylus avellana* L.	Bondogh	Fruit	Up to 63.67142	
37	*Crocus sativus* L.	Zafarān	Stigma	Up to 6.367142	

Table 3. Continued

No.	Botanical name	Traditional name	Effective part	Dose in PM (g/day)
38	*Cucumis melo* L.	Bettikh	Seed	6.367142-15.917855
39	*Cucurbita pepo* L.	Ghar	Seed	Up to 31.835706
40	*Cydonia oblonga* Mill.	Safarjal	Fruit	Juice up to 95.50713
41	*Cymbopogon olivieri* (Boiss.) Bor	Ezkher	Flower, Root	2.273979 - 4.547958
42	*Datura stramonium* L.	Jaoz e māthel	Seed	Up to 0.5306
43	*Daucus carota* L.	Jazar	Root	727.67328
			Seed	6.367142
44	*Descurainia sophia* (L.) Webb ex Prantl	Khobbah	Seed	9.095916 - 13.643874
45	*Dorema ammoniacum* D.Don	Oshagh	Oleogum resin	2.273979 - 4.547958
46	*Doronicum hyrcanum* Widder & Rech.f.	Darunaj	Root	3.183571-6.367142
47	*Elettaria cardamomum* (L.) Maton	Hamāmā	Fruit	Up to 6.367142
48	*Eugenia caryophyllata* Thunb.	Gharanfol	Flower	4.547958
49	*Ferula persica* Willd.	Sakbinaj	Oleo gum resin	Up to 3.183571
50	*Ficus carica* L.	Tin	Fruit	Dried: 136.43874
51	*Foeniculum vulgare* Mill.	Rāziānaj	Seed	4.547958
			Root	Decoction 9.095916 - 13.643874
52	*Gentiana lutea* L.	Jentiānā	Root	4.547958
53	*Glycyrrhiza glabra* L.	Sos	Root	15.917855
54	*Hyoscyamus niger* L.	Bang	Seed	Up to 1.0612
55	*Hypericum perforatum* L.	Hufārighoon	Seed, Leaf	3.183571- 6.367142
56	*Iris germanica* L.	Irsā	Root	Up to 9.095916
57	*Lactuca sativa* L.	Khas	Leaf	juice Up to 95.50713
58	*Lawsonia inermis* L.	Henā	Leaf	Max: 4.547958
59	*Malus domestica* Borkh.	Toffāh	Fruit	31.835706
60	*Mandragora officinarum* L.	Yabruh	Root	0.2653-1.0612
61	*Mentha spicata* L.	Nanā	Aerial parts	9.095916
62	*Myrtus communis* L.	Ās	Leaf	Dried UP to 9.550713
				juice UP to 102.32907
63	*Nerium oleander* L.	Deflā	Leaf	1.5917855
64	*Nigella sativa* L.	Shoniz	Seed	1.5917855 - 6.367142
65	*Origanum vulgare* L.	Marzanjush	Aerial parts	Decoction 31.835706
				Dried 9.095916
66	*Papaver somniferum* L.	Afyun	Latex	Up to 1.0612
67	*Peganum harmala* L.	Hormal	Seed	4.547958 - 9.095916
68	*Phyllanthus emblica* L.	Amlaj	Fruit	Decoction Up to 31.83571
				Dried 9.550713- 15.917855
69	*Physalis alkekengi* L.	Kākanaj	Seed	Up to 15.917855
70	*Pimpinella anisum* L.	Anisun	Seed	6.367142-15.917855
71	*Piper longum* L.	Dārfelfel	Fruit	Up to 4.547958
72	*Piper nigrum* L.	Felfel	Fruit	Up to 4.547958
73	*Plantago major* L.	Lesānolhamal	Leaf	Juice 45.47958- 204.658135
			Seed	9.550713
74	*Plantago ovata* Forssk.	Bazreghatoonā	Seed	6.367142- 31.83571
75	*Portulaca oleracea* L.	Baghlatolhomghā	Seed	15.917855
76	*Prunus amygdalus* Batsch	Laoz e mor	Kernel oil	18.191832
77	*Prunus armeniaca* L.	Meshmesh	Kernel oil	Up to 13.643874
78	*Punica granatum* L.	Jolnār	Flower	3.183571- 6.367142
79	*Quercus infectoria* G.Olivier	Ballut	Fruit peel	4.547958
			Fruit	4.547958- 68.21937
80	*Quercus infectoria* G.Olivier	Afs	Gal	4.547958

Table 3. Continued

No.	Botanical name	Traditional name	Effective part	Dose in PM (g/day)	
81	*Raphanus sativus* L.	Fojl	Seed	3.183571	
			Tuber	Dried	63.67142
				Juice	95.50713
82	*Rhus coriaria* L.	Somāgh	Fruit	15.917855	
83	*Rosa gallica* L.	Vard	Flower	Fresh	31.83571
				Dried	12.734284
84	*Rubia tinctorum* L.	Fovvatossabgh	Root	4.547958	
				Decoction	13.643874
85	*Rumex conglomeratus* Murray	Hammāz	seed	Up to 6.367142	
			Aerial parts	57.304278	
86	*Ruta graveolens* L.	Sodāb (Fijen)	Aerial parts	Up to 13.643874	
87	*Saccharum spontaneum* L.	Tabāshir	Stem	6.367142	
88	*Saponaria officinalis* L.	Satrunion	Root	1.5917855	
89	*Drimia maritima* (L.) Stearn.	Esghil	Bulb	Up to 6.367142	
90	*Semecarpus anacardium* L.f.	Belādor	Fruit	0.79589275 - 1.5917855	
91	*Sesamum indicum* L.	Semsem	Seed	15.917855	
92	*Spinacia oleracea* L.	Esfānākh	Leaf	Juice	9.095916
			Seed	6.367142	
93	*Tamarindus indica* L.	Tamr e hendi	Fruit	31.835706-136.43874	
94	*Terminalia bellirica* (Gaertn.) Roxb.	Balilaj	Fruit	Up to 9.550713	
95	*Terminalia chebula* Retz.	Ehlilaj	Fruit	Up to 15.917855	
96	*Tribulus terrestris* L.	Hasak	Fruit	15.91785	
97	*Viola odorata* L.	Banafsaj	Flower	Decoction	Up to 45.47958
				Dried	22.73979
98	*Zingiber officinale* Roscoe	Zanjabil	Rhizome	6.367142	

*Adapted from references 5, 14 and 16

It is crucial to bear in mind that the texts of PM has generally outlined the average dosage of medicinal plants, which allows researchers to choose either these doses or other values in estimated dosage ranges following conversion of human doses to animal equivalent doses. There is, of course, some evidence in the PM texts that the recommended doses described in these ancient references are the maximum doses for some medicinal plants; thus, the starting dose for such medicinal plants should be lower. The comparison of therapeutic and toxic effects of doses delineated in PM with doses used in other studies can help understand the potential efficacy of this method and modify it if needed.

Acknowledgments

This study is part of a PhD thesis of Amirsaeed Hosseini. Funding for this study was provided by the Mazandaran University of Medical Sciences, Sari, Iran.

Author contributions

Amirsaeed Hosseini was the main study investigator and contributed to the collection of the data; Seyed Afshin Shorofi participated in the data interpretation and revised the manuscript; Ali Davoodi participated in the data interpretation and revised the manuscript. Mohammad Azadbakht was the study investigator, contributed to the collection of the data and critically revised the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

References

[1] Yuan R, Lin Y. Traditional Chinese medicine: an approach to scientific proof and clinical validation. *Pharmacol Ther*. 2000; 86(2): 191-198.

[2] Patwardhan B, Mashelkar RA. Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward? *Drug Discov Today*. 2009; 14(15): 804-811.

[3] World Health Organization. WHO publishes list of top emerging diseases likely to cause major epidemics. Geneva: World Health Organization, 2015.

[4] Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug

discovery. *Environ Health Perspect*. 2001; 109(1): 69-75.

[5] Azadbakht M, Hosseini AS, Fakhri M. Necessity of standardization of medicinal plant extracts in investigations and the manner to perform it. *Razi J Med Sci*. 2017; 23(152): 8-17.

[6] Mirzaee F, Hosseini A, Jouybari HB, Davoodi A, Azadbakht M. Medicinal, biological and phytochemical properties of *Gentiana* species. *J Tradit Complement Med*. 2017; 7(4): 400-408.

[7] Davoodi A, Ebrahimzadeh MA, Fathalinezhad F, Khoshvishkaie E. Antibacterial activity of *Mespilus germanica* leaf extract. *J Mazandaran Univ Med Sci*. 2017; 26(146): 173-178.

[8] Patwardhan B, Warude D, Pushpangadan P, Bhatt N. Ayurveda and traditional Chinese medicine: a comparative overview. *Evid Based Complement Alternat Med*. 2005; 2(4): 465-473.

[9] Fakhri M, Davoodi A, Parviz M, Ghadi ZS, Mousavinasab SN, Farhadi R, Azadbakht M. Characterization and HPLC analysis of manna from some *Cotoneaster* species. *Int J Pharm Sci Res*. 2017; 8(12): 5360-5366.

[10] Blondeau S, Do Q, Scior T, Bernard P, Morin-Allory L. Reverse pharmacognosy: another way to harness the generosity of nature. *Curr Pharm Des*. 2010; 16(15): 1682-1696.

[11] Do QT, Bernard P. Reverse pharmacognosy: a new concept for accelerating natural drug discovery. *Adv Phyt*. 2006; 2(1): 1-20.

[12] Le Tourneau C, Stathis A, Vidal L, Moore MJ, Siu LL. Choice of starting dose for molecularly targeted agents evaluated in first-in-human phase I cancer clinical trials. *J Clin Oncol*. 2010; 28(8): 1401-1407.

[13] Hosseini A, Azadbakht M, Yousofpoor M. 'Maoljobon' a drug in Iranian traditional medicine. *J Mazandaran Univ Med Sci*. 2017; 26(146): 269-278.

[14] Aghili Khorasani M. Makhzan ol Advieh. Tehran: Tehran University of Medical Sciences Press, 2009.

[15] Freireich EJ, Gehan E, Rall D, Schmidt L, Skipper H. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. *Cancer Chem Rep*. 1966; 50(4): 219-225.

[16] Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. *Fed Am Soc Exp Biol J*. 2008; 22(3): 659-661.

[17] Food & Drug Administration. Estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers. Rockville: Food & Drug Administration, 2005.

Abbreviations

PM: Persian Medicine; LD: Lethal Dose; FDA: Food & Drug Administration