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Review article

Wallflower (*Erysimum cheiri* (L.) Crantz) from Past to Future

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Abstract

Wallflower (*Erysimum cheiri* (L.) Crantz) is a common medicinal plant in Persian medicine and nowadays some traditional products from wallflower are consumed on global markets. The aim of the present study was to study the phytochemical constituents of wallflower and discuss safety evaluations related to the traditional wallflower preparations. Major Persian scholars (e.g. Avicenna) books, Persian manuscripts (e.g. Makhzan-al-advia) and Arabic medical manuscripts (e.g Alshamel-fi alsanaat altebya) of the medieval Islamic era as well as current search engines including Pubmed, Scopus, Siencedirect, and Google Scholar were included in the study from 1700 up to 2018 A.D. In traditional medicine manuscripts, various topical and oral dosage forms of wallflower were administered in low doses. After renaissance, phytochemical investigations reported cardiac steroids in wallflower and it might be the reason that next medical investigations on the herb have been interrupted. According to in vivo studies, topical indications of cardiac steroids in doses lower than their inhibitory concentration 50 (IC_{50}) should be safe and effective in some cutaneous disorders. Wallflower is reported to have several different classes of compounds including: 11 types of cardenolides (such as strophanthidin, bipindogenin, uzarigenin, cannogenol and digitoxygenin derivatives), two flavonoids, a cyanidin and two glucosinolates. Therefore, for safety guarantee, wallflower products require dose adjustment based on IC_{50} and probable cardenolide soluble content in that dosage forms.

Keywords: *Erysimum cheiri*; phytochemistry; wallflower

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Introduction

Wallflower (*Erysimum cheiri* (L.) Crantz), synonyms: *Cheiranthus cheiri* L. from Brassicaceae family [1], is a common medicinal plant in Persian medicine (PM) while, it is not popular in modern medicine. Wallflower is an ornamental herb which is native to Europe, especially Mediterranean region and is extensively cultivated around the world [2]. It is a perennial herb that grows up to 25-80 cm (figure 1). Botanically, the leaves are lanceolate shaped and are 5-10 cm in long, the flowers have four sepals and six stamens [3] have a pleasant fragrance and are arranged in dense racemes. The color of flowers is golden yellow to orange yellow. The fruit is a silique which has distinct ribs and the seeds are arranged in one row [4]. The inner surface of the fruit has trichomes and on its valves are usually 4-5-rayed, few 3-rayed,

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and infrequently 6-7-rayed [5]. Seeds are sub-orbicular, pale brown and about 3 mm long [3]. Wallflower description in the traditional medical manuscripts is in agreement with the above botanical description [6-12]. Some traditional preparations are available in global herbal markets containing wallflower as an ingredient. Because of cardiotonic constituents of wallflower organs, toxicity and safety of corresponding products should be mentioned in detail [13-27]. This study has been conducted to provide information on phytochemistry, traditional and current medicinal properties of wallflower preparations and it emphasizes the necessity of safety considerations for wallflower products.

Figure 1. Wallflower (*Erysimum cheiri* (L.) Crantz) (photographed by authors)

Methods

PM literature including, "Al hawi", the Canon of medicine, "Tohfeh al- momenin", "Makhzan-al-advia" and "Mohit-e azam" as well as medicinal manuscript from Arabian scholars i.e.: "Alshamel-fi alsanaat altebya", "Hadiqat ol-azhar" were searched with terms of cheir-e zard and cheir-e asfar [6-12]. Main part of this study was performed via electronic search on Pubmed, Scopus, Siencedirect, and GoogleScholar with terms of *Cheiri*, *Erysimum*, *Cheiranthus*, wallflower and goldlack (German common name), from 1700 up to 2018 A.D. History of phytochemical investigations on wallflower was provided and summarized in a diagram according to available articles [13-27]. Drawing of the molecular structures was done by ChemDraw Pro 8.0 software.

Results and Discussion

Wallflower from past to present

A brief history of wallflower investigations has been demonstrated in figure 2. Wallflower was well known as a medicinal plant in Persian and Arabic medical manuscripts of the medieval Islamic era [6-12]. Later, a large number of studies have been directed on phytochemical studies of wallflower [13-27]. In 1899, an isolated cardiac glycoside (cheiranthin) was introduced as a new remedy extracted from wallflower [17]. In 1932, in vivo toxicological studies on cheiranthin made some safety concerns [22]. Cheiranthin and cheirinine were reported as wallflower chemical compounds in the early phytochemical investigations [14]; however, they has not been identified as pure chemical compounds by current phytochemistry In 1994, a review on wallflower cardiac glycosides [25]. And in 2001, a pharmacological in vivo study on wallflower were published. It introduced wallflower as a medicinal plant which was used clinically in some skin diseases [26]. Based on Persian and Arabic medical manuscripts of the medieval Islamic era, various wallflower dosage forms have different medicinal effects. Wallflower had oral, topical and vaginal but no parenteral indications in Persian medicine. Topical dilute decoction of the flower was recognized as a good remedy for aphthous and inflammations. Topical oil of flower has been reported as analgesic, anti-inflammation and hair tonic. Cerate dosage form is suggested as anti-fissure (both anal and skin fissure) and wound healer. Root in a topical decoction or poultice has been reported as analgesic and anti-inflammatory agent. The seeds in the form of sitz bath or vaginal suppository have been administered as emmenagogue, abortifacient and labor inducer [6-12]. Nowadays, wallflower preparations are available in herbal markets for traditional medicine requests. In Iran, there is a traditional medicine ointment compound from *E. cheiri* and *Helianthus annuus* which is used for anal fissure treatment [28]. In Indian markets there is a multi-component tablet containing wallflower for breastfeeding mothers to improve lactation [29].

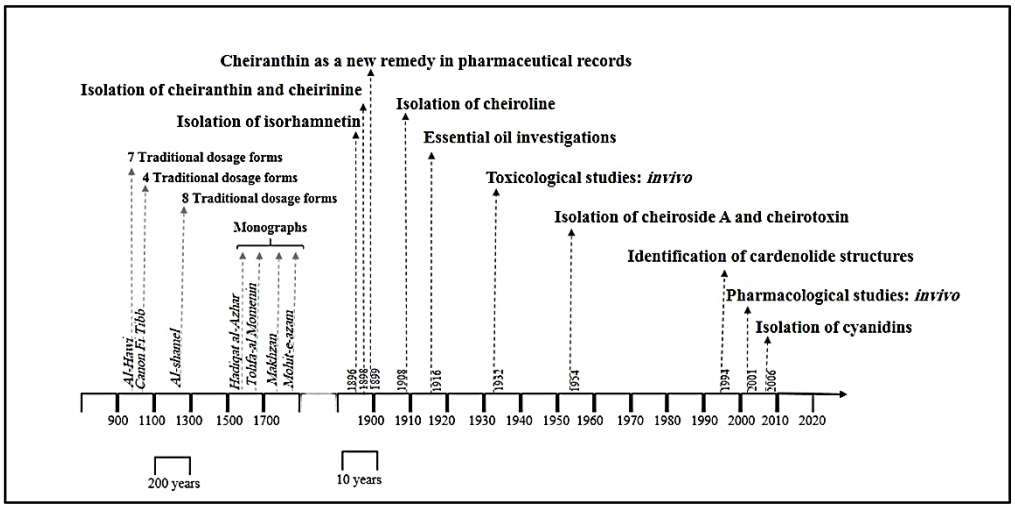


Figure 2. A brief history of wallflower investigations

In traditional societies of present India, wallflower is still used as an abortifacient agent [30]. In Indian medicine, flowers are recommended as cardioactive, antispasmodic, purgative, emmenagogue, deobstruent and tonic. Besides, wallflower seeds are known as stomachic, diuretic, expectorant, but goitrogenic, and the extracts of leaves and the seeds are antibacterial [31]. Wallflower is used as cardioactive, emmenoguge, fertilizer and anti-paralysis agent in Pakistan [32]. The leaves and flowers are listed in herbal ingredients of "Asian medicines", which are used in west as fertilizer agent, anti-paralysis, emmenagogue, cardiotonic and expectorant [33]. In German phytotherapy, the dried flowers as well as the seeds and roots are considered to be anti-itching, emmenoguge, fertilizer and anti-tumor [34].

Phytochemistry of wallflower

According to literature, different parts of the herb have special profiles of compounds. Table 1 has explained chemical composition of wallflower organs in details. Molecular structures of wallflower chemical compounds have been presented in figure 1.

Wallflower pharmacology and toxicology

Despite the safety concerns, there is no report of health hazard or side effects about oral administration of wallflower [4,42]. Dried flowers, dried ripe seeds and fresh aerial parts of the plant before flowering, are reported to have medicinal properties as internal drops, infusion and multi-component preparations. Infusion is permitted in the form of mixing 2-3 g dried flower in 100 mL water (3-4 cups daily) [4]. Although oral administration of wallflower is considered to have low resorption rate (absorption into the circulation of cells or tissue), its parenteral dosage form is considered to have strong efficacy and probably poisoning effects [4]. According to European Food Safety Authority (EFSA) cheirotoxin (cardiotonic and antineoplastic agent) is a chemical of concern [13,35]. In addition to cheirotoxin, cheirosid A and glucocheirolin are categorized as moderately hazardous compounds [35,43] and wallflower is identified to have cytotoxic action [44]. Hazard and toxicity of cheiroside A is described by lethal dose of 0.681 mg/kg in cats by intravenous administration, and lethal dose of cheiroline is reported as 3-7 mg/kg in Mus (a subgenus of the rodent genus) by intravenous administration [13]. There is a suspect for goitrogenic properties of cheiroline [45]. In vitro, cheiroline increases activation and expression of Nrf2 as well as expression of hemeoxygenase 1 and γ-glutamylcysteine. In addition, cheiroline is an antibacterial and antifungal agent. Also in vitro anti-bacterial effects of cheiroline on *H. pylori* has been proved [13,46,47]. The minimum lethal dose of cheiranthin for the frog has been reported to be 2.2×10^{-7} g/g [22]. Cheiranthin showed the characteristics of systolic rest in frogs [48]. Wallflower root intravenously applied in anaesthetized rabbits has resulted in obvious vasodilation and bradycardia that eventually led to the animal's death [49].

Table 1. Natural components from wallflower

No.	Compounds and molecular formula	Plant part(s)	References
	Terpenoides		
	- Cardenolides		
(1)	Cheirotoxin ($C_{35}H_{52}O_{15}$)	Seed, Aerial parts	[4,35]
(2)	Deglucocheirotoxin ($C_{29}H_{42}O_{10}$)	Seed	[25]
(3)	Erysimoside ($C_{35}H_{52}O_{14}$)	Seed	[4,25]
(4)	Glucoerysimoside (C_{41} $H_{62}O_{19}$)	Seed	[4]
(5)	Alliside ($C_{29}H_{44}O_{10}$)	Seed	[25]
(6)	Glucoalliside ($C_{36}H_{56}O_{15}$)	Seed	[25]
(7)	Glucobipindogulomethyloside ($C_{35}H_{54}O_{15}$)	Seed	[25]
(8)	Cheiroside A ($C_{35}H_{54}O_{13}$)	Seed	[4]
(9)	Neouzarin ($C_{35}H_{54}O_{14}$)	Seed	[25,36]
(10)	Erycordin ($C_{35}H_{54}O_{14}$)	Seed	[25]
(11)	Digifucocellobioside ($C_{41}H_{64}O_{18}$)	Seed	[25]
	-Monoterpenoids		
(12)	Geraniol: 3,7-Dimethyl-2,6-octadien-1-ol ($C_{10}H_{18}O$) *(E) form*	Essential oil of flower	[37]
(13)	Nerol: 3,7-Dimethyl-2,6-octadien-1-ol ($C_{10}H_{18}O$) *(Z)* form	Essential oil of flower	[37]
(14)	Linalool ($C_{10}H_{18}O$)	Essential oil of flower	[37]
	Phenylpropanoids		
	-Flavonoids		
(15)	Isorhamnetin ($C_{16}H_{12}O_7$)	Herb	[13]
(16)	Isorhamnetin 3,7-diglycosides ($C_{27}H_{30}O_{15}$)	Herb	[13]
(17)	Kaempferol ($C_{15}H_{10}O_6$)	Flower	[31]
	-Cyanidins		
(18)	Cyanidin 3,5-diglycosides ($C_{41}H_{45}O_{22}{}^{+1}$)	Flower	[27,38]
	- Others		
(19)	Anis aldehyde ($C_8H_8O_2$)	Essential oil of flower	[37]
(20)	Benzyl alcohol (C_7H_8O)	Essential oil of flower	[37]
(21)	Salicylic acid ($C_7H_6O_3$)	Essential oil of flower	[37]
	Glucosinolates and isothiocyanates		
(22)	Cheiroline ($C_5H_9NO_2S_3$)	Essential oil of flower, seed, leaf, fruit, flower	[4,19,40]
(23)	Glucocheirolin ($C_{11}H_{21}NO_{11}S_3$)	Seed	[41]
(24)	Iberin ($C_5H_9NOS_2$)	Seed	[4]
(25)	Glucoiberin ($C_{11}H_{21}NO_{10}S_3$)	Seed	[4]
(26)	Ibervirin	Seed	[13]
	Miscellaneous nitrogen containing groups		
(27)	Choline ($C_5H_{14}NO$)	Seed	[15]
(28)	Anthranilic acid ($C_7H_7NO_2$)	Essential oil of flower	[39]
	Aliphatics		
(29)	Acetic acid (CH_3COOH)	Essential oil of flower	[37]
(30)	Palmitic acid ($C_{16}H_{32}O_2$)	Seed	[39]
(31)	Lignoceric acid ($C_{24}H_{48}O_2$)	Seed	[39]
(32)	Linolenic acid ($C_{18}H_{30}O_2$)	Seed	[39]
(33)	Oleic acid ($C_{18}H_{34}O_2$)	Seed	[39]

Toxicity concerns of cardiac glycosides are due to inhibition of Na^+ K^+ ATPase mechanism. There are various factors affecting the amount of cardenolide absorption in transdermal indications. Area and nature of wound are two important parameters responsible for cardenolide toxicity. Also cutaneous circulation, frequency, duration and formulation characteristics are other parameters affecting absorption of cardenolides [50]. On the other hand, application of cardenolide containing herbs in dermal dosage forms has a profound history [8,51]. Topical application of cardenolides in the safe doses lower than their inhibitory concentration 50% (IC_{50}) could accelerate dermal collagen synthesis [52]. An in vivo study on wallflower has shown anti-tumor properties of topical wallflower extract on murine skin. It has introduced wallflower as a medicinal plant, used clinically in some skin diseases like inflammations [26].

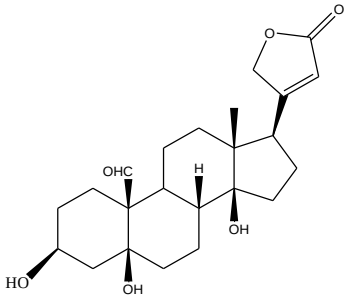
Conclusion

In Persian and Arabic medical manuscripts of the medieval Islamic era, various topical dosage forms of wallflower (in low doses) have been recommended for wound healing, analgesic and anti-inflammatory purposes. Although parenteral rout of administration was not suggested in traditional medicine, oral or vaginal dosage forms mostly have been indicated for emmenoguge, abortifacient and anti-endometriosis activities [6-12]. Phytochemical investigations have reported some cardiac glycosides from wallflower organs and concomitantly safety concerns of medicinal application of the herb fell into a doubt [17,22]. Probably it became the reason that wallflower is not popular in current medicine. Nowadays, there are some traditional medicine preparations around the world, still applying wallflower as an ingredient [28,32]. Recently, topical dosage forms of wallflower has been suggested for clinical skin diseases [26]. According to new in vitro/ in vivo pharmacological studies, cardiac steroids in low doses (below their IC_{50}) have shown stimulatory effects on Na+/K+ ATPase pumps that occurs in safe dose below their minimum toxic concentrations [52-54]. Therefore, dose adjustment of wallflower products are necessary in order to decrease side effects of probable cardenolide constituents. It is suggested that IC_{50} value of cardenolide extract from the whole product could be a good criteria to evaluate safety of wallflower preparations. For

this purpose, IC_{50} value of an extract of wallflower product could be compared with IC_{50} value of a known cardiac steroid (for example digoxin) as an indicator. On the other hand, cardenolide's amount fraction could be estimated according to HPTLC-densitometry calibration curve to a standard cardiac steroid (e.g. digoxin). This method may provide information about safety degree of wallflower traditional products.

Terpenoides → Cardiac steroids

Group of "Strophanthidin"



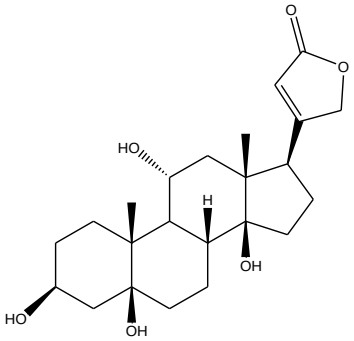
(1) 3-*O*-[β-D-Glucopyranosyl-(1→4)-6-deoxy-β-D-glucopyranoside]

(2) 3-*O*-(6-Deoxy-β-D-glucopyranoside)

(3) 3-*O*-[β-D-Glucopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranoside]

(4)3-*O*-[β-D-Glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranoside]

Group of "Bipindogenin"



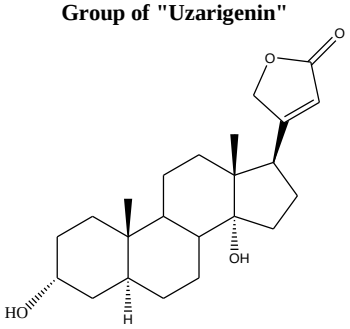
(5) 3-*O*-(6-Deoxy-α-L-glucopyranoside)

(6) 3-*O*-[3-*O*-Methyl-β-D-glucopyranosyl-(1→4)-6-deoxy-α-L-glucopyranoside]

(7) 3-*O*-[β-D-Rhamnopyranosyl-(1→4)-β-D-glucopyranoside]

Figure 1. Chemical structure of natural compounds in wallflower (see table 1)

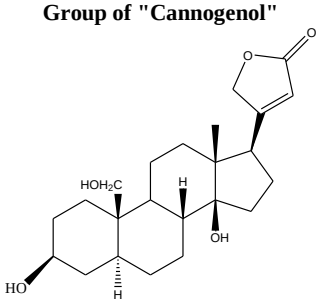
Group of "Uzarigenin"



(8) 3-*O*-[β-D-Glucopyranosyl-(1→4)-β-D-fucopyranoside]

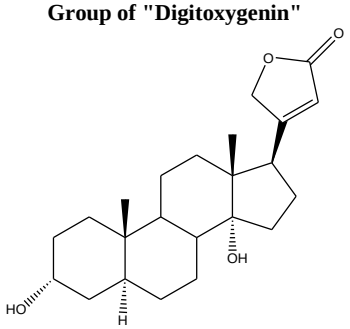
(9) 3-*O*-[β-D-Glucopyranosyl-(1→4)-β-D-glucopyranoside]

Group of "Cannogenol"



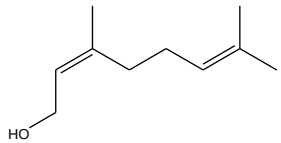
(10) 3-*O*-[β-D-Glucopyranosyl-(1→4)-6-deoxy-β-D-glucopyranoside]

Group of "Digitoxygenin"



(11) 3-*O*-[β-D-Glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→4)-β-D-fucopyranoside]

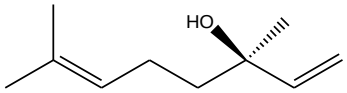
Monoterpenoids



3,7-Dimethyl-2,6-octadien-1-ol ($C_{10}H_{18}O$)

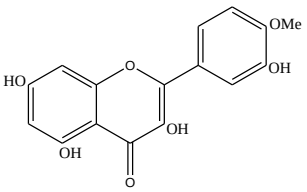
(12) *(E)* form: Geraniol **(13)** *(Z)* form: Nerol

Figure 1. Continued

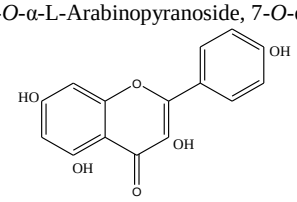


(14) *(R)* form: Linalool

Flavonoids

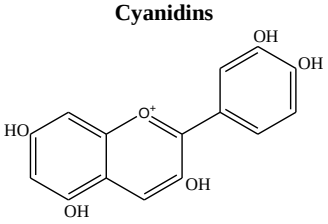


(15) Isorhamnetin ($C_{16}H_{12}O_7$)
(16) Isorhamnetin: 3-*O*-α-L-Arabinopyranoside, 7-*O*-α-L-rhamnopyranoside



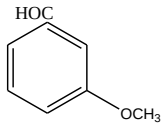
(17) Kaempferol ($C_{15}H_{10}O_6$)

Cyanidins

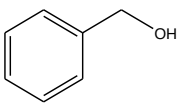


(18) *(E)* derivative:
3-*O*-[β-D-Xylopyranosyl-(1→2)-[4-hydroxy-*E*-cinnamoyl-(→6)]-β-D-glucopyranoside],
5-*O*-β-D-glucopyranoside
(Z) derivative:
3-*O*-[β-D-Xylopyranosyl-(1→2)-[4-hydroxy-*Z*-cinnamoyl-(→6)]-β-D-glucopyranoside],
5-*O*-β-D-glucopyranoside

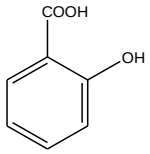
Minor phenylpropanoids:



(19) Anis aldehyde ($C_8H_8O_2$)

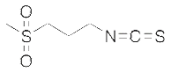


(20) Benzyl alcohol (C_7H_8O)

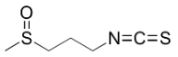


(21) Salicylic acid ($C_7H_6O_3$)

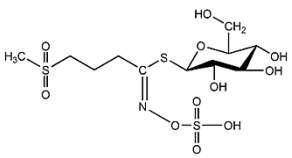
Glucosinolates and isothiocyanates



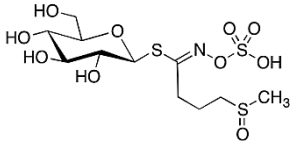
(22) Cheiroline($C_5H_9NO_2S_3$)



(24) Iberin ($C_5H_9NOS_2$)

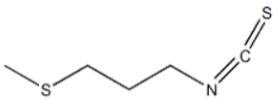


(23) Glucocheirolin$C_{11}H_{21}NO_{11}S_3$)



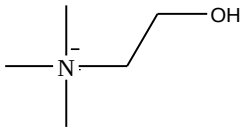
(25) Glucoiberin($C_{11}H_{21}NO_{10}S_3$)

Figure 1. Continued

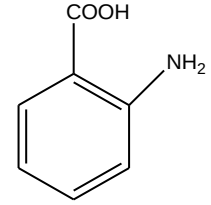


(26) Ibervirin ($C_5H_9NS_2$)

Miscellaneous nitrogen-containing structures

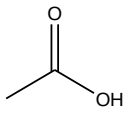


(27)

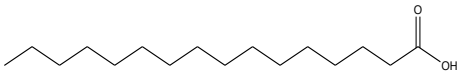


(28) Anthranilic acid ($C_7H_7NO_2$)

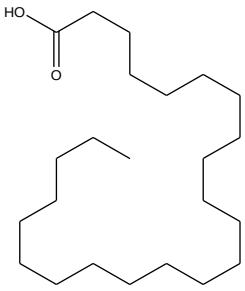
Aliphatics



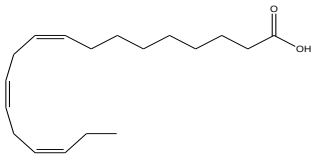
(29)



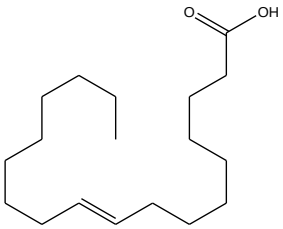
(30)



(31)



(32)



(33)

Figure 1. Continued

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Author contributions

Ghazaleh Mosleh contributed as Ph.D. student and the main study investigator; Amir Azadi, Parmis Badr, Zohreh Abolhassanzadeh, Seyed Vahid Hosseini and Abdolali Mohagheghzadeh contributed as supervisors of the whole project. All authors approved the final draft of 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.

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Abbreviations

PM: Persian medicine; IC_{50}: Inhibitory concentration 50