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Original article

Formulation of a Traditional Polyherbal Product to a Standard Pharmaceutical Syrup and Development of Its Quality Control Methods

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Abstract

Background and objectives: People interest in traditional medicine has increased recently; however, traditional herbal medicines should be transformed into modern forms of medicine to increase patient acceptance. In this investigation, a polyherbal traditional combination "Monzej-e-balgham" has been based on according to Iranian traditional medicine (ITM) manuscripts and its quality control evaluations have been performed. **Methods**: The main ingredients of the formulation including *Vitis venifera* L., *Ficus carica* L., *Foeniculum vulgare* Mill., *Glycyrrhiza glabra* L., *Adiantum capillus-veneris* L., *Rosa damascena* Herrm. and *Onopordum acanthium* L. were crushed, mixed and extracted with distilled water by decoction method. The mixture was used to prepare formulations of the syrup. Physicochemical, microbiological properties and rheological behavior of the syrup were studied and total phenolics content of the formulation was determined. The syrup was evaluated in accelerated stability test during 6 months. **Results:** The product was light brown semitransparent syrup with appropriate taste and odor. There was no cap locking and precipitation. Dry residue, sedimentation, pH, viscosity, density and total phenolics were found to be 14.82%, 0.015%, 5.40, 4.6 cP, 1.076 g/mL and 127.34 mg/100 mL, respectively. Microbial evaluations of syrup were consistent with the WHO protocol. The rheogram of the product represented the Newtonian behavior. In the accelerated stability tests, no significant changes were observed. Total phenolics content reduced to 2.50% within 6 months in 40 ºC. **Conclusion:** The outcome of this research was a pharmaceutical standardized formulation from the traditional "Monzej-e-balgham" which supports the idea of drug discovery based on traditional knowledge.

Keywords: formulation; Iranian traditional medicine; Monzej-e-balgham; quality control; syrup

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Introduction

Traditional medical systems are potential resources to discover new medicines. The popularity of traditional, complementary, and alternative medicine has grown throughout the world [1]. Iranian traditional medicine (ITM)

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with its majestic background and efficient treatments has attracted the attention of many scholars in Iran and worldwide. Existing treatments mentioned in Iranian old manuscripts have studied in many experiments and clinical trials [2]. Among various traditional medical systems, ITM is a well-known health care system due to its basic concept of humors. It believes that balance in the four humors (phlegm, black bile, yellow bile and blood) creates a healthy body and imbalance causes the disease [3]. "Balgham" (phleghm) (with cold and wet qualities) is one of these humors and the imbalance of this humor causes many disorders such as stroke [4,5], hemiplegia due to ischemic stroke [6], cardiovascular disease risk factors such as metabolic abnormalities like abdominal obesity, high cholesterol, high blood pressure and high blood glucose [7], overweight [8], atherosclerosis [9], vitiligo [10,11], impotency [12-14], polycystic ovary syndrome (PCOS) [15] and premature ovarian failure (POF) [16] in human body according to modern research. Treatment would include the evacuation of morbid or excess humors from the body [17,18]. "Monzej-e-balgham" formulations are known to be useful to evacuate morbid matters produced due to excess or putrefaction of phlegm and is widely used for diseases with cold and moist temperament (diseases occurring due to phlegm accumulation) [17].

Different formulations of "Monzej-e-balgham" were found in ITM textbooks, among diverse prescriptions, a combination of liquorice, fennel, maidenhair fern, large raisins, fig, damask rose and cotton thistle have been used in this study in the form of decoction according to "Mizan-al-teb*"* , an ITM reference book, prescription [19]. Since "Monzej-e-balgham" is still used as a traditional cure, it is needful to prepare a suitable formula for facilitating its use for patients [2]. Traditional pharmaceuticals should be transformed into new drug forms for easier use and better patient acceptance compared to the traditional formulations that are needed to be prepared for each turn of use. Also, it is necessary to use a standard dosage form to achieve an appropriate and repeatable therapeutic response [3,20]. In the present research, a syrup was prepared in accordance with ITM manuscripts and its quality control analysis was conducted.

Material and Methods

Ethical considerations

The present research was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (SBMU) (IR.SBMU.RETECH.REC.1396.1138, 2017)

Plant materials

All required plants for formulation of the syrup were purchased from Tehran local market in 2017. They were authenticated by the botanists of the Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Herbal market samples (HMS) of the roots of *Glycyrrhiza glabra* L., liquorice, (Paplionaceae), fruits of *Foeniculum vulgare* Mill., fennel, (Apiaceae), whole parts of *Adiantum capillus-veneris* L., maidenhair fern, (Polypodiaceae), fruits of *Vitis venifera* L., large raisins, (Vitaceae), fruits of *Ficus carica* L., fig, (Moraceae), flowers of *Rosa damascena* Herrm., damask rose, (Rosaceae) and seeds of *Onopordum acanthium* L., cotton thistle, (Asteraceae) (No. 494 , 492, 491, 489, 490, 488 and 493, respectively), were stored at the Herbarium of TMRC for future references.

Chemicals

Folin-Ciocalteu, pyrogallol and glycerin were purchased from Merck Co., Germany. Sodium benzoate, potassium sorbate and sodium bicarbonate were provided from Sigma-Aldrich Co., UK.

Quality control assessment of the plants

Quality control tests for the plants were carried out according to their monographs in pharmacopoies [21-23].

Preparation of the polyherbal syrup

According to the selected traditional resource [19], large raisins (1 part), fennel and cotton thistle (1.3 parts), damask rose and liquorice (2 parts), maidenhair fern (3 parts), fig (6 parts) were crushed, coarsely powdered and extracted by decoction method with distilled water (plant: water 1:10 w/v) for 30 min. The mixture was filtered. Finally, sodium benzoate and potassium sorbate (0.3 and 0.2%, respectively) were added to the mixture as microbial preservatives. In order to achieve appropriate viscosity for formulation, carbomer 940 (0.5-1%), carboxy

methyl cellulose (CMC) (0.5-1%), hydroxy propyl methyl cellulose (HPMC) (0.5-1%), poly vinyl pyrrolidone (PVP) (5%), propylen glycol (PG) (8,12,16 and 20%) and glycerin (8,12,16 and 20%) were examined and various experimental formulations with the mentioned ingredients (F1-F15) were prepared.
Formulations containing glycerin were acceptable; so, F8- F11 formulations were prepared and their physicochemical properties were evaluated. Based on the results, F10 was chosen as the best formulation.

Physicochemical quality control of the polyherbal syrup
Various physiochemical tests and pharmaceutical parameters, including macroscopic characteristics, crystallization evaluation, cap locking, sedimentation, dried residue, pH, density, viscosity measurement and evaluation of rheological properties, Short term thermal stability and microbial evaluations were performed on the prepared syrup [24].

Total phenolics content
The concentration of total phenolics content in the product was measured with Folin-Ciocalteu reagent according to British Pharmacopeia [21]. Briefly, 1 mL of the syrup was adjusted to 10 mL with distilled water. One mL of Folin-Ciocalteu reagent was added to 2 mL of the diluted syrup, then 10 mL distilled water was added to the mixture. The solution was diluted with sodium carbonate (29% w/v) up to 25 mL and then stored at room temperature for 30 min. The absorbance was recorded at 760 nm. Total phenolics content was calculated using calibration curve of pyrogallol as the standard. All measurements were carried out at room temperature in triplicate.

Short term thermal stability
Three bottles of syrup were placed in refrigerator (4° C) and another three samples in incubator at 40° C. Seven days later, the samples were replaced. After the fourteen-day's cycle, the samples were periodically evaluated for changes like sedimentation, taste, odor and color.

Accelerated stability tests
Six bottles of the syrup were placed in an oven (40 °C). They were evaluated according to the above mentioned measurements after 3 and 6 months [25].

Statistical analysis
All data were analyzed by one-way ANOVA test using SPSS Software (22.0.0.2). Differences were considered significant at $p < 0.05$, and data were presented as means ± SD.

Results and Discussion
Herbal medicines have been used since ancient times as effective ways for prevention and treatment of different illnesses. In recent years their use has increased dramatically [26,27]. "Monzej-e-balgham" formulation is an oral medication which is widely used in ITM in decoction form. Although traditional drugs can be used as new therapies for researches, they need to be reformulated to access pharmacopoeia standards for modern drugs. Lack of the quality control profiles for the plant formulations drives scientists to explore more about the plant products. Formulation quality control plays an important role in confirming the safety and efficacy of the product.
The results of raw materials analysis including total ash, acid insoluble ash, loss on drying, alcohol soluble extractive and water soluble extractive have been summarized in table 1. Physicochemical tests results of all plants were in acceptable range for each plant confirming to be proper enough for further processing of the formulation.
In the present study, various formulations of syrup were prepared according to Iranian traditional medicine. Experimental syrups contained active ingredients and required suitable excipients including preservative, viscosity-increasing and sweetening agents.
In order to obtain appropriate viscosity for the polyherbal syrup, carbomer 940, CMC, HPMC, PVP, PG and glycerin were used and various experimental formulations were prepared. By adding carbomer, CMC and HPMC (0.5, 1%) in the syrup, turbidity and particles were observed that indicated incompatibility between these polymers and other components of the formulation. Therefore, the use of these polymers to increase the viscosity of this herbal syrup was not logical although these polymers at 1% concentrations gave suitable viscosity to the syrup (formulations F1- F6). On the other hand, PVP was soluble in water and the prepared syrup showed uniformity with clear appearance, but the syrup did not show suitable viscosity (F7).

Table 1. Physicochemical analysis of ingredients of the polyherbal syrup

Ingredients	Total ash %	Acid insoluble ash %	Foreign matter %	Loss on drying %	Alcohol soluble extractive %	Water soluble extractive %	Assay %
Glycyrrhiza glabra	6.01± 0. 38 (NMT 10)[a]	0.46 ± 0.03 (NMT 2)	-	5.95% (NMT 10%)	-	-	7.40 ± 0. 28 Glycyrrhizin, (NLT 4)
Adiantum capillus-veneris	9.66± 0.34 (NMT 10)	-	9.5 ± 0.45 (NMT 10)	-	11.72± 0. 85[b]	-	1.62± 0. 14 mucilage
Foeniculum vulgare	8.42± 0.25 (NMT 10)	0.71± 0.05 (NMT 1.5)	0.18 ± 0.01 (NMT 1.5)	-	-	-	80.50 ± 0. 63 Anethole, (NLT 80)- 3.00± 0. 00 Essential oil, (NLT 2)
Vitis venifera	2.41± 0.22 (NMT 3)	0.06± 0.00 (NMT 0.2)	0.0± 0.00 (NMT 2)	10.09± 0.41	20.54 ± 1. 23	56.64 ± 2.15	-
Ficus carica	2.58± 0.17 (NMT 4)	0.09± 0.01 (NMT 1)	0.0 ± 0.00 (NMT 2)	-	15.79± 0. 76	44.39± 1.06	-
Rosa damascena	5.13± 0.46 (NMT 6)	0.85± 0.03 (NMT 2)	0.2 ± 0.01 (NMT 2)	-	14.54± 0. 89	28.73± 0.83	-
Onopordum acanthium	5.45± 0.37	0.90± 0.02	0.35% ± 0.02	-	-	-	0.5± 0. 00 Essential oil

NMT: Not More Than; NLT: Not Less Than; [a] The data in parenthesis are acceptable ranges in Pharmacopoeia (BP/ Iranian Herbal Pharmacopoeia/ Unanian Pharmacopoeia); [b] No acceptable range have been reported

Table 2. Physicochemical characteristics of F8-F11 formulations

Tests	formulations			
	F8	F9	F10	F11
Color	Light brown	Light brown	Light brown	Light brown
Taste	Bitter	Bitter sweet	Sweet	Very sweet
Appearance	Semi transparent	More transparent than F8	More transparent than F9	More transparent than F10
Viscosity (cP)	3.9 ± 0.33	4.3 ± 0.42	4.6± 0.30	5.1± 0.26
Density (g/cm^3)	1.048± 0.002	1.064± 0.001	1.076± 0.001	1.092± 0.001
pH	5.17± 0.03	5.29± 0.05	5.40± 0.03	5.49± 0.04

F8: 8% Glycerin, F9: 12% Glycerin, F10: 16% Glycerin, F11: 20% Glycerin

Glycerin and PG also increased the relative viscosity and improved the transparency of the syrup, but various concentrations of PG were not acceptable due to its undesirable taste (F12- F15). Glycerin gave a clear viscose liquid with sweet tastes that caused increase in viscosity and improved the transparency of the syrup and also masked the taste (F8- F11).

In order to access the best formulation, the syrups were prepared using different amounts of glycerin. Table 2 shows physicochemical properties of various amounts of glycerin based syrup used in the experimental formulations.

Investigating the properties of experimental formulations showed that increasing the glycerin ratio improved the taste and appearance and increased the viscosity of the syrup (F10-F11). Since high level of glycerin (F11) produced very sweet flavor that was not desirable, formulation F10 was chosen as the most appropriate formulation for preparation of the polyherbal syrup. Therefore, glycerin as sweetener, viscosity-increasing agent, co-solvent, stabilizer and transparency enhancer was used in the syrup. Sodium benzoate and potassium sorbate were used as antimicrobial preservatives; while, adding additional components like flavoring and coloring agents was avoided to prepare a product similar to the traditional version as much as possible. The details of the final formula have been presented in table 3.

The evaluation of syrup quality control has shown that it has the optimum visual properties without any indications of cap locking and crystallization. There was no indication of physical changes were observed during short term thermal stability tests and centrifugation. Also, the rheological behavior of the polyherbal syrup was determined. Rheology deals with the viscosity characteristics of powders, fluids and semisolids. Materials are divided into two general categories, Newtonians and non-Newtonian, depending on their flow characteristics.

Table 3. Final formulation of polyherbal syrup

Ingredients	Amount (%)	Function
Glycyrrhiza glabra	2.65	Active constituent
Adiantum capillus-veneris	4.42	Active constituent
Foeniculum vulgare	1.77	Active constituent
Vitis venifera	1.40	Active constituent
Ficus carica	8.35	Active constituent
Rosa damascena	2.65	Active constituent
Onopordum acanthium	1.77	Active constituent
Glycerin	16	Co-solvent, Viscosity-increasing agent, Enhanced transparency, Preservative, Sweetener
Sodium benzoate	0.3	Preservative
Potassium sorbate	0.2	Preservative
Water	qs to 100	Solvent

Table 4. Evaluation of physicochemical parameters and results of accelerated stability testing of polyherbal syrup

Specification	Start	3rd Months	6th Months
Appearance	Light brown semitransparent liquid	Conforming	Conforming
Taste	appropriate	Conforming	Conforming
Odor	Characteristic	Conforming	Conforming
pH	5.40±0.03	5.33±0.05	5.29±0.09
Dried residue (%)	14.82±0.73	14.88±0.32	14.91±0.45
Sedimentation (%)	0.015±0.000	0.016±0.000	0.016±0.001
Density (g/mL)	1.076±0.001	1.076±0.002	1.077±0.001
Viscosity (cP)	4.6±0.3	4.8±0.2	4.8±0.2
Total phenolics content (mg/100 mL)	127.34±0.42	125.66±1.03	124.15±0.76
Conclusions on stability		**Stable**	**Stable**

Newtonian flow is characterized by constant viscosity, regardless of shear rate applied. A Newtonian fluid will plot as a straight line with the slop of the line being viscosity [28]. The rheogram of polyherbal syrup has been presented in figure 1. Base on the figure, the rheogram was linear indicating Newtonian behavior.

The results of accelerated stability test have been shown in table 4 after three and six months. Total phenolics content was measured as the marker using Folin-Ciocalteu reagent. The syrup was found to contain 6.37 mg/5 mL total phenolics as pyrogallol.

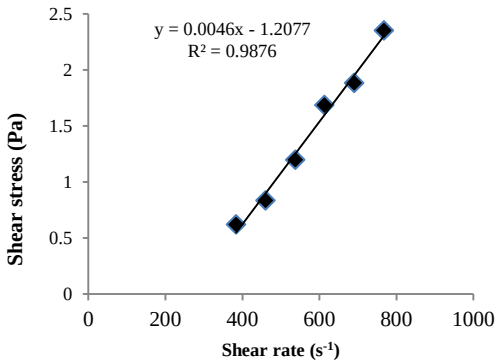

Figure 1. Rheogram of the polyherbal syrup, showing the presence of a Newtonian behavior (n = 3, data points are presented as mean ± SD).

After three and six months, the decrease in the phenolics contents has been reduced to 1.31% and 2.50%, respectively after three and six months, that is proper according to the maximum allowed reduction (5%) [25].The results of the microbiological tests were in accordance with WHO guideline within six months. Based on the results of accelerated stability test, no statistically significant changes ($p>0.05$) were found about the measured parameters during six months which confirm the stability of the product. It could be concluded that the polyherbal syrup showed suitable stability after the 6 month period at 40 °C regarding physical characteristics and microbiological quality control tests and was acceptable for an oral product.

In this study, "Monzej-e-balgham" syrup was reformulated with appropriate physicochemical characteristics and its quality control methods were developed. This formulation can be used in clinical trials to present a new traditional formulation of "Monzej-e-balgham".

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Author contributions

Maedeh rezghi performed the experimental parts; Seyed Alireza Mortazavi supervised the pharmaceutical parts; Rasool Choopani and Shirin Fahimi were involved in the traditional aspects; Mohammad Abbas Sheihkoleslami was involved in data analysis; Maryam Hamzeloo-Moghadam designed and supervised the study. 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 accuracy and integrity of the paper content.

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Abbreviations

ITM: Iranian traditional medicine; COPD: chronic obstructive pulmonary disease; POF: premature ovarian failure; PCOS: polycystic ovary syndrome; HMS: herbal market samples; (PVP): poly vinyl pyrrolidone; CMC: carboxy methyl cellulose; HPMC: hydroxy propyl methyl cellulose; PG: propylen glycol; TVC: total viable count; NMT: not more than; NLT: not less than