Phytopharmacology and phytotherapy of regulatory T cells: A new approach to treat multiple sclerosis

Article · March 2016

CITATIONS
0

READS
37

1 author:

Mohamadreza mahmoodian sani
Hamadan University of Medical Sciences
10 PUBLICATIONS **30** CITATIONS

SEE PROFILE

Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (3):215-220
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Phytopharmacology and phytotherapy of regulatory T cells: A new approach to treat multiple sclerosis

Mohammad Reza Mahmoudian Sani[1], Majid Asadi-Samani[2], Hojjat Rouhi-Boroujeni[*2] and Mehdi Banitalebi-Dehkordi[3]

[1]Hamedan University of Medical Sciences, Hamedan, Iran
[2]Student Research Committee, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]Cellular and Molecular Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

---

ABSTRACT

Multiple sclerosis (MS) is a disorder of central nervous system characterized by demyelination, inflammation, and axonal injury. Regulatory T cells (Tregs) have been defined as CD4+CD25+FoxP3+ T-cells that play a critical role in maintaining self-tolerance and preventing autoimmune diseases. Dysfunction and decreased numbers of Tregs may lead to MS. Web of Science and PubMed databases were searched using the Endnote software for the publications about the role of Tregs in MS published from 2000 to February 2016. The medicinal plants and their derivatives, including Hypericum perforatum, Astragalus membranaceus, Pterodon emarginatus Vogel, curcumin, resveratrol, matrine, Bu Shen Yi Sui Capsule, and Hyungbangpaedok-san have been reported to regulate the function of Tregs in MS. The medicinal plants and their derivatives reported in this study might be useful for up-regulation of Tregs through suppressing the activation of autoreactive T cells and hence controlling MS. They should be investigated in clinical trials to help to prevent and treat MS.

Keywords: Multiple sclerosis, Regulatory T cells, Medicinal plants, Phytochemicals, Herbal drugs

---

INTRODUCTION

Multiple sclerosis (MS), an inflammatory demyelinating disease of central nervous system (CNS), is characterized by multifocal inflammation, demyelination, and neuronal damage [1]. A variety of drugs are used to modify the conditions of MS including interferon beta (IFN-β), natalizumab, glatiramer acetate, alemtuzumab, fingolimod, teriflunomide, and dimethyl fumarate. However, the use of MS drugs may cause certain side effects in long term. In addition, because these drugs are costly, MS patients may face economic problems [2, 3]. Adverse effects, including depression, cardiotoxicity, infection, nausea, and anemia, have been reported to be associated with long-term therapy. MS is caused by damage to myelin sheath at plaques due to infiltration of autoimmune Th17 cells and lack of regulatory T cells (Tregs) [4, 5]. In this regard, some strategies such as inhibiting Th17 cells activity and stimulating the regulation of Tregs activity have been suggested to control and treat MS.

Tregs are negative immune regulatory cells that mediate immune tolerance. The interactions between Th17 and Tregs are regulated by the secretion of some cytokines such as interleukin (IL)-17 and transforming growth factor-β 1, and specific transcription factors, including retinoic acid-related orphan receptor (ROR) γt and forkhead box P3 (FoxP3) [6-8]. Tregs have been defined as CD4+CD25+FoxP3+ T-cells that play a crucial role in maintaining self-tolerance and preventing autoimmune diseases [9, 10]. Tregs may play a critical role in maintaining immune tolerance and controlling the destructive self-reactive T cells found in MS [11, 12]. In addition to the increased number of autoimmune T-cells, the decreased number and dysfunction of Treg-cells contribute to the pathogenesis of MS [13]. Given the role of Tregs in preventing and controlling MS as well as the side effects of the present drugs,

researchers are investigating to find out more effective drugs with less side effects to regulate the activity of Tregs. In this regards, medicinal plants are reliable source for preparation of new drugs. They have been frequently used in the traditional medicine by local people [14-19] and have been investigated for prevention and treatment of hyperlipidemia [20], cardiovascular diseases [21, 22], kidney disorders [23-25], neurological disorders [26], and even cancer [27]. So, they can be considered as a useful source for production of effective drugs in the treatments of various diseases [28-34].

Regarding the significance of inflammatory diseases, especially MS, and the necessity of preventing and treating this disease, the aim of this review article is to report medicinal plants and their nature-based derivatives that are effective on regulation of Tregs' activity in MS patients. In this regards, Web of Science and PubMed databases were searched for the publications about the role of Tregs in MS published between 2000 and February 2016 using the EndNote software. The used search terms were multiple sclerosis and medicinal plant or herb or herbal medicine or natural compound or phytochemical or herbal drugs and regulatory T cell or Treg or Treg in Title/Keywords/Abstract. Each database was searched independently. The articles retrieved from both databases were analyzed once. Abstracts were reviewed based on predefined inclusion and exclusion criteria. When necessary, full texts were retrieved to assess study eligibility. The articles without English abstract and English available full texts were excluded. Only the articles directly addressing the effect of the medicinal plants and their derivatives were selected and analyzed.

From the Web of Science, 27 articles were retrieved and from the PubMed, 19 articles retrieved. Overall, 22 articles were retrieved from both databases and 24 were included in the final analysis. After reviewing the abstracts, we excluded two articles from the analysis as they did not meet the inclusion criteria. Twenty two articles investigated the role of the medicinal plants and their derivatives in regulating Tregs. These plants were *Hypericum perforatum*, *Astragalus membranaceus*, *Pterodon emarginatus* Vogel, the compounds curcumin, resveratrol, matrine, and the drugs Bu Shen Yi Sui Capsule and Hyungbangpaedok-san. Table 1 gives further details.

Hypericum perforatum (HP) or St. John's wort, from Hypericaceae family, is used in traditional medicine for treatment of mild to moderate depression. HP has also been used as an antioxidant, anti-inflammatory and wound-healing agent. The results indicated that HP extract reduced the incidence and severity of EAE, an outcome that is closely correlated with an inhibition of pathological characteristics (leukocyte infiltration and demyelination) and antigen-specific T-cell proliferation. These results indicate that HP extract can attenuate EAE autoimmune responses by inhibiting immune cell infiltration and expanding Treg cell, and therefore may be considered as a potential choice of MS treatment [35].

P. emarginatus is a medicinal plant which is used in Brazilian traditional medicine as a folk therapy because of its immunosuppressive, anti-inflammatory, healing, antirheumatic, tonic and depurative features. The essential oil of *P. emarginatus* (100 mg/kg) significantly attenuated neurological signs and EAE development. In addition, it inhibited Th1 cell-mediated immune response and upregulated Treg response in vitro. Moreover, the essential oil of *P. emarginatus* inhibited both microglial activation and expression of iNOS, associated with inhibition of axonal demyelization and neuronal death throughout the disease development [36].

Curcumin (diferuloylmethane) is a naturally occurring yellow pigment obtained from the rhizomes of the plant *Curcuma longa* (turmeric) commonly found in south Asia [37, 38]. It is used as a coloring and flavoring spice in foods. Curcumin has traditionally been used to treat inflammatory disorders and to heal wounds. The antioxidant, antitumor and anti-inflammatory properties of curcumin are well recognized as it is under preclinical trials for the treatment of cancer and inflammation [39, 40]. The inhibition of EAE by curcumin is related to an up-regulation of CD4+CD25+-Foxp3+ Tregs in the lymphoid organs and CNS. These findings confirm that curcumin differentially regulates CD4+ T helper cell responses in EAE [41].

Matrine (MAT), a quinolizidine alkaloid derived from the herb *Radix Sophorae* Flave, has been used to treat hepatitis B in clinical trials, with excellent safety [42, 43]. The use of natural products for the treatment of MS may be more effective as they have fewer side effects. Oriental herbal medicines have been reported to improve neurological signs, clinical symptoms, and immune function and reduce the frequency of recurrence in MS patients [44]. The results showed that administration of MAT significantly increased serum Tregs and expression of Foxp3, a Treg transcription factor, in the spinal cord. Moreover, treatment with MAT significantly upregulated CNS expression of Nrf2 and HO-1, which contribute importantly to inhibiting oxidative stress and CNS inflammation. Together, the findings represent MAT as an immunosuppressive and potent immunomodulatory natural product for the treatment of EAE which could be a novel therapeutic option for MS [43].

Bu Shen Yi Sui Capsule (BSYSC, originally named Erhuang Capsule) is a phlegm-resolving, yin-nourishing and blood-activating formula used in traditional Chinese medicine. The clinical studies showed that BSYSC had the ability to markedly reduce and eliminate the symptoms such as limbs weakness and paresthesia, reduce the frequency and intensity of relapses and the dose of the medication required, to improve the quality of life in MS patients [45, 46]. Results showed that BSYSC improved neurological function and reduced inflammatory cell infiltration and damage to the axons and myelin in the spinal cord and brain. BSYSC down-regulated the ratio of CD4 + IL-7+/CD4 + CD25 +FoxP3+ T cells in the spleen greatly, and reduced the ratio of IL-17A and FoxP3 mRNA and protein in the brain or spinal cord at different stages. BSYSC had a strong neuroprotective effect on EAE mice. The protective mechanisms of BSYSC might be associated with mediating the regulation of Th17/Tregs [1].

Hyungbangpaedok-san (HBPDS) is extensively used in traditional medicine, which is composed of 10 herbs: *Ostericum koreanum*, *Bupleurum falcatum*, *Aralia continentalis*, *Schizonepeta tenuifolia*, *Angelica decurs* iva, *Saposhikovia divaricata*, *Poria cocos*, *Rehmannia glutinosa*, *Lycium barbarum*, and *Plantago asiatica*. HBPDS has traditionally been used for patients with fever and chills that are not sweating, generalized body aches and pain, pain and stiffness of the head and neck, and redness and swelling of the eyes [47]. HBPDS decreases tumor necrosis factor-α (TNF-α) and signal transducer and activator of transcription 4 expression and increases proliferation of CD4+ T cells, which are associated with the immunomodulatory effects and anti-inflammatory activity. Taken together, HBPDS could alleviate the development/progression of EAE by regulating the recruitment/infiltration and activation of microglia and peripheral immune cells (macrophages, Th1, Th17, and Tregs) in the spinal cord. These findings could help to develop protective strategies by means of HBPDS for the treatment of autoimmune disorders including MS [48].

Table 1: The effects of medicinal plants and phytochemicals on regulatory T cells in multiple sclerosis

Medicinal plants/ phytochemicals	Study	Dosage	Main results	Ref.
Matrine	*In vivo*	low dose (150 mg/kg) high dose (250 mg/kg)	Increased production of regulatory T cell (Treg) as well as expression of Foxp3	[43]
Hypericum perforatum	*In vivo*	1, 5 and 10 mg/kg (low, intermediate and high doses)	Increased Tregs levels in the spleen	[35]
Resveratrol	*In vivo*	20 mg/kg	Controlling Th17 activity through increased Tregs activity	[49]
Pterodon emarginatus Vogel	*In vivo*	50 and 100 mg/kg	Upregulation of T reg cells and inhibition of Th17 and Th1 cells polarization	[36]
Bu Shen Yi Sui Capsule (BSYSC)	*In vivo*	3.02 g/kg	Down-regulated markedly the ratio of CD4 + IL-17+/CD4 + CD25 +FoxP3+ T cells in the spleen	[50]
Curcumin	*In vivo*	100μg curcumin in 25 μl dimethyl sulfoxide	Up-regulation of activated receptor γ and CD4+CD25+Foxp3+Tregs in the CNS and lymphoid organs	[41]
Astragalus membranaceus	*In vivo*	20 mg/kg	Significant enhance of T-bet and Foxp3 mRNA levels	[51]
Hyungbangpaedok-san	*In vivo*	20g each/200g in total	Increased the elevated population of CD4+/CD25+/Foxp3+	[48]

DISCUSSION

There is no available cure for MS. However, crtain therapies may be used to treat the disease symptomatically, including IFN β-1a, IFN β-1b, glatiramer acetate, natalizumab, fingolimod and dimethyl fumarate. In addition, anti-inflammatory Tregs have been found to be important CD4 cells for controlling the development of autoimmune diseases [49]. In this regard, seeking out new drugs that specifically target Tregs is important for the development of more effective MS treatments [50]. Therefore, novel biological mechanisms and pharmacological targets are still being identified through analysis of the biochemical characteristics natural/herbal compounds and their derivatives. Natural compounds continue to be a treasure for new drugs development for the future [52-57]. Actually, medicinal plants are important sources used to find new compounds with immunomodulatory and anti-inflammatory potential [58-62]. However, one important limitation in using nature-based derivatives to treat diseases is limited knowledge about their mechanisms of action, which adds to our misgivings about clinical use. Therefore, the present study reviewed the medicinal plants and their derivatives that play a role in stimulating Tregs to detect their effect mechanisms better. The findings of this study indicated that the plants and compounds such as matrine, *Hypericum perforatum*, Resveratrol, *Pterodon emarginatus* Vogel, the essential oil, Bu Shen Yi Sui Capsule, Curcumin, *Astragalus membranaceus*, and Hyungbangpaedok-san cause increase in the number of Tregs in the MS patients and therefore help to prevent and treat this disease.

It has been shown that, in the active period of disease, the number of CD4+CD25+Foxp3+ Tregs in the peripheral blood of MS patients decreased compared with the inactive period [51]. Moreover, in the early stage of EAE, the number of CD4+CD25+Foxp3+ Tregs in target organs and peripheral lymphoid organs of mice was significantly

lower than the recovery phase, representing that CD4+CD25+Foxp3+ Tregs correlate partially with MS [63] Furthermore, several studies have shown that decreased number of Tregs in patients with MS led to an expansion of autoreactive T-cells [64]. Therefore, an up-regulation of Foxp3+ Tregs might help to suppress the activation of autoreactive Tcells, because Tregs are involved in the pathogenesis of autoimmune diseases [35]. In addition, immune dysfunction is related to down-regulation of the Tregs and the upregulation of Th17 cells [65, 66]. Therefore, the aim of novel drug targets for the treatment of MS is the regulation of immunity balance between Th17 and Tregs.

The results of this review article indicate that the onset of treatment with medicinal plants increases the recruitment/migration of thymus-derived Tregs, production of Tregs, expression of Foxp3, and inhibition of Th17 and Th1 cells polarization through increased Tregs activity, significantly enhances T-bet mRNA levels, up-regulation of activated receptor γ and CD4+CD25+Foxp3+ Tregs in the CNS and lymphoid organs, and down-regulates the ratio of CD4 + IL-17+/CD4 + CD25 +FoxP3+ T cells markedly in the spleen in EAE/MS. Medicinal plants have antoxidant and immunomodulatory properties in vivo and in vitro and, most interestingly, they have good bioavailability and can be given orally, which may reduce the costs of therapy and painful administration of drug and contribute to adherence to the treatment by patients [67-72].

Finally, this review article provides great implications for ethnomedicine and clinical research, as well as strongly supports the applicability of the medicinal plants and their constituents to develop an effective treatment, alone or in combination with existing therapies, for MS. This may be an explanation of the use of this plant to treat peripheral and central autoimmunity disorders in folk medicine. This study provides a basis for further research on the efficacy of medicinal plants and their active ingredients in the treatment of MS. However, the formula of medicinal plants is complicated and the compounds exert multipurpose effects; therefore, other mechanisms by which medicinal plants influence MS in EAE require further investigation.

REFERENCES

[1] Q Zheng, T Yang, L Fang, L Liu, H Liu, H Zhao, Y Zhao , H Guo , Y Fan , L Wang . *BMC Complement Altern Med*. **2015**, 15, 60. doi: 10.1186/s12906-015-0572-0.
[2] A Finkelsztejn. *Perspect Med Chem*. **2014**, 6, 65-72.
[3] A Minagar. *Scientifica*. **2013**, 249101. doi: 10.1155/2013/249101.
[4] Castro-Borrero W, Graves D, Frohman TC, Flores AB, Hardeman P, Logan D, M Orchard, B Greenberg, EM Frohman. *Ther Adv Neurol Disord*. **2012**, 5(4), 205-20. doi: 10.1177/1756285612450936.
[5] DA Hafler, HL Weiner. *Immunol Rev*. **1987**, 100(1), 307-32.
[6] DC Wraith, KS Nicolson, NT Whitley. *Curr Opin Immunol*. **2004**, 16(6), 695-701.
[7] H Park, Z Li, XO Yang, SH Chang, R Nurieva, Y-H Wang, Y Wang, L Hood, Z Zhu, Q Tian, C Dong. *Nat Immunol*. **2005**, 6(11), 1133-41.
[8] XO Yang, BP Pappu, R Nurieva, A Akimzhanov, HS Kang, Y Chung, L Ma, B Shah, AD Panopoulos, KS Schluns, SS Watowich, Q Tian, AM Jetten, C Dong. *Immunity*. **2008**, 28(1), 29-39.
[9] S Sakaguchi, M Ono, R Setoguchi, H Yagi, S Hori, Z Fehervari, J Shimizu, T Takahashi, T Nomura. *Immunol Rev*. **2006**, 212(1), 8-27.
[10] E Corsini, M Oukka, R Pieters, NI Kerkvliet, R Ponce, DR Germolec. *J Immunotoxicol*. **2011**, 8(4), 251-7.
[11] J Goverman. *Nat Rev Immunol*. **2009**, 9(6), 393-407.
[12] J Reddy, H Waldner, X Zhang, Z Illes, KW Wucherpfennig, RA Sobel, VK Kuchroo. *J Immunol*. **2005**, 175(9), 5591-5.
[13] H Batoulis, K Addicks, S Kuerten. *Ann Anat*. **2010**, 192(4), 179-93.
[14] A Mohsenzadeh, Sh Ahmadipour, S Ahmadipour, M Asadi-Samani. *Der Pharm Lettre*. **2016**, 8(1), 129-34.
[15] A Mohsenzadeh, Sh Ahmadipour, S Ahmadipour, M Asadi-Samani. *Der Pharm Lettre*. **2016**, 8(1), 90-6.
[16] S Ahmadipour, Sh Ahmadipour, A Mohsenzadeh, M Asadi-Samani. *Der Pharm Lettre*. **2016**, 8(1), 61-6.
[17] M Asadi-Samani, M Bahmani, M Rafieian-Kopaei. *Asian Pac J Trop Med*. **2014**, 7(Suppl 1), 22-8.
[18] M Asadi-Samani, N Kafash-Farkhad, N Azimi, A Fasihi, E Alinia-Ahandani, M Rafieian-Kopaei. *Asian Pac J Trop Biomed*. **2015**, 5(2), 146-57.
[19] M Asadi-Samani, M Rafieian-Kopaei, N Azimi. Pak J Biol Sci. **2013**, 16, 1238-47.
[20] W Kooti, M Ghasemiboroon, M Asadi-Samani, Ahangarpoor A, M Noori Ahmad Abadi, R Afrisham, N Dashti. *Adv Environ Biol*. **2014**, 8(9), 325-30.
[21] K Ghatreh Samani, E Farrokhi, N Mohandes Samani. *J Zanjan Univ Med Sci*. **2014**, 23(97), 103-11.
[22] T Ghanavati, K Ghatreh-Samani, E Farrokhi, E Heydarian, M Nikookar. *J Mazandaran Univ Med Sci*. **2015**, 25(129), 17-25.
[23] MR Tamadon, A Baradaran, M Rafieian-Kopaei. *J Renal Inj Prev*. **2014**, 3(2), 41-2.
[24] A Asgari. *J Nephropharmacol*. **2014**, 3(1), 5-6.

[25] MR Tamadon, M Zahmatkesh. *J Parathyr Dis*. **2015**, 3(2), 34-6.
[26] Z Rabiei, MR Bigdeli, M Asadi-Samani. *Zanjan Univ Med Sci J*. **2013**, 21(86), 56-64.
[27] M Asadi-Samani, W Kooti, E Aslani, H Shirzad. *J Evid Based Complementary Altern Med*. **2015**. PubMed PMID: 26297173.
[28] M Bahmani, A Sarrafchi, H Shirzad, M Rafieian-Kopaei. *Curr Pharm Des*. **2016**, 22(3), 277-85. doi: 10.2174/1381612822666151112151529.
[29] A Sarrafchi, M Bahmani, H Shirzad, M Rafieian-Kopaei. *Curr Pharm Des*. **2016**, 22(2), 238-46. doi: 10.2174/1381612822666151112151653 .
[30] E Shayganni, M Bahmani, S Asgary, M Rafieian-Kopaei. *Phytomedicine*. **2015**. doi: 10.1016/j.phymed.2015.11.004.
[31] M Rafieian-Kopaei, M Setorki, M Doudi, A Baradaran, H Nasri. *Int J Prev Med*. **2014**, 5, 927-46.
[32] M Mirhosseini, A Baradaran, M Rafieian-Kopaei. *J Res Med Sci*. **2014**, 19, 758-61
[33] M Rafieian-Kopaei, N Shahinfard, H Rouhi-Boroujeni, M Gharipour, P Darvishzadeh-Boroujeni. *Evid Based Complement Alternat Med*. **2014**. Doi: 10.1155/2014/680856.
[34] Z Rabiei, M Rafieian-kopaei, E Heidarian, E Saghaei, S Mokhtari. *Neurochem Res*. **2014**, 39(2), 353-60.
[35] R Nosratabadi, M Rastin, M Sankian, D Haghmorad, N Tabasi, S Zamani, A Aghaee, Z Salehipour, M Mahmoudi. *J Immunotoxicol*. **2015**, 1-11.
[36] TB Alberti, R Marcon, MA Bicca, NR Raposo, JB Calixto, RC Dutra. *J Ethnopharmacol*. **2014**, 155(1), 485-94.
[37] R Lodha, A Bagga. *Ann Acad Med*. **2000**, 29(1), 37-41.
[38] R Srimal, B Dhawan. *J Pharm Pharmacol*. **1973**, 25(6), 447-52.
[39] C Araujo, L Leon. *Mem Inst Oswaldo Cruz*. **2001**, 96(5), 723-8.
[40] P Claeson, A Panthong, P Tuchinda, V Reutrakul, D Kanjanapothi, W Taylor, T Santisuk. *Planta Med*. **1993**,59(5), 451-4.
[41] S Kanakasabai, E Casalini, CC Walline, C Mo, W Chearwae, JJ Bright. *J Nutr Biochem*. **2012**, 23(11), 1498-507.
[42] Z Wang, J Zhang, Y Wang, R Xing, C Yi, H Zhu, X Chen, J Guo, W Guo, W Li, L Wu, Y Lu, S Liu. *Carcinogenesis*. **2013**, 34(1), 128-38.
[43] N Liu, Q-c Kan, X-j Zhang, Y-m Xv, S Zhang, G-X Zhang, L Zhu. *Exp Molr Pathol*. **2014**, 97(3), 470-6.
[44] J-p Liu, L Feng, M-h Zhang, D-y Ma, S-y Wang, J Gu, Q Fu, R Qu, SP Ma. *J Ethnopharmacol*. **2013**, 150(1), 371-81.
[45] Y Fan, P Wang, X Zhang, H Gong, L Zhou, X Liu, L Wang. *Chin J Trad Chin Med Pharm*. **2007**, 22(1), 25-9.
[46] Y Fan, P Wang, X Zhang. *J Beijing Univ Trad Chin Med*. **2006**, 29(4), 273.
[47] J-W Park, B-W Lee, J-U Baek. *J Korean Med Classics*. **2012**, 25(1), 17-29.
[48] JH Choi, MJ Lee, M Jang, E-J Kim, I Shim, H-J Kim, S Lee, SW Lee, YO Kim, IH Cho. *PloS one*. **2015**, 10(10), e0138592.
[49] J Reddy, Z Illes, X Zhang, J Encinas, J Pyrdol, L Nicholson, RA Sobel, KW Wucherpfennig, VK Kuchroo. *Proc Nat Acad Sci U S A*. **2004**;101(43), 15434-9.
[50] X Qin, BT Guo, B Wan, L Fang, L Lu, L Wu, YQ Zang, JZ Zhang. *J Immunol*. **2010**, 185(3), 1855-63.
[51] P Gaur, GA Qadir, S Upadhyay, AK Singh, NK Shukla, SN Das. *Cell Oncol*. **2012**, 35(5), 335-43.
[52] M Bahmani, A Zargaran, M Rafieian-Kopaei. *Rev Bras Farmacogn*. **2014**, 24(4), 468-80.
[53] G Rahimian, MH Sanei, H Shirzad, F Azadegan-Dehkordi, A Taghikhani, L Salimzadeh, M Hashemzadeh-Chaleshtori, M Rafieian-Kopaei, N Bagheri. *Microb Pathog*. **2014**, 67-68, 1-7. doi: 10.1016/j.micpath.2013.12.006.
[54] M Bahmani, Z Eftekhari, K Saki, E Fazeli-Moghadam, M Jelodari, M Rafieian-Kopaei. *J Evid Based Complementary Altern Med*. **2015**. pii: 2156587215599105.
[55] M Bahmani, H Shirzad, M Mirhosseini, A Mesripour, M Rafieian-Kopaei. *J Evid Based Complementary Altern Med*. **2015**. pii: 2156587215583405.
[56] M Ebrahimie, M Bahmani, H Shirzad, M Rafieian-Kopaei, K Saki. *J Evid Based Complementary Altern Med*. **2015**, 20(4), 302-9. doi: 10.1177/2156587215577896.
[57] A Azadmehr, R Hajiaghaee, A Afshari, Z Amirghofran, M Refieian-Kopaei, H Yousofi Darani, H Shirzad. *J Med Plants Res*. **2011**, 5(11), 2365-8.
[58] S Asgary, A Sahebkar, M Afshani, M Keshvari. *Phytother Res*. **2013**. doi: 10.1002/ptr.4977.
[59] S Asgary, R Kelishadi, M Rafieian-Kopaei, S Najafi, M Najafi, A Sahebkar. *Pediatr Cardiol*. **2013**, 34(7), 1729-35. doi: 10.1007/s00246-013-0693-5.
[60] A Khoshdel, F Famuri, E Keivani, M Lotfizadeh, KA Kasiri, M Rafieian. *J Herbmed Pharmacol*. **2014**, 3(1), 53-56.
[61] M Kafeshani. *Renal Endocrinol*. **2015**, 1, e04.
[62] E Heidarian, G Movahed-Mohammadi, J Saffari, K Ghatreh-Samani. *J Mazandaran Univ Med Sci*. **2013**, 23(102), 78-90.
[63] S Brahmachari, K Pahan. *J Immunol*. **2010**, 184(4), 1799-809.

[64] M Koutrolos, K Berer, N Kawakami, H Wekerle, G Krishnamoorthy. *Acta Neuropathol Commu*. **2014**, 2(1), 163.
[65] M Oukka. *Ann Rheum Dis*. **2007**, 66(Suppl 3), 87.
[66] R Zhang, A Tian, H Zhang, Z Zhou, H Yu, L Chen. *J Mol Neurosci*. **2011**, 44(1), 31-40.
[67] M Rafieian-Kopaei, A Baradaran, M Rafieian. *J Nephropathol*. **2013**, 2(2), 152-3.
[68] S Khodadadi. *Immunopathol Persa*. **2015**, 1(1), e01.
[69] H Nasri. *J Prev Epidemiol*. **2016**, 1, e01.
[70] A Baradaran. *Angiol Persica Acta*. **2016**, 1(1), e01.
[71] W Kooti, A Ahangarpoor, M Ghasemiboroon, S Sadeghnezhadi, Z Abbasi, Shanaki Z, Z Hasanzadeh-Noohi, M Asadi-Samani. *J Babol Univ Med Sci*. **2014**, 16 (11), 44-50.
[72] A Beyrami-Miavagi, F Farokhi, M Asadi-Samani. *Adv Environ Biol*. **2014**, 8(9), 942-7.