Send Orders for Reprints to reprints@benthamscience.net

Current Cancer Therapy Reviews, XXXX, *XX,* 1-11

RESEARCH ARTICLE

Preventive Effects of *Achillea Millefolium*, *Rosa Damascena* and *Origanum Majorana* Hydroalcoholic Extracts on Breast Cancer in Female Mice

Fariba Nabatchian[1,#], Mojtaba Ashtiani[1,#] , Amir Teimourpour[2], Negin Davoudi[3], Sara Niknam[4] and Reza Afrisham[1,*]

[1]*Department of Clinical Laboratory Sciences, Faculty of Allied Medicine, Tehran University of Medical Sciences, Tehran, Iran;* [2]*Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran;* [3]*Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran;* [4]*Department of Clinical Biochemistry, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*

Abstracts: ***Introduction*:** Breast cancer is overall considered the second most frequently recognized cancer worldwide. Several studies have recently reported the antitumoral properties of some medicinal herbs such as Yarrow (*Achillea millefolium*), Marjoram (*Origanum majorana*), and Rose (*Rosa damascena Mill L*). Therefore, the current study aimed to evaluate the effect of the hydroalcoholic extract of these plants on breast cancer prevention in female mice.

***Methods*:** Mice were classified into five ten-mice groups: normal control (untreated group), tumor group (treated with 4T1 cells), and treatment groups (treated with 4T1 cells+ Yarrow or Rose and Marjoram plants). Then, the levels of cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA), superoxide dismutase (SOD), and total antioxidants were determined. Finally, the tumor size was evaluated.

***Results*:** The hydroalcoholic extract of Yarrow herb significantly decreased the levels of CA-15-3 and CEA (*P*-value = 0.008 and *P*-value = 0.018, respectively). In addition, hydroalcoholic extracts of Yarrow, Rose, and Marjoram plants significantly reduced tumor size in comparison with the tumor group (*P*-value < 0.001 for Yarrow, and *P*-value = 0.004 for Rose and Marjoram plants). Yarrow herb had the significantly highest effect on tumor size in comparison with Rose and Marjoram plants (*P*-value = 0.011 for both plants). However, no significant differences were found among the groups treated with the plants in comparison with the tumor mice in terms of SOD and total antioxidants (*P*-value > 0.05).

***Conclusion*:** Our findings revealed that *A. millefolium* had the greatest antitumor effects on mice with breast cancer in comparison with *O. majorana* and *R. damascena* herbs. However, more complementary studies are needed in this regard.

ARTICLE HISTORY

Received: April 28, 2022
Revised: October 19, 2022
Accepted: November 11, 2022

DOI:
10.2174/1573394719666221228110443

Keywords: Breast cancer, hydroalcoholic extract, herbal medicine, marjoram, rose, yarrow.

1. INTRODUCTION

Cancer disease is a major health concern in modern societies [1] and breast cancer is overall regarded as the second most frequently recognized cancer worldwide. More importantly, this type of cancer commonly affects the female population [2]. There has recently been an increasing interest in the application of dietary derived compounds and phytochemicals for cancer prevention and treatment [3, 4]. In this regard, several phytochemicals have extensively shown antitumoral properties *in vivo* and *in vitro* [4-8]. For example, researchers have reported that *Patrinia scabiosaefolia* stimulated the death of human renal cell carcinoma 786-O cells *via* mTOR and SIRT-1 signaling, which provided a novel insight into the application of natural extracts for cancer therapy [9]. Besides, Trametes robiniophila Murr(Huaier) polysaccharide showed anticancer influences against clear cell renal cell carcinoma [10]. It is noted that some phytochemicals obtained from natural origins, such as camptothecin and taxol, are highly applied in clinics to treat cancers [11, 12]. However, breast tumors remain one of the most resistant [2].

In the last years, several studies have reported the antitumoral properties of some medicinal herbs such as Yarrow (*Achillea millefolium*), Marjoram (*Origanum majorana*), and Rose (*Rosa damascena Mill L*) [13-15]. *A. millefolium* is a natural remedy that is considered a major medicinal herb for several centuries to treat bleeding, headache, inflammation, wounds, gastrointestinal disorders,

*Address correspondence to this author at the Department of Clinical Laboratory Sciences, Faculty of Allied Medicine, Tehran University of Medical Sciences, Tehran, Iran; E-mail: rafrisham@sina.tums.ac.ir;
Tel: +982164432369
[#]*These authors contributed equally to this work.*

1573-3947/XX $58.00+.00

and pains [16, 17]. Nowadays, many investigations have established strong antioxidants [17], wound healing [18], anti-inflammatory [19], skin lightening [20], and skin rejuvenating [21] potential of *A. millefolium* hydro-alcoholic or alcoholic extracts. Moreover, it has antimicrobial, antibacterial, immunological, antiplatelet, and anti-proliferative activity [22]. Another plant is *O. majorana* commonly known as marjoram [23]. This herb is primarily distributed in the Mediterranean areas and belongs to the family of Lamiaceae [23]. Its leaves are applied to treat asthma, insomnia, nervousness, and gastritis [24]. Many investigations reported that marjoram revealed anti-microbial [25] and antitumor activity [26, 27] and inhibited platelet adhesion and aggregation [28]. Furthermore, it has been shown that this herb induced apoptosis, inhibited metastasis, migration and tumor growth as well as promoted mitotic arrest in breast cancer [26, 27].

On the other hand, *R. damascena* (Damask rose) is one of the most significant species of the Rosaceae family. This ornamental plant is mainly cultivated for application in perfumes and food industries [29]. Also, *R. damascena* is used to manufacture Iranian traditional medicine [15]. A number of isolated constituents and products from petals, flowers, and seeds of this plant have been investigated *in vitro* and *in vivo* [30]. This plant is mainly consumed to enhance the brain [31] and cardiovascular function [32] and is used as a gentle laxative [33] and cough reliever [34]. The anti-ageing, antimicrobial, antidiabetic [35], anti-HIV [36], anti-inflammatory [37], antitumoral [38-40] and antioxidant [41] activities of this herb have been well-documented.

However, the effect of *A. millefolium*, *R. damascena* and *O. majorana* plants on breast cancer remains unclear. To the best of our knowledge, no studies have compared the preventive effects of these plants on breast cancer in female mice. Hence, the aim of the current study was to evaluate the effect of hydroalcoholic extract of Yarrow, Rose, and Marjoram plants on breast cancer prevention in female mice.

2. METHODS

2.1. Cell Culture

Mouse mammary tumor (4T1 cell lines) was purchased from the Iranian Biological Resource Center (IBRC). Cells were cultured in RPMI 1640 medium supplemented with 10% FBS and 1%penicillin-streptomycin solution and then they were maintained at 37°C in a humidified atmosphere with 95% air and 5% CO_2. The culture medium was changed every 2-3 days, and cells were passaged with 0.25% trypsin/EDTA [42].

2.2. Animals and Treatments

Fifty female BALB/c mice, 5 weeks old and weighing 16-20 g, were obtained from the National Animal Center (Pasteur Institute of Karaj). In addition, the murine breast cancer cell line, 4T1, was purchased from the Pasteur Institute of Iran (Tehran, Iran). All the mice were housed in standard cages and maintained under standard conditions (35%-60% relative humidity; 23 ± 2ºC temperature; 12 h light/dark cycle). Before the treatments, the mice were randomly classified into five ten-mice groups:

Normal control (untreated group): Mice having undergone laboratory measurements without any treatment.

Tumor group: Mice treated with 100 µl of 4T1 cell suspension at a cell density of 2.5×10^5 cells/ml in 1× PBS in order to induce breast cancer (injected into the inguinal mammary fat pad subcutaneously).

Treatment group 1: Mice treated with 4T1 cells + the hydroalcoholic extract of *A. millefolium* (in the form of gavage) in a dose of 100 mg/Kg body weight.

Treatment group 2: Mice treated with 4T1 cells + the hydroalcoholic extract of *O. majorana* in a dose of 100 mg/Kg body weight.

Treatment group 3: Mice treated with 4T1 cells + the hydroalcoholic extract of *R. damascena* in a dose of 100 mg/Kg body weight.

The hydroalcoholic extract of all three plants was used for 2 months (daily). After one month, 100 µl of 4T1 cell suspension at a cell density of 2.5×10^5 cells/ml in 1× PBS was applied to induce breast cancer. After one month, all mice were anesthetized and blood samples were taken from them. In the next stage, blood samples were centrifuged at 2000×g for 7 min for the isolation of serum and finally, serum samples were kept at -70°C until future examination.

2.3. Preparation of Hydroalcoholic Extraction

The Yarrow (*Achillea millefolium*), Marjoram (*Origanum majorana*), and Rose (*Rosa damascena*) herbals were taken from the Faculty of Agriculture, University of Tehran, Tehran, Iran. The plants were approved by a registered pharmacologist as *Achillea millefolium*, *Rosa damascena,* and *Origanum majorana*. The hydro-alcoholic extract of three plants was prepared by the maceration protocol. Maceration is a liquid-solid separation method, with water and an organic solvent as the liquid phase. Water, ethanol, and methanol, or a mixture of these solvents were applied for the isolation of phenolic compounds [43]. At first, 120 grams of the powdered herbal was soaked in 600 mL of 70% ethanol and stirred intermittently for two days at 25 ^{o}C. In the next stage, the solution was passed through Whatman's filter paper. Finally, the filtered extract was fed to a rotary evaporator for drying. The extract was kept at a temperature of -20°C until further analyses [44].

2.4. Measurement of Biochemical Parameters in Serum

Initially, tumor markers of cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) were measured using the chemiluminescence method according to Nima Pouyesh Teb Co. Ltd., kit instructions (Tehran, Iran). Then, superoxide dismutase (SOD) levels were determined based on Navand Salamat kit instructions (no. TAC-az22, Urmia, Iran). In addition, total antioxidants were measured using the high-performance liquid chromatography (HPLC) technique according to Navand Salamat kit (no. NS-15032, Urmia, Iran) following the manufacturer's instructions. Finally, the tumor size was determined using a manual caliper twice a week [45].

2.5. Statistical Analysis

Descriptive statistics including mean ± SD, first, second and third quartile along with minimum and maximum are reported for each treatment. In order to compare measured criteria, including CA15.3, CEA, SOD, total antioxidants and tumor size, a One-way ANOVA procedure was performed. In cases where One-way ANOVA assumptions (homogeneity of variance, Normality of Errors) were violated, the Kruskal-Wallis test was used. Pairwise comparison was conducted by independent samples t-test or Wilcoxon sum rank test with a false discovery rate adjustment. All statistical analyses were performed using the R software version 4.0.5 and P-value < 0.05 was considered statistically significant.

3. RESULTS

Table **1** demonstrates the effect of hydroalcoholic extracts of Yarrow, Rose, and Marjoram plants on the variables measured in female mice. Moreover, (Figs. **1**-**5**) indicate the effect of hydroalcoholic extracts of Yarrow, Rose, and Marjoram plants on the factors of CA15-3, CEA, SOD, total antioxidants, and tumor size, respectively. Based on (Figs. **1** and **2**), CA15-3 and CEA levels were significantly elevated in the tumor group in comparison with the untreated mice, respectively. However, the hydroalcoholic extracts of all three plants alleviated the levels of CA-15-3 and CEA in comparison with the tumor group but only the Yarrow herb significantly decreased the levels of these tumor markers (P-value = 0.008 for CA-15-3, P-value = 0.018 for CEA). In addition, another finding showed that hydroalcoholic extracts of Yarrow, Rose, and Marjoram plants significantly reduced tumor size in comparison with the tumor group (P-value<0.001 for Yarrow, P-value = 0.004 for Rose and Marjoram plants). More importantly, the Yarrow herb had the significantly highest impact on tumor size in comparison with the other plants (P-value = 0.011 for both plants).

Table1. The effect of hydroalcoholic extracts of Yarrow, Rose and Marjoram plants on the variables related to breast cancer (tumor markers and tumor size) and antioxidant factors in female mice. CA 15-3: Cancer antigen 15-3, CEA: Carcinoembryonic antigen, SOD: Superoxide dismutase, SD: Standard deviation, Min: Minimum, Max: Maximum.

Criterion	Treatments	Mean	SD	Min	Q1	Median	Q3	Max	*P*-value
CA15.3 (U/ml)	Yarrow	7.660	2.418	4.20	5.775	7.750	8.550	12.20	0.017
	Marjoram	8.530	4.445	3.60	4.400	7.450	12.475	14.90	
	Rose	7.660	5.023	3.40	3.900	5.800	10.150	16.30	
	Tumor	12.000	1.810	9.60	10.900	11.500	12.575	15.30	
	Healthy	7.337	0.124	7.17	7.222	7.385	7.425	7.51	
CEA (ng/ml)	Yarrow	0.174	0.063	0.112	0.128	0.154	0.191	0.314	0.012
	Marjoram	0.318	0.169	0.124	0.176	0.300	0.433	0.618	
	Rose	0.270	0.185	0.124	0.145	0.206	0.335	0.712	
	Tumor	0.357	0.136	0.000	0.353	0.392	0.418	0.486	
	Healthy	0.179	0.007	0.165	0.178	0.180	0.183	0.186	
SOD (U/ml)	Yarrow	91.21	45.162	21.6	54.975	98.25	118.775	169.4	0.003
	Marjoram	47.80	22.575	12.3	28.500	49.70	65.450	74.6	
	Rose	67.31	29.277	32.6	42.375	65.60	80.450	125.9	
	Tumor	62.52	24.471	25.3	45.575	61.15	73.750	106.5	
	Healthy	90.38	4.675	79.3	89.425	91.30	93.475	95.6	
Total Antioxidants mmol/L	Yarrow	591.9	278.167	129	395.00	597.5	794.25	984	0.17
	Marjoram	658.1	317.144	129	434.00	730.5	914.50	1025	
	Rose	726.8	228.683	254	654.75	739.5	882.25	984	
	Tumor	503.2	330.976	122	265.25	403.5	786.50	1012	
	Healthy	857.6	42.568	754	849.25	866.5	872.75	923	
Tumor size mm^3	Yarrow	165.11	99.376	100.8	106.175	120.20	192.075	410.6	<0.001
	Marjoram	302.53	141.503	118.4	212.475	245.65	412.750	541.9	
	Rose	332.81	211.404	126.8	177.550	317.35	391.350	845.6	
	Tumor	477.07	9.285	451.9	476.750	479.20	482.150	483.9	

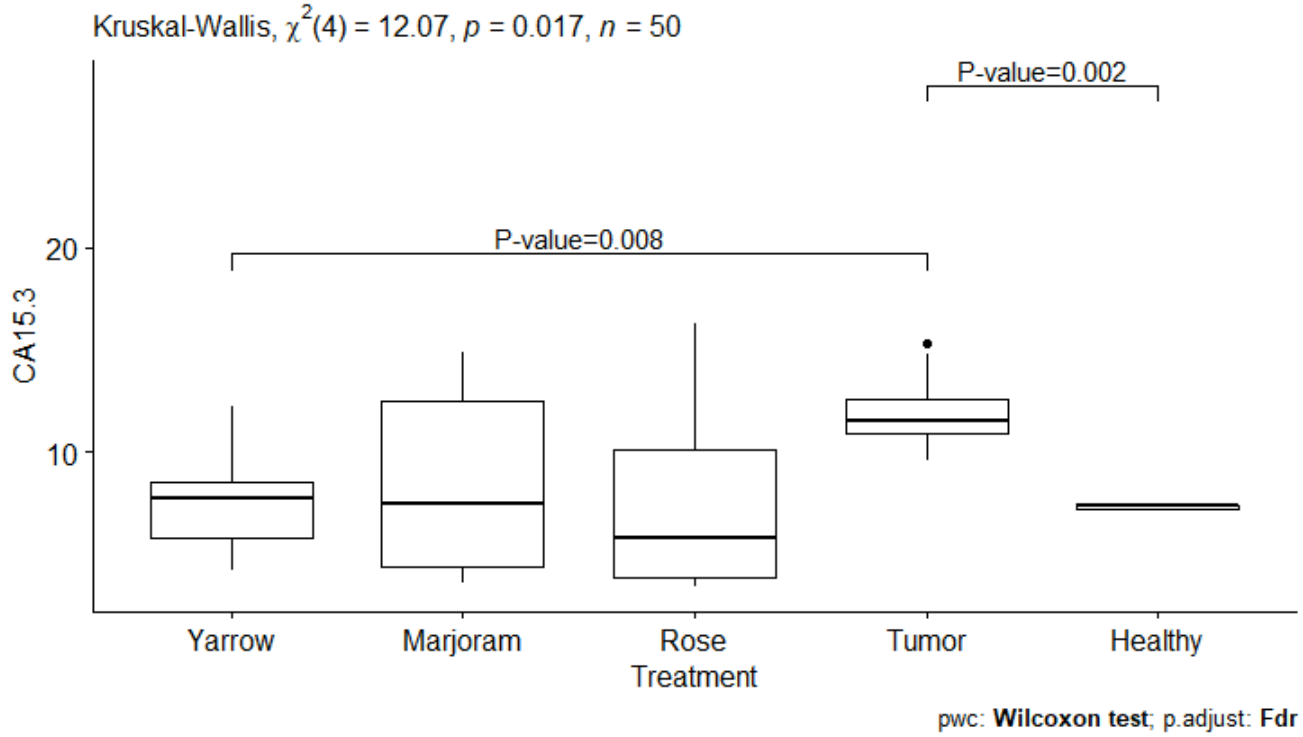

Fig. (1). Comparison of the effect of hydroalcoholic extracts of Yarrow, Rose and Marjoram plants on tumor marker of cancer antigen 15-3 (CA15-3, U/ml) in female mice with breast cancer. CA15-3 levels were significantly elevated in the tumor group in comparison with the untreated mice (*P*-value = 0.002). The hydroalcoholic extract of Yarrow herb significantly decreased the levels of CA15-3 (*P*-value = 0.008).

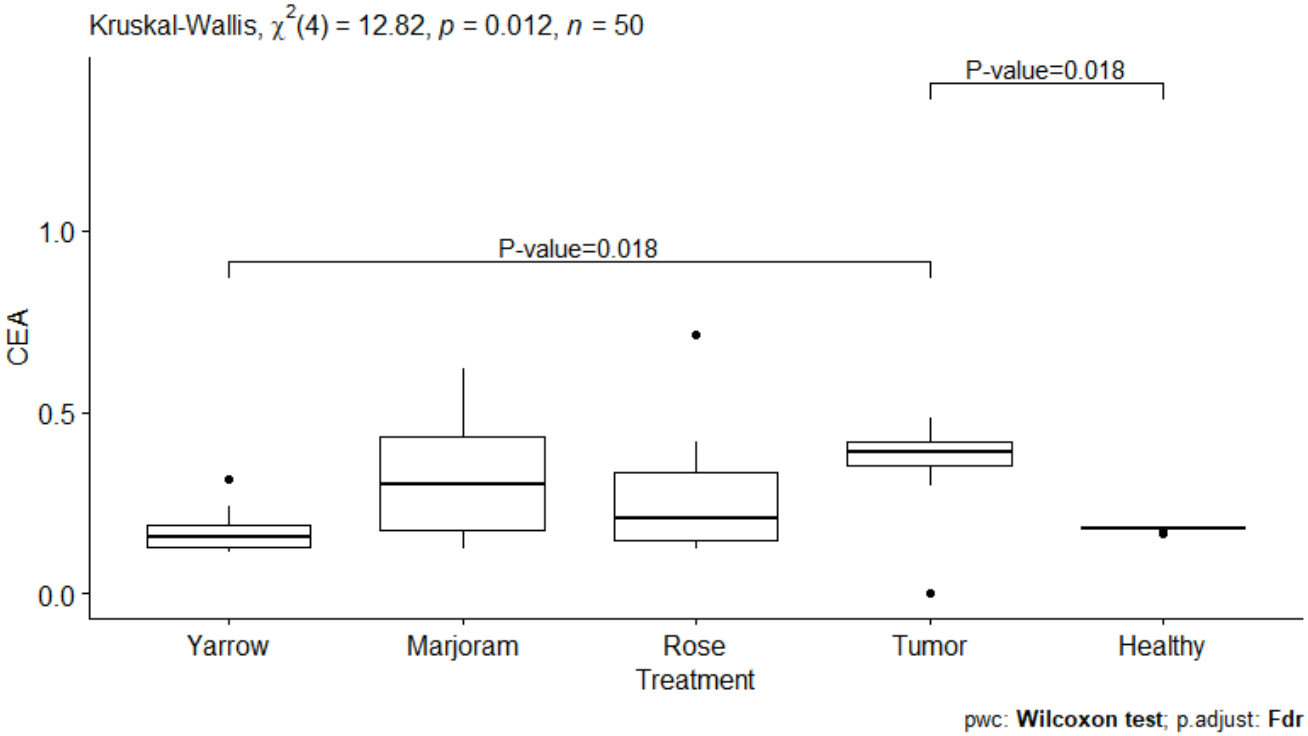

Fig. (2). Comparison of the effect of hydroalcoholic extracts of Yarrow, Rose and Marjoram plants on tumor marker of carcinoembryonic antigen (CEA, ng/ml) in female mice with breast cancer. CEA levels were significantly elevated in the tumor group in comparison with the untreated mice (*P*-value = 0.018). The hydroalcoholic extract of Yarrow herb significantly reduced the levels of CEA (*P*-value = 0.018).

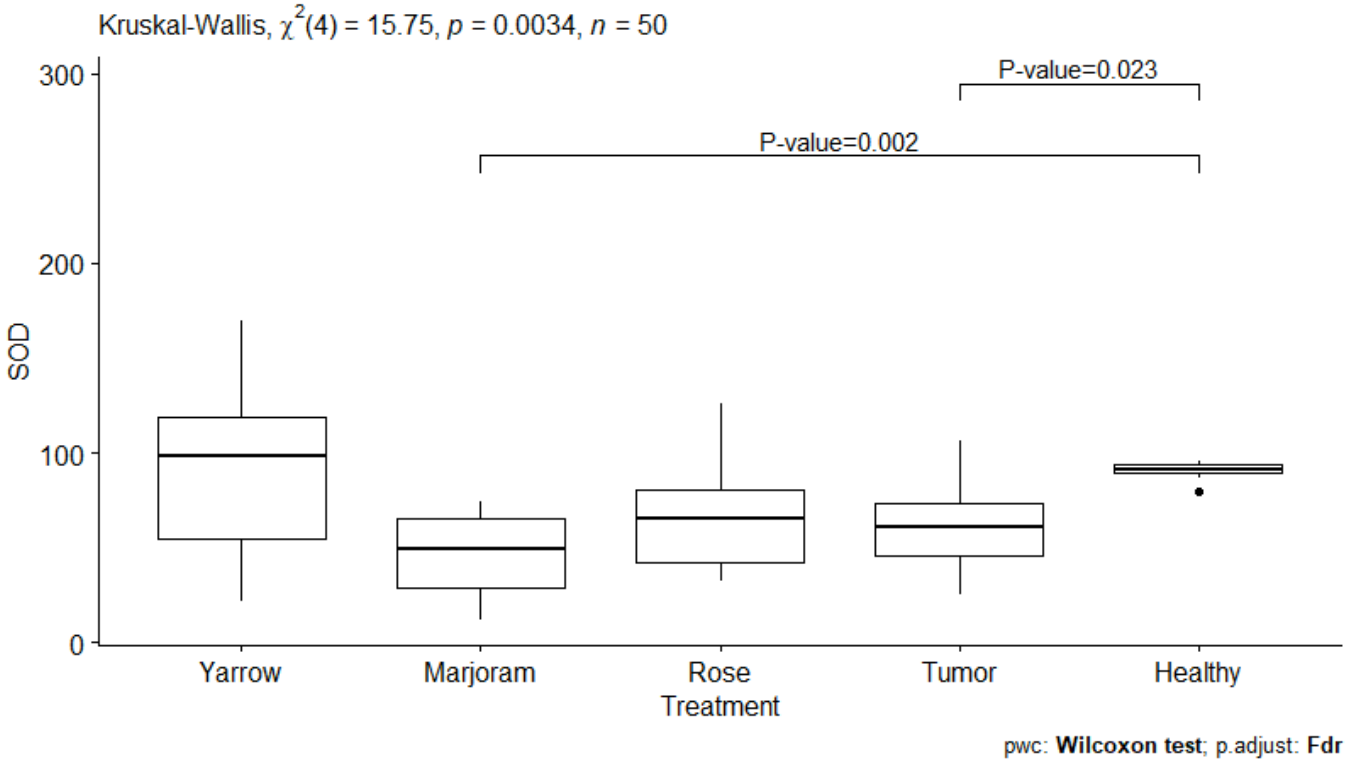

Fig. (3). Comparison of the effect of hydroalcoholic extracts of Yarrow, Rose and Marjoram plants on superoxide dismutase (SOD, IU/mg protein) in female mice with breast cancer. SOD levels were significantly reduced in the tumor group in comparison with the untreated mice (*P*-value = 0.023). No significant differences were found among the groups treated with the plants in comparison with the tumor mice in term of SOD (*P*-value>0.05).

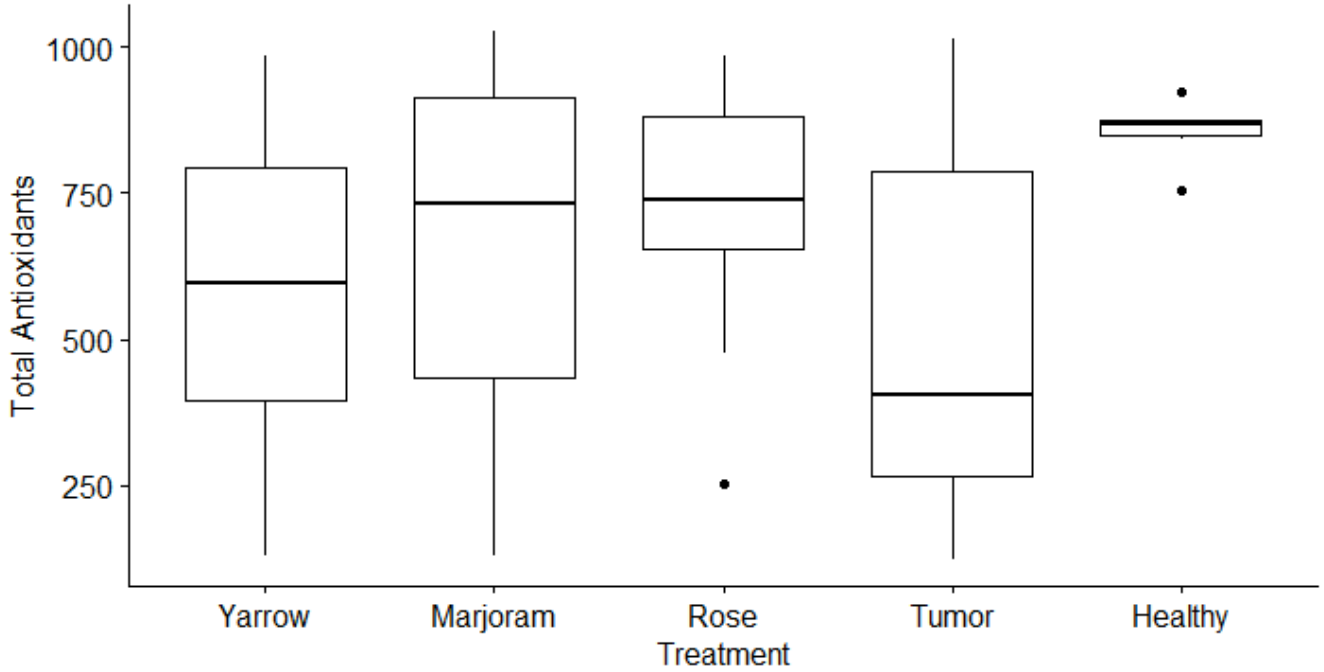

Fig. (4). Comparison of the effect of hydroalcoholic extracts of Yarrow, Rose and Marjoram plants on total antioxidants (mmol/L) in female mice with breast cancer. No significant differences were found among the groups treated with the plants in comparison with the tumor mice in term of total antioxidants (*P*-value>0.05).

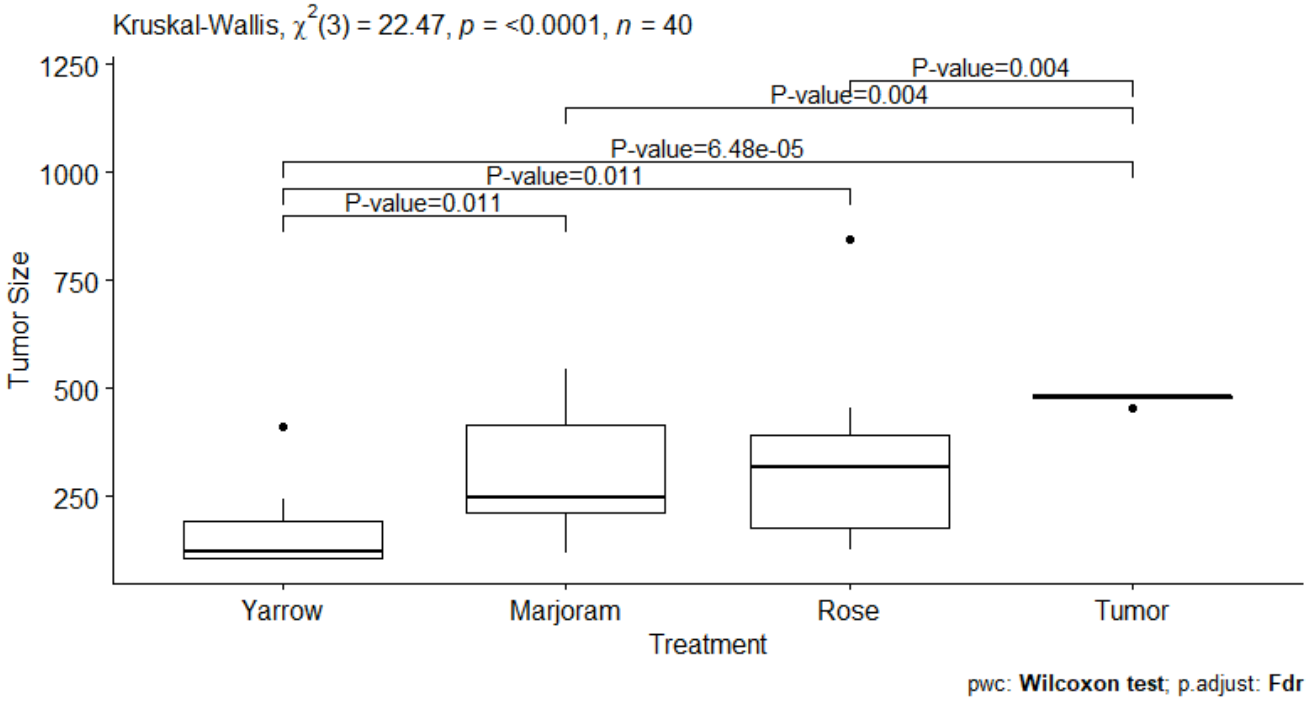

Fig. (5). Comparison of the effect of hydroalcoholic extracts of Yarrow, Rose and Marjoram plants on tumor size in female mice with breast cancer. Hydroalcoholic extracts of Yarrow, Rose and Marjoram plants significantly reduced tumor size in comparison with the tumor group (*P*-value<0.001 for Yarrow, *P*-value = 0.004 for Rose and Marjoram plants). Yarrow herb significantly had the highest effect on tumor size in comparison with the other plants (*P*-value = 0.011 for both the plants).

However, despite the great effects of these herbs on SOD and total antioxidants, no significant differences were found among the groups treated with the plants in comparison with the tumor mice in terms of SOD and total antioxidants (*P*-value > 0.05).

4. DISCUSSION

Nowadays, despite advancements in manufacturing synthetic drugs, there is a growing tendency in the use of herbal treatments because of their limited side effects, high efficacy, reasonable price, and easy access [46]. To the best of our knowledge, no studies have compared the preventive effects of *A. millefolium*, *O. majorana* and *R. damascena* herbs on breast cancer in female mice. Therefore, in the current study, we compared the preventive effect of hydroalcoholic extracts of these herbs on breast cancer in female mice for the first time.

The results of the present study showed that the hydroalcoholic extract of *A. millefolium* herb significantly decreased the levels of CA-15-3 and CEA. In addition, hydroalcoholic extracts of *A. millefolium*, *R. damascena,* and *O. majorana* plants significantly reduced tumor size in comparison with the tumor group. *A. millefolium* herb had a significantly high impact on tumor size in comparison with *R. damascena* and *O. majorana* plants. Some of the findings in this study are in line with those conducted earlier. For example, Ghavami *et al.* [47] investigated the cytotoxic activities of *A. millefolium* herb on breast cancer cells *in vitro* (MCF-7 cells). They showed that this plant had a cytotoxic effect against MCF-7 cells with IC50 = 64.058 µg/mL after 24 h incubation. In another study, cytotoxic effects of aqueous, aqueous-methanol, N-hexane, and chloroform extracts of the aerial parts of this herb on MCF-7 cell lines were reported [48]. These effects are probably related to the phytochemical profile of *A. millefolium* that is primarily characterized by the presence of apigenin flavonoid glycosides, rutin, rosmarinic, luteolin as well as chlorogenic acid and its caffeoylquinic derivatives [49-51].

On the other hand, Dhaheri *et al.* [27] in 2013 evaluated the effect of *O. majorana* on the proliferation, invasion, and migration of breast cancer cells *in vitro* (MDA-MB-231 cells). They showed that non-cytotoxic doses of this plant significantly inhibited tumor growth as well as the invasion and migration of breast cancer cells through suppressing vascular endothelial growth factor (VEGF) as well as the activities of matrix metalloproteinase-9 and -2 (MMP-9 and MMP-2). It has also been established that *O. majorana* can result in the hyperacetylation of histone H4 and H3 [26]. In addition, this herb consists of a dietary flavonoid (luteolin) that can inhibit histone deacetylase activity, leading to the suppression of inversion [27]. In another study, Dhaheri *et al.* [26] showed that *O. majorana* enhanced apoptosis through the extrinsic pathway, including the activation of caspase 3, caspase 8, tumor necrosis factor-a (TNF-α), depletion of the mutant p53 and downregulation of survivin in MDA-MB-231 cells [26]. In line with our studies, a few studies revealed that *R. damascena* oils and extracts induced cytotoxic effects against some tumor cells *in vitro* [38-40]. Furthermore, Hagag *et al.* in 2014 [52] reported that *R. damascena* had antitumor potential against both HepG2 and breast tumor cells (MCF-7). Moreover, other studies have

shown cytotoxic activities of the essential oil of this herb against human lungs, prostate, and MCF-7 [53]. In addition to breast cancer, Al-Oqail *et al.* [15] in 2021 revealed that the methanolic extract of Rose at 100 µg/ml and larger inhibited the cell viability of human cervical cancer HeLa Cells.

We also found that despite the increasing influences of *A. millefolium*, *R. damascena,* and *O. majorana* plants on SOD and total antioxidants**,** no significant differences were found among the groups treated with the plants in comparison with the tumor mice regarding SOD and total antioxidants. However, several studies have reported the antioxidant properties of these traditional herbs [17, 25-27, 41]. In addition, two studies approved that R. damascena can reduce oxidative stress injuries and improve antioxidant capacity in rats receiving CdC_{l2}. These properties are related to rich antioxidant content like Apigenin, Gallic acid, quercetin, and phenolic compounds [54, 55]. The differences between our study and others may be related to the smaller sample size in mice groups and the duration of intervention. Another limitation of the current study was the lack of evaluating signaling pathways associated with breast cancer. For this reason, it is recommended that future researchers investigate how *A. millefolium* and even *R. damascena* and *O. majorana* could affect breast tumors.

CONCLUSION

In the current study, we compared the preventive effect of hydroalcoholic extracts of *Achillea millefolium* (Yarrow), *Origanum majorana* (Marjoram), and *Rosa damascena* (Rose) herbs on breast cancer in female mice for the first time. Our findings revealed that the hydroalcoholic extracts of all three plants significantly reduced tumor size in comparison with the tumor group. More importantly, the Yarrow herb had the highest antitumor effects on mice with breast cancer in comparison with the other herbs. However, more complementary studies are needed in this regard.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocols were carried out in compliance with the Declaration of Helsinki and were approved by the Ethics Committee of Tehran University of Medical Sciences (with IR.TUMS.SPH.REC.1400.123 code).

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author [RA], upon reasonable request.

FUNDING

The current study was funded by the Tehran University of Medical Sciences, Tehran, Iran with the code 99-3-102-50337.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGMENTS

The current paper is taken from the research project with the code 99-3-102-50337, so we would like to thank the Tehran University of Medical Sciences, Tehran, Iran for the funding support.

REFERENCES

[1] Liaudanskas M, Žvikas V, Petrikaitė V. The potential of dietary antioxidants from a series of plant extracts as anticancer agents against melanoma, glioblastoma, and breast cancer. Antioxidants 2021; 10(7): 1115. http://dx.doi.org/10.3390/antiox10071115 PMID: 34356348

[2] Sadegh-Nejadi S, Afrisham R, Emamgholipour S, *et al.* Influence of plasma circulating exosomes obtained from obese women on tumorigenesis and tamoxifen resistance in MCF ‐7 cells. IUBMB Life 2020; 72(9): 1930-40. http://dx.doi.org/10.1002/iub.2305 PMID: 32542981

[3] Surh YJ. Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer 2003; 3(10): 768-80. http://dx.doi.org/10.1038/nrc1189 PMID: 14570043

[4] Mouhid L. Improving *in vivo* efficacy of bioactive molecules: An overview of potentially antitumor phytochemicals and currently available lipid-based delivery systems. J Oncol 2017: 7351976.

[5] Kotecha R, Takami A, Espinoza JL. Dietary phytochemicals and cancer chemoprevention: A review of the clinical evidence. Oncotarget 2016; 7(32): 52517-29. http://dx.doi.org/10.18632/oncotarget.9593 PMID: 27232756

[6] González-Vallinas M, González-Castejón M, Rodríguez-Casado A, Ramírez de Molina A. Dietary phytochemicals in cancer prevention and therapy: A complementary approach with promising perspectives. Nutr Rev 2013; 71(9): 585-99. http://dx.doi.org/10.1111/nure.12051 PMID: 24032363

[7] Jokar F. Preparation of etoposide loaded poly butyl cyano acrylate nanoparticles and it's effect on human brain carcinoma cells BE (2)-C. Pharm Lett 2016; 8(16): 96-100.

[8] Sajjadiyan SZ. Preparation of silibinin loaded pegylatedniosomal nanoparticles and investigation of its effect on MCF-10A human breast cancer cell line. Pharm Lett 2016; 8(16): 70-5.

[9] Li Z, Tang Y, Zhu S, *et al.* Ethanol extract of Patrinia scabiosaefolia induces the death of human renal cell carcinoma 786-O cells *via* SIRT-1 and mTOR signaling-mediated metabolic disruptions. Oncol Rep 2018; 39(2): 764-72. PMID: 29251317

[10] Fang L, Zhang Y, Zang Y, *et al.* HP-1 inhibits the progression of ccRCC and enhances sunitinib therapeutic effects by suppressing EMT. Carbohydr Polym 2019; 223: 115109. http://dx.doi.org/10.1016/j.carbpol.2019.115109 PMID: 31427001

[11] Cragg GM, Newman DJ. Plants as a source of anti-cancer agents. J Ethnopharmacol 2005; 100(1-2): 72-9. http://dx.doi.org/10.1016/j.jep.2005.05.011 PMID: 16009521

[12] Ouyang L, Luo Y, Tian M, *et al.* Plant natural products: From traditional compounds to new emerging drugs in cancer therapy. Cell Prolif 2014; 47(6): 506-15. http://dx.doi.org/10.1111/cpr.12143 PMID: 25377084

[13] Mouhid L, Gómez de Cedrón M, García-Carrascosa E, Reglero G, Fornari T, Ramírez de Molina A. Yarrow supercritical extract exerts antitumoral properties by targeting lipid metabolism in pancreatic cancer. PLoS One 2019; 14(3): e0214294. http://dx.doi.org/10.1371/journal.pone.0214294 PMID: 30913248

[14] Athamneh K, Alneyadi A, Alsamri H, *et al. Origanum majorana* essential oil triggers p38 MAPK-mediated protective autophagy, apoptosis, and caspase-dependent cleavage of P70S6K in colorectal cancer cells. Biomolecules 2020; 10(3): 412. http://dx.doi.org/10.3390/biom10030412 PMID: 32155920

[15] Al-Oqail MM. Oxidative stress mediated cytotoxicity, cell cycle arrest, and apoptosis induced by *Rosa damascena* in human cervical cancer HeLa cells. Oxidative Medicine and Cellular Longevity 2021. http://dx.doi.org/10.1155/2021/6695634

[16] Gaweł-Bęben K, Strzępek-Gomółka M, Czop M, Sakipova Z, Głowniak K, Kukula-Koch W. *Achillea millefolium* L. and *Achillea biebersteinii* Afan. hydroglycolic extracts–bioactive ingredients for cosmetic use. Molecules 2020; 25(15): 3368. http://dx.doi.org/10.3390/molecules25153368 PMID: 32722270

[17] Ali SI, Gopalakrishnan B, Venkatesalu V. Pharmacognosy, phytochemistry and pharmacological properties of *Achillea millefolium* L.: A review. Phytother Res 2017; 31(8): 1140-61. http://dx.doi.org/10.1002/ptr.5840 PMID: 28618131

[18] Pain S, Altobelli C, Boher A, *et al.* Surface rejuvenating effect of *Achillea millefolium* extract. Int J Cosmet Sci 2011; 33(6): 535-42. http://dx.doi.org/10.1111/j.1468-2494.2011.00667.x PMID: 21711463

[19] Tadić V, Arsić I, Zvezdanović J, Zugić A, Cvetković D, Pavkov S. The estimation of the traditionally used yarrow (*Achillea millefolium* L. Asteraceae) oil extracts with anti-inflamatory potential in topical application. J Ethnopharmacol 2017; 199: 138-48. http://dx.doi.org/10.1016/j.jep.2017.02.002 PMID: 28163113

[20] Zengin G, Aktumsek A, Ceylan R, *et al.* Shedding light on the biological and chemical fingerprints of three Achillea species (*A. biebersteinii*, *A. millefolium* and *A. teretifolia*). Food Funct 2017; 8(3): 1152-65. http://dx.doi.org/10.1039/C6FO01847E PMID: 28174780

[21] Ghobadian Z, Ahmadi M, Rezazadeh L, Hosseini E, Kokhazadeh T, Ghavam S. *In vitro* evaluation of *Achillea millefolium* on the production and stimulation of human skin fibroblast cells (HFS-PI-16). Med Arh 2015; 69(4): 212-7. http://dx.doi.org/10.5455/medarh.2015.69.212-217 PMID: 26543303

[22] Mohammadhosseini M, Sarker SD, Akbarzadeh A. Chemical composition of the essential oils and extracts of Achillea species and their biological activities: A review. J Ethnopharmacol 2017; 199: 257-315. http://dx.doi.org/10.1016/j.jep.2017.02.010 PMID: 28179115

[23] Benhalilou N, Alsamri H, Alneyadi A, *et al. Origanum majorana* ethanolic extract promotes colorectal cancer cell death by triggering abortive autophagy and activation of the extrinsic apoptotic pathway. Front Oncol 2019; 9: 795. http://dx.doi.org/10.3389/fonc.2019.00795 PMID: 31497536

[24] Vasudeva N. *Origanum majorana* L.-Phyto-pharmacological review. 2015.

[25] Leeja L, Thoppil JE. Antimicrobial activity of methanol extract of *Origanum majorana* L. (Sweet marjoram). J Environ Biol 2007; 28(1): 145-6. PMID: 17718003

[26] Al Dhaheri Y, Eid A, AbuQamar S, *et al.* Mitotic arrest and apoptosis in breast cancer cells induced by *Origanum majorana* extract: upregulation of TNF-α and downregulation of survivin and mutant p53. PLoS One 2013; 8(2): e56649. http://dx.doi.org/10.1371/journal.pone.0056649 PMID: 23451065

[27] Al Dhaheri Y, Attoub S, Arafat K, *et al.* Anti-metastatic and anti-tumor growth effects of *Origanum majorana* on highly metastatic human breast cancer cells: Inhibition of NFκB signaling and reduction of nitric oxide production. PLoS One 2013; 8(7): e68808. http://dx.doi.org/10.1371/journal.pone.0068808 PMID: 23874773

[28] Yazdanparast R, Shahriyary L. Comparative effects of *Artemisia dracunculus*, *Satureja hortensis* and *Origanum majorana* on inhibition of blood platelet adhesion, aggregation and secretion. Vascul Pharmacol 2008; 48(1): 32-7. http://dx.doi.org/10.1016/j.vph.2007.11.003 PMID: 18069068

[29] Jabbarzadeh Z, Khosh-Khui M. Factors affecting tissue culture of Damask rose (*Rosa damascena* Mill.). Sci Hortic 2005; 105(4): 475-82. http://dx.doi.org/10.1016/j.scienta.2005.02.014

[30] Boskabady MH, Shafei MN, Saberi Z, Amini S. Pharmacological effects of *Rosa damascena*. Iran J Basic Med Sci 2011; 14(4): 295-307. PMID: 23493250

[31] Awale S. Protective effects of *Rosa damascena* and its active constituent on Aβ (25–35)-induced neuritic atrophy. Evid-based Complement Altern Med 2011.

[32] Boskabady MH. Effect of aqueous-ethanolic extract from *Rosa damascena* on guinea pig isolated heart. Iran J Basic Med Sci 2011; 14(2): 116-21.

[33] Arezoomandan R, Kazerani HR. The laxative and prokinetic effects of *Rosa damascena* Mill in rats. Iran J Basic Med Sci 2011; 14(1): 9-16.

[34] Shafei MN, Rakhshandah H, Boskabady MH. Antitussive effect of *Rosa damascena* in guinea pigs. Iran J Pharm Res 2010; (4): 231-4.

[35] Gholamhoseinian A, Fallah H, Sharifi far F. Inhibitory effect of methanol extract of *Rosa damascena* Mill. flowers on α-glucosidase activity and postprandial hyperglycemia in normal and diabetic rats. Phytomedicine 2009; 16(10): 935-41. http://dx.doi.org/10.1016/j.phymed.2009.02.020 PMID: 19380218

[36] Mahmood N, Piacente S, Pizza C, Burke A, Khan AI, Hay AJ. The anti-HIV activity and mechanisms of action of pure compounds isolated from *Rosa damascena*. Biochem Biophys Res Commun 1996; 229(1): 73-9. http://dx.doi.org/10.1006/bbrc.1996.1759 PMID: 8954085

[37] Latifi G, Ghannadi A, Minaiyan M. Anti-inflammatory effect of volatile oil and hydroalcoholic extract of *Rosa damascena* Mill. on acetic acid-induced colitis in rats. Res Pharm Sci 2015; 10(6): 514-22. PMID: 26779271

[38] Zamiri-Akhlaghi A, Zamiri-Akhlaghi A, Rakhshandeh H, Tayarani-Najaran Z, Mousavi SH. Study of cytotoxic properties of *Rosa damascena* extract in human cervix carcinoma cell line. Avicenna J Phytomed 2011; 1(2): 74-7.

[39] Venkatesan B, Subramanian V, Tumala A, Vellaichamy E. Rapid synthesis of biocompatible silver nanoparticles using aqueous extract of *Rosa damascena* petals and evaluation of their anticancer activity. Asian Pac J Trop Med 2014; 7: S294-300. http://dx.doi.org/10.1016/S1995-7645(14)60249-2 PMID: 25312140

[40] Abdel-Hameed ESS, Bazaid SA, Hagag HA. Chemical characterization of *Rosa damascena* Miller var. *trigintipetala* Dieck essential oil and its *in vitro* genotoxic and cytotoxic properties. J Essent Oil Res 2016; 28(2): 121-9. http://dx.doi.org/10.1080/10412905.2015.1099120

[41] Kumar N, Bhandari P, Singh B, Bari SS. Antioxidant activity and ultra-performance LC-electrospray ionization-quadrupole time-of-flight mass spectrometry for phenolics-based fingerprinting of Rose species: *Rosa damascena*, *Rosa bourboniana* and *Rosa brunonii*. Food Chem Toxicol 2009; 47(2): 361-7. http://dx.doi.org/10.1016/j.fct.2008.11.036 PMID: 19100811

[42] Guan X, Bryniarski MA, Morris ME. *In vitro* and *in vivo* efficacy of the monocarboxylate transporter 1 inhibitor AR-C155858 in the Murine 4T1 breast cancer tumor model. AAPS J 2019; 21(1): 3. http://dx.doi.org/10.1208/s12248-018-0261-2 PMID: 30397860

[43] Cacique AP, Barbosa ÉS, Pinho GP, Silvério FO. Maceration extraction conditions for determining the phenolic compounds and the antioxidant activity of *Catharanthus roseus* (L.) G. Don. Cienc Agrotec 2020; 44: e017420. http://dx.doi.org/10.1590/1413-7054202044017420

[44] Mansouri E, Asadi-Samani M, Kooti W, *et al.* Anti-fertility effect of hydro-alcoholic extract of fennel *(Foeniculum vulgare* Mill *)* seed in male Wistar rats. J Vet Res (Pulawy) 2016; 60(3): 357-63. http://dx.doi.org/10.1515/jvetres-2016-0052

[45] Becherini P, Caffa I, Piacente F, *et al.* SIRT6 enhances oxidative phosphorylation in breast cancer and promotes mammary tumorigenesis in mice. Cancer Metab 2021; 9(1): 6. http://dx.doi.org/10.1186/s40170-021-00240-1 PMID: 33482921

[46] Afrisham R. Inhibitory effect of *Heracleum persicum* and *Ziziphus jujuba* on activity of alpha-amylase. J Bot 2015; 2015(1): 1-8. http://dx.doi.org/10.1155/2015/824683

[47] Ghavami G, Sardari S, Shokrgozar MA. Anticancerous potentials of Achillea species against selected cell lines. J Med Plants Res 2010; 4(22): 2411-7.

[48] Csupor-Löffler B, Hajdú Z, Zupkó I, *et al.* Antiproliferative effect of flavonoids and sesquiterpenoids from *Achillea millefolium* s.l. on

cultured human tumour cell lines. Phytother Res 2009; 23(5): 672-6.
http://dx.doi.org/10.1002/ptr.2697 PMID: 19107850

[49] Vitalini S, Beretta G, Iriti M, *et al.* Phenolic compounds from *Achillea millefolium* L. and their bioactivity. Acta Biochim Pol 2011; 58(2): 203-9.
http://dx.doi.org/10.18388/abp.2011_2266 PMID: 21503279

[50] Agar O, Dikmen M, Ozturk N, Yilmaz M, Temel H, Turkmenoglu F. Comparative studies on phenolic composition, antioxidant, wound healing and cytotoxic activities of selected *Achillea* L. species growing in Turkey. Molecules 2015; 20(10): 17976-8000.
http://dx.doi.org/10.3390/molecules201017976 PMID: 26437391

[51] Bobis O. Influence of phytochemical profile on antibacterial activity of different medicinal plants against gram-positive and gram-negative bacteria. Appl Biochem Microbiol 2015; 51(1): 113-8.
http://dx.doi.org/10.1134/S0003683815010044

[52] Hagag HA, Bazaid SA, Abdel-Hameed ESS, Salman M. Cytogenetic, cytotoxic and GC–MS studies on concrete and absolute oils from Taif rose, Saudi Arabia. Cytotechnology 2014; 66(6): 913-23.
http://dx.doi.org/10.1007/s10616-013-9644-5 PMID: 24101441

[53] Zu Y, Yu H, Liang L, *et al.* Activities of ten essential oils towards *Propionibacterium acnes* and PC-3, A-549 and MCF-7 cancer cells. Molecules 2010; 15(5): 3200-10.
http://dx.doi.org/10.3390/molecules15053200 PMID: 20657472

[54] Hamza RZ, Al-Malki NA, Alharthi S, Alharthy SA, Albogami B, El-Megharbel SM. Chemical characterization of Taif Rose (*Rosa damascena*) methanolic extract and its physiological effect on liver functions, blood indices, antioxidant capacity, and heart vitality against cadmium chloride toxicity. Antioxidants 2022; 11(7): 1229.
http://dx.doi.org/10.3390/antiox11071229 PMID: 35883718

[55] Refat MS, Hamza RZ, Adam AMA, *et al.* Potential therapeutic effects of new ruthenium (III) complex with quercetin: Characterization, structure, gene regulation, and antitumor and anti-inflammatory studies (RuIII/Q novel complex is a potent immunoprotective agent). Crystals 2021; 11(4): 367.
http://dx.doi.org/10.3390/cryst11040367