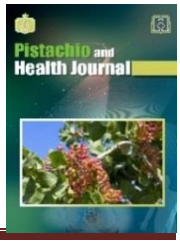

Potential Anticancer Activity of the Genus Pistacia through Apoptosis Induction in Cancer Cells

Maryam Mohamadi (PhD) [1], Mojgan Noroozi Karimabad (PhD) [2]*

[1] Pistachio Safety Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[2] Molecular Medicine Research Center, Institute of Basic Medical Sciences Research, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Information

Article Type:
Review Article

Article History:
Received: 05.05.2020
Accepted: 28.08.2020
DOI: 10.22123/phj.2021.265934.1072

Keywords:
Apoptosis
Anticancer
Pistachios
Herapy
Cytotoxicity

Corresponding Author:
Dr. Mojgan Noroozi Karimabad
Email: mojgan.noroozi@yahoo.com
Tel: +98-343-1315000

Abstract

Cancer is one of the most significant global challenges threatening health. Accordingly, cancer management is one of the most important issues in the world. Evading apoptosis is a route through which a cancerous cell becomes malignant. Thus, designing novel apoptotic drugs against cancer is of high importance because deficiencies in the regulation of apoptotic pathways lead to cancer chemotherapy resistance. Apoptosis can be induced by inhibiting anti-apoptotic factors or stimulating pro-apoptotic molecules. On the other hand, chemotherapy complications have caused medical plants to be considered as potential alternatives for the treatment of tumors. Pistachios have been proved to have a wide range of pharmacological benefits, including anti-microbial, anti-oxidant, and anticancer properties. Evidence shows that anticancer effects of pistachios result from their influence on numerous apoptosis-related pathways in tumor cells. In this paper, we aim to introduce anticancer properties of pistachios, particularly those connected with targeting apoptosis-related pathways.

►Please cite this article as follows:

Mohamadi M, Noroozi Karimabad M. Potential Anticancer Activity of the Genus Pistacia through Apoptosis Induction in Cancer Cells. Pistachio and Health Journal. 2020; 3 (3): 18-32.

1. Introduction

Cancer is one of the most serious health challenges in the world. In the human body, new cells are frequently produced to repair damaged tissues. Under normal circumstances, the death and proliferation process of cells takes place in a balanced way. However, in tumor cells, the growth, division, and death of cells are irregular. Tumor formation occurs as a result of this irregularity [1, 2]. Apoptosis, i.e. programmed cell death, is controlled by various proteins and genes categorized into apoptotic proteins and genes. The former has a positive effect on apoptosis, which makes the cellular process further progress, yet the latter has a negative effect that blocks apoptosis [3]. Although apoptosis induced by chemotherapy is the main mechanism of various anticancer therapies, many of the drugs used have had different side effects and treatment resistance [4]. Understanding mechanisms associated with apoptosis is important for discovering novel therapies for cancer [1]. The genus Pistacia is a member of the family Anacardiaceae, which is comprised of about 70 genera and over 600 species. Species of this genus (*Pistacia khinjuk* Stocks, *Pistacia terebinthus* L., *Pistacia atlantica* Desf., *Pistacia vera* L., and *Pistacia lentiscus* L.) are deciduous or evergreen resin-bearing trees and shrubs that grow up to 8–10 m height [5, 6]. Iran is the natural habitat of *P. vera* L., *P. khinjuk* Stocks., *P. atlantica* Desf., and *P. atlantica* [7, 8]. Pistacia, as a traditional herbal medicine, has been found to show different biological activities, such as anticancer and antioxidant properties, being able to improve glucose metabolism, reduce blood pressure, and control weight. Moreover, it can induce apoptosis [7]. This article aims to review Pistachios' potentials for influencing various apoptosis signaling pathways.

2. Cancer and apoptosis induction

Resistance to the induction of cell death is one of the signs of cancer. Thus, understanding essential mechanisms regulating different events of cell death, such as endoplasmic reticulum stress, apoptosis, necroptosis, and autophagy can help develop new agents for interfering with these pathways. Dysregulation of apoptosis allows the survival of neoplastic cells, even under conditions of oxidative stress and hypoxia, thereby noticeably contributing to pathogenesis [1]. Tumors can be formed as result of a series of genetic changes transforming normal cells to malignant ones [9]. In a study, Karimabad et al showed that a novel indole derivative triggered apoptosis and anti-cancer activity in NB4 cells by modulating the bax/bcl-2 (B-cell

lymphoma2) ratio [10]. Apoptosis can be induced as a non-surgical therapy for cancer by means of the agents that return apoptotic signaling pathways to normal patterns. It has been reported that apoptosis is associated with progression of tumors, hyperplasia, and formation of abnormal cells in an inverse manner [11]. Besides, it has been demonstrated that an abnormal cell can repress programmed cell death to become apoptosis-resistant through numerous mechanisms. Generally, apoptosis evasion mechanisms are categorized into three classes. These classes include imbalance between anti-apoptotic and pro-apoptotic proteins, a caspase activity decrease (cysteine-aspartic proteases, cysteine aspartases, or cysteine-dependent aspartate-directed proteases), and disruption of signaling pathways of death receptors. The ratio of the pro-apoptotic protein level to that of anti-apoptotic proteins is considered a fundamental factor in cell death modulation. Additionally, apoptosis modulation through down- or up-regulation of particular genes has been shown to play a significant role in carcinogenesis. Caspases are a type of these genes, which are generally categorized into two classes. The first class includes caspases 1, 4, 5, 13, and 14 that contribute to the cytokine processing during inflammation. The other class includes caspases 2, 3, 6, 7, 8, 9, and 10 that play the main role in apoptosis. Caspases 2, 8, 9, and 10 are known as "initiator caspases" because they initiate apoptosis; on the other side, "effector caspases" are comprised of caspases 3, 6, and 7 that interpose the cleavage of cellular components during the apoptosis process. In fact, caspases are involved in both initiation and execution of apoptosis. Consequently, disruption to the function or regulation of caspases can result in impaired apoptosis and carcinogenesis [13]. In their study, Mohammadizadeh *et al* confirmed that such disruption complicated activities of apoptosis from intrinsic and extrinsic apoptotic routes in malignant cells. However, because of the lack of considerable modifications to the bax/bcl-2 ratio in cells (L929) and the increase in the expression of caspase-8 and bid genes, this complication mainly activates apoptosis through the most effective extrinsic apoptotic pathways in regular cells [14]. There are various molecular mechanisms through which tumor cells suppress apoptosis. Decreased bax and increased bcl-2 in a tumor cell make it resistant to apoptosis [16, 17]. In addition, death receptors and their ligands have a substantial impact on external apoptosis signaling pathways. TNFR1, referred to as Fas, includes DR1, DR3, DR4, DR5, DR6, NGFR, and EDAR, being death receptors.

3. Pistachio applications in cancer cell treatment

The rising trend of cancers requires further studies to find more efficient therapies [18]. Radiotherapy, immunotherapy, chemotherapy, and transplantation of stem cells are the most popular methods used in treating tumors [18]. However, each of these modalities has its own limitations. For instance, chemotherapy and radiotherapy, being the most prevalent cancer treatment methods, have two main barriers, including side effects and disease recurrence [18]. Hence, the use of natural dietary elements, especially phytochemicals and medicinal plants, has received a lot of attention in recent decades [19, 20]. The highest rate of cytotoxicity of resins was observed against APL among 13 human cell line types [21]. Another study indicated antioxidant activities of green hull extracts of the Ahmadaghaei variety of pistachios [22]. Mastic gum extract delayed proliferation of colorectal cancers that progressed from colon tumor cells and xenografted into mice [23]. In this research, the hulls of ripe pistachios were extracted using methanol and ethanol, with their phenolic composition as well as antioxidant and cytoprotective activities determined. In both extracts, 20 compounds were identified, with the most abundant constituent having been gallic acid. The highest yields among all compounds were obtained using methanol as the extracting solvent. The results of this study highlighted the intense cytoprotective and anticancer activities of the components of pistachios [24]. Additionally, they have been reported to enhance expression of maspin (an inhibitor of mammary serine proteases in the cells of prostate cancer), thereby preventing growth of cell lines and blocking progression of the cell cycle [25, 26]. According to research, mastic oil of *P. lentiscus* significantly prevented proliferation of cancer cells in immune-competent mice with no signs of toxicity. This effect was exerted as a result of the induction of apoptosis, a reduction in neovascularization, and inhibition of chemokine expression [27]. In this regard, anticancer effects of various parts of Pistacia species have been examined. Accordingly, the extract of the *P. atlantica* sub. kurdica fruit exerted inhibitory effects on the growth of colon cancer cells, similar to those observed for doxorubicin [28]. Oleoresin extracted from *P. vera* exerted moderate cytotoxic effects on hepatocellular carcinoma, cervical tumor, breast tumor cells, and normal melanocytes [29]. In the same vein, the gum of *P. lentiscus* var. chia prevented growth of colorectal cancer cell lines and induced apoptosis [30]. Moreover, research showed pro-apoptotic and anti-proliferative effects of mastic oil on leukemia cell lines, which inhibited release of the vascular endothelial growth factor from these cells [31]. Furthermore, various

parts of P. lentiscus have been reported to show radical scavenging activities [21, 32, 33]. Cyanidin-3-O-glucoside, quercetin, epicatechin, luteolin, naringenin, and kaempferol are the main constituents of pistachio hull [34]. Concerning the extract of *P. terebinthus* leaves, an antioxidant capacity of approximately 12 times that of Butylated hydroxyanisole and ascorbic acid was observed [35]. Another study considered the mastic gum of the leaves and stem of *Pistacia lentiscus* as "conglomeration of effective anticancer drugs" and focused on different mechanisms of anticancer properties of its triterpenoids. This report considered anticancer properties for the resinous exudate and its major compounds [26]. The antioxidant property of *P. vera* (known as pistachio) nuts was observed to be similar to that of the synthetic antioxidant [36]. Interestingly, the antioxidant activity of the hydrophilic extract of *P. vera* nuts was significantly higher than that of its lipophilic extract [37]. The results obtained from four different assays indicated that the hull of *P. vera* had a stronger antioxidant activity than its kernel. That is because the hull has higher amounts of phenolic compounds acting as antioxidants [38]. According to research, other parts of *P. vera* show antioxidant properties as well [39]. Pistachio hull has been demonstrated to have antioxidant, enzyme-inhibitory, antimicrobial, and radical scavenging activities [40]. In addition, destructive effects of dietary kaempferol on cancers have been frequently reported [41]. In a research, anticancer properties of epicatechin have been reported [42]. The study conducted by Seifaddinipour *et al* demonstrated that the ethyl acetate extract of pistachio hull had no significant cytotoxic effects on normal fibroblast cells; however, it significantly affected all five tested human cancer cells, including HT-29, HCT-116, MCF-7, H23, and HepG2. Among these cell lines, HepG2 was the most resistant cell line, and MCF-7 was the most sensitive one [43]. Different *in vitro* and *in vivo* studies indicated anti-tumor effects of the flavonoid quercetin [42]. Besides, various *in vitro* antioxidant assays revealed that the leaves and fruit of *P. atlantica* showed antioxidant activities similar to or considerably higher than those of standard antioxidant compounds [44- 46].

4. Pistachio targets during apoptosis induction in cancer cells

Table 1 shows the plant parts used as well as pharmacological activities of *Pistacia* from different regions. Growing evidence shows that pistachios exert their anticancer effects by influencing different apoptosis-related intrinsic and extrinsic pathways in cancerous cells (Fig.1).

Table 1- Shows the plant parts used as well as pharmacological activities of Pistacia from different regions

Species	Region	Plant part(s) used	Pharmacological activities	Assay	Model	Cell line Type of cancer	Reference
Pistacia lentiscus	Japan	Resin	Cytotoxicity	MTT	In vitro	13 human cell line types (HSC-2, HSC-4, HSC-3, HepG2, T98G, U87MG, HGF, HPC, HPLF, HL-60, K-562, ML-1, KG-1)	[21]
Pistachia vera	Iran	Green hull extracts	Antioxidant, anti-microbial and antimutagenic	ABTS assay, DPPH assay, and β-carotene bleaching (BCB)	In vitro	Bacillus cereus	[22]
Lentiscus	Greece	Mastic gum	Induces p53- and p21-independent G1-phase arrest followed by apoptosis	Immunodeficient mice and tumor measurement	In vitro and in vivo	Colorectal cancers colon cancer/immunodeficiency, mouse model	[23]
Lentiscus	China	Mastic gum	Inhibits the ARE binding activity and increases the Sp1 binding activity in the Maspin promoter	RT-PCR and Western blotting	In vitro	Prostate cancer cells	[25]

Lentiscus	China	Mastic gum	Blocks the PC-3 cell cycle in the G1 phase; Mastic gum decreases the p-AKT protein level and increases the IκBα protein level	MTT RT-PCR and western blotting	In vitro	Prostate cancer cells	[26]
Lentiscus	Greece	Mastic Oil	Blocks relevant signaling and transcription pathways	Immunohistochemistry and ELISA	In vivo	Lung carcinoma	[27]
Atlantica	Iran	Pericarp polyphenol-rich extract	Anti-proliferative, apoptosis induction, and cell cycle	MTT	In vitro	Human colon carcinoma, HT29 cells	[28]
Lentiscus	USA	Mastic gum	Apoptosis induction by CMG is not inhibited in the HCT116 cell.	CMG-treatment induces cell arrest at G1.	In vitro	Human colon cancer cells	[30]
Lentiscus	Greece	Mastic Oil	Anti-proliferative and proapoptotic	ELISA angiogenesis assays western blotting	In vitro	K562 Leukemia Cells	[31]
Vera	Italy	Pistachio nut	Antioxidant	TAA test	In vitro	Biological models	[37]
Atlantica	Iran	Flavonoid and flavonol content of the extract	Anticancer	MTT	In vitro	AGS, HeLa, and HDFs cells	[47]

Vera	Iran	Pistachio rosy hull (PRH)	Expression of both pro-apoptotic and anti-apoptotic genes associated with extrinsic and intrinsic apoptosis signaling pathways	MTT PCR array Flow cytometry	In vitro	HepG2	[48]
Vera	Iran	Extract of pericarp of pistachio fruit	Cytotoxic and apoptotic effects	MTT Realtime PCR	In vitro	HepG2	[53]
Vera	Iran		Cytotoxicity and apoptotic effects	MTT Realtime PCR	In vitro	MCF7	[54]

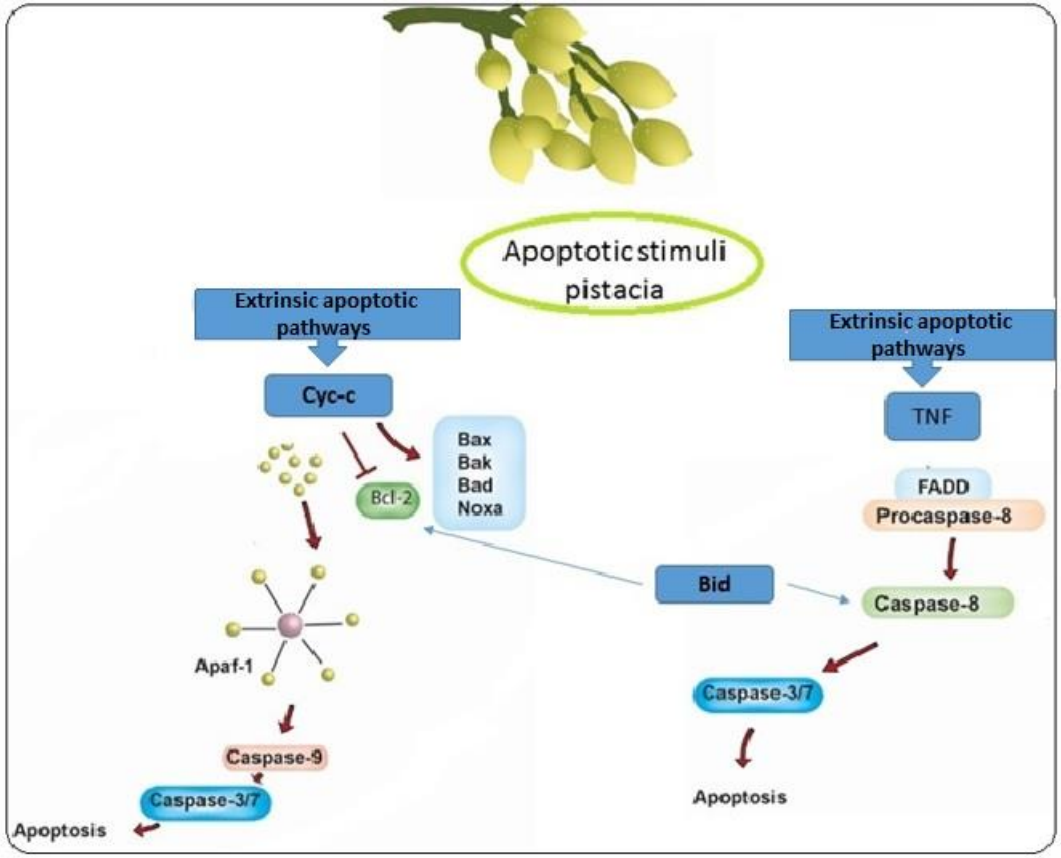

Fig. 1- Effects of pistachios on apoptosis-related intrinsic and extrinsic pathways in cancer cells

This finding promises discovery of novel anticancer drugs for treating cancer by inducing apoptosis. Accordingly, the data obtained from the study of Hashemi *et al* on MCF-7 cell lines treated with three doses of F13b1/PV-EA indicated the dose-dependent effect of the compound on cell viability, which induced some apoptotic morphological changes to the cell lines [47]. Fathalizadeh *et al* examined the apoptotic effects of the aqueous extract of pistachio rosy hull (PRH) on HepG2 cells. Accordingly, they observed that the extract significantly reduced viability of the cell lines by inducing apoptosis. Besides, expression of many apoptosis-related intrinsic and extrinsic signaling pathways in cancerous cells was found out to alter in the cell lines treated with the PRH. The results of the polymerase chain reaction (PCR) array showed that 8 pro-apoptotic genes (CD27, lta, faslg, bag4, t, pycard, casp14, and casp6) were upregulated; in contrast, the remaining 9 pro-apoptotic genes (tnfrsf21, tnfrsf10a, bcl2l11, bax, casp3, casp4, casp7, casp10, and cradd) were downregulated. Besides, 5 anti-apoptotic genes (birc3, bcl2a1, xiap, cflar, and traf2) were downregulated. Downregulation of CFLAR (CASP8 and the FADD-like Apoptosis Regulator) is an interesting subject for cancer therapies because this cellular FLICE-like inhibitory protein (c-FLIP) plays an important role in apoptosis regulation [48, 49]. Research shows that p43-FLIP or the N-terminal fragment of the c-FLIP long isoform (c-FLIPL) interacts with TNF receptor-associated factor 2 (TRAF2), thereby activating NF-κB (the nuclear factor kappa-light-chain-enhancer of activated B cells) [49]. As a result, activation of NF-κB upregulates anti-apoptotic genes, which results in the survival of the cells [50]. Many cancers occur when the natural process of apoptosis is deregulated. Additionally, this dysregulation could cause resistance to chemotherapy among cancerous cells. Thus, one of the most efficient strategies for fighting cancer is to develop new drugs that regulate apoptotic molecules [51, 52]. In another study carried out by Harandi *e al* [53], the hydro-alcoholic extract of pistachio hull regulated the intrinsic apoptosis pathways in HepG2 cells by balancing the expression of bax/bcl-2 genes. The bax gene causes the release of cytochrome C and the subsequent apoptosis, while Bcl-2 protein blocks the cytochrome C channel. In their study, Ahmadirad *et al* examined anti-tumor effects of the hydro-alcoholic extract of wild pistachio leaves on breast cancer (MCF-7 cell line). Analysis results of the obtained data showed the IC50 values of 250 µg/mL and 400 µg/mL for cancerous MCF-7 and normal L929 cell lines, respectively, after treatment with the extract for 48 h. DNA fragmentation assays and morphological analysis

demonstrated apoptosis induction in both cell lines as a result of treatment at the concentration of IC50. Accordingly, upregulation of caspases -8 and -3, as well as bax and p53 reduced expression of bcl-2, which indicates that the extract induced apoptosis through extrinsic and intrinsic pathways in the MCF-7 cells. In fact, upregulation of p53, bax, and p21 as well as suppression of the expression of the bcl-2 gene induced apoptosis in the Hep G2 cell line. The P53 protein promotes expression of the bax gene, thereby directly activating transcription of the bax gene and inducing apoptosis [55]. Koyuncu *et al* studied anticancer properties of different extracts of pistachio hull. Accordingly, they found out that the n-hexane fraction arrested the cell cycle at the G1 sub-phase and induced apoptosis through oxidative pathways in cancerous cell lines [56]. Seifaddinipour *et al* evaluated cytotoxicity of different fractions of the ethyl acetate extract of pistachio hull using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay. F13b1/PV-EA was found to be the most cytotoxic fraction, with the most abundant active compounds having been gallic acid and quercetin. Besides, the IC_{50} value of F13b1/PV-EA against MCF-7 cell lines was calculated to be 15.2± 1.35 µg/mL. This fraction increased expression of SOD, CAT, bax, as well as caspases 3 and 8 genes, yet it decreased that of bcl-2, according to the RT-PCR method. *In vivo* studies on cancer-induced mice revealed that F13b1/PV-EA inhibited development of the tumor [57].

5. Conclusion

The rising prevalence of malignant cancers worldwide, on the one hand, and various side effects of present treatments, on the other, have made it urgent to find novel treatments. Complementary and alternative therapeutic agents originated from herbal sources have attracted much attention due to their efficiency in interfering with oncogenic molecular signaling pathways. According to the results of the present research, phytochemicals of pistachios possess anticancer properties. This study focused on the role of the mentioned agents in apoptosis regulation. However, further studies are required to fully determine mechanisms of the anti-tumor activity of pistachios, especially their apoptotic activity.

Conflict of Interest

It is not applied to this study.

Acknowledgement

This project was financially supported by Rafsanjan University of Medical Sciences.

References

1- Wong RS. Apoptosis in cancer: From pathogenesis to treatment. Journal of Experimental & Clinical Cancer Research. **2011**;30: *87*.

2- Jaafari-Ashkvandi Z, Shirazi SY, Rezaeifard S, Hamedi A, Erfani N. Cytotoxic Effects of Pistacia Atlantica (Baneh) Fruit Extract on Human KB Cancer Cell Line. Acta medica (Hradec Kralove). **2019**;62: *30-4*.

3- Mullauer L, Gruber P, Sebinger D, Buch J, Wohlfart S, Chott A. Mutations in apoptosis genes: A pathogenetic factor for human disease. Mutation Research/Reviews in Mutation Research. **2001**;488: *211-31*.

4- Funahashi H, Imai T, Tanaka Y, Tsukamura K, Hayakawa Y, Kikumori T, et al. Wakame seaweed suppresses the proliferation of 7, 12-dimethylbenz (a)-anthracene-induced mammary tumors in rats. Japanese Journal of Cancer Research. **1999**;90: *922-27*.

5- Mozaffarian V. Trees and shrubs of Iran: Farhang Moaser Publ.; **2005**.

6- Kole C. Wild crop relatives: Genomic and breeding resources: legume crops and forages: Springer; **2014**.

7- Mozaffarian V. A dictionary of Iranian plants names. Tehran. Farhang Moaser Publishers; **1998**.

8- Pasban-Aliabadi H, Sobhani V, Esmaeili-Mahani S, Najafipour H, Askari A, Jalalian H. Effects of Baneh (Pistacia atlantica) Gum on Human Breast Cancer Cell Line (MCF-7) and Its Interaction with Anticancer Drug Doxorubicin. Iranian Journal of Pharmaceutical Research: IJPR. **201**9;18: *1959-66*.

9- Hanahan D, Weinberg R. The hallmarks of cancer. cell, 100. Transpl Immunol. **2000**;5: *179-83*.

10- Karimabad MN, Mahmoodi M, Jafarzadeh A, Darehkordi A, Hajizadeh MR, Khorramdelazad H, et al. The novel Indole-3-formaldehyde (2-AITFEI-3-F) is involved in processes of apoptosis induction? Life Sciences. **2017**;181: *31-44*.

11- YATES C. Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. Ann Intern Med. **1997**;126: *608-14*.

12- Fink SL, Cookson BT. Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. Infection and Immunity. **2005**;73: *1907-16*.

13- Shen XG, Wang C, Li Y, Wang L, Zhou B, Xu B, et al. Downregulation of caspase-9 is a frequent event in patients with stage II colorectal cancer and correlates with poor clinical outcome. Colorectal Disease. **2010**;12: *1213-18*.

14- Mohammadizadeh F, Mahmoodi M, Rezaei A, Mohamadi M, Hajizadeh MR, Mirzaei MR, et al. A new copper complex enhanced apoptosis in human breast cancerous cells without considerable effects on normal cells. Gene Reports. **2019**;17: *100475*.

15- Ahmadirad H, Mahmoodi M, Rahmatian F, Bakhshi M, Hajizadeh M, Mirzaei M, et al. The hydroalcoholic extract of baneh leaves (pistacia atlantica) induces apoptosis in the breast cancer cells.

16- Miyashita T, Krajewski S, Krajewska M, Wang HG, Lin HK, Liebermann DA, et al. Tumor suppressor p53 is a regulator of bcl-2 and bax gene expression in vitro and in vivo. Oncogene. **1994**;9: *1799-805*.

17- Vaux DL. Immunopathology of apoptosis-introduction and overview. Springer seminars in immunopathology: Springer; **1998**: *271-78*.

18- Şermet MO. Antioxidant, antimicrobial activity and phytochemical analysis of Pistacia Vera L. skin: Middle East Technical University; **2015**.

19- Durmaz G, Gokmen V. Changes in oxidative stability, antioxidant capacity and phytochemical composition of Pistacia terebinthus oil with roasting. Food chemistry. **2011**;128: *410-14*.

20- Karimabad MN, Mahmoodi M, Jafarzadeh A, Darekordi A, Hajizadeh MR, Hassanshahi G. Molecular targets, anti-cancer properties and potency of synthetic indole-3-carbinol derivatives. Mini reviews in medicinal chemistry. **2019**;19: *540-54*.

21- Sakagami H, Kishino K, Kobayashi M, Hashimoto K, Iida S, Shimetani A, et al. Selective antibacterial and apoptosis-modulating activities of mastic. In vivo. **2009**;23: *215-23*.

22- Rajaei A, Barzegar M, Mobarez AM, Sahari MA, Esfahani ZH. Antioxidant, anti-microbial and antimutagenicity activities of pistachio (Pistachia vera) green hull extract. Food and Chemical Toxicology. **2010**;48: *107-12*.

23- Dimas K, Hatziantoniou S, Wyche JH, Pantazis P. A mastic gum extract induces suppression of growth of human colorectal tumor xenografts in immunodeficient mice. In vivo. **2009**;23: *63-8*.

24- Borchani C, Fonteyn F, Jamin G, Paquot M, Thonart P, Blecker C. Physical, functional and structural characterization of the cell wall fractions from baker's yeast Saccharomyces cerevisiae. Food Chemistry. **2016**;194: *1149-55*.

25- He Ml, Chen WW, Zhang PJ, Jiang AL, Fan W, Yuan HQ, et al. Gum mastic increases maspin expression in prostate cancer cells. Acta Pharmacologica Sinica. **2007**;28:*567-72*.

26- He ML, Li A, Xu CS, Wang SL, Zhang MJ, Gu H, et al. Mechanisms of antiprostate cancer by gum mastic: NF-κB signal as target. Acta Pharmacologica Sinica. **2007**;28: *446-52*.

27- Magkouta S, Stathopoulos GT, Psallidas I, Papapetropoulos A, Kolisis FN, Roussos C, et al. Protective effects of mastic oil from Pistacia lentiscus variation chia against experimental growth of lewis lung carcinoma. Nutrition and Cancer. **2009**;61: *640-48*.

28- Rezaei PF, Fouladdel S, Hassani S, Yousefbeyk F, Ghaffari SM, Amin G, et al. Induction of apoptosis and cell cycle arrest by pericarp polyphenol-rich extract of Baneh in human colon carcinoma HT29 cells. Food and Chemical Toxicology. **2012**;50: *1054-59*.

29- Almehdar H, Abdallah HM, Osman A-MM, Abdel-Sattar EA. In vitro cytotoxic screening of selected Saudi medicinal plants. Journal of Natural Medicines. **2012**;66: *406-12*.

30- Balan K, Prince J, Han Z, Dimas K, Cladaras M, Wyche J, et al. Antiproliferative activity and induction of apoptosis in human colon cancer cells treated in vitro with constituents of a product derived from

Pistacia lentiscus L. var. chia. Phytomedicine. **2007**;14: *263-72*.

31- Loutrari H, Magkouta S, Pyriochou A, Koika V, Kolisis FN, Papapetropoulos A, et al. Mastic oil from Pistacia lentiscus var. chia inhibits growth and survival of human K562 leukemia cells and attenuates angiogenesis. Nutrition and Cancer. **2006**;55: *86-93*.

32- Gardeli C, Vassiliki P, Athanasios M, Kibouris T, Komaitis M. Essential oil composition of Pistacia lentiscus L. and Myrtus communis L: Evaluation of antioxidant capacity of methanolic extracts. Food Chemistry. **2008**;107: *1120-30*.

33- Barra A, Coroneo V, Dessi S, Cabras P, Angioni A. Characterization of the volatile constituents in the essential oil of Pistacia lentiscus L. from different origins and its antifungal and antioxidant activity. Journal of Agricultural and Food Chemistry. **2007**;55: *7093-98*.

34- Kolluru GK, Siamwala JH, Chatterjee S. eNOS phosphorylation in health and disease. Biochimie. **2010**;92: *1186-98*.

35- Kavak DD, Altıok E, Bayraktar O, Ulku S. Pistacia terebinthus extract: As a potential antioxidant, antimicrobial and possible β-glucuronidase inhibitor. Journal of Molecular Catalysis B: Enzymatic. **2010**;64: *167-71*.

36- Goli AH, Barzegar M, Sahari MA. Antioxidant activity and total phenolic compounds of pistachio (Pistachia vera) hull extracts. Food Chemistry. **2005**;92: *521-25*.

37- Gentile C, Tesoriere L, Butera D, Fazzari M, Monastero M, Allegra M, et al. Antioxidant activity of Sicilian pistachio (Pistacia vera L. var. Bronte) nut extract and its bioactive components. Journal of Agricultural and Food Chemistry. **2007**;55: *643-48*.

38- Tomaino A, Martorana M, Arcoraci T, Monteleone D, Giovinazzo C, Saija A. Antioxidant activity and phenolic profile of pistachio (Pistacia vera L., variety Bronte) seeds and skins. Biochimie. **2010**;92: *1115-22*.

39- Hosseinzadeh H, Tabassi SAS, Moghadam NM, Rashedinia M, Mehri S. Antioxidant activity of Pistacia vera fruits, leaves and gum extracts. Iranian Journal of Pharmaceutical Research: IJPR. **2012**;11: *879*.

40- Ozcan MM, Tzakou O, Couladis M. Essential oil composition of the turpentine tree (Pistacia terebinthus L.) fruits growing wild in Turkey. Food Chemistry. **2009**;114: *282-85*.

41- Koutsoudaki C, Krsek M, Rodger A. Chemical composition and antibacterial activity of the essential oil and the gum of Pistacia lentiscus Var. chia. Journal of Agricultural and Food Chemistry. **2005**;53: *7681-85*.

42- Baghel SS, Shrivastava N, Baghel RS, Agrawal P, Rajput S. A review of quercetin: Antioxidant and anticancer properties. World J Pharm Pharmaceutical Sci. **2012**;1: *146-60*.

43- Seifaddinipour M, Farghadani R, Namvar F, Mohamad J, Abdul Kadir H. Cytotoxic effects and anti-angiogenesis potential of pistachio (Pistacia vera L.) hulls against MCF-7 human breast cancer cells. Molecules. **2018**;23: *110*.

44- Peksel A. Antioxidative properties of decoction of Pistacia atlantica Desf. Leaves. **2008**.

45- Farhoosh R, Khodaparast MHH, Sharif A. Bene hull oil as a highly stable and antioxidative vegetable oil. European Journal of Lipid Science and Technology. **2009**;111: *1259-65*.

46- Farhoosh R, Tavassoli-Kafrani MH, Sharif A. Antioxidant activity of the fractions separated from the unsaponifiable matter of bene hull oil. Food Chemistry. **2011**;126: *583-9*.

47- Hashemi L, Asadi-Samani M, Moradi M-T, Alidadi S. Anticancer activity and phenolic compounds of Pistacia atlantica extract. International Journal of Pharmaceutical and Phytopharmacological Research. **2017**;7: *26-31*.

48- Fathalizadeh J, Bagheri V, Khorramdelazad H, Kazemi Arababadi M, Jafarzadeh A, Mirzaei M, et al. Induction of apoptosis by pistachio (Pistacia vera L.) hull extract and its molecular mechanisms of action in human hepatoma cell line HepG2. Cell Mol Biol. **2015**;61: *128-34*.

49- Shirley S, Micheau O. Targeting c-FLIP in cancer. Cancer Letters. **2013**;332: *141-50*.

50- Hoesel B, Schmid JA. The complexity of NF-κB signaling in inflammation and cancer. Molecular Cancer. **2013**;12: *1-15*.

51- Justin A, Eckhardt S, Camidge D. Targeted manipulation of apoptosis in cancer therapy. Lancet. **2008**;9: *1002-11*.

52- Fesik SW. Promoting apoptosis as a strategy for cancer drug discovery. Nature Reviews Cancer. **2005**;5: *876-85*.

53- Harandi H, Majd A, Falahati-Pour SK, Mahmoodi M. Anti-cancer effects of hydro-alcoholic extract of pericarp of pistachio fruits. Asian Pacific Journal of Tropical Biomedicine. **2018**;8: *598-603*.

54- Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. Nature Reviews Cancer. **2002**;2: *647-56*.

55- Raisova M, Hossini AM, Eberle J, Riebeling C, Orfanos CE, Geilen CC, et al. The Bax/Bcl-2 ratio determines the susceptibility of human melanoma cells to CD95/Fas-mediated apoptosis. Journal of investigative dermatology. **2001**;117: *333-40*.

56- Koyuncu I, Gonel A, Temiz E, Karaogul E, Uyar Z. Pistachio Green Hull Extract Induces Apoptosis Through Multiple Signaling Pathways by Causing Oxidative Stress on Colon Cancer Cells. Anti-cancer agents in medicinal chemistry. **2020**.

57- Seifaddinipour M, Farghadani R, Namvar F, Bin Mohamad J, Muhamad NA. In Vitro and In Vivo Anticancer Activity of the Most Cytotoxic Fraction of Pistachio Hull Extract in Breast Cancer. Molecules. **2020**;25: *1776*.