## REVIEW ARTICLE

# THE GENUS AS, A POTENTIAL SOURCE OF ANTICANCER AGENT: AN UPDATED REVIEW

Zuneera Akram1*

**ABSTRACT**

On the list of the world's most significant health problems, cancer rates are high. As a consequence, cancer treatment is a global priority. A cell may acquire malignant characteristics by learning how to avoid apoptosis. Defects in regulating apoptotic pathways enable cancer cells to become chemoresistant, highlighting the need to develop new anti-apoptotic drugs to combat the disease. Apoptosis can be induced by inhibiting anti-apoptotic factors or by activating pro-apoptotic molecules. However, the adverse side effects of chemotherapy have prompted researchers to investigate whether medicinal plants could replace chemotherapy in cancer treatment. Pistachios have antioxidant, antifungal, antimicrobial, and anticancer properties, among many other pharmacological benefits. The ability of pistachios to inhibit tumor growth is supported by data indicating that they do so by modulating multiple apoptotic pathways in tumor cells. This article introduces pistachios and discusses their potential anticancer effects, mainly targeting apoptosis-related pathways.

**Keywords:**Antimicrobial, Cancer, Anticancer,Chemoresistant, Antioxidant,

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**1***Assistant Professor, Department of Pharmacology, Baqai Institute of Pharmaceutical Sciences, Baqai Medical University.

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## INTRODUCTION

**Genus** *Pistacia*

Approximately twenty species of evergreen or deciduous plants, shrubs, and small trees ranging in height from 5 to 15 meters make up the genus [1-2]. *Pistaciavera, Pistacia. khinjuk, Pistacia. palaestina, Pistacia. lentiscus, Pistacia. terebinthus, Pistacia. chinensis, Pistacia. mexicana, Pistacia. texana, Pistacia. saporte, Pistacia. atlantica,Pistacia. weinmannifolia*, etc. are common Pistacia species [3].Ê*Stewart's Pistacia.integerrimais a subspecies of P. chinensis[4]. The fruits of P. chinensisripen in October and are planted as an attractive plant in the South California desert.*Studies on the Pistacia genus have led to the discovery of numerous secondary metabolites and high mineral and vitamin concentrations. Recent pharmaceutical interest has been drawn to this genus as a source of phenolic compounds, fatty acids, alkaloids, flavonoids, terpenoids, monoterpenes, saponins, and sterols [5]. The genus Pistacia's phytochemical profiles, ethnomedical applications, and pharmacological validations are all rigorously evaluated in the current review.

**Pistacia Genus: Distribution, Morphology, and Life Cycle**

Genus Pistaciais found in Southern Europe, Asia, North America, and Africa. These trees thrive in a moist environment[6].They are widespread throughout the Mediterranean sink. *P. lentiscus* is one of the numerous species adapted to Mediterranean semiarid climates and saline desert soil [7]. Because of the salt stress, they have adapted by becoming bushes [8]. The genus has separate trees that bear male and female flowers, making this a dioecious species [9]. Some *P. atlantica* specimens

*Corresponding Author:* Zuneera Akram, Assistant Professor, Department of Pharmacology, Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Karachi, Pakistan. Email: dr.zunaira@baqai.edu.pk

are monoecious, though [10]. The complex, pinnate whorls of the leathery, alternating leaves are a vibrant, deep green. Clusters of unisexual flowers are displayed. According to research, it takes the Pistacia genus between 15 and 20 years to reach maturity and another 7 to 10 years before it generates fruit. The fruits of the female trees ripen around August. The round fruit is a juicy drupe that changes colour from red to brown to indicate ripeness. Due to resins, the uncooked red fruits are poisonous. The endocarp and the absence of an endosperm characterize these seeds. The main agents of spread are frugivorous birds. Only P. vera, a species of commercial significance, produces edible nuts [2]. Popular cultivars of P. vera include Bronte, Damghan, II, III, Kerman, Ohadi, Kaleh, Momtaz, etc. [11]. The nuts other species produce are either not commercially viable or are grown solely for aesthetic purposes. Insects, most notably aphids and chalcidoid wasps, cause leaf galls on some Pistacia species [12]. Aphids use the leaves and buds as a haven for their developing larvae by manipulating them into tumorous galls. Slavumwertheimae and Baizongiapistaciae L. are common aphid species [13]. The shapes of the galls range from random to cauliflower-like to spicy to coral-like to curved. Galls contain high concentrations of volatiles, such as terpenes, which are antibacterial against bacteria, viruses, and fungi [14]. Galls have been found to provide essential biological functions according to their unique phytochemistry compared to the plant. The galls had ten to sixty times the average amount of total terpene, primarily comprised of the monoterpenes a-pinene and limonene [14]. In contrast, the healthy leaves contained more sesquiterpenes, particularly E-caryophyllene, germacrene D, and d-cadinene [15]. Aphids were found to have modified the secondary metabolite synthesis pathways of the plant to their advantage[16].

**Phytochemistry of Genus *Pistacia*Ê**

Diverse bioactive phytochemicals, including gum and essential oils, have been isolated from several species of Pistacia. Several crucial elements supported by established or ongoing empirical research are discussed in this article. Typical of other members of the Anacardiaceae family, Pistacia trees secrete large amounts of chemicals through their woody structures. The *P. lentiscus*var. chia plant is the source of Chios mastic gum[17]. This resin, a complex mixture of many distinct substances, can yield essential oil. Rich in phytochemicals, both the gum and the oil have diverse pharmacological effects. Antimicrobial, immunity-correcting, hypocholesterolemic, anti-inflammatory, anticancer, antiatherogenic, digestive, etc., are just some of its many applications. Numerous in-depth analyses of mastic gum and its constituents have been conducted [17,18]. The essential oil contains a high concentration of triterpenoids, which have been linked to the oil's anticancer properties [19]. The triterpenic acids 24Z-isomasticadienonic acid (IMNA) and 24Z-isomasticadienolic acid are beneficial [20]. Essential oils have been shown to include a wide variety of compounds, including carvacrol, limonene, a-terpineol, alpha-pinene, b-caryophyllene, beta-pinene, camphene, verbenone, and linalool, to name a few [21,22]. According to a review, this gum has been used as a medicine and a food item in various cultures, including the Greeks, Romans, Byzantines, Arabs, and Europeans [18]. Only a few Pistacia species have been analyzed for their essential oil content. Hence there is a lack of information in the literature. Essential oils can have vastly different aroma profiles based on species, tree gender, plant part (mastic gum, fruits, leaves, andgall), region, extraction solvent, and process. Monoterpenes and oxygenated sesquiterpenes are abundant in the oil. a-humulene, myrcene, delta-3-carene, muurolene, terpinen-4-ol, a and b-pinene, camphene, b-gurjunene, spathulenol, limonene, germacrene, a-humulene, epi-bicyclosesquiphellandrene, etc. are just some of the frequent components. [15,23,24]. Hydrodistillation is typically the preferred extraction technique [25]. Gas chromatography-mass spectrometry (GC-MS) has contributed to the accessibility of this field. Based on their chemical composition, essential oils from Pistacia can be divided into severalchemotypes [25]. The categorization of chemotypes was facilitated by principal component analysis (PCA)

[26]. The most abundant compounds were flavan-3-ols, myricetin,luteolin, g-tocopherol, cyanidin-3-galactose, chlorophyll a, b-carotene, and g-tocopherol [27]. The*P. lentiscus* essential oil contains thunbergol, germanicol, terpinyl propionate,himachalene, trans-squalene, 3,3-dimenthol, and cadinyl-1.4-diene. Different plant regions showed qualitative and quantitative differences [28]. Fresh, unripe pistachio fruits contained more essential oil than foliage[29]. The nut's skin is rich in phenolics, whereas the nutmeat has lipophilic components [30]. The nuts provide a lot of healthy fats, including monounsaturated fatty acids(MUFA) andpolyunsaturated fatty acid (PUFA).

**Ethnopharmacological Aspects of the Genus Pistacia**

Various *Pistacia*species have long been valued for their functional resin, leaves, fruits, and aerial parts. Resin from *P. lentiscus*has been used for as long as 5,000 years, making it the most widely used species. In the Mediterranean and Middle Eastern countries, *P. lentiscus*resin has been used to treat a wide range of stomach problems for over three thousand years [31]. It has been used as a preservative and a breath sweetener [32], and it was burned as incense in ancient Egypt. The resin of *P. atlantica*has been used traditionally in Iran to treat gastrointestinal, liver, and kidney disorders [33]. The*pistachio* (*P. vera*) fruit is prevalent in many different cultures. Pistachios have been a food source since at least 7,000 BC [34]. Pistachios are grown in the Mediterranean, the Middle East, and the United States. Iran is a significant pistachio nut exporter and producer [35].

Fruit kernels of *Pistaciakhinjuk*, *Pistaciaatlantica*, and *Pistaciaterebinthus*are used as aphrodisiacs and for treating kidney, liver, heart, and respiratory disorders. *Pistacialentiscus* gum resin is used as a pain reliever and anti-inflammatory. Multiple constituents and portions of.*Pistacialentiscus* has demonstrated radical-scavenging activity in vitro [36–39]. Human LDL was well protected from oxidation in vitro by *P. terebinthus* var. chia resins and *Pistacialentiscus* var. chia [40]. Antioxidant activity in *P. atlantica* leaf and fruit have been measured, and it is comparable to or even exceeds that of reference compounds in in vitro experiments [41]. Antioxidant activity in *P. vera* fruit was similar to that of a synthetic antioxidant [42]. The roasting method may increase the fruits' antioxidant activity [43]. Many Gram-negative and Gram-positive microorganisms are vulnerable to the potent antibacterial properties of Pistacia species. The plaque was reduced on teeth using *P. lentiscus* gum, which was shown to have antibacterial action against *Prevotellamelaninogenica* and *Porphyromonasgingivalis* [39]. Significant antifungal activity was demonstrated by the essential oil of *P. lentiscus*leaf and gum, several extracts of *P. khinjuk*leaf, and the essential oil of *P. vera*gum [22]. Leaf extract inhibited *Plasmodium falciparum* without harming mammalian cells, whereas *P. vera* branch extract inhibited *Leishmaniadonovani* significantly [44]. The antiprotozoal action of *P. atlantica* leaves and twigs, as well as its active component 3-methoxycarpachromene, was described by Adams et al. [45]. Mice infected with Leishmania major had their cutaneous leishmaniasis under control after being given gum from *P. atlantica* [46]. In a double-blind, placebo-controlled study, *P. lentiscus* gum significantly mitigated the intensity of functional dyspepsia symptoms reported by study participants [47]. Several in vivo acute and chronic inflammation models showed anti-inflammatory action in *P. terebinthus* gall [48]. The anti-inflammatory activity of *P. lentiscus* var. chia gum has been linked to its potential role in reducing superoxide and hydrogen peroxide generation by NADPH oxidase [49]. Strong acetylcholinesterase (AChE) inhibition was observed in aqueous preparations of the leaves of both *P. atlantica* and *P. lentiscus*[50]. *Pistaciapalaestina* fruit extract silver nanoparticles promote wound healing in rats[51].

**Anticancer Potential of a Genus Pistacia**

*The P. lentiscus* has been studied more than any other Pistacia species for its potential anticancer effects[1]. In a study using human colon cancer cells xenografted into mice, the gum showed anticancer efficacy by inhibiting the development of colorectal

tumors [31]. The human breast cancer MCF-7 cell line was evaluated with fractions generated from *P. integerrima* crude extract. A 200mg/ml concentration indicated 100 and 97.4% inhibition in the ethyl acetate and chloroform fractions, respectively. The results appeared to be dose-dependent. This discovery paved the way for future cytotoxic studies of Pistacia extracts for their ability to fight cancer [52].

*In Vitro Studies of a Genus Pistacia*

The chia gum from *P. lentiscus* reduced the growth of human colorectal tumor cells in vitro [53] and caused some of those cells to commit suicide. *P. lentiscus* leaf essential oil and various preparations strongly inhibited mutagenicity in vitro [54]. *P. lentiscus*fruit extracts inhibited genotoxicity and mutagenicity in vitro [37]. The cytotoxic activity of *P. vera*oleoresin was moderate against several cancer cell lines, including those of the normal melanocytes, cervix, hepatocellular carcinoma, and breast carcinoma [55]. Significant In-vitro anticancer potentials were discovered for AgNPs when tested on AGS and MCF-7 cell lines using the MTT assay [56]**..**

*In Vivo Studies of a Genus Pistacia*

The resin inhibited the normal apoptosis of oral polymorphonuclear leukocytes and had the most significant cytotoxic effect of 13 human cell types against promyelocyticleukemia [39]. In a study using human colon cancer cells xenografted into mice, the gum showed anticancer efficacy by inhibiting the development of colorectal tumors [31]. Cell proliferation was suppressed, and cell cycle progression was halted [57]. It also upregulated the production of maspin (a mammary serine protease inhibitor with tumor suppressive action for prostate malignancies) in sensitive prostate cancer cells. A high dose of P. lentiscus gum was shown in an in vivo study to promote the development of preneoplastic lesions in rat liver with increasing relative liver weight, suggesting that the desirable anticarcinogenic effects of mastic could be obtained at relatively low doses despite the many reports of its antitumor activities [58]. *Pistaciakhinjuk* samples have the potential to be used as an Anticancer agent[59]

*In Silico Studies of a Genus Pistacia*

The essential oil of pistachio hulls contains chemicals that may be effective in treating gastrointestinal malignancies, according to an insilico study[60]. In a computational study, the anticancer activity of *Pistaciaintegerrima* was found to be indicated[61]. In-silico analysis [62] showed that rhodamine123 is bound to the exact location of the compounds naringenin and dihydrokaempferol.

**Clinical Studies**

Various components of Pistacia species, such as resin, leaves, fruits, and aerial parts, have long been employed in diverse clinical applications, drawing upon their inherent material properties. The growth inhibitory effects reminiscent of doxorubicin were observed in human colon cancer cells after exposure to a fruit extract derived from *P. atlantica* sub. Kurdica[63**].**Breast cancer cell lines, hepatocellular carcinoma, cervical cancer cell lines, and normal melanocytes were all somewhat sensitive to *P. vera* oleoresin's cytotoxic effects [64]. The resin impeded the typical programmed cell death of oral polymorphonuclear leukocytes and exhibited the highest degree of toxicity towards promyelocyticleukemia among a set of 13 distinct human cell types [31]. The utilization of *Pistaciakhinjuk* samples exhibits promising potential as an agent for combating cancerous growth [59].

**Molecular Mechanism**

There is mounting proof that pistachios induce apoptosis in cancer cells by modulating intrinsic and extrinsic mechanisms. Accordingly, the results from Hashemi et al.'s investigation on MCF-7 cell lines treated with three dosages of F13b1/PV-EA showed that the chemical had a dose-dependent influence on cell viability, causing the cell lines to undergo certain apoptotic morphological alterations [65]. Fathalizadeh et al. investigated the apoptotic effects of *pistachio rosy* hull (PRH) aqueous extract on HepG2 cells. They concluded that the extract caused apoptosis in the cell lines, drastically decreasing their viability. Additionally, it was shown that PRH treatment of cancer cell lines caused changes in the expression of numerous intrinsic and

extrinsic signaling pathways relevant to apoptosis. The PCR array revealed upregulation of 8 proapoptotic genes (CD27, lta, faslg, bag4, t, pycard, casp14, and casp6) and the downregulation of 9 others (tnfrsf21, tnfrsf10a, bcl2l11, bax, casp3, casp4, casp7, casp10, and cradd) [66]. Also, the expression of 5 anti-apoptotic genes (birc3, , traf2xiap, bcl2a1, and cflar) was reduced. As a cellular FLICE-like inhibitory protein (c-FLIP) with a crucial role in apoptosis regulation, the downregulation of CFLAR (CASP8 and the FADD-like Apoptosis Regulator) is an intriguing topic for cancer therapy [67-68]. TNF receptor-associated factor 2 (TRAF2) is known to interact with p43-FLIP or the N-terminal portion of c-FLIP long isoform (c-FLIPL), leading to NF-B (the nuclear factor kappa-light-chain-enhancer of activated B cells) activation [66]. Therefore, NF-B activation upregulates anti-apoptotic genes, ultimately leading to cell survival[67].Deregulation of the natural mechanism of apoptosis is a common cause of cancer. Cancer cells may become resistant to chemotherapy as a result of this imbalance. As a result, creating novel medications to control apoptotic molecules is one of the most promising ways to combat cancer [68]. Harandi et al. [69] found that the hydroalcoholic extract of pistachio hull balanced the expression of bax/bcl-2 genes, hence regulating the intrinsic apoptosis pathways in HepG2 cells. The apoptosis-inducing bax gene releases cytochrome C, and the anti-apoptotic Bcl-2 protein blocks the cytochrome C channel. The antitumor effects of a hydroalcoholic extract of wild pistachio leaves were investigated by Ahmadirad et al. in a study conducted on the breast cancer (MCF-7) cell line. After 48 hours of treatment with the extract, the IC50 values were determined to be 250 µg/mL for the malignant MCF-7 cell line and 400 µg/mL for the normal L929 cell line. DNA fragmentation assays and morphological examination showed that treatment at the IC50 concentration induced apoptosis in both cell lines. The extract caused apoptosis in MCF-7 cells via extrinsic and intrinsic mechanisms, as evidenced by the overexpression of caspases -8 and -3, bax and p53, and the corresponding reduction in bcl-2 expression. When the expression of the bcl-2 gene was downregulated alongside that of p53, bax, and p21, apoptosis was promoted in the Hep G2 cell line. Direct activation of bax gene transcription and subsequent induction of apoptosis is facilitated by the P53 protein, which enhances the expression of the bax gene [70]. Koyuncu et al. investigated the anticancer properties of various pistachio hull extracts. Accordingly, they discovered that the n-hexane fraction arrested the cell cycle at the G1 sub-phase and induced apoptosis in malignant cell lines via oxidative pathways[71]. Using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay, Seifaddinipour et al. assessed the cytotoxicity of various fractions of the ethyl acetate extract of pistachio hull. F13b1/PV-EA was the most cytotoxic fraction, with gallic acid and quercetin being the most abundant active compounds. In addition, the calculated IC50 value of F13b1/PV-EA against MCF-7 cell lines was 15.2 1.35 g/mL. Using the RT-PCR technique, this fraction increased the expression of SOD, CAT, bax, and caspases 3 and 8 but decreased that of bcl-2. F13b1/PV-EA inhibited tumor development in cancer-induced mice [72], according to in vivo investigations.

*Toxicological Studies*

The essential oil of *P. lentiscus* inhibited tumor growth in immunocompetent rodents without causing toxicity through apoptosis induction, reduced neovascularization, and chemokine expression inhibition [59]. Toxicity test results ofÊ*pistaciavera* produced by the admetSAR online server confirmed that all compounds have no toxicity effect[60].

## CONCLUSION

The escalating prevalence of malignant malignancies worldwide, coupled with the multitude of adverse effects associated with existing therapies, has expedited the quest for more efficacious alternatives. Because of their potential to disrupt carcinogenic molecular signaling pathways, many people are interested in herbal-based complementary and alternative medicines. The phytochemicals in pistachios have anticancer properties, according to the current review. This review was centered on the function of these factors in regulating apoptosis. However, additional research is required to determine

the precise mechanisms by which pistachios inhibit tumor growth, primarily via their apoptotic effect.

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*Author's Contribution*

ZA: Conception and design of the work; writing and final approval of the manuscript

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