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REVIEW

Anticancer Effects of Punicalagin

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Abstract

Side effects of treatments such as chemotherapy, radiotherapy, and immunotherapy, which are widely used today, negatively affect the cancer treatment process. In particular, the need for new treatments with less side effects but with higher therapeutic power is increasing day by day due to the resistance developing in patients against antineoplastic drugs and radiation therapy. From this point of view, natural compounds of plant origin attract attention because of their bioavailability, less side effects, and most importantly, because they can be either an auxiliary or an alternative treatment to traditional cancer treatments due to their low cost.

Pomegranate (*Punica granatum*) is a fruit that is abundant in our country, has anticancer bioactive components such as phenolic compounds, and has medicinal value. The pomegranate fruit peel that constitutes approximately 30% of the weight of pomegranate fruit, which is unfortunately discarded, is actually particularly rich in phenolic compounds such as Punicalagin (PN) and Ellagic acid (EA) and various minerals. There are studies revealing that PN has direct or indirect anti-oxidant, anti-tumor, anti-atherosclerosis, anti-inflammatory, anti-viral, anti-fungal, and anti-bacterial effects. Its positive effects on health and its non-toxic structure enable the multifunctional use of PN compound. In this review, the therapeutic use of PN phenolic compound as an anti-cancer agent is discussed.

Keywords: Cancer; phenolic compounds; pomegranate; punicalagin.

Cancer is defined as the progression of damaged and/or mutant cells through the cell cycle, which must die due to the accumulation of functional disorders and mutations in the cell cycle[1]. Cancer is a genetic disease caused by the disruption of information in DNA, the genetic material of the cell, and causes abnormalities in gene expressions. In this process, the effects of genes that control functions such as growth, survival, and invasion/motility in a healthy cell during the normal life cycle increase, while genes that suppress these functions become dysfunctional[2]. Although epigenetic changes that are not related to mutations appear to be quite important factors, the main mechanism in the process of cancer is also considered to be mutational changes[3].

Programmed cell deaths, which are regarded as apoptosis, autophagy, and programmed necrosis, are considered to be the death of a cell in any pathological condition mediated by an intracellular program. These three programmed forms of death can jointly decide the fate of the cell; While apoptosis and programmed necrosis always direct the cell toward death, autophagy can play a pro-survival or pro-death role. Recent evidence suggests that researching and understanding the complex interaction between these three different types of cell death may give clues about cancer initiation and progression[4].

With the efforts made in the past 50 years, many studies have been conducted to develop new therapeutic ap-

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proaches against cancer, many potential chemotherapeutic agents have been put on the market and have been successfully used in clinical applications. However, cancer is still one of the leading causes of death in most countries. Today, it is observed that the primary research of pharmaceutical companies and independent research organizations are carried out to develop new therapeutic agents to treat cancer. The common goal of all research in this field is to develop new therapeutic agents that have selective cytotoxic and/or antiproliferative effects on cancer cells and that do not induce toxic responses in normal cells. Therefore, the development of new agents that are both effective and safe is extremely important for cancer treatment[5].

When the relation of herbal-derived agents with cancer is examined, the fact that each of these agents has a potential within itself for anticancer drugs draws the researches in this direction. Natural compounds obtained from plants and herbs are used for therapeutic purposes against many diseases. Many scientific studies have revealed that plants can be useful in the treatment of many diseases that affect human life and quality of life, such as infections, metabolic diseases, and cancer. The pharmacological examination of natural compounds obtained from plants, revealing the mechanism providing the aforementioned effect, and identifying the component or components responsible for these effects will guide the studies in this field. Flavonoids are among the natural compounds that have been involved in many clinical trials. Considering the number of studies investigating the anticancer effects of flavonoids, it is seen that flavonoids are potential anti-cancer agents[5-7].

Pomegranate (*P. granatum* L.) is a fruit that is consumed around the world in fresh form or in processed forms such as extract and is well known to have numerous therapeutic effects and is included in the daily diets of many people. Besides its anti-oxidant, anti-diabetic, and anti-atherosclerotic properties, it is also observed that pomegranate has anti-cancer effects in experimental models of lung, prostate, and skin cancer. Pomegranate contains a wide range of phytochemicals, mainly Punicalagin (PN) and Ellagic acid (EA). As a result of detailed literature review on pomegranate fruit and its peel, it has been observed that pomegranate fruit extract has growth suppressing and cytotoxic effects on many cancer cell lines[8].

PN (2,3-hexahydroxydiphenylgallagil-D-glucose), *P. granatum* is a bioactive tannin compound that can be isolated in large quantities and that forms the characteristic yellow color of the pomegranate peel. It is the largest water-soluble ellagitannin molecule with high level of bioavailability. PN makes up the bulk of the pomegranate fruit component, and its isomers are mostly known to be responsible for the high antioxidant potential of pomegranate juice. There are also findings suggesting anti-hepatocellular and anti-angiogenic effects, and especially anti-inflammatory effects[9]. In this review, the anti-cancer efficacy of PN will be discussed.

Flavonoids and Their Anti-Cancer Effects

The current drugs used today are insufficient in the treatment of cancer due to accumulating mutations. For this reason, there is a great need for research to discover new molecules or to increase drug efficacy in cancer treatment. As a result of many studies conducted in recent years, many potential chemotherapeutic agents have been put on the market to develop new therapeutic approaches against cancer that have started to be used successfully in clinical applications. However, it is a fact that there is a need for new agents that can be used as alternatives to existing chemotherapeutic agents due to the side effects and the developing drug resistance. The common goal of all research in this field is to discover new therapeutic agents that have selective cytotoxic and/or antiproliferative effects on cancer cells and that do not result in toxic responses from normal cells. Therefore, the discovery of new alternative agents that are both effective and safe is very important for cancer treatment. At this point, we encounter plant-derived extracts or metabolites isolated from plants[5].

The relationship between cancer and nutrition is currently supported by epidemiological studies conducted at national and international levels. There are examples of how a diet rich in fruits and vegetables can lead to a reduction in the risk of common types of cancer and may be beneficial in cancer prevention, particularly revealing that certain phytochemical classes have benefits in both basic and clinical studies[10]. Many studies have revealed that plants are used for treatment against infectious (bacterial, fungal, parasitic, and viral), immunological, cardiovascular, neurological, inflammatory diseases, and cancer[7].

Flavonoids are heat-resistant polyphenolic compounds commonly found in nature. They usually consist of two aromatic rings, each bearing at least one hydroxyl group, connected through a three-carbon "bridge" to a six-membered heterocyclic pyran ring[11]. Flavonoids are divided into six subgroups according to the way an aromatic ring is attached to the heterocyclic ring: flavones, flavanones, flavanols, flavonols, isoflavones, and anthocyanins (Fig. 1). Compounds of each subclass are characterized by specific hydroxylation and conjugation patterns. Certain

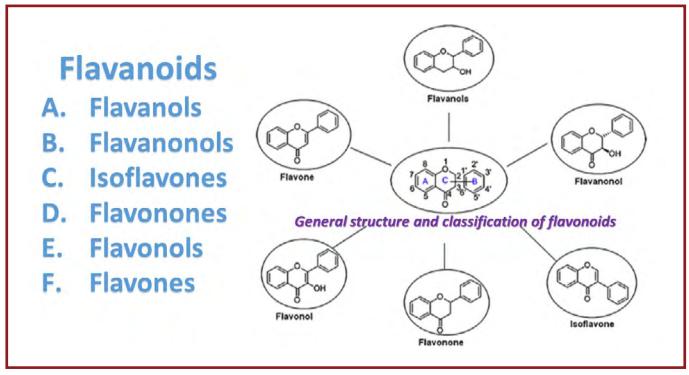

Figure 1. General structure and classification of flavonoids[15]

food groups are often rich sources of one or more of these polyphenols[12]. Flavonoids are the source of yellow, red, and purple colored pigments in plants, and they are abundant in fruits such as apples, grapes, pomegranates, citrus fruits, blackberries, in vegetables such as tomatoes, lettuce, broccoli, radishes, beans, and in plants such as tea, turmeric, and others[10-14]. Flavonoids are valuable biological components and are consumed in significant amounts in daily diets. It is estimated that humans ingest about 100 mg of flavonoids per day[13,14]. It is supported by many studies that flavonoids have various biological effects such as antiallergic, anti-inflammatory, antioxidant, antimutagenic, and anticarcinogenic effects[15-17]. Flavonoids have become prominent natural agents in anti-cancer studies in recent years because they suppress cell cycle, induce apoptosis, inhibit mitotic spindle formation, and inhibit angiogenesis. Their different structural features indicate that each may be a potential anti-cancer agent[18-21]. It is known that dietary flavonoids, along with other components such as various vitamins, play an important role in cancer prevention. The effects of flavonoids on cell signal transduction pathways associated with reactive oxygen derivatives, cellular proliferation, apoptosis, and angiogenesis make them an interesting topic in molecular studies. The mechanisms of the effects of flavonoids on cancer cells continue to be investigated. Studies suggesting that dietary flavonoids can be used in a new approach for cancer prevention are promising[5,14,17,22,23].

PN and Anti-Cancer Mechanisms of Action

Pomegranate (*P. granatum* L) is a primitive, mystical, and different fruit that has medicinal value due to its unique structure and phytochemical content. The reported health benefits include anticancer properties (prostate cancer, colon cancer, breast cancer, lung cancer, skin cancer, and leukemia), treatment of cardiovascular diseases, prevention and management of diabetes, and contribution to hormonal balance and skin nutrition. Pomegranate has many active ingredients that unfortunately cannot be fully utilized since most of them are discharged from the body[24]. Pomegranate peel is a natural vegetable-based dye due to its yellow pigment content. There are records of pomegranate being used by the public for years as a natural dye. The main source of these natural pigments is the numerous polyphenols found in the structure of pomegranate, primarily PN. In addition, the fact that pomegranate peel is very rich in minerals such as magnesium, sodium, potassium, calcium, phosphorus, and nitrogen makes it medicinally valuable[24,25].

The peel, which is rich in phenolic components, constitutes 26–30% of the total weight of the fruit. Pomegranate peel contains many phenolic compounds such as flavonoids (anthocyanin, catechin, and other complex flavonoids) and tannins (EA, gallic acid [GA], PN, and punicalin)[26]. The various medicinal properties of pomegranate peel are actually attributed to the high-molecular-weight polyphenols found in its structure. These phenolic compounds protect the human body by neutralizing the destructive effects of free radicals and oxidative stress on cell membrane, organelles, and DNA surface[27,28].

In terms of bioavailability, it has been observed that the amount of phenols and hydrolysable tannins is greater in the peel than in the flesh, the best examples of these being phenolic compounds such as PN and EA. PN, known as the largest molecular weight polyphenol, is also the most common polyphenol in pomegranate. PN is one of the unique members of the ellagitannin family[22]. Especially when the dry parts of the flesh of the pomegranate are examined, it is observed that PN, EA derivatives, and GA are abundant in the peel, while protopathic acid and GA compounds are generally found in the seeds. The average amount of PN in dry matter has been reported to be 78.79 mg per gram of pomegranate peel[29]. This ratio can be considered valuable compared to the total weight of the pomegranate. PN is a high-molecular-weight (1081), medical, and bioactive component, it is a water-soluble phenolic compound that is primarily obtained from pomegranate peel, as well as being abundant in pomegranate seeds and juice. PN can only be obtained by natural extraction methods[30]. There are studies that report direct or indirect anti-oxidant, anti-tumor, anti-atherosclerosis, anti-inflammatory, anti-viral, anti-fungal, and anti-bacterial effects of PN. It is known that its antioxidant activity is due to the 16 hydroxyl (OH) groups in its structure (Fig. 2)[26,30-33].

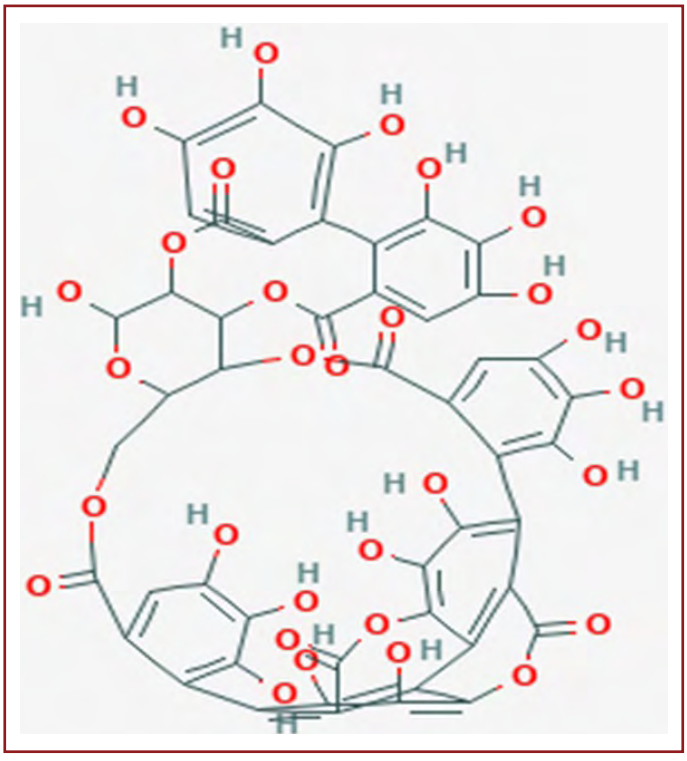

Figure 2. Molecular structure of Punicalagin (taken from PubChem).

There are many studies that show the anti-cancer effects of PN. It suppresses the growth of tumor cells and also has anti-proliferative and apoptotic effects. There are studies reporting that PN slows down the progression of cancer types such as human papillary thyroid, ovarian carcinoma, and colon cancer. Its positive effects on health and its non-toxic nature enable a multifunctional use of the PN compound[34-37].

In a study showing that PN, which is a dietary phytochemistry, changes various cell signal transduction pathways associated with cell apoptosis and proliferation, it may have an effect on some Bcl-2 family proteins and caspase family members on human cervical cancer cells, and also may have an effect through p53, one of the cell cycle regulatory proteins, and NF-κB signaling. This study demonstrated that PN inhibits cervical cancer cell proliferation and induces mitochondria-mediated cell apoptosis by suppressing NF-kappa B activity in ME-180 cells[38]. In another study investigating the effect of PN on PCa cells, which are prostate cancer cells, its anti-proliferative effects and its effects on the extrinsic pathway of apoptosis have been examined. As a result, it has been reported that PN induces apoptosis by caspase-3 and caspase-8 activity in PCa cells and has antiangiogenic effects[39].

Cytotoxic effects of PN on lung cancer cell line A549 and lung epithelial cell line MRC-5 have been evaluated and it was found to be an effective agent for apoptosis at concentrations of 50 μM, 75 μM. While PN has cytotoxic effects on A549 cell line, the fact that it does not cause toxic response in epithelial cell line indicates that PN has selective toxicity, which is very important for cancer treatments. In addition to these, it has been reported that cytoplasmic ROS production decreased and release of superoxide radicals from mitochondria increased, causing changes in cell morphology, and PARP cleavage by activating caspases, as results that support the induction of the apoptosis pathway[40].

In a study conducted by Tang et al.[37] in 2017, they suggested that PN may have chemopreventive and chemotherapeutic effects against cervical cancer in humans through the inhibition of the β-catenin signaling pathway in the application of PN in HeLa cells, a human cervical cancer cell line. In another study, it was demonstrated that PN inhibits MMP-2, MMP-9, and N-Cadherin expressions in MCF-7 and MDAMB 231 human breast cancer cells, triggers E-Cadherin expression, thereby suppressing cell viability, migration, and invasion in cells. Researchers have reported that PN causes cell death in breast cancer cells by significantly inhibiting Golgi phosphoprotein-3 expression, which supports the survival of cells. Current findings provide a potential therapeutic approach that PN may exert anti-cancer activity through different mechanisms as well as its apoptotic effects[41].

PN activates the MAPK pathway and inhibits mTOR signaling pathways in human papillary thyroid carcinoma breast cancer cells, causing apoptosis-independent autophagic cell death[42]. Luo et al.[43] (2020) found that PN increases Beclin-1 expression by preventing the phosphorylation of AKT/FOXO3a in L02 liver cancer cells and thus activates autophagy. PN has been suggested to induce both apoptotic and autophagic cell death in U87MG human glioma cells[44]. In another study carried out in human osteoblast cell line (hFOB1.19) and human osteosarcoma cell lines (U2OS, MG63, and $SaOS_2$), the inhibitory effect of PN on proliferation and invasion of cells has been examined by Huang et al.[45] PN treatment significantly reduced osteosarcoma cell proliferation while triggering apoptosis. While it has been emphasized in this study that PN significantly downregulates interleukin (IL)-6 and IL-8 levels, this has been associated with inhibition of NF-kB signaling. With the tumor xenograft mouse model, it has also been revealed *in vivo* that PN exposure inhibits osteosarcoma growth and angiogenesis. These observations showed that PN has a suppressive effect against osteosarcoma malignancies. Ganesen et al.[46] examined the expression of Annexin A1 (Anx-A1) in HCT 116 colorectal adenocarcinoma cells and the role

of PN in modulating the interaction between apoptosis and autophagy. PN demonstrated its anti-cancer effect by modulating the apoptosis-autophagy switch through down-regulation of the Anx-A1 protein in the colorectal cancer cell line HCT 116. PN therapy also appears to alter the expression of proteins involved in apoptosis and autophagy mechanisms, particularly in the presence of FPR inhibition, suggesting that these proteins may play a role in their transcription, translation, and localization.

PN is the major bioactive component of pomegranate peel and is known to have antioxidant, anti-inflammatory, antiviral, antiproliferative, and anticancer properties[37]. In numerous studies, PN treatment has been revealed to have effects such as inhibiting proliferation, invasion and angiogenesis, and triggering both apoptotic and autophagic cell death in many cancer types such as breast, ovarian, cervix, prostate, colon, colorectal, lung, liver, and papillary thyroid[38-46]. In this context, it is hoped that the use of PN in pomegranate peel, which is a natural value that unfortunately goes to waste, in cancer treatments will be discussed, and it is hoped that this photochemical will draw attention to the value of this photochemical in herbal medicine, and perhaps shed light on new treatment methods.

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