



REVIEW ARTICLE

Punicic Acid: A Versatile and Promising Nutraceutical with Potential Health Benefits

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A B S T R A C T

Fruits are an important part of the human diet because they not only provide basic nutrients but also have a therapeutic effect against different diseases. Pomegranate is an ancient fruit and has several versatile proactive such as puniceic acid, commonly known as omega 5; a polyunsaturated fatty acid and an isomer of conjugated linolenic acid (CLnA). It is mostly found in pomegranate seed oil (PSO) extracted by different methods including superheated hexane extraction method, cold pressing, soxhlet method, and supercritical fluid extraction method. It is readily metabolized into conjugated linoleic acid in the human body and does not affect lipid metabolism and the process of oxidation. This 9c, 11t-conjugated linoleic acid has an important biological role in biological role in the body and is the natural source of CLA in the body which is made through the breakdown of CLnA. It has many health benefits as an anti-oxidant by reducing the level of reactive oxidative species (ROS) and anti-carcinogenic and anti-diabetic activities by reducing the activity of tumor necrosis factor TNF- α and nuclear factor kappa B (NF κ B) and up-regulation of peroxisome proliferator-activated receptor- α (PPAR α) gene involved in glucose homeostasis. In addition, this versatile proactive induces apoptosis and reduces proliferation and anti-inflammatory by lowering the level of pro-inflammatory cytokines.

Keywords: Punicic Acid, Conjugated Linolenic Acid, Anti-Diabetic, Anti-Oxidant, Anti-Carcinogenic, Anti-Inflammatory.

1. INTRODUCTION

Human uses fruits as a main part of food but their uses for the treatment of diseases regarding therapeutic concern are also important (Mile *et al.*, 2017). This is because they not only provide the basic nutrients to the human body but also have several versatile proactive (Dillard *et al.*, 2000). The use of natural products as an alternative to medicines is now increasing day by day (Dewil *et al.*, 2017). Some vital medicinal products such as quinine, vinca alkaloids and digoxin are formulated by using herbs (Awuchi, 2019). Plants naturally produce various chemical compounds as a byproduct of their metabolic processes, which can be extracted and used for medicinal purposes (Nwonu *et al.*, 2019). Pomegranate is an ancient fruit and is majorly found in Iran. It belongs to the Pinaceae family, which is a shrub or small multi-stem tree that grows approximately 16 to 26 feet tall (Pande and Akoh, 2016). Furthermore, it is considered a holy fruit known as the jewel of winter throughout the world has 500 types with different characteristics that vary in size, shape, color, flavor, and taste (Mahesar *et al.*, 2019). A well-ripened pomegranate contains fat (0.1%), mineral matter (0.7%), fiber (5.1%), carbohydrate (14.5%), protein (1.6%), phosphorus (70 mg/100g), magnesium (12mg/100g), calcium (10mg/100g) and boron (0.3 mg/100g) it contains a good concentration of vitamins, vitamin C (20 mg/100g), riboflavin (0.1 mg/100g), thiamine (0.06 mg/100g) and Nicotinic Acid (0.3 mg/100g). Pomegranate fruit has a digestible carbohydrate content of 12-16% in the form of glucose and fructose, with an acidity level of 1.3-3%. Additionally, it provides 65 calories per 100g serving (Venkatasamy *et al.*, 2019). Seeds make 3% of fruit weight and seeds of the

pomegranate contain conjugated fatty acid in the range of 20-22 % in different concentrations in the pomegranate seed oil the concentration of the conjugated fatty acid is high in the foam of puniceic acid (Table 2) (Mahesar *et al.*, 2019). Pomegranate seeds are usually considered waste and after usage, they are disposed of but they contain very beneficial ingredients oil which is extracted from its seeds contain a complex array of fatty acids almost 80 % of which are 18 carbon molecule with 3 alternating double bonds called trienoic acid research reveal that trienoic acid present in the (PSO) have potent physiological activities as compare to dienoic acid having two alternating double bond and the specific trienoic acid present in the (PSO) is puniceic acid (PA) it is also known as omega 5 (Pamisetty *et al.*, 2020). It is a polyunsaturated fatty acid (18:3 n-5) an isomer of conjugated α -linolenic acid (CLnA) (Garaiova *et al.*, 2017) similar in structure to linoleic acid (CLA) and linolenic acid (LnA) it is also called super conjugated linoleic acid (CLA) (Aruna *et al.*, 2016) with molecular formula $C_{18}H_{30}O_2$ a melting point of 44-45°C, and molar mass of 278.43 g/mol as shown in Table 2 (Shabbir *et al.*, 2017; Song *et al.*, 2017).

Pomegranate seed oil (PSO) is a natural product and extracted from *Punica granatum* which is an ancient fruit containing shrub. It comprises of a mixture triacylglycerol TAG, a high percentage of conjugated fatty acids, and specifically a good amount of Punicic acid (PA) (Pamisetty *et al.*, 2018). About 72% of seed oil consists of Punicic Acid (Carvalho, 2014) and a small number of geometric isomers such as α -eleostearic acid, β -eleostearic acid, and catalytic (Fig 1) (Adu-Frimpong *et al.*, 2019). It is also found in bitter melon, T. kirilowii, M. charantia, and snake gourd seed oil (Table 1) (Aruna *et al.*, 2016).

Although pomegranate seeds are a natural and abundant source of punicic acid (Carvalho, 2014) but it is not feasible for large-scale industrial use due to restricted extraction process, low yield and problems in cultivation due to tropical and sub-tropical climate (Durante *et al.*, 2017). Consequently, because of its effective natural bio-actives and less availability, efforts are made to develop a biotechnological platform for the high-scale production of PSO (Tirado-Gallegos *et al.*, 2021).

Table 1. Sources of Punicic Acid from Pomegranate and *Trichosanthes Kirilowii* Seed Oil

Parameters	Pomegranate Seed Oil	<i>Trichosanthes Kirilowii</i> Seed Oil
Saturated	10%	7.50%
Di-Unsaturated	10%	32.70%
Mono-Unsaturated	10%	22.91%
Punicic Acid and Isomer (C18: 3-9c,11t,13c)	70%	35.89%

(Source: Shabbir *et al.*, 2017)

1.1. Isolation of Punicic Acid Using Various Extraction Modes

Many types of extraction methods are used including normal stirring, Microwave irradiation, Soxhlet method, superheated hexane method, supercritical fluid extraction method, cold pressing, petroleum benzene as a solvent, and ultrasound irradiation.

1.2. Microwave Pretreatment

Pomegranate seeds were grounded and placed in the Pyrex Petri dish of 9cm in a microwave oven. The sample in the microwave rotates at (NN-GD 469M, Panasonic). This specific configuration maintains an equal electromagnetic field inside the oven. The frequency was set at 2450MHz at three levels of power 100, 250, and 600W for two times (2 to 6 min). Temperature is set at 63 to 136°C. After this, the seeds were placed in another apparatus for the extraction process the seeds not given microwave treatment were placed in a controlled group to check the difference in the extraction (Durdevic *et al.*, 2017b).

1.3. Super-Heated Hexane Extraction Method

This method is carried out in a laboratory by using ground seeds. The apparatus consists of a feed reservoir, a coil to preheat the solvent, to check the pump suction rate a burette high-pressure pump and an extractor that is 20.7 volume stainless steel cylinders. After the preheating of the coils, a three-way line was made by using high resistant high-pressure needle valves. Some components were present in the oven they work at 200 °C. For the immediate cooling of the extract, a double-pipe heat exchanger with water is used. The 2.2m to 1mm stainless steel was used before Back Pressure Regulator (BPR) (Eikani *et al.*, 2012).

1.4. Cold Pressing

In the sample of 20 g is placed in a laboratory made extraction vessel for 72 hours with 10 tones using a standard mechanical press that make pellet (Eikani *et al.*, 2012). The extraction vessel was made

using SS304 with 50 ml of volume the extractor is collected at the bottom of the vessel by pressing the seeds then the oil is weighted and efficiency is calculated after the replication of the process (Hatami *et al.*, 2018).

1.5. Soxhlet Method

The Soxhlet method is done in a typical apparatus for 24 hours by using the standard method within 3 days (38hour) by taking 20g sample ground seeds using organic solvent hexane of 200 ml. the extracted sample is evaporated by using the same two methods as mentioned in the superheated hexane extraction method first rotatory evaporator and then completely by using nitrogen. The oil is weighted and the efficiency is calculated by repeating the method twice (De Castro and Garcia-Ayuso, 1998).

1.6. Supercritical Fluid Extraction Method

Supercritical fluid extraction is performed at the high-pressure unit. Take 10g of ground pomegranate seeds which are pretreated with microwave radiations place them in a stainless steel basket having a perforated top and bottom then fix it in a stainless steel extraction vessel (Pamisetty *et al.*, 2018). Then through the siphon tube provide liquid CO₂ through a cylinder the flow rate is 0.3 kg/h the tube is cooled cryostat between the pump and cylinder outlet to avoid the vaporization of CO₂ (Durdevic *et al.*, 2018). When the system becomes heated CO₂ is supplied by a liquid metering pump until the desired pressure is obtained. The extraction started after opening the valve. The process is performed at 37.9 MPa pressure which is attained by using backpressure valve BPR and 47°C temperature. After the completion of the process, the extracted material is preserved at -20°C (Durdevic *et al.*, 2017b).

Table 2. The Sources and Molecular Weight of Punicic Acid.

Constituent	Molecular Weight	Formula	Pomegranate Part
Punicic acid (41)	278.43	C ₁₈ H ₃₀ O ₂	Pericarp, flower, root, seed oil and bark

(Source: Puneeth and Chandra, 2020)

1.7. Fatty Acid Composition

After the extraction of pomegranate seed oil by supercritical fluid extraction from pretreated microwaved seeds the PSO are further analyzed by using Mass Spectrometry and Gas Chromatography. Total of 11 fatty acids were detected in this which is a mixture of all saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acid. The ratio of fatty acid is PUFA>MUFA>SFA. Main PUFA is punicic acid found in PSO having many health benefits there were (53.6%) CLnA (Amri *et al.*, 2017).The 2nd most important PUFA in PSO is linoleic acid which is 6.7%. Linoleic acid was in a small amount. Among the MUFA elaidic and oleic acid were present in PSO 1.1% and 7.3% respectively. From SFA stearic acid 2.9% and palmitic acid 3.3% were observed the minor level of saturated heptadecanoic 0.06%, lignoceric acid 0.3%, behenic acid 0.11% and arachidic acid 0.58% were also present (Durdevic *et al.*, 2018).

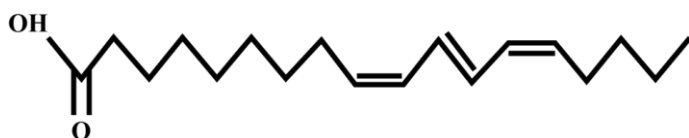


Figure 1. Chemical structure of punicic acid (C₁₈H₃₀O₂)

(Khajebishak *et al.*, 2019b)

1.8. Health Claims

Pomegranate is nature's beautiful gift that grows in tropical climates having many bioactive ingredients and not only provides the nutrients to body but also use as a functional food as it provides health benefits beyond the basic nutrients and uses as therapeutic food as well to treat many diseases especially its seeds and peel are used for medical purpose. As, it contains a huge quantity of vitamins, minerals, phytochemicals, flavonoids, ellagic acid, punicic acid punicalagin, and ellagitannins. traditionally it has been used in treating sore throat, skin disorders, arthritis, cough, reducing pain, expelling tapeworm, and digestive disorders (Guerrero-Solano *et al.*, 2020) It also can treat many serious diseases such as different types of cancer diabetes, arthritis, osteoarthritis, and Alzheimer disease (Emami *et al.*, 2015; Vučić *et al.*, 2019b; Morzelle *et al.*, 2019). As it has the potential to thin the blood it reduces the blood pressure increases the blood flow to the heart inhibits plaque formation in the arteries and reduces the level of bad cholesterol in the body by increasing the concentration of good cholesterol. Its juice affects the reduction of inflammation by lowering the level of C-reactive protein (Suman and Bhatnagar, 2019; Faria and Calhau, 2010).

It contains a high number of anthocyanins and has antioxidant properties having anti-carcinogenicity properties (Sevilla *et al.*, 2008; Andrade *et al.*, 2019). It has an effective role in the health of the reproductive system it increases the level of the reproductive system increases the level of luteinizing hormone, testosterone, and follicle-stimulating hormones by the injection of carbon tetrachloride (CCl₄). It reduces the destruction of sperm numbers due to the effect of lead acetate. It increases the epidermal sperm concentration and sperm mortality it improves erectile response and smooth muscle relaxation in erectile dysfunction as it increases the testosterone number it improves the men's health outside and inside (Esmailinezhad *et al.*, 2019; Puneeth and Chandra, 2020).

It has very effective health benefits during pregnancy it protects the placenta from oxidative stress and protects from birth defects as it has some amount of folate and enhances milk production (Abdolhosseini *et al.*, 2017). It improves the health of the urinary bladder and reduces the acidity of the urine by preventing the entry of harmful bacteria from outside, prevents inflammation decreases the chances of placental injury (Suman and Bhatnagar, 2019) pomegranate seed oil is extracted from the seeds of pomegranate having many active ingredients the main punicic acid have many health benefits in metabolic and inflammatory diseases it downregulated the inflammation in mucosal immune and epithelial cells (Vučić *et al.*, 2019a). It also increases the absorbance of other active ingredients like resveratrol (Liu *et al.*, 2018). The punicic acid present in the seed oil also maintains liver health and reduces its inflammation by blocking the activity of the desaturases enzyme (Bialek *et al.*, 2017a). The punicic acid in a

mixture of ellagic acid and luteolin inhibits the metastasis of cancer cells (Bonesi *et al.*, 2019).

Punicic acid shows anti-obesity properties as well by reducing the level of leptin production in the body and increasing the activity of the carnitine palmitoyl transferase enzyme which is involved in the beta-oxidation of fats (Fig 2) (Bialek *et al.*, 2017b).

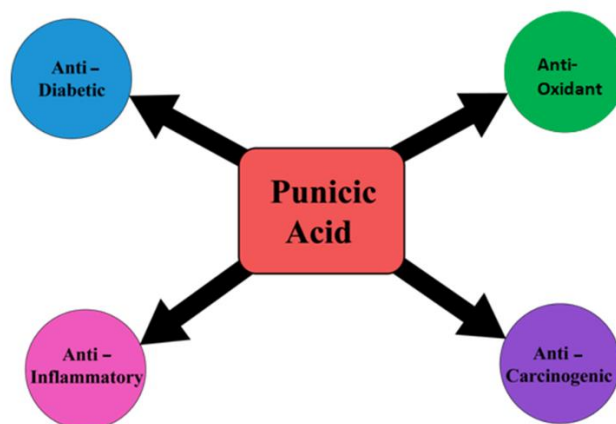


Figure 2. Therapeutic properties of punicic acid

(Bedel *et al.*, 2017)

1.9. Anti-Oxidant Properties of Punicic Acid

Punicic acid an isomer of conjugated linolenic acid (Chojnacka *et al.*, 2016) is the active ingredient of pomegranate seed oil as seeds are normally wasted but their oil has many functional ingredients (Khoddami *et al.*, 2014). It has many health claims one of the most important is the anti-oxidant property. The use of artificial anti-oxidants has negative effects on health because they increase the risk of oxidative stress disorders in the body. In addition, studies reveal to use the of natural sources of anti-oxidant to avoid side effects. The body also has its defense anti-oxidant defense system but when the amount of anti-oxidant in the body decreases they must be given from external sources it will be more healthful if they must be supplied from the diet in place of supplements so the importance of natural sources is increasing the extracts of the pomegranate have anti-oxidant abilities, induce apoptosis in tumor cells (Zarfeshany *et al.*, 2014).

It is proven from many studies that punicic acid has the potential to minimize the harmful effects of the oxidative mechanism mostly the free radicle foam as a result of lipid peroxidation (Aruna *et al.*, 2016). To verify this effect various animal studies were conducted in the experiment snake gourd seed oil was used as a source of punicic acid. It was given to rats in the foam of blend with soybean. The results of the study suggested that there was a significant decrease in the total body weight gain, triglyceride, energy requirement and total cholesterol level also lowered then after the supplementation of the pomegranate leaf extract containing punicic acid cause the increase in the total cholesterol to high-density lipoprotein ratio TC/HDL ratio as the oxidation the of the LDL is very fast and make free radicles leading towards the oxidative stress and damages the body (Fernandes *et al.*, 2015).

Punicic acid showed antioxidant properties and lowered the total cholesterol TC and LDL levels as compared to the group given a control diet without punicic acid (Maghsoudi *et al.*, 2018). After this the

mixture of puniceic acid the isomer of conjugated linolenic acid with the vitamin E alpha-tocopherol on the lipid peroxidation the results showed that significant reduction in the erythrocyte lipid peroxidation (Saha and Ghosh, 2011) and LDL concentration in the serum of the rats having diabetes mellitus and decrease of the peroxidation in the liver and membrane were significant. They increase the activity of the antioxidant enzymes in the body to make the natural body anti-oxidant defense system strong such as catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD) and decrease the activity of the nitric oxide (NO). It improves renal oxidative stress by making better the lipid profile of the renal system (Shabbir *et al.*, 2017).

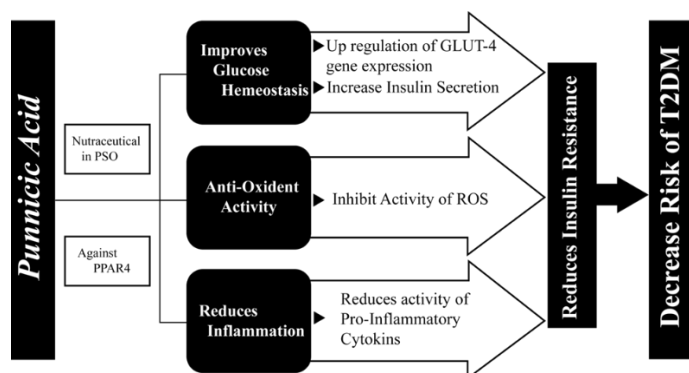


Figure 3. Anti-diabetic activity of puniceic acid

(Khajebishak *et al.*, 2019b)

1.10. Anti-Diabetic Properties of Punicic Acid

According to the world health organization (WHO), diabetes is the 3rd most prevalent disease in the world. This disease is not completely cured but managed through diet and natural sources nature provides many fruits one of them is pomegranate having many functional ingredients found in its peel, flower, and seed and shows a hypoglycemic effect. Due to the negative effects of antidiabetic-medicines nutraceutical present in natural fruits is gaining attention as a complementary therapy. Punicic acid the nutraceutical present in pomegranate has anti-diabetic properties through different mechanisms as regulating glucose homeostasis by increasing insulin secretion and upregulation of GLUT-4 gene expression, suppressing inflammatory cytokines and reducing inflammation and anti-oxidant activity by inhibiting ROS species reducing oxidative stress as shown in Fig 3 (Viuda-Martos *et al.*, 2010).

Insulin is the key hormone responsible for the homeostasis of glucose in the body it controls its regulation by suppressing the glucose production in the kidney, small intestine, and liver and ensuring the uptake of glucose in the insulin-sensitive tissues such as skeletal, muscle and adipose tissues (Khajebishak *et al.*, 2019a). Insulin resistance has now become an important factor in public health. Many risk factors lead to insulin resistance which includes a sedentary lifestyle, obesity, and a high-fat diet. Inflammation plays a significant role in the development of metabolic syndrome by down-regulating glucose transporters and disrupting insulin signaling pathways. This ultimately leads to metabolic dysfunction. Inflammation due to insulin resistance mostly occurs in adipocytes and this inflammation in humans leads to the dysfunction of mitochondria and oxidative stress and this stress further activates the stress-responsive genes such as IKK, JNK, NFκβ, *etc.* All these pro-inflammatory cytokines have a role

in inflammation as shown in Fig 3 but NFκβ role is most prominent in obesity, insulin resistance and obesity (Anusree *et al.*, 2018).

Punicic acid reduces insulin resistance in diabetic patients. The inflammatory cytokine tumor necrosis factor-alpha (TNFα) plays important role in inflammation-inducing obesity and increasing insulin resistance in type 2 diabetic patients by making reactive oxidative species (ROS). TNFα causes a decrease in ATP production, changes in the mitochondrial membrane potential to transfer the nutrients overall, makes the level of ROS high in the body and downregulates the activity of aconitase the enzyme of Krebs Cycle but the puniceic acid downregulates its expression of the TNFα restore all these functions and increase glucose uptake by the cells (Boroushaki *et al.*, 2016a).

Type 1 diabetes is a chronic metabolic disease usually due to the body's autoimmune response which may be genetic or due to environmental factors or viruses the body in the condition is not able to produce insulin in the body and treatment includes taking insulin from external sources for the whole life but its prevalence is very low as compared to type 2 diabetes only 5% out of 415 million people diagnosed with diabetes have type 1 diabetes so due to the increasing prices of insulin natural ways are implemented. puniceic acid is also effective in the management of type 1 diabetes in adolescence the patient is given puniceic acid with insulin and the results are very positive. There is improved blood glucose level, reduction in visceral body fat and improved peripheral blood cell (PBC) functioning. After administering insulin with puniceic acid to rats in an animal study, the blood glucose levels were monitored for 16 weeks and the results demonstrated a favorable glucose profile (Grimes, 2019).

The research-based studies suggest that the administration of puniceic acid decreases the concentration of blood glucose level, TC and triglyceride levels and raises the HDL and hemoglobin levels of the blood (Suman and Bhatnagar, 2019). The research was conducted on genetically obese mice who were fed with dietary puniceic acid the concentration.e.1g/100g of the fed rats for 30 days lowers the level of fasting blood glucose concentration. The ability to normalize the blood glucose level was greater in the mice fed with puniceic acid as compared to the control group rats. Results suggest that the puniceic acid suppresses the activity of tumor necrosis factor-α, expression of NF-κβ and upregulates the activity of gamma-responsive genes, PPAR-α- in the genes that are responsible for the regulation of the glucose homeostasis found in skeletal muscles and adipose tissues (Banihani *et al.*, 2013).

The downregulation in the PPR-α- gene decreases the ability of the dietary puniceic acid to maintain glucose homeostasis. The medications used in diabetes have their action by activating the receptors of the peroxisome proliferator-activated receptor PPAR-α- as Thiazolidinedione or TZD. The supplementation of the dietary puniceic acid increases glucose tolerance and reduces the inflammation in the body due to type 2 diabetes in obese mice by acting similar to the PRAR-α-. puniceic acid delays the development of atherosclerosis in diabetes type 2 patients by enhancing the catalytic activity of the paraoxonase 1 antioxidant enzyme and increasing the amount of HDL (Khajebishak *et al.*, 2019b).

1.11. Anti-Carcinogenic Properties of Punicic Acid

Uncontrolled cell growth is simply defined as cancer (Ghaffari *et al.*, 2015) and for its treatment in addition to medication, the concept of the use of natural products and nutraceuticals is increasing because they do not have negative effects on health (Prasad *et al.*, 2017). For centuries, plant-based conjugated linolenic acids (CLnA) are studied for their therapeutic and preventive effect against diverse diseases, for example, cancer (García-Montero *et al.*, 2021). Particularly Punicic acid found in pomegranate exerts great anti-cancerous properties (Khawairakpam *et al.*, 2018).

A study has shown that the exact mechanism behind the cytotoxic activity of punicic acid is not clear but mostly it follows the process of ferroptosis (Vermonden *et al.*, 2021). It is a process in which cell death occurs due to the accumulation of lipid peroxides (Li *et al.*, 2020). Several studies have been conducted to check the anti-cancer properties of the nutraceutical present in pomegranate seed oil which is punicic acid. Many types of long-chain polyunsaturated fatty acids show anti-carcinogenic properties but PA showed a significant effect (Touihri *et al.*, 2019). It shows cytotoxic activity a trial was conducted on different cancer cell lines such as HeLa, A549, LS174 and normal cell lines as well MRC-5 results showed that the best cytotoxic activity was observed in HeLa, weaker in LS174 and A549 but there was no effect in MRC-5 which is normal (Đurđević *et al.*, 2018). Its most effective result is observed in the prevention of breast cancer it shows apoptotic and anti-proliferative properties. It stops the proliferation of breast cancer by two mechanisms. First, by inhibiting the protein kinase C pathway and the second way is by lipid peroxidation. It inhibits the proliferation and secretion of inflammatory cytokines as well (Holic *et al.*, 2018).

It not only inhibits proliferation in breast cancer but also its effect is seen in different human cancer cell lines. It shows good effects on the insensitive breast cancer cell line (MDA-MB-231) and estrogen-sensitive (MDA-Era-7) PA stopping the growth of these cells by 92% and 96%, respectively. Mode of action includes the impairment of cellular mitochondrial membrane potential and induction of apoptotic effect in them. it has a cytotoxic effect on the MCF-7 mammary cancer cell line as well it reduces the cell viability reduces the tumor activity and blocks the activity of ornithine decarboxylase enzyme in the human cancer cell line (Grossmann *et al.*, 2010).

Furthermore, the effect of punicic acid on prostate and colon cancer was investigated as prostate cancer is the 2nd most common type of cancer in the world so there needs to find a natural therapeutic agent for its treatment (Wang *et al.*, 2014). Many types of oil acid including punicic acid block the accumulation of steroid 5-R reductase type, dihydrotestosterone-induced androgen receptor in cell and suppresses the expression of prostate-specific antigens contributing to cancer. It stimulates cell cycle arrest, DNA fragmentation and internal apoptotic activity by a caspase-dependent pathway in the prostate cancer cells line LNCap, PC3, DU145 (Gafar *et al.*, 2016). Punicic acid stops the activity of the arachidonic acid metabolism pathway in the cancer cell and reduces the level of dihydrotestosterone and testosterone in LNCaP. It reduces the development and progression of cancer metastasis by blocking the signaling pathways, inhibits prostaglandin production, reduces invasion of PC3 and stops growth of LNCap and DU145 cell line. Punicic acid inhibits chemotaxis, proliferation and

angiogenesis and metastasis by decreasing cell migration and increasing cell adhesion and by blocks the hyaluronan signaling pathway (Bedel *et al.*, 2017). Punicic acid is also effective in controlling glioblastoma which is an aggressive type of cancer in the brain or spinal cord it induces apoptosis and block signaling pathways in its cell line (Mete *et al.*, 2019).

1.12. Anti-Inflammatory Properties

The frontline physiological defense system of the human body (inflammation) is the protection of the body against physical wounds, injury, poison, and many other factors. It is also known as short-term inflammation and can fight against infectious microorganisms that can maintain normal physiological functions of the body and also protect against irritants. But if persist long-lasting inflammation has negative effects on health and can create many health problems that can disturb normal physiology and can cause rheumatic arthritis, chronic obstructive pulmonary disease, inflammatory bowel disease, and asthma. Inflammation is initiated by many biological aspects, chemicals, cytokines, pro-inflammatory enzymes, enzymatic damage to the tissues and eicosanoids that have a low molecular weight (Viuda-Martos *et al.*, 2010).

Punicic acid shows anti-inflammatory properties as well it blocks the activity of neutrophils, lipid peroxidation, lipoxygenase (LOX) and cyclooxygenase-2 (COX-2) this is the isoform of cyclooxygenase enzyme which catalyzes arachidonic acid into prostaglandin E2 (PGE2), which is the key mediator of inflammation contribute in the onset of vascular heart diseases and cancer but Punicic acid down-regulates the overexpression of this enzyme. Another form of this enzyme cyclooxygenase-1 (COX-1) has a role in the regulation of homeostasis (Borouhaki *et al.*, 2016b). It decreases the activity of IL-6 and TNF α which are inflammatory markers that play a vital role in acute hepatic damage so it stops the inflammation in the liver (Adu-Frimpong *et al.*, 2019).

A study was conducted on the anti-inflammatory effect of punicic acid on rats having rheumatic arthritis they were fed with pomegranate extracts containing a prominent amount of PA the treatment decreased the severity of the inflammation as compared to the control group. The level of inflammatory cells in the joints was lowered, IL-6, down-regulation of the mediators, and blockage of multiple signaling pathways were observed. It also reduces inflammation in osteoarthritis (Maghsoudi *et al.*, 2018). Beneficial effects are also observed in IBD which presents a group of chronic inflammatory disorders of the digestive tract including ulcerative colitis. The results showed that the intensity of the disease is decreased by reducing the activity of the Lighter Colitis Activity Index (LCAI) (Viuda-Martos *et al.*, 2010).

2. CONCLUSION

Natural and plant-based food products are gaining attention over synthetic products gaining attention in the global nutrition market. Because they have biological active biomolecules and nutraceuticals in them which does not have any health hazard effect. Several natural foods are explored in this context: punicic acid a nutraceutical found in natural foods pomegranate seeds majorly usually its seeds are considered waste but they have this special ingredient. Its health effects are well known it can be effective in many diseases having many therapeutic effects as an anti-oxidant by blocking the activity of

reactive oxidative species, anti-diabetic by regulating the pathway of glucose metabolism, anti-inflammatory by reducing the activity of pro-inflammatory cytokines, anti-carcinogenic properties by reducing proliferation and inducing apoptosis in tumor cells as documented in this paper. While we have discussed the numerous health benefits and therapeutic effects of this substance, it is important to note that its bioavailability is currently low. As a result, additional research is needed to improve its oral bioavailability in the future.

3. ACKNOWLEDGMENT

None.

4. CONFLICTS OF INTERESTS

Authors declare no conflict of interest.

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