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A REVIEW ON BIOACTIVE PHYTOCHEMICALS IN PUNICIC ACID FOR THE VARIOUS TREATMENT

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ABSTRACT

The positional and geometric isomers of octadecatrienoic acid also known as Punicic acid (C18:3) with conjugated double bonds are collectively referred to as conjugated -linolenic acids (CLnAs). Conjugated fatty acids have garnered a lot of attention recently due to reports of their health benefits in a variety of models of metabolic diseases and chronic inflammatory diseases, but some work is controversial and there is still no consensus in the literature regarding their effects on animal and human organisms. This article provides a review of pomegranate seed oil and the potential health effects of conjugated -linolenic acid. Nutraceuticals and plant extracts are the oldest and most popular kind of medicine used by the general public. According to current research, pomegranate components such as ellagitannins, anthocyanins, anthocyanidins, flavonoids, estrogenic flavanols, and flavones are the most medicinally helpful. Additionally, 64–83%PUA of pomegranate seed, snake gourd which contains 32-40%PUA and *Trichosanthes Kirilowii* seeds contains 32-40%PUA. Thus, punicic acid's effects especially those that have been documented, like its anti-inflammatory, anti-carcinogenic, antioxidant, and antidiabetic properties were the main focus of this review. Given that nutraceuticals seem to be important for preventing a number of illnesses, punicic acid may significant and phytoconstituent in these substances. Most people agree that using nutraceuticals is safe and has fewer negative effects.

Keywords: Punicic Acid, Pomegranate Seed Oil *(Punica Granatum L), Trichosanthes Kirilowii* Seeds, Conjugated Fatty Acid, Therapeutic Uses.

1. INTRODUCTION

Pomegranate (*Punica granatum L.*) is a unique fruit due to its many reported functional properties [1], such as its high antioxidant activity and its juice, which have been shown to have positive health effects and have prompted more research into its nutraceutical potential and its uses in the food industry [2]. Its plentiful seeds, which are typically waste products from pomegranate processing, are also of great interest once their oil has a particularly rich composition [3].

When Melo [4] examined the composition of pomegranate seed oil, he found a significant concentration of phytosterols, tocopherols, and a distinct fatty acid composition, primarily punicic acid (55%). An omega-5 long chain polyunsaturated fatty acid, punicic acid (also called trichosanic acid) is an isomer of conjugated α-linolenic acid (CLnA) and shares structural similarities with both α-linolenic acid (LnA) and conjugated linoleic acid (CLA) [5], including carbon composition, atomic arrangement, and the number of carbon double bonds. Because of their numerous possible health advantages, these conjugated fatty acids have drawn more and more attention from scientists. [6] The possible health effects of conjugated α-linolenic acid are reviewed in this article under the heading of pomegranate seed oil, along with their antioxidant, anticancer, immunomodulatory, anti-atherosclerotic, and serum lipid-lowering properties. [7]

In addition to polyphenols, pomegranate seeds contain a variety of other components that may contribute to their beneficial effects [8]. Pomegranate seed oil (PSO), which makes up 12–20% of the whole seed mass, has recently drawn a lot of dietary attention. Its main bioactive constituent, PA, a conjugated linolenic acid (CLA), which made up 64–83% of PSO [9], [10], has been linked to the oil's potential benefits. Conjugated fatty acid (CFA), a general term for positional and geometric isomers of polyunsaturated fatty acids with conjugated double bonds, has been shown to have anti-inflammatory, anti-atherosclerotic, anti-obesity, anti-tumor, and antihypertensive effects [11], [12].

Punicic Acid (PA):

Pomegranate juice, peel, and seed's antioxidative qualities have been investigated for their therapeutic potential, which has led nutritionists to further explore their nutraceutical and industrial application [2]. Pomegranate seed and peel, which are typically regarded as agro-waste obtained during industrial processing of pomegranate juice, are gaining attention from researchers these days due to the presence of numerous nutraceutics in them. Pomegranate seed is abundant and of great interest to scientists due to its rich oil composition [3].

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This review summarizes PA and its role as a nutraceutical health substance. According to Melo [4], pomegranate seed oil has a rich composition of polyunsaturated fatty acids, with punicic acid (~55%) making up the majority. PA is also known as "Trichosanic acid," with a molecular formula of C18H30O2, a molar mass of 278.43 g/mol, and a melting point of 44–45 degrees Celsius. Punicic acid is an isomer of conjugated α-linolenic acid and an ω-5 polyunsaturated fatty acid that share structural similarities.

According to Melo [4], pomegranate seed oil has a rich composition of polyunsaturated fatty acids, with punicic acid making up the majority (around 55%). PA's function as a nutraceutical health substance is summed up in this review. With the chemical formula C18H30O2, PA is also known as "trichosanic acid." Its molar mass is 278.43 g/mol, and its melting point is between 44 and 45 oC. Punicic acid is a structurally similar isomer of conjugated α-linolenic acid and an ω-5 polyunsaturated fatty acid.

for example, the number of double bonds and atomic arrangement with conjugated α-linolenic and linoleic acid. Scientists are very interested in investigating the functional and nutraceutical qualities of punicic acid against different metabolic disorders because of the health benefits linked to these fatty acids [13], [14].

Based on its three double bonds (cis9, trans11, and cis13), the International Union of Pure and Applied Chemistry (IUPAC) assigned its nomenclature as 9Z, 11E, 13Z-octadeca-9,11, and 13-trienoic acid. It is primarily an isomer of conjugated linoleic acid (c9t11), distinguished by the presence of a double bond on its tail side. Catalpic acid (trans9, trans11, cis13), alpha-eleostearic acid (cis9, trans11, trans13), calendic acid (trans8, trans10, cis12), and jacaric acid (cis8, trans10, cis12) are additional isomers of lenolic acid.

Pomegranate seed oil (PSO) is the most abundant source of PA among all the sources, with the remaining sources being snake gourd seed oil [15] and *Trichosanthes kirilowii* Maxim (TK) seeds Table 1, which contain 32 to 40% PA out of total seed weight [50: 9: 32]. The fatty acid profile of PSO contains conjugated linoleic acid up to 74–85% PA [16], with the remaining 14–25% being its isomers [17]. PA can be chemically synthesized by dehydration and isomerization of secondary oxidation products of linoleic and alpha-linolenic acids [18], [19].

Since lipolytic enzymes deactivate during heat processing, the lipid portion of pomegranate seeds (the main by-product) was investigated after juice extraction because PA is primarily effective against conditions like obesity, diabetes, inflammation, and metabolic syndromes in a variety of in vivo experiments Table 2 [20].

Metabolism of Punicic acid:

The way that punicic acid breaks down Animals have been the subject of numerous pharmacokinetic studies to evaluate PA's metabolism and bioavailability, effectiveness trial results provided strong evidence that PA is easily converted to circulating conjugated linoleic acid (c9t11) [21], [22].

Table 1: So*urces of Punicic acid*

Sources of punicic acid (PA)		Authors
Pomegranate (Seed oil)		[23]
Saturated	10%	
Mono-unsaturated	10%	
Di-unsaturated	10%	
Punicic acid and isomer (C18: 3-9c,11t,13c)	70%	
Trichosanthes kirilowii (seed oil)		[24]
Saturated	7.50%	
Mono-unsaturated	22.91%	
Di-unsaturated	32.70%	
Punicic acid and isomer (C18: 3-*9c,11t,13c*)	35.89%	

Table 2: Summary of health effects of punicic acid (PA) on animal and human model

Level of PA	Study model system	Mechanism of activity	Outcomes	Authors
5% punicic acid	ICR CD-1 mice	↑ CPTI activity	Decreased perirenal and epididymal fat	[25]
5% pomegranate seed (punicic	OLEFT rats	↓ Δ9 desaturase activity	Adipose tissues weight	[26]

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acid)			reduction	
1% punicic acid	C57Bl/J6 mice	-	Adipose tissues weight reduction	[16]
10-100 µM mixture of CLnA isomers (*cis*-9, *trans*- 11, *cis*-15, and *cis*-9, *trans*-13, *cis*-15)	3T3-L1 cells	↑ HSL and ATGL gene expression	Decreased triglyceride content	[5]
10 and 50 µg/mL pomegranate seed (punicic acid)	3T3-L1 cells	↓ $PPAR_Y$ and C/EBP_β↓ FAS	Decreased adipogenesis and preadipocyte differentiation	[27]
Punicic acid	C57Bl/J6 mice	-	Insulin sensitivity enhanced in peripheral area	[28]
Punicic acid	3T3-L1 cells and obese mice	PPARα and PPARβ activation	Improved glucose tolerance, with diabetes improvement	[29]
Punicic acid	HepG2 cells	↓ apoB100 secretion. Inhibition of stearoyl CoA desaturase	↓ Plasma triacyl glycerides. Upgraded saturated/ monounsaturated fatty acid ratio	[30]
Catalpic acid, jacaric acid, calendic acid, eleostearic acid and punicic acid,	Microsomes from sheep vesicular glands	Inhibition of cyclooxygenase activity (inhibition of prostaglandin synthesis)	Anti-inflammatory activity	[31]
Punicic acid	Sheep	Inhibit cyclooxygenase and lipoxygenase activity	Anti-inflammatory activity	[32]
Pomegranate extract (punicic acid)	3T3-L1 cells	PPARY receptor activator and agonist (inhibit NF-κβ expression, declined serum IL-6 and TNF-α)	Decreased chronic inflammation	[29]
Alpha-Eleostearic and punicic acid	Diabetic rats	Inhibit NF-κβ expression. Declined serum IL-6 and TNF-α.	Anti-inflammatory activity	[33]
Punicic acid (70% pomegranate seed oil)	-	Decreased expression PPARγ and C/EBPs, and fatty acid synthase	Suppresses adipocyte differentiation and lipid accumulation	[27]
Punicic acid	Ovariectomized (OVX) mice	Down-regulate the expression of osteoclast differentiation markers and RANK-RANKL downstream signaling targets in osteoclast-like cells (RAW264.7)	Improved bone mineral density and prevented trabecular micro-architecture impairment	[34]
Dietary mono-conjugated alpha-linolenic acid isomers	Neonatal pig	-	Safe for animals	[35]
Pomegranate seed oil	Rats	-	Improved insulin secretion	[36]

There have been more reports on PA recently.

In fact, our group found a novel impact: PA had a vasodilatory effect in the rat's aortic arteries that was mediated by nitric oxide [37]. As a result, we discuss the effects of PA in this review, specifically its anti-inflammatory, anti-carcinogenic, antioxidant, and antidiabetic activities Error! Reference source not found.

PA's anti-inflammatory and antioxidant properties:

It is commonly known that oxidative stress contributes significantly to the aetiology of a number of illnesses. The antioxidant effect of PA has been the subject of numerous experimental and clinical investigations. PSO and fermented pomegranate juice have been shown to have antioxidant properties by Schubert et al. [38]. According to Saha et al., PA had hydroxyl radical scavenging activity, reducing qualities, and metal chelation, which was especially evident in the trans isomer of the CLA compounds. Additionally, they noted that PA was a strong antioxidant that reduced lipid peroxidation and scavenged free radicals in toxicity caused by arsenic [33].

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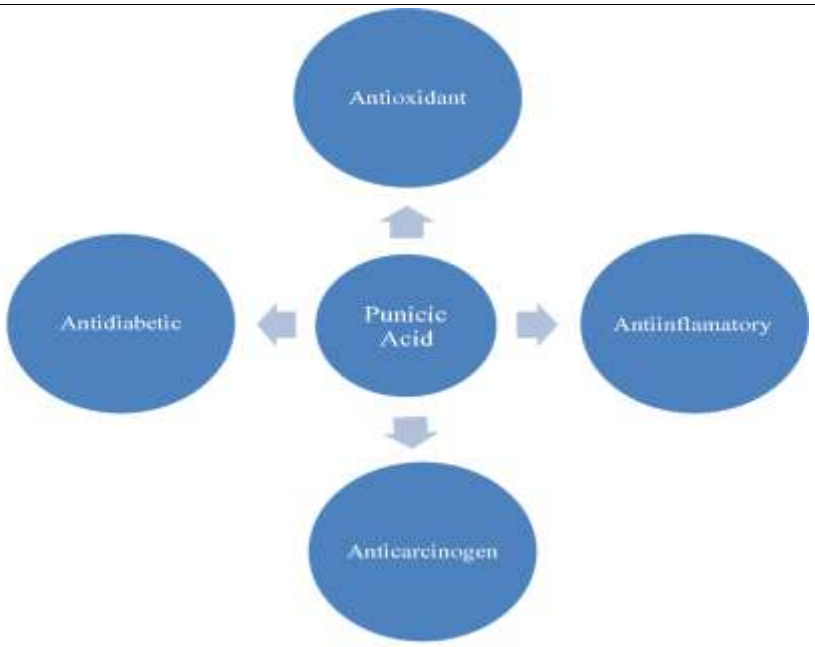

Figure 1: Effects of punicic acid

According to Saha et al., PA's high cis components may be the reason for its greater hypocholesterolaemia and anti-inflammatory effects [39]. Furthermore, urolithins, which are metabolites of PA, were found to have a notable antioxidant effect and to promote the proliferation of human gut flora by Bialonska et al.[40] . Additionally, because of its antioxidant properties, Binyamin et al. suggested in an experimental animal investigation that PSO in nano-drop form might be taken into consideration for the treatment of demyelinating illnesses [41]. It has been suggested that people in Asia and the Middle East who consume big amounts of CFA seem to have a decreased incidence of illnesses that are inflammatory [42]. According to recent research, PA reduces colitis in an experimental rat model and has a potent anti-inflammatory impact by blocking the increase of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase brought on by tissue necrosis factor α (TNF-α). By modifying T-cell and macrophage activity via peroxisome proliferator activated receptors (PPAR-γ) and δ-dependent processes, PA also improved experimental inflammatory bowel illness, according to in vivo molecular evidence presented by Bassaganya Riera et al. [5]. In dextran sodium sulphate colitis, intestinal inflammation was recognized to be strongly inhibited by PPAR-γ and δ [43]. PA was shown to reduce spontaneous pan enteritis and inflammatory colitis brought on by dextran sodium sulphate in interleukin-10 (IL-10) knockout mice.

The primary cause of newborn mortality and morbidity is necrotizing enterocolitis, whose pathogenesis is unknown. In a rat model of necrotizing enterocolitis, it was shown that administering PA reduced intestinal damage [44]. Additionally, Caplan et al. showed that PA decreased the rat's incidence of inflammatory intestinal disorders and necrotizing enterocolitis [45]. A recent study also demonstrated that PSO provided protection against necrotizing enterocolitis in this model. It was proposed that PSO's anti-inflammatory properties and restoration of epithelial homeostasis through a reduction in TNF-α, IL-6, and IL-8 levels may be the cause of this effect. Furthermore, they hypothesized that PA significantly improves the integrity of the gastrointestinal mucosa. According to this study, PA is a crucial dietary component for the future [46].

Pomegranate (*Punica granatum L.*) seed oil:

Since ancient times, pomegranates (*Punica granatum L.*) have been utilized medicinally due to their strong antioxidant potential [47]. Their possible antiproliferative, anti-invasive, and pro-apoptotic properties against several human cancer cell lineages and in animal models were examined by Syed et al. [47]. More than 50 compounds with phytoestrogenic and antioxidant properties have so far been identified in the fruit's seeds, juice, and peel, as well as in the tree's leaves and flowers. The dried peel of ripe pomegranates has been shown to be useful in avoiding lipoperoxidation and is used to cure stomach aches. Fruit extracts have been successful in preventing influenza and herpes viruses from spreading, as well as in reducing the growth of human breast and prostate cancer cells. decreases in the degree of depression and bone degradation in Following the administration of pomegranate juice concentrate and a seed extract, ovariectomized rats were seen [2], [48]. Products made from pomegranates have also been shown to have anti-inflammatory, antibacterial, and immunosuppressive properties, as well as protective benefits on lipid and glucose metabolism and liver function [49], [50]. Pomegranate juice or extracts taken regularly as supplements may

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help prevent or even treat obesity, diabetes, and cardiovascular problems, claim Al-Muammar and Khan [51]. According to their review, reducing energy intake, oxidative stress and inflammation, and intestinal absorption of dietary lipids by blocking pancreatic lipase may all be significant pathways for the anti-obesity effects of pomegranate foods in general [51] **Error! Reference source not found.** was shown.

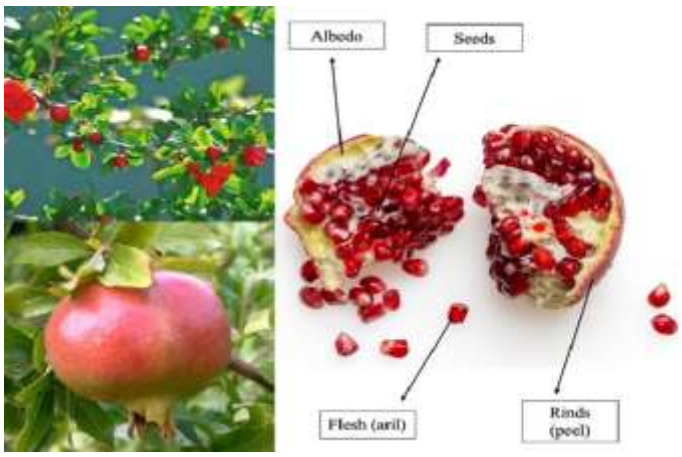
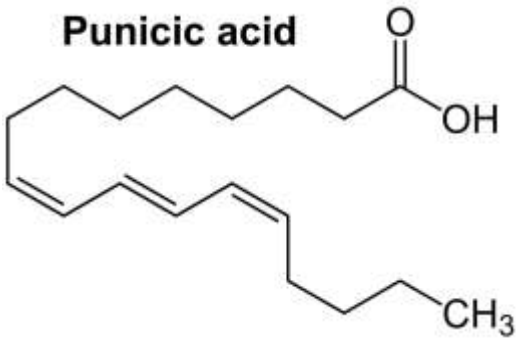


Figure 2: Pomegranate seed

Three components make up the fruit: the seeds, which make up around 3% of the total weight and contain 20% oil; the juice, which makes up about 30% of the whole weight; and the pericarp, which includes the skin and inner membrane walls and makes up around 67% of the entire weight [1]. Typically, pomegranate seeds are leftovers from fruit preparation. fruit weight, which varies by cultivar [3]. The seeds are rich in carbohydrates, polyunsaturated fatty acids, vitamins, polysaccharides, polyphenols, and minerals, and they have a notable antioxidant capacity [1]. Pomegranate seeds cultivated in Brazil had an average carbohydrate content of 43.97%, followed by moisture content of 38.03% and high lipid content of 14.06% [52].



Characteristics that prevent diabetes:

Experimental research has thus far produced conflicting findings about the impact of PA on insulin resistance, glucose metabolism, and serum lipid levels. The administration of a diet containing 1% α-ESA and/or PA for six weeks produced non-significant results for both body and tissue weight [33]. When the mice were fed a diet containing 0.12% and 1.2% PSO for three weeks, similar outcomes were observed [53]. Rats fed a diet consisting of 1% PSO and 9% safflower oil for two weeks showed non-significant weights of abdominal white adipose tissue [26]. In another study, hamsters were fed a diet consisting of PA and α-ESA for six weeks, and while there was a decrease in the TG levels in their liver tissue, there was no discernible Serum TC findings were discovered [54]. The outcomes of a few other experimental investigations, however, contradicted the aforementioned conclusions [28], [55], [56]. Researchers discovered that PA significantly decreased the levels of TC, apoB-100, and TG in liver tissue.

In comparison to the control group, rats fed PSO exhibited increased serum levels of insulin and glutathione peroxidase (GOP) activity, but there was no discernible change in blood glucose levels [36]. Glycosylated total blood cholesterol (TC), triglycerides (TG), and glycosylated haemoglobin (HbA1C) levels were reduced in mice treated with peony seed oil high in PA, whereas weight growth, high density lipoprotein cholesterol (HDL-C), serum insulin, and liver glycogen levels were increased [57].

Another study found that giving rats PSO for 21 days raised their serum levels of phospholipids and total triacylglycerol (TAG), but did not significantly raise their levels of TC [56]. The levels of PA in the liver, serum, epididymal, and peri-renal adipose tissues rise in tandem with the dietary intake of PSO. In comparison to the same

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amount of PA extracted directly from pomegranates, mice fed with dietary genetically modified rapeseed oil (GMRO) at 0.25% weight of the entire diet showed improvements in hepatic lipid metabolism and a decrease in the body lipid ratio.

PSO consistently significantly decreased liver TG levels, but no discernible changes were seen in serum TG, TC, LDL-C, or HDL-C levels [4]. Serum TNF-α levels dropped from 15 to 13.08 pg/ml in the PSO group after four weeks of PSO administration for dyslipidaemia individuals [58]. When PSO was administered to high-fat induced patients for four (04) weeks, a similar situation occurred. The concentrations of serum TC, LDL-C, glucose, and body composition factors remained unchanged [59]. It was discovered that giving hyper lipidemic patients PSO supplements for a month showed encouraging results on their lipid profiles, particularly TAG and the TAG: HDL-C ratio. In contrast, the *Trichosanthes kirilowii* Maxim did not significantly alter fasting serum glucose, insulin, or sensitivity levels.

Homeostasis model assessment-insulin resistance (HOMA-IR) was used to examine diet supplements [60]. However, compared to a glucose tolerance test, rats with diet-induced obesity showed improvements in plasma glucose and insulin levels as well as glucose-normalizing capacity when PA was administered [61]. Consuming PSO (av. 61 mg/day) improved insulin sensitivity in CD-1 mice, suggesting that the risk of developing type-II diabetes may be reduced [62]. Furthermore, it was observed that PSO ingestion increases mice's insulin and glucose sensitivity as well as obesity brought on by a fat diet.

For three months, taking PA (1% PSO) as a supplement caused lipids to drop, which was followed by a decrease in body weight, which in turn caused a decrease in total body mass [63]. enhanced peripheral insulin sensitivity while leaving liver insulin sensitivity unaffected. Therefore, regardless of changes in food consumption or energy expenditure, dietary supplementation of PA is beneficial in relation to insulin resistance and fat-induced obesity in mice. The precursor of PA is xanthogens, a bioactive substance obtained from pomegranates that is well known for its ability to decrease cholesterol in both humans and animals, though its exact mode of action is still unknown. When compared to its separate constituents, fucoxanthin and PSO, xanthogens significantly and dose-dependently inhibited the production of lipid droplets in adipocytes [64].

Xanthogens can be used as a potential treatment for diabetes patients by overwhelming the accretion of triacyl glycerides and adipocyte differentiation through a variety of ways. Mice were given a mixture of PA, xanthogens, and fucoxanthin acid (70% in PSO) to examine any potential inhibitory effects on 3T3-L1 pre-adipocyte development. In 3T3-L1 pre-adipocytes treated with punicic acid, a reduction in the expression of the gene that controls the differentiation process that increases TG accumulation was noted [65].

***Trichosanthes Kirilowii* seeds:**

Numerous bioactive substances found in the medicinal plant *Trichosanthes kirilowii* have been studied. Its connection to punicic acid, a bioactive substance mostly present in pomegranates *(Punica granatum)* but also discovered in *T. kirilowii*, is one topic of investigation. The conjugated linolenic acid (CLnA) structure of punicic acid gives it a number of pharmacological characteristics, such as anti-inflammatory, antioxidant, and anticancer actions.

Figure 3: Trichosanthes kirilowii seeds

Punicic acid and *T. kirilowii* are related. Studies on *T. kirilowii* have revealed that its extracts might include substances that work with or enhance punicic acid's action. The bioactive elements of the plant, such as flavonoids and saponins, may improve punicic acid's medicinal effects, especially when it comes to lowering oxidative stress and regulating immunological responses. Benefits of Pharmacology Antioxidant and Anti-Inflammatory Properties Punicic acid is commonly used in acknowledged for its capacity to lessen oxidative damage and inflammation, which makes it beneficial in diseases like cancer and cardiovascular disease. With its active ingredients, *T. kirilowii* may enhance these benefits in concert. Anticancer Characteristics Punicic acid and T. kirilowii have both demonstrated promise in cancer studies, with punicic acid potentially inducing apoptosis and preventing tumour growth. It may increase

antitumor activity when combined with *T. kirilowii* extracts. expansion. When coupled with extracts from *T. kirilowii*, it may enhance anticancer activity.

T. kirilowii's chemicals have the potential to work in concert with punicic acid, particularly in terms of anti-inflammatory, antioxidant, and anticancer properties, but further research is needed to determine how the two substances interact directly. This interaction has to be investigated further in order to validate their combined therapeutic potential.

Cancer and Punicic acid:

Over the past ten years, the use of nutraceuticals in the treatment of cancer has increased. There are studies on the usage of PA in cancer. Early research looked on the anticancer properties of chemicals found in pomegranate juice. Pomegranate juice's antiproliferative and apoptotic properties in breast cancer were demonstrated by Dikmen et al. [66], [67]. Numerous fatty acid types exist, including long-chain polyunsaturated fatty acids, which may have anticancer properties [68], [69]. One excellent example of this class of fatty acids is PA, which is being researched for use in the treatment of cancer. According to a study, PA's lipid peroxidation has prevented the growth of breast cancer cells.

characteristics as well as through influencing the protein kinase C pathway [6]. Pomegranate components, such as PA, have been shown by Rocha et al. to suppress the release of proinflammatory cytokines and the growth of cell lines [70]. PSO has been shown to prevent various human cancer cell lines from invading and proliferating. For instance, it has recently been discovered that pomegranate CLA has cytotoxic effects on MCF 7 mammary cancer cells and increases apoptosis in MDA-MB-435 human breast cancer cells [71].

Grossmann et al. looked into how PA affected the oestrogen-sensitive (MDA-ERa7) and insensitive (MDA-MB-231) breast cancer cell lines. In comparison to control cells, they discovered that PA decreased the proliferation of MDA-ERa7 and MDA-MB-231 cells by 96% and 92%, respectively. Additionally, PA decreased the mitochondrial membrane potential of cells and had an apoptotic effect on both cell lines. Lipid peroxidation and the protein kinase C pathway are linked to PA's breast cancer inhibitory properties [6].

According to Costantini et al., PA significantly reduced cell viability in two distinct breast cell lines (MCF-7 and MDA-MB-231) but not in liver and colon cancer cell lines [72]. PSO and fermented juice polyphenols have been demonstrated by Toi et al. to inhibit the growth and invasion of breast cancer cells, increase apoptosis in breast cancer cells, and delay oxidation and prostaglandin generation. Additionally, they initially demonstrated that pomegranate fractions had antiangiogenic properties [73]. By blocking the enzyme ornithine decarboxylase, which is active in mouse skin cancer cell lines, PA reduced tumour activity in mouse skin cancer cells and served as a preventive measure [74].

Prostate and colon cancers have also been researched in relation to PA.

Not dosage dependently, PA reduced the expression of PPARc in the colon mucosa and the incidence of chemically induced colon carcinogenesis in F344 rats [75]. Prostate cancer is considered to be the second leading cause of cancer-related fatalities among men. In order to cure prostate cancer, less harmful yet more potent therapeutic molecules must be discovered. Prostate-specific antigen expression, steroid 5R-reductase type, and dihydrotestosterone-induced androgen receptor nuclear accumulation are all inhibited by a variety of oil acids, including PA. Additionally, they demonstrated that PA stimulated intrinsic apoptotic activity and DNA fragmentation via a caspase-dependent mechanism [76].

The search for natural treatments, such pomegranate extract, to combat prostate cancer has recently redoubled [77]. It was demonstrated that pomegranate extracts stimulate apoptosis and cell cycle arrest, which results in pro-apoptotic and antiproliferative actions [78], [79]. Pomegranate extracts may inhibit the growth of human prostate cancer cell lines in vitro, according to a substantial body of research. In vitro studies have shown that pomegranate extracts have a beneficial effect on all of the various prostate cancer cell lines. Numerous investigations demonstrated that pomegranate extracts cause LNCaP, PC3, and DU145 prostate cancer cells to undergo apoptosis and decrease their ability to proliferate and invade Matrigel [80].

Pomegranate extracts have more recently been demonstrated to suppress the levels of testosterone and dihydrotestosterone in prostate cancer cell lines (22RV1) and LNCaP [81]. Additionally, in vivo research demonstrated that pomegranate extracts prevent the onset and spread of prostate cancer, potentially via inhibiting the PI3K/Akt/mTOR signalling pathways in a transgenic mice model of the disease [82]. By obstructing the arachidonic acid metabolism pathway in metastatic cell lines, PA may also inhibit the invasion of prostate cancer cells [83].

PSO's antiangiogenic actions and suppression of prostaglandin synthesis may be linked to its anticarcinogenic qualities. Additionally, it has been demonstrated that dietary PSO dramatically lowers the invasiveness of the PC-3 cell

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line and inhibits the growth of human prostate cancer LNCaP and DU 145 cells [80]. According to Wang et al., pomegranate extracts, such as PA, prevent the spread of prostate cancer by focusing on the CXCL12/CXCR4/AKT signalling axis [77]. Pomegranate extracts, such as luteolin, ellagic acid, and PA, have been shown to have enhanced anticancer action when administered together in recent years. **Error! Reference source not found.** By reducing cell migration and CXCL12 chemotaxis, enhancing cell adhesion, blocking the epithelial-mesenchymal transition, and preventing angiogenesis and proliferation, PA has anticancer action [77]. Consuming pomegranate juice normalized prostate-specific antigen in a two-year phase II clinical trial involving patients with prostate cancer [84]. PA has been shown to have beneficial benefits on patients with prostate cancer in a more recent phase II clinical trial [85].

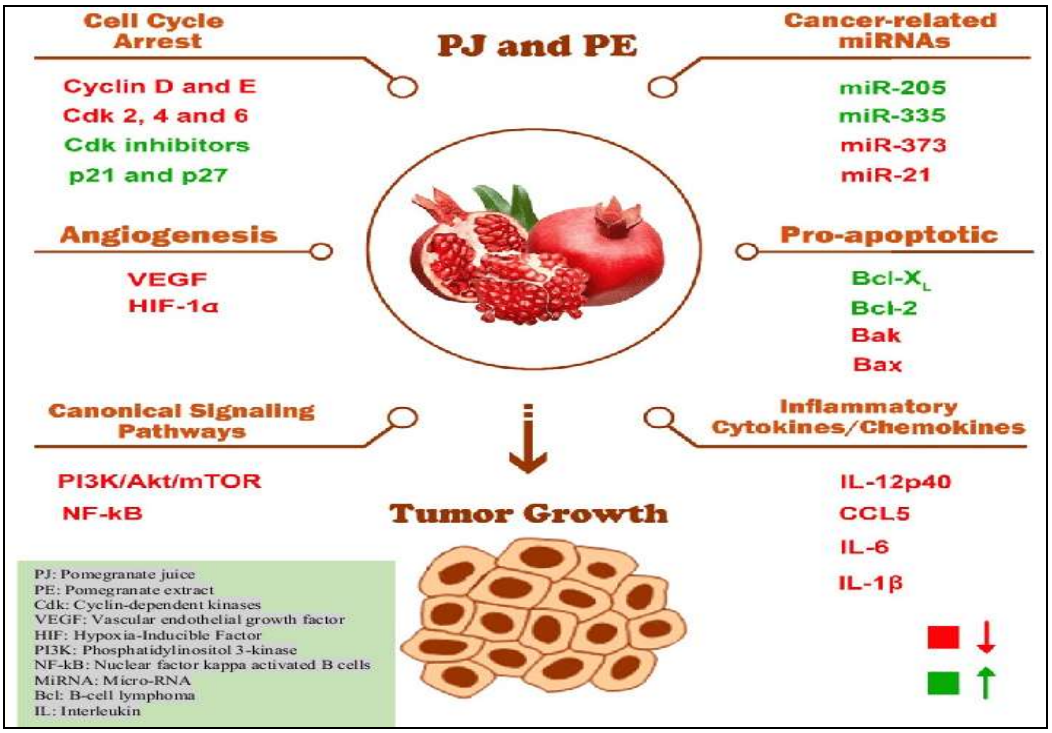

Figure 4: Pomegranate Juice (PJ) and pomegranate extract (PE) against prostate cancer (adapted from Wang and Martins-Green 2014)

Bioactive compound	IUPAC name	Molecular Formulae	Molecular weight (g/mol)	Structure	Effect on human body	References
Gallic acid	3,4,5-Trihydroxybenzoic acid	$C_7H_6O_5$	170.12		GA in pomegranate plays a significant role as anti-carcinogenic activities	Elango et al. (2011)
Rutin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-[[(2*R*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl] oxymethyl]oxan-2-yl] oxychromen-4-one	$C_{27}H_{30}O_{16}$	610.5		Rutin promotes a defensive impact against impairment of spatial memory escorted by neuron loss of pyramidal hippocampus	Koda et al. (2008)
Anthocyanins	2-Phenylchromenylium	$C_{15}H_{11}O^+$	207.25		The anthocyanins is used specifically as human medicinal application in models of animal as well as supplements of diet or as novel effective drugs to prevent cardio-vascular disorder	Reis et al. (2016)
Pelargonidin	2-(4-Hydroxyphenyl)chromenylium-3,5,7-triol	$C_{15}H_{11}O_5^+$	271.24		Pelargonidin reserves inducement of H_2O_2 for the peroxidation of lipid in homogenates brain of rat	Noda et al. (2002)

Figure 1: Bioactive compounds present in different compartments of pomegranate and their effect on human body [86]

The function of PA in metastatic prostate cancer has also been studied. By enhancing cell adherence and reducing cell migration, pomegranates stop metastases. Figure 1

However, PA exhibits its antimetastatic properties through various routes. The stroma of a solid tumour contains the majority of hyaluronan, which promotes tumour invasion. metastasis and cell migration [87]. By specifically targeting the hyaluronan signalling pathways in prostate cancer cells, PA and pomegranate extract have an antimetastatic impact. Among other potential processes, cytokines and chemokines can be mentioned. PA has beneficial effects and blocks this route [70], [77].Based on the data presented above, it can be said that nutraceuticals play a big part in preventing a number of illnesses, and PA in particular is a crucial component with a lot of promise. These substances have a low frequency of adverse effects and are safe to use. To fully realize their potential, more clinical research is needed.

2. CONCLUSION

Punicic acid, a major bioactive compound found in pomegranate (*Punica granatum L*) seed oil, *Trichosanthes Kirilowii* seeds has demonstrated significant therapeutic potential due to its various biological activities. These include antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, and cardiovascular protective effects, making it an attractive candidate for natural therapeutic interventions. Its ability to modulate key biological pathways, such as those involved in oxidative stress, inflammation, and lipid metabolism, underpins its wide range of health benefits. Additionally, the potential synergy between punicic acid and other phytochemicals in pomegranate suggests that whole plant extracts could offer enhanced therapeutic effects. However, while promising results from in vitro and animal studies are reported, clinical evidence in humans remains limited. More rigorous clinical trials are needed to establish its safety, efficacy, and optimal dosage for various treatments. Nonetheless, the growing body of evidence suggests that punicic acid could play a crucial role in the development of novel, natural therapeutic agents for managing chronic diseases, particularly those associated with inflammation and metabolic disorders. In conclusion, punicic acid presents a promising avenue for research and potential therapeutic use, but further studies are necessary to confirm its benefits in human health and treatment.

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