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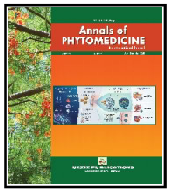

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Phenolic composition, antioxidant, antidiabetic, and cytotoxic activities of the pomegranate extracts

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Abstract

Pomegranate (*Punica granatum* L.) is widely recognized for its health-promoting potential, primarily attributed to its rich phenolic profile, including flavonoids, tannins, and phenolic acids. These bioactive compounds, particularly abundant in the peel and seeds, exhibit potent antioxidant, antidiabetic, and cytotoxic activities. More than 35 phenolic constituents have been identified, with gallic acid, ellagic acid, and punicalagin showing notable biological effects. The strong antioxidant capacity of pomegranate is associated with mitigating oxidative stress and reducing the risk of chronic conditions such as diabetes and cardiovascular diseases. Its antidiabetic effects are linked to mechanisms like Nrf2 pathway activation, enhancing antioxidant defenses and improving metabolic regulation. Furthermore, compounds such as punicalagin display cytotoxic activity against various cancer cell lines, highlighting potential therapeutic applications in oncology. Nonetheless, variability in phenolic content across cultivars and extraction methods poses challenges for standardization. Continued research is essential to clarify molecular mechanisms and substantiate the therapeutic utility of pomegranate.

1. Introduction

Pomegranate (*Punica granatum* L.) is a fruit widely recognized for its diverse health benefits, largely attributed to its rich phenolic composition. This includes flavonoids, tannins, and phenolic acids, which have attracted significant scientific attention for their antioxidant, antidiabetic, and cytotoxic properties. These bioactive compounds play a pivotal role in mitigating oxidative stress, a key factor in the pathogenesis of chronic diseases, thereby supporting the therapeutic potential of pomegranate in health promotion and disease prevention (Armstrong and Kricker, 2001; Cadet and Douki, 2018; Mouret *et al.*, 2006). Phenolic compounds are concentrated mainly in the peel and seeds of pomegranate, with their levels influenced by cultivar differences and extraction methods. Up to thirty-five distinct phenolics have been identified, among which gallic acid, ellagic acid, and punicalagin exhibit significant biological activity (Fan *et al.*, 2003; Mouret *et al.*, 2006; Paulo *et al.*, 2023). The diversity and extraction of these compounds determine the antioxidant efficacy of pomegranate extracts, which have been shown to alleviate conditions such as diabetes and cardiovascular disorders (Gobba *et al.*, 2019; Ling *et al.*, 2001; Glass and Hoover, 1989). In addition to antioxidant potential, pomegranate demonstrates antidiabetic effects through mechanisms such as activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, thereby strengthening antioxidant defenses (Bajdik*et al.*, 1996; de Winter *et al.*, 2001). Experimental findings reveal its ability to lower blood glucose levels and improve metabolic profiles in diabetic models, underscoring its role in diabetes management (Bajdik *et al.*, 1996; Cadet *et al.*, 1992). Furthermore, compounds such as punicalagin exert cytotoxic effects against cancer cell lines, inducing apoptosis *via* multiple cellular pathways, thus suggesting potential in cancer therapeutics (Beani, 2014; Anderson *et al.*, 1997). Despite these promising outcomes, variations in phenolic content due to cultivar and extraction differences pose challenges for standardization. Current research continues to focus on unravelling the molecular mechanisms underlying these bioactivities, reinforcing the importance of pomegranate in nutritional and pharmaceutical sciences (Protiæ Sabljiæ *et al.*, 1986; Ley, 1985; Narayanan *et al.*, 2010).

2. Primary phenolic compounds in pomegranate extracts

Pomegranate extracts are rich in phenolic compounds that contribute significantly to their antioxidant, antidiabetic, and cytotoxic activities. The major phenolics identified include ellagic acid, gallic acid, punicalagin, and a wide range of anthocyanins. Ellagic acid is distributed across various parts of the fruit, including the juice, peel, and seeds (Wang *et al.*, 2001; Ley, 1985). Punicalagin, particularly abundant in the peel, is a key bioactive compound known for its antioxidant, anti-inflammatory, and hepatoprotective effects (de Winter *et al.*, 2001; Anderson *et al.*, 1997). The concentrations of phenolic compounds vary considerably among pomegranate cultivars. For example, the 'Vietnam' variety has been reported to contain the

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highest phenolic content (4.3 µg/ml), followed by the 'EG' (4.1 µg/ml) and 'Molla Nepes' (3.8 µg/ml) cultivars (Gobba *et al.*, 2019). Similarly, the 'Pust Sefeede Shirin' cultivar showed the highest total phenolics among several studied varieties, followed by 'Pust Ghermeze Shirin' and 'Yazdi' (Paulo *et al.*, 2023). Differences in phenolic composition translate into variations in antioxidant capacity, which has been reported to range from 31.16% to 66.82% across cultivars (Cadet and Douki, 2018; Mouret *et al.*, 2006). Anthocyanins, which can constitute 20% - 82% of the total phenolic content, represent another major contributor to the antioxidant potential of pomegranate (Narayanan *et al.*, 2010). Comparative analyses of pomegranate juice have further demonstrated wide variability in total phenolic content, ranging from 0.78 to 9.47 mg/ml, depending on the cultivar (Armstrong and Kricker, 2001). Moreover, phenolic distribution varies among different fruit parts, with the peel generally containing higher concentrations compared to seeds and arils (de Winter *et al.*, 2001). Overall, the phenolic composition of pomegranate is complex and strongly influenced by cultivar type, genetic factors, and the specific fruit part analyzed. Ellagic acid, gallic acid, punicalagin, and anthocyanins remain the most prominent bioactive constituents, underscoring their importance in the therapeutic potential of pomegranate extracts.

3. Phenolic compounds and antioxidant potential of pomegranate extract

Pomegranate extracts are abundant in phenolic compounds that play a crucial role in their antioxidant activity. The principal phenolics include ellagic acid, gallic acid, punicalagin, anthocyanins, and ellagitannins. Among them, ellagic acid and gallic acid are widely distributed throughout the juice, peel, and seeds (Wang *et al.*, 2001; de Winter *et al.*, 2001). Punicalagin, predominantly concentrated in the peel, is particularly noteworthy for its strong antioxidant and other biological effects (de Winter *et al.*, 2001; Beani, 2014).The antioxidant potential of pomegranate is largely attributed to these compounds. Anthocyanins, comprising glycosides of delphinidin, cyanidin, and pelargonidin, represent a substantial fraction of the total phenolic content and contribute significantly to antioxidant activity (Fan *et al.*, 2023; Anderson *et al.*, 1997). The total phenolic content in pomegranate juice has been reported to range between 784.4 and 1551.5 mg GAE/l, reflecting its strong free radical scavenging capacity (Wehner *et al.*, 2012; Mouret *et al.*, 2006).Variability in phenolic composition has been observed across cultivars and fruit parts. For example, the 'Pust Sefeede Shirin' cultivar demonstrated the highest phenolic content compared to other varieties (Paulo *et al.*, 2023), while peels generally contained higher concentrations than seeds and arils (Ling *et al.*, 2001). Such differences influence the overall antioxidant capacity of pomegranate extracts. Additionally, ellagitannins and flavonoids account for a substantial proportion of the total phenolic content, further strengthening their antioxidant potential (Narayanan *et al.*, 2010; Bajdik *et al.*, 1996).

A study profiled the phenolic composition of pomegranate peel from nine cultivars across China using UHPLC-QTOF-MS and UPLC-QQQ-MS, identifying 64 compounds, including 23 reported for the first time. Dominant phenolics such as punicalagin (28.03-104.14 mg/g), ellagic acid, gallocatechin, and punicalin were quantified with high precision. Principal component analysis revealed cultivar-specific phenolic profiles, with sweet with green seed (SGS) showing unique flavonoid abundance. These findings underscore the peel's rich phytochemical diversity and suggest its potential for targeted nutraceutical applications. The study also highlights UHPLC-QTOF-MS as a robust tool for comprehensive phenolic profiling and cultivar differentiation (Man *et al.,* 2022). A study by Toledo-Merma *et al.* (2022) evaluated the recovery of phenolic compounds from pomegranate peel and carpelar membranes using pressurized liquid extraction (PLE) at moderate temperatures and pressures. The optimal conditions-60°C and 40 bar yielded extracts rich in α- and β-punicalagin (48 ± 2 and 146 ± 11 mg 100 g) and ellagic acid (25.6 ± 0.3 mg 100 g). These compounds exhibited strong antioxidant potential. Notably, lower pressure enhanced compound recovery while reducing energy costs. The study demonstrated that PLE is a sustainable and efficient method for valorizing agro-industrial pomegranate waste, offering promising applications in food and pharmaceutical industries (Toledo-Merma *et al.,* 2022).

Pomegranate peel extract exhibits strong antioxidant activity, primarily due to its rich phenolic content, including punicalagin and ellagic acid. Using DPPH and ABTS assays, the extract showed IC_{50} values comparable to Trolox, a standard antioxidant. These findings highlight its potential as a natural antioxidant source for therapeutic and nutraceutical applications (Bakhti *et al.,* 2024). A research comparing antioxidant activity across pomegranate fruit parts revealed that wild pomegranate peel extract (WPPE) exhibited the highest efficacy, with IC_{50} values of 12.2 µg/ml (DPPH) and 3.2 µg ml (ABTS), closely matching Trolox, a standard antioxidant. Cultivated peel and membrane extracts also showed strong hydroxyl radical inhibition (41 µg ml). These effects correlate with high phenolic and flavonoid content, particularly punicalagin, ellagic acid, and epicatechin. The findings underscore WPPE's superior radical-scavenging potential and support its use as a natural antioxidant source for nutraceutical and therapeutic applications (Miloševiæ *et al.,* 2023). In summary, the diverse array of phenolic compounds particularly ellagic acid, gallic acid, punicalagin, and anthocyanins, forms the biochemical basis of pomegranate's antioxidant activity and highlights its potential role in mitigating oxidative stress related diseases (Ling *et al.*, 2001; Ley, 1985).

4. Antidiabetic potential of pomegranate extracts

Pomegranate extracts exhibit notable antidiabetic effects, primarily through mechanisms associated with blood glucose regulation and improved insulin sensitivity. These effects are largely attributed to their rich phenolic composition, including ellagic acid, punicalagin, gallic acid, anthocyanins, and ellagitannins. Such compounds possess strong antioxidant activity, which plays a critical role in reducing oxidative stress and lipid peroxidation pathological processes closely linked to diabetes and insulin resistance (Armstrong *et al.*, 2001; Mouret *et al.*, 2006; de Winter *et al.*, 2001). By scavenging free radicals and preventing oxidative damage, pomegranate polyphenols contribute to enhanced insulin signaling and glucose metabolism (Mouret *et al.*, 2006). Experimental evidence indicates that pomegranate extracts modulate molecular pathways involved in insulin sensitivity, such as the nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor kappa B (NF-κB) pathways (Bajdik*et al.*, 1996). Additionally, they may promote insulin release and protect pancreatic tissue, thereby supporting glucose homeostasis (de Winter *et al.*, 2001). Animal studies have shown that pomegranate supplementation improves insulin sensitivity, suggesting its potential role as an adjunct therapy for type 2 diabetes

(Seebode *et al.*, 2016). Fresh pomegranate juice has also been reported to exert synergistic effects with oral hypoglycemic agents by creating an antioxidant environment that mitigates diabetes-related complications (Ling *et al.*, 2001). Although, some investigations indicate that flower and peel extracts do not directly influence glucose homeostasis, they nonetheless exhibit significant antioxidant and anti-inflammatory effects that may indirectly benefit blood glucose regulation (Gobba *et al.*, 2019; Glass and Hoover, 1989). Furthermore, improvements in homeostasis model assessment of insulin resistance (HOMA-IR) values have been observed in individuals with metabolic disorders, indicating enhanced insulin sensitivity (Protiæ Sabljiæ *et al.*, 1986; Narayanan *et al.*, 2010). Several experimental studies support these findings. For instance, pomegranate phenolic extracts demonstrated strong radical-scavenging activity in the DPPH assay, confirming their antioxidant potential (Mohan and Chang, 2014). In alloxan-induced diabetic rats, administration of pomegranate peel extract (200 mg, 10 days) reduced fasting glucose levels, increased insulin secretion, and showed anti-lipid peroxidation effects (Armstrong *et al.*, 2001). Similarly, pomegranate peel extract combined with L-carnitine showed efficacy against streptozotocin-induced diabetes (Paulo *et al.*, 2023). However, a meta-analysis revealed that pomegranate supplementation did not produce significant improvements in metabolic status or oxidative stress markers among diabetic patients, highlighting variability and the need for further clinical validation (Cadet and Douki, 2018).

In vitro assays revealed that PP-Sr NPs significantly inhibited α-amylase and α-glucosidase activities, with maximum inhibition rates of 79.28% and 76.17%, respectively, at 160 µg ml comparable to standard acarbose. These effects suggest a concentration-dependent mechanism that may help regulate postprandial glucose levels. Prior research also supports the extract's role in improving insulin sensitivity and reducing oxidative stress, positioning PP-Sr NPs as a viable candidate for future diabetes therapeutics (Royapuram *et al.,* 2023). Ethanol-based extracts demonstrated significant inhibition of α-amylase and α-glucosidase enzymes, with IC_{50} values of 5.86 mg/ml and 6.58 mg/ml, respectively. LC-MS analysis revealed ten bioactive compounds, including punicalagin, ellagic acid, and gallic acid, which are linked to glucose metabolism modulation (More *et al.,* 2024). Another study demonstrated that aqueous extract of *P. granatum* fruits significantly ameliorates hyperglycemia and hyperlipidemia in alloxan-induced diabetic Wistar rats. Oral administration of the extract at 350 mg/kg body weight led to a 67.9% reduction in fasting blood glucose and a marked increase in insulin secretion. Molecular analysis revealed upregulation of IRS-1, Akt, Glut-2, and Glut-4 mRNA expression, enhancing glucose uptake and storage. Additionally, triglyceride and free fatty acid levels were lowered, while glycogen content in liver, heart, and skeletal muscle improved. These findings suggest that pomegranate extract modulates insulin signaling and lipid metabolism effectively (Gharib and Kouhsari, 2019). A study by Elsaid (2022) investigated the protective effects of pomegranate peel extract (PPE) on diabetes-induced testicular damage in rats. Diabetic rats exhibited severe histopathological changes, including thickened tunica albuginea, disrupted basement membranes, depleted germ cells, and elevated caspase-3 expression. Ultrastructural analysis revealed ballooned mitochondria and cytoplasmic vacuolations. However, PPE treatment (500 mg/kg/day for 8 weeks) significantly restored normal testicular architecture, reduced apoptotic markers, and improved serum testosterone levels. These findings suggest that PPE exerts potent antioxidant and anti-apoptotic effects, offering therapeutic potential as an adjuvant in mitigating diabetes-related reproductive dysfunction (Elsaid, 2022). Overall, the antidiabetic activity of pomegranate extracts is multifaceted, involving oxidative stress modulation, insulin sensitivity enhancement, and glucose metabolism regulation. Continued research is warranted to fully elucidate the molecular mechanisms and establish their therapeutic applications in diabetes management.

5. Cytotoxic effects observed in pomegranate extracts against cancer cell lines

Pomegranate extracts have demonstrated significant cytotoxic effects against various cancer cell lines, primarily attributed to specific phenolic compounds. Studies have highlighted the effectiveness of pomegranate peel extracts, particularly against breast cancer (MCF-7) and colon cancer (HT29) cells, where they exhibited significant antiproliferative and cytotoxic activities. For instance, one study indicated that pomegranate peel extract had a notable cytotoxic effect on MCF-7 cancer cells, even surpassing the effects of vitamin D (Seebode *et al.,* 2016). The primary phenolic compounds responsible for these cytotoxic effects include punicalagin and other polyphenolic constituents. Punicalagin, in particular, has been noted for its ability to induce apoptosis in cancer cells at high concentrations (Beani, 2014). Additionally, the cytotoxic potential of various solvent extracts of pomegranate fruits has been validated through cytotoxicity assays, further reinforcing the role of phenolic compounds in combating cancer (Beani, 2014). Research has also pointed towards the pomegranate peel extract as a potent antiproliferative agent, suggesting its potential for not only reducing cancer cell viability but also inhibiting cancer cell invasion (Wehner *et al.,* 2012). Furthermore, the antioxidant properties of these phenolic compounds contribute to their overall effectiveness in reducing oxidative stress within cancer cells, thereby enhancing their cytotoxic potential (Ley, 1985). Pomegranate extracts, particularly from the peel, exert significant cytotoxic effects on various cancer cell lines through their rich phenolic composition, prominently featuring compounds like punicalagin, which facilitate apoptosis and inhibit proliferation in cancer cells. These findings suggest a promising avenue for the use of pomegranate extracts in cancer therapy and prevention.

Recent research has underscored the potent anticancer effects of polyphenolic compounds extracted from pomegranate peel (PP), particularly against cervical (HeLa), breast (MDA-MB), and lung (A549) cancer cell lines. Teniente *et al.* (2025) demonstrated that PP extracts exhibited significant antiproliferative and cytotoxic activity in a dose-dependent manner, while showing minimal impact on non-cancerous Hek-293 cells, indicating selective toxicity. Complementary studies have identified punicalagin and ellagic acid major constituents of PP as key bioactives responsible for inducing apoptosis, disrupting mitochondrial function, and arresting the cell cycle at G_0 G_1 or G_2 M phases. Methanolic PP extracts have shown exceptional potency, with IC_{50} values as low as 0.1 µg/ml against prostate cancer PC3 cells, and similarly strong effects across other cancer types including breast and ovarian cancers (Teniente *et al.,* 2025). Dwarf pomegranate extracts peel, juice, and seed oil exhibited dose-dependent cytotoxicity in DU145 prostate cancer cells, with seed oil showing the lowest IC_{50} (0.12 mg/ml). All extracts induced apoptosis *via* DNA fragmentation, PARP cleavage, and COX-2 inhibition, with peel extract demonstrating the strongest pro-apoptotic effect (Amri *et al.,* 2019). A study highlights the potent anti-inflammatory and cytotoxic effects of the hydrophilic fraction of pomegranate seed oil (PSO), particularly

rich in punicic acid. In breast cancer cell lines MCF-7 and MDA-MB-231, PSO extracts significantly reduced cell viability and induced G - G cell cycle arrest without markedly increasing apoptosis. Moreover, cytokine profiling revealed dose-dependent down regulation of VEGF and nine pro-inflammatory markers, suggesting PSO's potential to modulate NF-κB and STAT1 pathways. These findings support PSO's synergistic antioxidant and anticancer properties (Costantini *et al.,* 2014).

A study highlighted the potent anticancer properties of pomegranate extracts, particularly against breast cancer cell lines. Turkish cultivar P7 (Izmir 1513), rich in cyanidin-3-O-glucoside and punicalagin, demonstrated strong cytotoxicity on MCF-7 cells with an IC_{50} of 49.08/ µg/ml. Additionally, seed oil extracts containing punicic acid showed anti-inflammatory effects and induced G-G cell cycle arrest. Across various studies, pomegranate extracts selectively targeted cancer cells while sparing normal cells, suggesting their promise as natural antioxidant and anticancer agents (Ozkan *et al.,* 2021). Pomegranate extracts induce cancer cell death through multiple complementary mechanisms. Apoptosis induction occurs via both intrinsic and extrinsic pathways, with consistent upregulation of pro-apoptotic proteins (Bax, caspase-3, caspase-8, and caspase-9) and downregulation of anti-apoptotic proteins (Bcl-2) (Peng *et al.,* 2021; Banerjee *et al.,* 2013; Amri *et al.,* 2019). Mitochondrial dysfunction represents a critical mechanism, with pomegranate extracts causing mitochondrial membrane potential disruption, ATP depletion, and mitochondrial DNA damage. This leads to cytochrome c release and activation of the intrinsic apoptotic pathway (Sun *et al.,* 2023).

6. Conclusion

Pomegranate extracts are rich in phenolic compounds, particularly ellagic acid, gallic acid, punicalagin, and anthocyanins, which contribute to their potent antioxidant, antidiabetic, and cytotoxic activities. The phenolic composition varies across cultivars and fruit parts, with the peel generally containing higher concentrations. Pomegranate's antioxidant potential is attributed to these compounds, which scavenge free radicals and prevent oxidative damage. The extracts exhibit antidiabetic effects by modulating molecular pathways involved in insulin sensitivity, promoting insulin release, and protecting pancreatic tissue. Animal studies have shown improved insulin sensitivity and glucose homeostasis with pomegranate supplementation. Pomegranate extracts also demonstrate significant cytotoxic effects against various cancer cell lines, particularly breast, colon, cervical, and lung cancers. Punicalagin and other polyphenolic constituents induce apoptosis, disrupt mitochondrial function, and arrest the cell cycle in cancer cells. Recent studies highlight the selective toxicity of pomegranate extracts towards cancer cells while sparing normal cells. However, variability in phenolic content across cultivars and extraction methods poses challenges for standardization. Further research is needed to elucidate the molecular mechanisms and establish the therapeutic applications of pomegranate extracts in managing diabetes and cancer.

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None to be declared.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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