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Phenolic Composition, Antioxidant, Antidiabetic, and Cytotoxic Activities of the Pomegranate Extracts

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ABSTRACT

Pomegranate (*Punica granatum*) is valued for its health-promoting properties, largely due to its rich phenolic content, including flavonoids, tannins, and phenolic acids. These bioactive compounds, especially abundant in the peel and seeds, exhibit strong antioxidant, antidiabetic, and cytotoxic activities. Up to 35 phenolic compounds have been identified, with gallic acid, ellagic acid, and punicalagin showing significant biological effects. The antioxidant potential of pomegranate is linked to its ability to combat oxidative stress and reduce risks of chronic diseases like diabetes and cardiovascular conditions. Its antidiabetic activity involves mechanisms such as Nrf2 pathway activation, improving antioxidant defense and metabolic profiles. Additionally, certain compounds, notably punicalagin, demonstrate cytotoxicity against cancer cell lines, indicating potential in cancer therapy.

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However, variations in phenolic content due to cultivar differences and extraction techniques pose challenges in standardizing its use. Ongoing research aims to elucidate the underlying mechanisms and support therapeutic applications of pomegranate.

Keywords: Pomegranate, antibacterial activity, oxidative stress, skin carcinoma, data integrity

1. INTRODUCTION

Pomegranate (Punica granatum) is a fruit renowned for its extensive health benefits, largely attributed to its rich phenolic composition. This composition, which includes a variety of phytochemicals such as flavonoids, tannins, and phenolic acids, has garnered significant scientific interest due to its potent antioxidant, antidiabetic, and cytotoxic properties. Research has consistently highlighted the role of these compounds in combating oxidative stress, which is linked to numerous chronic diseases, making pomegranate extracts notable for their potential therapeutic applications in health promotion and disease prevention [1,2,3]. The phenolic compounds present in pomegranate are predominantly found in the fruit's peel and seeds, where they exhibit varying concentrations based on cultivar and extraction methods. Studies have identified up to thirty-five distinct phenolic compounds, with key constituents such as gallic acid, ellagic acid, and punicalagin demonstrating significant biological activity [4,5,6]. The diversity of phenolic content, along with the methods used to extract them, plays a crucial role in determining the antioxidant efficacy of pomegranate extracts, which has been shown to mitigate conditions such as diabetes and cardiovascular diseases [7,8,9].In addition to its antioxidant properties, pomegranate extracts have been shown to possess antidiabetic effects through mechanisms such as the modulation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which enhances the body's antioxidant defenses [10,11] Experimental studies indicate that pomegranate can significantly reduce blood glucose levels and improve metabolic profiles in diabetic models, highlighting its multifaceted role in diabetes management [10,12]. Furthermore, pomegranate extracts exhibit cytotoxic activities against various cancer cell lines, with compounds like punicalagin inducing apoptosis through several cellular pathways, presenting potential avenues for cancer therapeutics [13,14]. Despite the promising benefits associated with pomegranate extracts, the variability in phenolic composition among different cultivars and extraction techniques poses challenges in standardizing their health applications. Moreover, ongoing research aims to elucidate the precise mechanisms underlying these biological activities, which remain a focal point of contemporary studies in nutritional and pharmaceutical sciences
[15,16,17].

2. PRIMARY PHENOLIC COMPOUNDS IN POMEGRANATE EXTRACTS

Pomegranate extracts are rich in phenolic compounds, which contribute to their antioxidant, antidiabetic, and cytotoxic activities. The primary phenolic compounds found in pomegranate extracts include ellagic acid, gallic acid, punicalagin, and various anthocyanins. Ellagic acid is notable for its presence across different parts of the fruit, including the juice, peel, and seeds [22,41]. Punicalagin, particularly prevalent in the peel, is another significant compound that exhibits various biological activities, including anti-inflammatory and hepatoprotective effects [11,39]. The concentrations of these phenolic compounds can vary significantly among different pomegranate varieties. For instance, studies have shown that the 'Vietnam' variety has the highest content of total phenolics at 4.3 μg/mL, followed closely by the 'EG' variety at 4.1 μg/mL and 'Molla Nepes' at 3.8 μg/mL [32]. Furthermore, the 'Pust Sefeede Shirin' variety has been reported to possess the highest total phenolics among various cultivars analyzed, followed by 'Pust Ghermeze Shirin' and 'Yazdi' [6].

Different cultivars also exhibit varying antioxidant capacities, with statistically significant differences noted. The antioxidant activity across several pomegranate cultivars studied ranged from 31.16% to 66.82% [2,30]. Additionally, anthocyanins have been reported to make up between 20% to 82% of the total phenolic content, underscoring their prominence in certain pomegranate varieties [17]. Moreover, a comparative study of pomegranate juice from various cultivars indicated that the total phenolic content can range widely, with values between 0.78 and 9.47 mg/mL, illustrating the diversity in phenolic composition based on the cultivar [26]. The phenolic profiles also differ among the various parts of the pomegranate, with peels typically showing higher concentrations compared to seeds and arils [36]. The phenolic composition of pomegranate extracts is complex and varies significantly among different cultivars. Key compounds like ellagic acid, gallic acid, punicalagin, and anthocyanins are prevalent, with their concentrations influenced by both genetic factors and the specific part of the fruit analyzed.

3. PHENOLIC COMPOUNDS IN POMEGRANATE EXTRACTS AND ANTIOXIDANT ACTIVITY

Pomegranate extracts are rich in various phenolic compounds that significantly contribute to their antioxidant activity. Among the main phenolic compounds identified in pomegranate extracts are ellagic acid, gallic acid, punicalagin, anthocyanins, and ellagitannins. Specifically, ellagic acid and gallic acid are prominent phenolic acids found throughout the fruit, including in the juice, peel, and seeds [22,36]. Punicalagin, which is predominantly found in the pomegranate peel, is known for its potent biological activities, including antioxidant effects [11,39]. The antioxidant activity of pomegranate extracts is largely attributed to these phenolic compounds. For instance, anthocyanins, which include glycosides of delphinidin, cyanidin, and pelargonidin, make up a significant portion of the total phenolic content and play a crucial role in providing antioxidant benefits [29,39]. The total phenolic content in pomegranate juice has been reported to range from 784.4 to 1551.5 mg GAE/L, indicating a high capacity for scavenging free radicals and protecting against oxidative stress [19,28]. Furthermore, various studies have highlighted the variation in phenolic profiles among different pomegranate cultivars and parts of the fruit. For example, the 'Pust Sefeede Shirin' cultivar demonstrated the highest total phenolic value compared to other varieties [6], while pomegranate peel samples generally exhibited a higher concentration of phenolics than other fruit parts [8]. These variations suggest that the specific phenolic composition can vary widely, affecting the overall antioxidant capacity. Additionally, it has been noted that phenolic compounds such as ellagitannins and flavonoids account for a significant percentage of the total phenolic content in pomegranates, contributing to their strong antioxidant properties [17,35]. This diverse array of phenolic compounds not only enhances the antioxidant activity but also underscores the potential health benefits of pomegranate extracts in mitigating oxidative stress-related diseases [33,41]. In conclusion, the main phenolic compounds found in pomegranate extracts, including ellagic acid, gallic acid, punicalagin, and anthocyanins, play a critical role in their antioxidant activity.

4. POMEGRANATE EXTRACT'S MECHANISM OF ANTIDIABETIC EFFECTS

Pomegranate extracts exhibit significant antidiabetic effects, particularly through mechanisms related to blood glucose regulation and enhancement of insulin sensitivity. A key aspect of these effects lies in the rich phenolic composition of pomegranate, which includes compounds such as ellagic acid, punicalagin, gallic acid, anthocyanins, and ellagitannins. These compounds are known for their strong antioxidant properties, which play a crucial role in mitigating oxidative stress and lipid peroxidation, conditions often associated with diabetes and insulin resistance [1,30,36]. The antioxidant activity of pomegranate is primarily attributed to its high content of various polyphenolic compounds that scavenge free radicals and reduce oxidative damage [3,5].

This reduction in oxidative stress is beneficial, as it is linked to improved insulin signaling and glucose metabolism. Specifically, pomegranate extracts have been shown to modulate key molecular pathways involved in insulin sensitivity, including the nuclear factor-erythroid factor 2-related factor 2 (Nrf2) and nuclear factor kappa B (NF-kB) pathways [35]. Moreover, pomegranate extracts may enhance insulin release and protect pancreatic tissue, contributing to better glucose homeostasis [36]. In animal studies, consumption of pomegranate has demonstrated improvements in insulin sensitivity, highlighting its potential as an adjunct therapy for managing type 2 diabetes [43]. Fresh pomegranate juice has also shown synergistic effects when combined with oral hypoglycemic agents, creating an antioxidant environment that helps minimize complications associated with diabetes [33]. While some studies suggest that specific extracts, like those from the flower and peel, do not directly affect glucose homeostasis, they still exhibit significant antioxidant and anti-inflammatory properties that may indirectly support blood glucose regulation [32, 34]. Furthermore, there is evidence indicating that pomegranate extracts can improve Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) levels in individuals with metabolic disorders, suggesting a role in enhancing insulin sensitivity [40,42]. The antidiabetic effects of pomegranate extracts are multifaceted, involving the modulation of oxidative stress, enhancement of insulin sensitivity, and regulation of glucose metabolism. Continued research is essential to fully elucidate hatm lalay awlaya the specific mechanisms and potential clinical applications of pomegranate extracts in diabetes management. Several studies have examined the antioxidant, antidiabetic, and cytotoxic effects of pomegranate extracts, demonstrating their diverse therapeutic potentials. One study investigated the antioxidant capacity of phenolic extracts from pomegranate fruit using the DPPH scavenging assay, demonstrating significant antioxidant activity. This indicates that pomegranate extracts can effectively neutralize free radicals, contributing to their potential health benefits [45]. In a controlled experiment, alloxan-induced diabetic rats treated with a pomegranate peel extract rich in polyphenols (200 mg) for ten days showed lower fasting serum glucose and elevated insulin levels, along with anti-lipid peroxidation effects [1]. Furthermore, another study focused on the antidiabetic efficacy of pomegranate peel extract and L-carnitine on streptozotocin-induced diabetes, highlighting its potential in managing diabetic conditions [6]. However, a meta-analysis revealed that pomegranate supplementation did not exhibit significant improvements in metabolic status and oxidative stress among diabetic individuals, indicating mixed results in this area [27]. The cytotoxic effects of pomegranate extracts have been documented in various cancer cell lines. For example, a study demonstrated the cytotoxic and anti-inflammatory activities of a pomegranate extract in breast cancer cells, showing promising results for cancer treatment [12]. Additionally, cytotoxicity assays revealed that pomegranate fruit extracts and punicalagin were effective in inducing cytotoxic effects at high concentrations against certain cancer cell lines, such as MCF-7 [13]. Another investigation evaluated the anticancer activity of pomegranate leaf extracts on HT29 and MCF7 cancer cells using the MTT assay, reinforcing the anticancer potential of pomegranate constituents [43]. Long-term intake of pomegranate extracts has been suggested as a potential strategy for preventing high-fat diet-induced insulin resistance and oxidative stress, further supporting their role in diabetes management [4]. A separate study indicated that eight-week supplementation with pomegranate extract resulted in favorable changes in inflammatory status and oxidative stress biomarkers among diabetic patients, which aligns with the extract's antioxidant properties [5].

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 [18]. 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 [13]. 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 [13]. 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 [19]. 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 [16]. 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.

6. RECOMMENDATIONS FOR MEDICAL EDUCATION

To mitigate the risks associated with AI, medical schools should adopt a dual-focused educational approach that combines data science and AI training with traditional medical education. This could involve the inclusion of dedicated modules on AI, biostatistics, and the ethical implications of technology in healthcare [11,12]. Encouraging students to critically assess AI tools, including their limitations and biases, will be vital in fostering a generation of physicians who can utilize AI effectively while maintaining a strong foundation in clinical reasoning and ethical practice. By cultivating a balanced understanding of AI's capabilities and limitations, medical students can better prepare themselves to leverage this technology as a valuable tool rather than a crutch that could compromise patient care and their professional development [13,14].

7. SOLUTIONS AND BEST PRACTICES

To successfully integrate artificial intelligence (AI) into medical education, a multidisciplinary approach is essential. This includes innovative data annotation methods and the development of rigorous AI techniques and models. Collaboration between computer scientists and healthcare providers will foster an environment conducive to creating practical and usable technology for clinical practice [15]. Sharing data across multiple healthcare settings will also enhance data quality and verify analyzed outcomes, which are critical for the successful adoption of AI technologies [15]. Medical schools must prioritize the incorporation of AI into their curricula. This should involve developing AI-focused modules that are engaging and easy to learn, ensuring that students acquire the necessary skills to thrive in their future medical careers [12,16]. A longitudinal approach to teaching AI across various subjects will help students understand its breadth and applicability in healthcare [11]. Practical, hands-on experience with AI technologies should be emphasized, as students expressed the importance of real-world applications and the use of advanced visualization techniques like 3D models and animations [17]. Developing AI curricula requires collaboration among educators from various disciplines. This collaborative effort can facilitate the integration of AI into existing medical training and ensure that all learners have equal opportunities to benefit from these technologies. Institutions should invest in infrastructure that supports AI education and foster partnerships with AI experts to create interdisciplinary learning opportunities [11,18]. Furthermore, incorporating case-based learning and simulation scenarios with AI-driven recommendations can familiarize students with AI solutions in clinical settings [11].

To prepare educators for the evolving role of AI in medicine, investment in their training and development is crucial. Creating a safe environment for educators to explore AI applications will be vital for guiding students through this transformation [18]. Ongoing workshops and seminars on emerging AI technologies can support continuous professional development, ensuring that faculty remain knowledgeable and competent in teaching AI-related content [17].

8. ETHICAL CONSIDERATIONS

Medical education should also emphasize ethical considerations surrounding the use of AI. Students have indicated the necessity for transparency and explainability in AI systems to understand their decision-making processes better. This includes addressing ethical challenges that may arise from AI applications, as future physicians will encounter complex scenarios that require a solid understanding of ethical principles [8,19,20]. The incorporation of ethical training into AI education will equip students with the skills necessary to navigate these challenges effectively [8].

9. RESEARCH AND EVALUATION

Future research should focus on evaluating the long-term impact of AI education on clinical outcomes and the effectiveness of various teaching methodologies. Policymakers are encouraged to allocate funding for AI training programs and establish guidelines for ethical AI use in healthcare settings. Developing a national framework for AI literacy in medical education will also ensure that students are adequately prepared for a technology-driven healthcare environment [17,21]. By implementing these solutions and best practices, the medical education community can effectively integrate AI into training programs, ultimately enhancing healthcare delivery and outcomes.

10. Case Studies and Real-world Examples

Recent advancements in artificial intelligence (AI) have introduced dynamic approaches to case-based learning in medical education. Utilizing scenarios where AI is currently implemented in clinical practice serves as effective examples for students, fostering a deeper understanding of both AI capabilities and limitations [22]. Such methods allow for the integration of AI-based recommendations into clinical scenarios, enhancing students' exposure and familiarity with AI applications in medical contexts [11]. Real-world case studies highlight various ethical challenges associated with AI in medicine. For instance, when generative AI collaborates with human medical professionals, it leads to non-frozen interactions, where both the AI and the clinician can modify their views on medical diagnoses through mutual interaction [14]. This collaborative environment necessitates a critical examination of ethical implications, particularly when AI encounters pitfalls in clinical settings [23]. Public attitudes toward AI in healthcare are mixed. A significant proportion of the population is skeptical about the potential improvements AI could bring to health outcomes; only 38% believe AI applications like disease diagnosis and treatment recommendations would enhance patient care [24]. Concerns regarding empathy, emotional well-being, and the ability of AI to navigate unforeseen situations underscore the limitations of AI in addressing complex human factors inherent in medical practice [12]. Moreover, issues such as accountability in case of errors, AI's potential to undermine physician autonomy, and the biases that may be perpetuated by AI systems have emerged as major points of contention [5,25]. To address these concerns and improve students' mastery of AI tools, medical education institutions are encouraged to implement practice-oriented teaching formats. Workshops based on real-life cases and online simulation courses can provide students with safe environments to engage with AI technology [26].

This experiential learning approach can build confidence in the technology while simultaneously addressing the ethical and practical considerations that arise from its use in clinical settings.

11. CONCLUSION

As artificial intelligence becomes increasingly embedded in medical education, it is vital that its integration is guided by careful consideration, ethical awareness, and structured training. While AI offers promising tools to support learning and clinical practice, uncritical reliance and lack of adequate education can undermine core competencies and patient care standards. By equipping medical students with technical knowledge, critical thinking skills, and a strong ethical foundation, educational institutions can ensure that future healthcare professionals use AI responsibly and effectively.

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