Texila International Journal of Public Health
Special Issue-2024
DOI: 10.21522/TIJPH.2013.SE.24.05.Art040

Polydatin: A Promising Natural Agent with Anti-Hepatocellular Carcinoma Properties

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Abstract

The review extensively examines the multifaceted anti-cancer properties of polydatin (PD), a stilbenoid compound sourced from fruits and vegetables. PD is known for its antioxidant capabilities, anti-inflammatory effects, and anti-cancer properties. The analysis delves into PD's impact on cancer characteristics such as cellular proliferation, metastasis, and apoptosis. It highlights PD's potential as a targeted therapeutic agent and its synergistic interactions with existing anti-cancer medications, aiming to enhance understanding and innovative strategies in cancer therapy. Ultimately, this review aims to provide a comprehensive analysis of PD's diverse anti-cancer attributes and intrinsic value in advancing novel paradigms in cancer treatment and prevention, instilling hope for the future of cancer therapy.

Keywords: *Cancer Therapy, Liver Cancer, Natural Product, Polydatin.*

Introduction

Liver cancer ranks as the fifth most prevalent form of malignancy in the human population and stands as the third leading cause of cancer-related mortality on a global scale [1]. Hepatocellular carcinoma (HCC) typically emerges because of conditions such as hepatitis and cirrhosis, responsible for approximately 80-90% of primary liver cancer cases [2]. Owing to its unique immunosuppressive characteristics, distinctive metabolic milieu, and anatomical location, the liver frequently becomes a target for colonizing metastatic tumor cells originating from adjacent organs, notably the colon [3]. While a significant proportion of individuals with HCC receive palliative care, curative strategies are implemented in around 30-40% of instances. Surgical resection and liver transplantation are recognized as the most efficacious interventions for liver cancer; nevertheless, a considerable number of cases are diagnosed at advanced stages, limiting the applicability of available treatments to a mere 15% of patients. Chemotherapy is generally not recommended

Received: 20.08.2024 ***Accepted: 16.09.2024*** ***Published on: 10.12.2024***

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for individuals with cirrhosis and extensive resections [1]. Therefore, the development of innovative chemotherapeutic agents with enhanced efficacy in treating liver cancer patients while minimizing toxicity and adverse effects is imperative. Doxorubicin (DOX), an anthracycline antibiotic, is utilized in the management of various cancer types, including haematological malignancies, liver cancer, and diverse solid tumors. However, its clinical utility is constrained by dose-dependent and irreversible cardiac toxicity, posing a substantial limitation. Patients receiving DOX are at heightened risk of congestive heart failure, thereby escalating the mortality rates among cancer survivors due to cardiovascular complications [4, 5]. Similarly, cisplatin (DDP) is an anticancer medication employed in treating a broad spectrum of malignancies such as lymphoma, lung, ovarian, and bladder cancers [6, 7]. Regrettably, its clinical application is hindered by severe adverse effects akin to many other therapeutic agents and the development of resistance over time [6]. Cisplatin is associated with various detrimental effects on patients, including neurotoxicity, cardiotoxicity, nephrotoxicity, and hepatotoxicity in a dose-dependent manner [8]. Historical utilization of natural substances for health advantages persists, and ongoing research aims to investigate the potential of phytochemicals from natural origins, including PD, a component derived from *Polygonum cuspidatum* roots [5, 9].

PD, a medicinal element, is famed for its analgesic and antipyretic attributes. Its potential in treating cancer has attracted attention owing to its distinctive molecular structure and varied pharmacological effects [10]. Investigations disclose the antioxidant features of PD and its capacity to influence cancer-associated signaling pathways, like the PI3K/AKT pathway. Studies demonstrate encouraging outcomes in cancer cell cultures, indicating PD as a wide-ranging anticancer substance [11]. It heightens the efficacy of 2-DG therapies by modulating glucose metabolism and obstructing specific routes. PD's favourable influence on glucose and lipid regulation further bolsters its promise in cancer treatment. Given its accessibility and cost-effectiveness, PD could be merged into cancer treatment protocols, particularly in resource-scarce settings. This examination explores PD's antineoplastic potential, underscoring its modes of operation and consequences for innovative therapeutic techniques in the battle against cancer, particularly in environments with limited resources [9, 11].

Polydatin: Sources, Benefits, and Therapeutic Potential

PD is a monocrystalline substance from the stilbene family, derived from resveratrol with a glucoside group at the C-3 position. Its trans-isomer form, including trans-PD, is known for higher bioactivity [12]. The biosynthesis of PD involves the polyketide and phenylpropanoid pathways [13]. Glucosyltransferases metabolize resveratrol into PD. Polydatin is present in multiple dietary sources, predominantly sourced from plants that are part of the Vitaceae, Liliaceae, and Leguminosae families. The primary plant from which Polydatin is derived is *Polygonum cuspidatum* [14]. Nevertheless, the invasive characteristics of this plant, especially in isolated mountainous areas, have the potential to disturb ecosystems and agricultural productivity, presenting ecological obstacles [15]. Polydatin was initially identified in grape skin and is primarily obtained from white, red, and grape juices. Another derivative known as Cis-PD is mainly found in rose and effervescent wines. The highest concentrations of trans-resveratrol, a precursor to polydatin, can be found in grapes, berries, peanuts, and pistachios. Furthermore, polydatin can be found in various fruits and vegetables, beer, cocoa-containing products, and chocolate [16-18]. PD has shown therapeutic advantages in various diseases,

including cancer, diabetes, neurodegenerative disorders, and cardiovascular diseases [9].

PD has potent antioxidative effects, increasing the activities of antioxidative enzymes in rats more effectively than resveratrol [9]. Though studied for its chemo preventive effects against various diseases, resveratrol has low bioavailability due to rapid metabolism. Both resveratrol and piceid exhibit cytotoxicity on tumor cells at high concentrations [9, 19]. PD has shown potential in inducing cell cycle arrest and differentiation in colorectal cancer cells [20]. PD may serve as a substitute for resveratrol in clinical antioxidant use due to its higher antioxidative effect. Overall, PD and resveratrol are natural compounds with distinct biological activities, with PD showing superior antioxidative effects and potential therapeutic benefits in cancer treatment [19, 20]. PD and DHS compounds have shown significant anti-tumor effects against various cancer types and can induce cell cycle arrest, inhibiting cell proliferation and growth [21]. The mechanisms of action differ, with PD modulating oxidative stress, inhibiting tumor growth, and inducing apoptosis through specific signalling pathways, while DHS compounds' mechanisms are less understood [22]. PD targets proteins like p21, p27, CDK2, and Cyclin D1, while the molecular targets of DHS compounds and their specific cancer types are not well-defined. Both compounds have shown promising potential as anti-tumour agents, with variations in their mechanisms, targeted cancers, and pathways involved in their therapeutic effects [23]. Its efficacy against cervical, nasopharyngeal, and liver cancers has been confirmed, making it a promising candidate for further exploration in cancer treatment and other medical applications.

Mechanism of PD in Hepatocellular Carcinoma

PD has been identified as an effective agent in reducing the invasion and migration of HCCLM3 cells, with its efficacy being dependent on the dosage administered [24, 25]. This compound induces epithelial-mesenchymal transition (EMT) in HCCLM3 cells by upregulating E-cadherin levels while downregulating the expression of N-cadherin and vimentin. Studies have suggested that the progression of hepatocellular carcinoma (HCC) and EMT are closely associated with the PI3K/AKT, JAK1/STAT3, and p38 signaling pathways [26-28]. Treatment with PD resulted in decreased levels of phosphorylated STAT3, AKT, and JAK1 in HCCLM3 cells without affecting p38 expression. P38's regulation of oxidative stress may modulate the impact of PD on intracellular ROS levels [24, 29, 30]. The protein FOXO1, known for its multifunctionality, is implicated in the EMT of HCC and is activated by the STAT3/JAK1 and AKT/PI3K pathways [5, 9, 31]. PD has the potential to modulate FOXO1, thereby influencing HCC cell apoptosis and EMT-related processes [24]. These findings prove that PD can impede EMT and metastasis in HCC by regulating critical signalling pathways and proteins [9].

PD treatment resulted in elevated levels of FOXO1 in HCCLM3 cells, potentially conferring therapeutic benefits by targeting the STAT3/JAK1 and AKT/PI3K signaling pathways. Administration of PD led to an increase in caspase-3 activity, levels of caspase-3 and -9 proteins, and Bax protein expression while reducing the levels of Bcl-2 protein. It impedes the motility and invasiveness of cancer cells, particularly in HCC cells [24, 32]. PD inhibits tumor growth in HCC cell lines by blocking the Wnt/beta-catenin signalling pathway, promoting apoptosis, and inhibiting proliferation. Furthermore, it downregulates the expression of genes that facilitate cell growth [32]. PD exhibits cytotoxic and chemoresistant properties against various agents, such as 2-DG, which may have adverse cardiac effects at high doses [5, 33]. Overall, PD shows promise for therapeutic effects by inhibiting the

migration, spread, and growth of HCC cells, inducing cell death, and suppressing pro-cancer gene expression. Its potential in cancer therapy is significant, and further research is warranted to explore its practical application and potential in combination therapies (Fig. 1) [9].

PD has demonstrated beneficial effects on vital organs and cardiovascular systems. In a study involving mice, PD enhanced the anticancer effects of 2-DG by inhibiting the AKT/PI3K pathway. Another study revealed that PD could decrease glycolysis in Parkinson's, improve cardiovascular health, and increase cancer cells' sensitivity to chemotherapy drugs [34]. PD is also associated with an extended lifespan and exhibits antioxidant properties. Its role in oxidative stress varies depending on the cell type; for instance, PD reduces stress in heart cells while increasing it in cancer cells. It has been observed that PD effectively retards the growth of liver cancer cells, with lower toxicity to normal liver cells compared to conventional chemotherapeutic agents. Importantly, PD's effects on vital organs are beneficial, as it reduces oxidative stress in heart cells and does not significantly affect normal liver cells. Various signalling pathways and target genes affected by PD have been identified, particularly in the mitotic processes of cancer cells. Overall, research suggests that PD influences spindle formation, which is crucial for cell division, and its impact on gene regulation could alter cancer treatment outcomes [9], has shown potential in reducing the detrimental effects on hearts and vital organs, as seen in xenograft mice models, where it enhanced anticancer effects by blocking the AKT/PI3K pathway. Additionally, PD administration decreased the glycolytic pathway, improved cardiac signs, and increased the susceptibility of certain cancer cells to chemotherapy. PD has been linked to a longer lifespan and acts as an antioxidant, but its oxidative state mediation varies depending on the cell type. It reduced oxidative stress in cardiomyocytes but increased it in nasopharyngeal cancer cells. In liver cancer cells, PD reduced cytotoxicity and specifically inhibited proliferation, showing promise as a cancer treatment in clinical settings. PD affects multiple signalling pathways and target genes, crucial for mitosis and spindle formation, potentially leading to better outcomes for patients with liver cancer. The study concluded that spindle formation is the primary mechanism PD targets, and increased expression of specific genes is related to poor clinical outcomes in liver cancer patients [5].

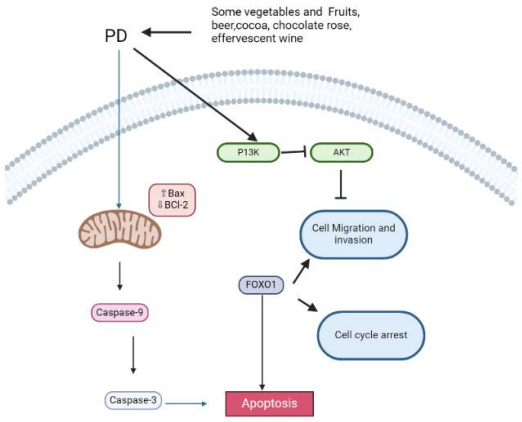

Figure 1. Molecular mechanism of PD in HCC.

PD treatment induces significant molecular changes in HCCs. It inhibits Akt activation, leading to increased FOXO1 expression and inhibits cell invasion, proliferation, and migration while also modulating apoptotic pathways. In addition, PD increases Bax expression and decreases Bcl-2 expression, leading to activation of caspase 3 and caspase 9, which initiates Apoptosis. Eventually, this inhibits HCC cell growth and survival. [↑ = upregulate, ↓= downregulate, ⊤ = Inhibit, ↑↓= regulate].

Limitations And Future Directions

While PD has shown encouraging anticancer effects in preclinical studies, translating these findings to clinical settings necessitates rigorous validation through properly controlled human trials. This validation process involves thoroughly assessing safety, dosage, and efficacy across a wide range of patient populations to ensure the generalizability of the results [9]. It is crucial to delve into the specificity of PD's mechanisms in targeting HCC, underscoring the importance of further investigations into its interactions with specific molecular targets and pathways. Moreover, a comprehensive evaluation of the long-term safety profile of PD, mainly when combined with other drugs, is essential to ascertain any potential side effects and impacts on the normal functioning of cells. The optimization of formulations and delivery systems is also a critical aspect that needs to be addressed to enhance the bioavailability and effectiveness of PD in cancer treatment [9]. Understanding the underlying resistance mechanisms, particularly in the context of combination therapies, is imperative for developing strategies to either overcome or prevent resistance from developing. Looking ahead, there is a need to explore combination therapies involving a broader spectrum of anticancer drugs and personalized medicine strategies tailored based on identifying relevant biomarkers. Conducting large-scale clinical trials that consider factors such as cancer stage, genetic diversity, and patient-specific characteristics is crucial for establishing the effectiveness of PD across diverse patient populations. Additionally, delving into detailed pharmacokinetic studies and investigating the efficacy of PD in treating rare cancers may unveil novel therapeutic opportunities that were previously unexplored.

Conclusion

In the current era marked by an escalating interest in phytomedicine, PD emerges as an up-and-coming agent in the realm of anticancer therapeutics owing to its unique ability to influence a multitude of signalling pathways that are closely linked to the development and progression of cancerous conditions. This compound's remarkable antioxidative characteristics and capacity to induce apoptosis and disrupt oncogenic pathways collectively underscore its efficacy as an anticancer agent. The critical analysis presented in the literature underscores the pressing necessity for comprehensive explorations into the precise mechanisms through which PD exerts its effects, thus highlighting the importance of conducting meticulously controlled human trials to effectively ascertain its therapeutic benefits within clinical environments. Upon synthesis of the available evidence, it becomes apparent that PD occupies a crucial position as a valuable constituent in the ongoing quest to innovate novel strategies in the fight against HCC, thereby supporting its significant role in advancing the field of oncology.

Conflict of Interest

All authors have no conflict of interest.

Acknowledgement

The authors like to thank Meenakshi Academy of Higher Education and Research (Deemed to be University), for providing research facilities.

Credit Authorship Contribution Statement

Deepan Sundararaj: Conceptualization, Vishnuvanditha Vuppuluri and Venkatachalam Bharathi Writing-original draft, Sakthivel Muthu: Review and editing, Nallusamy Duraisamy: Writing- review and editing.

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