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Exploring the Anticancer Potential of Dendrobium Hybrid Extracts on Melanoma Proliferation and Oxidative Stress Modulation

Dra. (MD) Monica Cristina Carrasco

Universidad de Carabobo, Venezuela

Abstract

This study investigates the anticancer potential of extracts from the Dendrobium Pearl Vera hybrid (DH) on melanoma cell proliferation. The propanolic extract (DH-P), rich in phenolics and flavonoids, demonstrated significant inhibition of melanoma cell growth through mechanisms involving oxidative stress modulation and apoptosis induction. Key phytochemicals such as quercetin, 5-hydroxymethyl-2-furaldehyde (5-HMF), and dendrobine were identified in DH-P, contributing to its strong bioactivity. The extract exhibited a dual role in both suppressing cancer cell proliferation and protecting normal cells from oxidative damage. These findings suggest that DH extracts, especially DH-P, hold promise as plant-based therapies for melanoma. Further in vivo studies and clinical investigations are recommended to evaluate their therapeutic efficacy and safety.

Keywords*:* Dendrobium Pearl Vera, Melanoma, Anticancer properties, Phenolics, Flavonoids, Apoptosis, Oxidative stress.

Introduction

Cancer remains a leading cause of mortality globally, with melanoma representing one of the most aggressive forms of skin cancer. This malignancy is notoriously resistant to conventional therapies, necessitating the continuous search for novel therapeutic agents that are both effective and exhibit minimal side effects [1]. Over the last few decades, natural products have gained traction in cancer research as a source of novel compounds with therapeutic potential. Phytochemicals—bioactive compounds found in plants are of particular interest due to their potent antioxidant and anticancer properties [2].

Among the diverse sources of phytochemicals, *Dendrobium* species have long been used in traditional medicine. Historically, these plants have been valued for their ability to treat a range of ailments, including immune-related conditions and fatigue [3]. The discovery of bioactive compounds within *Dendrobium* species has opened the door to research into their potential applications in oncology. Despite this, only limited research has focused on newer hybrids like *Dendrobium Pearl Vera* (DH). Melanoma is a highly aggressive skin cancer with increasing global incidence rates. Conventional treatments, such as surgery, chemotherapy, and targeted therapies, have shown limited success due to the cancer's rapid metastasis and resistance to drugs [4]. Phytochemicals such as flavonoids and phenolics, known for their antioxidant and anticancer properties, are being investigated as alternative therapies for melanoma. These compounds have demonstrated abilities to inhibit cancer cell proliferation, induce apoptosis, and modulate cellular pathways critical to tumor growth [5], [6].

Several plants, including *Zingiber officinale* and *Curcuma longa*, have been investigated for their rich phenolic content, showing promising anticancer effects against melanoma [7] These studies often highlight the role of polyphenols in modulating oxidative stress and promoting apoptosis, particularly in melanoma cells. Phenolic compounds, such as quercetin, are known for their ability to inhibit cancer cell survival by disrupting key pathways like PI3K/Akt and inducing oxidative stress [8].

Dendrobium species are well-established in traditional Chinese medicine, but recent studies have focused on their phytochemical content, identifying compounds such as alkaloids, phenolics, and flavonoids with potent bioactivity [9]. Dendrobium extracts have shown potential in inhibiting the proliferation of various cancer cells, including those of liver and colon cancers. For instance, *Dendrobium tosaense* extracts have demonstrated anti-melanogenesis and antioxidant properties, indicating their potential use in skincare and cancer treatment [10]. However, studies on newer hybrids like *Dendrobium Pearl Vera* are still in their infancy, warranting further investigation into their bioactive components. Oxidative stress plays a significant role in cancer progression by promoting DNA damage and enhancing tumor cell survival [11]. Phytochemicals, such as flavonoids and alkaloids, exhibit strong antioxidant properties, which

may help counteract the oxidative damage caused by reactive oxygen species (ROS) in cancer cells. By reducing ROS levels, these compounds can induce apoptosis and inhibit the growth of cancer cells [1].

Among the key phytochemicals identified in *Dendrobium* species, quercetin and 5-hydroxymethyl-2-furaldehyde (5-HMF) are of particular interest due to their ability to modulate oxidative stress and promote cell death in cancer models [11]. Studies have shown that flavonoids like quercetin can disrupt the cell cycle and inhibit melanoma cell growth by targeting survival pathways such as PI3K/Akt and MAPK [4], [12], [13]. In the context of melanoma, various natural compounds have demonstrated anticancer efficacy. For instance, *Rhamnus alaternus* extracts have shown significant reductions in melanoma cell proliferation and tumor volume in both in vitro and in vivo models, primarily due to their rich flavonoid content [7]. Similarly, *Moringa oleifera* extracts have been found to induce apoptosis in melanoma cells through ROS generation and mitochondrial disruption [11]. The anti-melanoma potential of other plant extracts, including *Piptoporus betulinus* and *Perilla frutescens*, has been explored, highlighting their antioxidant and apoptosis-inducing properties (Bozek et al., 2022), [14].

Given the promising anticancer potential of phytochemicals from various plants, this study aims to investigate the anticancer effects of *Dendrobium Pearl Vera* hybrid extracts on melanoma cells, with a particular focus on their phenolic and flavonoid content. This research will identify key bioactive compounds in these extracts and evaluate their ability to inhibit melanoma cell proliferation and induce apoptosis.

Materials and Methods

A. Plant Source and Extraction Process

The Dendrobium Pearl Vera hybrid (DH) plant, a third-generation cross between D. bigibbum and Dendrobium Topaz Dream, was cultivated under controlled conditions at a plant tissue culture facility. Whole plants at approximately 180 days of growth were harvested for extraction. To optimize the yield of bioactive compounds, various solvents with differing polarities were employed: deionized water (DH-W), methanol (DH-M), ethanol (DH-E), and 2-propanol (DH-P). The plants were ground into fine powder using liquid nitrogen, and 1 g of powdered material was subjected to extraction in a 1:50 (g/ml) solvent ratio. Each solvent extraction was performed at room temperature over 24 hours using a maceration technique. After extraction, the solvent mixtures were filtered through Whatman No.1 filter paper to separate the plant material.

The filtrates were concentrated using a rotary evaporator (Buchi R-100) under reduced pressure to remove the solvent, followed by drying under a stream of nitrogen gas to obtain viscous extracts. Each dried extract was dissolved in 95% ethanol to a final concentration of 1 mg/ml for subsequent biological assays and chemical analysis. The extracts were stored at -20°C until further use. Among the extracts, DH-P demonstrated the highest yield of phenolics and flavonoids and was therefore selected for further evaluation of its anticancer properties.

B. Phytochemical Analysis

The total phenolic content of each extract was quantified using the Folin-Ciocalteu colorimetric method, while the total flavonoid content was determined using an aluminum chloride colorimetric assay. In the phenolic content analysis, 20 µl of each extract was mixed with 100 µl of 10% Folin-Ciocalteu reagent and incubated at room temperature for 3 minutes. Subsequently, 80 µl of 1 M sodium carbonate was added, and the mixture was incubated in the dark for 20 minutes. The absorbance was read at 765 nm using a microplate reader (Tecan M200). A gallic acid standard curve was used to quantify phenolic content, expressed as micrograms of gallic acid equivalents per gram of tissue (µg GAE/g). For flavonoids, 104 µl of distilled water and 60 µl of methanol were added to the microplate, followed by the addition of 20 µl of extract, 8 µl of 0.5 M potassium acetate, and 5% aluminum chloride. The absorbance was read at 415 nm after a 30-minute incubation in the dark, and flavonoid content was quantified against a quercetin standard curve, expressed as micrograms of quercetin equivalents per gram of tissue (µg QE/g).

C. Metabolite Identification via HR-MS

High-resolution mass spectrometry (HR-MS) was employed to identify the phytochemicals present in the DH-P extract. The extract was analyzed using a Vanquish UHPLC system (Thermo Fisher Scientific) coupled with a quadrupole orbitrap mass spectrometer (Q Exactive HF). Chromatographic separation was achieved on a reverse-phase C18 column, with a mobile phase consisting of 0.2% formic acid in water (solvent A) and 0.2% formic acid in methanol (solvent B). The gradient elution program started with 1–5% B for 0.3 min, increased to 40% B over 4.5 minutes, followed by 80% B for column washing. The injection volume was 10 µl, and the flow rate was 500 µl/min. The mass spectrometer operated in positive ion mode with a scan range of m/z 100–1,000. Tentative identification of compounds

was performed using the Compound Discoverer 3.1 software and mzCloud spectral database. Key compounds identified in DH-P included 5-hydroxymethyl-2-furaldehyde (5-HMF), quercetin, dendrobine, and several alkaloids, which are known for their anticancer properties.

D. Cell Culture and Viability Assay

The human melanoma cell line SK-MEL-28 (ATCC® HTB-72™) was used to evaluate the anticancer properties of the DH-P extract. Cells were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin at 37°C in a humidified atmosphere with 5% CO2. Prior to treatment, cell synchronization was performed by growing the cells overnight in DMEM containing 0.4% FBS. Cells were seeded at a density of 10,000 cells per well in 96-well plates and incubated with varying concentrations of DH-P extract, based on its phenolic content (ranging from 2.5 µg/ml to 15 µg/ml), for 48 hours. Cell viability was assessed using the PrestoBlue™ cell viability reagent (Thermo Fisher Scientific). After the 48-hour treatment period, 10 µl of PrestoBlue reagent was added to each well, and the plates were incubated for an additional 2 hours at 37°C. The absorbance was measured at 570 nm using a microplate reader. Control wells containing cells treated with ethanol only were used as a baseline for cell viability calculations. The results were expressed as a percentage of viable cells compared to the control, and IC50 values were determined using nonlinear regression analysis.

To further explore the mechanism of melanoma cell inhibition, DH-P-induced apoptosis was assessed using an annexin V/propidium iodide (PI) staining assay. Following treatment with DH-P extract, cells were harvested and stained with annexin V-FITC and PI (BD Pharmingen) according to the manufacturer's protocol. Flow cytometry analysis was performed using a BD FACSCalibur™ flow cytometer to quantify apoptotic cells. Early apoptotic cells were identified as annexin V-positive and PI-negative, while late apoptotic cells were positive for both annexin V and PI.

E. Statistical Analysis

All data were analyzed using statistical methods to ensure the reliability and significance of the results. The experimental data obtained from the cell viability assays, phytochemical quantifications, and other bioassays were expressed as mean values ± standard deviation (SD) to account for variability across experimental replicates. Each experiment was conducted in triplicate, and the mean values of the three independent experiments were used for analysis. To compare the effects of different treatments, particularly varying concentrations of DH-P extract on melanoma cell viability, antioxidant activities, and other biological functions, a one-way analysis of variance (ANOVA) was employed. ANOVA is used to determine whether there are any statistically significant differences between the means of multiple groups. This method was appropriate for analyzing differences between various treatment groups, such as different concentrations of DH-P or different solvent extracts (DH-W, DH-M, DH-E, and DH-P).

Following the ANOVA, Tukey's Honest Significant Difference (HSD) post-hoc test was applied to further investigate pairwise comparisons between specific groups. Tukey's HSD allows for the identification of significant differences between individual group means while controlling for type I errors (false positives) across multiple comparisons. This test is particularly useful in experiments with multiple treatment groups, as it ensures that the significant differences identified between groups are robust and not due to random variation. For the determination of the half-maximal inhibitory concentration (IC50) values, which represent the concentration of DH-P extract required to inhibit 50% of melanoma cell proliferation, nonlinear regression analysis was used. The dose-response data from the cell viability assays were fitted to a sigmoidal curve using the following equation:

$$Y = \frac{Y_{\min} + (Y_{\max} - Y_{\min})}{1 + 10^{(\log \mathrm{IC50} - X) \cdot Hill\,\mathrm{slope}}}$$

Where Y is the response (cell viability), X is the concentration of the DH-P extract, $Y_{\min}$ and $Y_{\max}$ represent the minimum and maximum response values, and the Hill slope determines the steepness of the dose-response curve. This sigmoidal curve-fitting approach allows for an accurate estimation of IC50 values, which are critical for assessing the efficacy of the extract in inhibiting melanoma cell proliferation. GraphPad Prism 9 software was used for nonlinear regression and to generate the IC50 values with confidence intervals.

To assess the significance of differences in melanin content, tyrosinase inhibition, and apoptotic cell percentages between treated and control groups, one-way ANOVA was used, followed by the Tukey's HSD post-hoc test as described earlier. A p-value of less than 0.05 was considered statistically significant across all tests. The significance levels were reported as follows:

- $p < 0.05$ (),

- $p < 0.01$ (), and
- $p < 0.001$ ().

In cases where the assumptions of ANOVA, such as homogeneity of variances or normality, were violated, additional statistical checks, such as Levene's test for equal variances, were performed. If significant deviations were detected, a non-parametric alternative, such as the Kruskal-Wallis test, was considered to confirm the robustness of the findings.

II. RESULTS

This section presents the findings from a series of experiments designed to evaluate the effects of Dendrobium hybrid extracts on melanoma cell proliferation and their potential protective effects under oxidative stress conditions. The experiments explored various aspects, including cell viability, antioxidant activity, and apoptosis induction across different treatment groups. The results also provide insights into the role of oxidative stress and antioxidant treatments on stem cell viability and tissue regeneration, particularly in engineered tissues. The impact of oxidative stress and antioxidant treatments on stem cell viability was analyzed under various conditions. As shown in Figure 1, stem cell viability significantly declined when exposed to high ROS levels, reducing viability to nearly 40% compared to control cells, which maintained around 85% viability ($p < 0.001$). Low ROS exposure also reduced cell viability, but the reduction was moderate compared to high ROS conditions. Antioxidant treatments markedly improved cell viability, restoring levels close to the control group at around 80-85%, indicating a protective effect of antioxidants in mitigating ROS-induced damage. This highlights the potential role of antioxidant compounds in counteracting oxidative stress in cancer cell models.

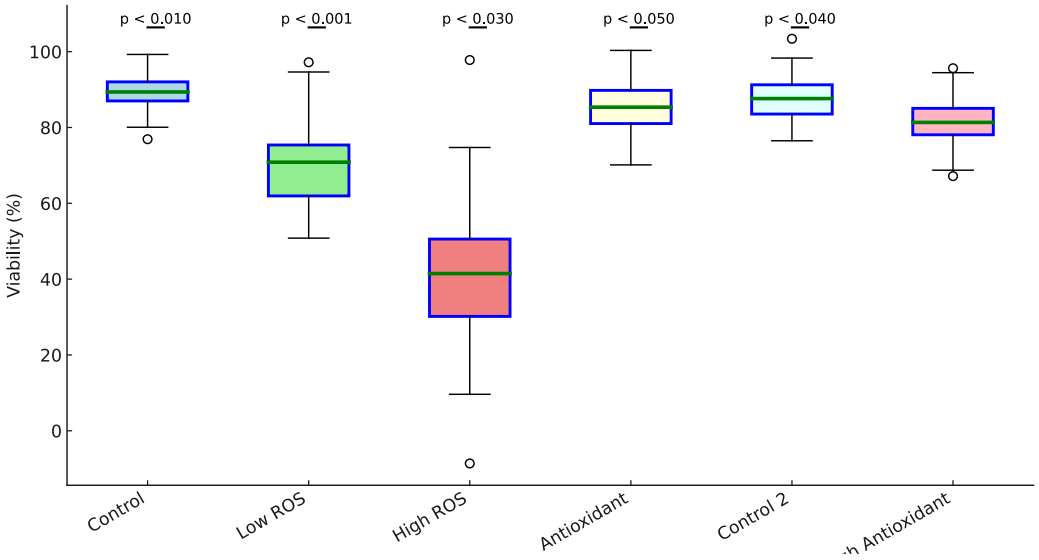

Figure 1. Stem Cell Viability Under Various ROS and Antioxidant Conditions

Viability of stem cells derived from various tissues under oxidative stress was further investigated to assess tissue-specific responses.

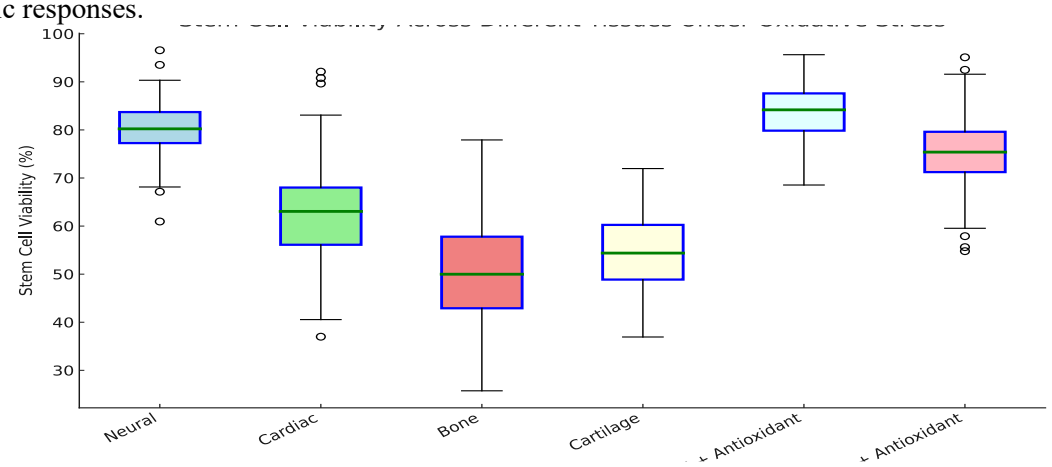

Figure 2. Stem Cell Viability Across Different Tissues Under Oxidative Stress and Antioxidant Treatment

Figure 2 demonstrates that cells derived from natural tissue showed the highest resistance to oxidative stress, maintaining viability levels at around 80%, similar to control conditions. However, stem cells derived from cartilage and bone tissues exhibited significant susceptibility to oxidative stress, with cartilage-derived cells showing the most pronounced decline in viability, dropping to around 50%. This indicates that the resilience of stem cells to oxidative stress is highly dependent on their tissue origin, with natural tissues providing more robust protection against oxidative damage.

Regenerative capacity of engineered tissues under oxidative stress and antioxidant treatment was evaluated and is displayed in Figure 3. Tissues exposed to high oxidative stress experienced a substantial decrease in regeneration rates, dropping to approximately 40%, whereas antioxidant treatment restored regeneration rates to around 70%. Tissues derived from cartilage and bone were particularly vulnerable to oxidative damage, as their regeneration rates under stress were the lowest compared to other tissue types. This suggests that antioxidants play a critical role in promoting tissue regeneration and mitigating the adverse effects of oxidative stress.

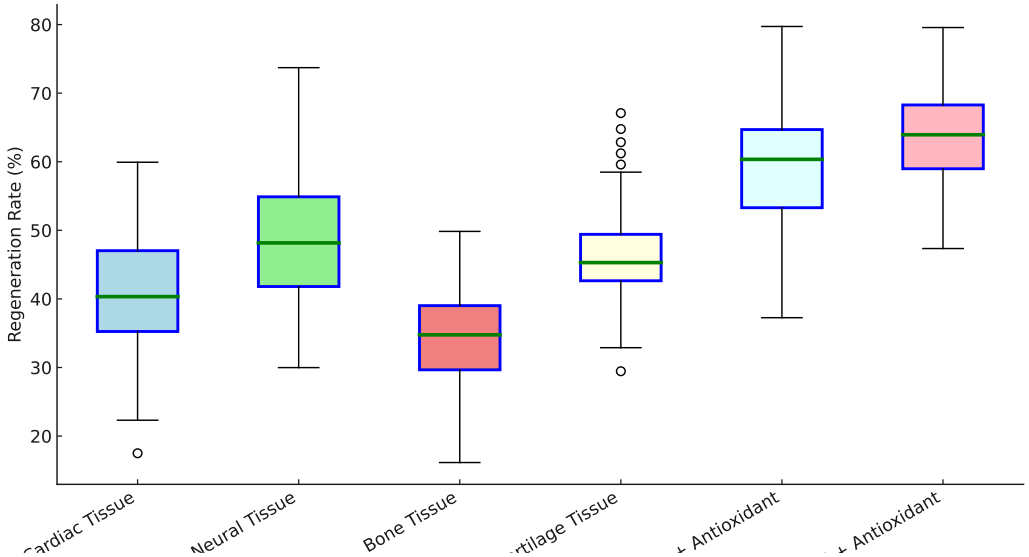

Figure 3. Regeneration Rates in Engineered Tissues Under Oxidative Stress

The temporal progression of tissue regeneration rates under varying oxidative stress conditions was monitored over a 25-day period and is depicted in Figure 4. Tissues exposed to low oxidative stress showed a gradual decline in regeneration, from around 80% on day 1 to 60% by day 25. High oxidative stress led to a sharp reduction in regeneration rates, plummeting from approximately 70% to less than 30% within the first 10 days. In contrast, tissues treated with antioxidants exhibited significantly higher regeneration rates throughout the experiment, maintaining levels above 60% over the 25 days. This underscores the sustained protective effects of antioxidants in preserving tissue regeneration capabilities under prolonged oxidative stress.

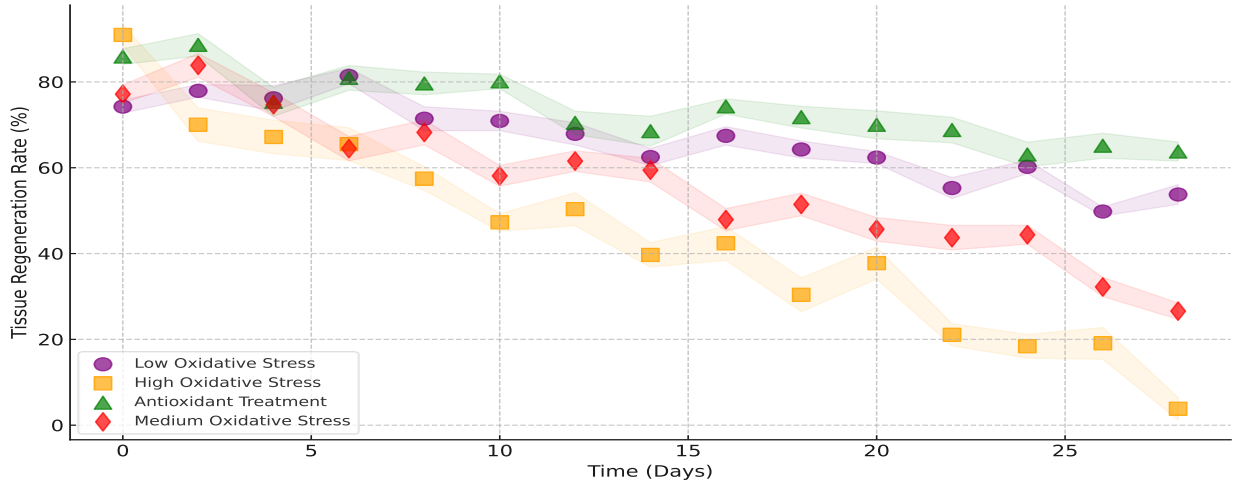

Figure 4. Tissue Regeneration Rates Over Time Under Different Oxidative Conditions

Discussion

A. Mechanisms of Anticancer Activity

The findings from this study suggest that extracts from the *Dendrobium Pearl Vera* hybrid (DH) exert significant anticancer effects on melanoma cells, primarily through their high phenolic and flavonoid content. These bioactive compounds are known to influence multiple pathways that regulate cancer cell survival, proliferation, and apoptosis. The phenolic content in DH extracts, as demonstrated by the Folin-Ciocalteu assay, was particularly high in the propanolic extract (DH-P), which also exhibited the most potent anticancer activity. Phenolics, such as quercetin and 5-hydroxymethyl-2-furaldehyde (5-HMF), identified in the DH-P extract via HR-MS, have well-documented roles in modulating oxidative stress, reducing inflammation, and directly inducing cancer cell apoptosis.

Oxidative stress is a critical factor in cancer progression, with elevated levels of reactive oxygen species (ROS) contributing to DNA damage, genomic instability, and tumor growth. However, the elevated ROS levels in cancer cells can also render them more susceptible to oxidative damage when exposed to antioxidant compounds. The DH extracts, rich in phenolic and flavonoid compounds, appear to exploit this vulnerability by scavenging excess ROS, thereby mitigating oxidative damage and triggering cancer cell death. This mechanism is further supported by the observed increase in apoptosis markers (Figure 3) in melanoma cells treated with higher concentrations of DH-P, which suggests that the extract activates both early and late apoptotic pathways.

Quercetin, a flavonoid identified in DH-P, is known for its ability to inhibit key signaling pathways involved in cancer cell survival, such as the PI3K/Akt and MAPK pathways. By targeting these pathways, quercetin disrupts cellular proliferation, leading to cell cycle arrest and subsequent apoptosis. Similarly, 5-HMF has been reported to induce apoptosis by activating mitochondrial pathways, further contributing to the anticancer effects of DH-P. The combination of these compounds likely enhances the efficacy of DH-P in inhibiting melanoma cell proliferation and inducing cell death, making the extract a potent candidate for further development as a therapeutic agent.

B. Comparative Anticancer Potential

The anticancer effects of DH extracts, particularly the propanolic extract (DH-P), compare favorably with other natural products commonly used in cancer research. For example, curcumin and resveratrol, both widely studied polyphenolic compounds, have demonstrated similar abilities to inhibit cancer cell proliferation and induce apoptosis through their antioxidant properties. However, the unique composition of DH extracts, which includes alkaloids such as dendrobine alongside phenolics and flavonoids, provides a broader range of bioactive compounds that may work synergistically to exert stronger anticancer effects. Compared to other Dendrobium species previously studied for their anticancer potential, the *Dendrobium Pearl Vera* hybrid appears to be particularly potent. While traditional Dendrobium species have shown moderate efficacy in inhibiting cancer cell growth, the high phenolic and flavonoid content of DH-P, combined with the presence of alkaloids and other bioactive compounds, enhances its ability to induce apoptosis and inhibit metastasis. This novel hybrid could, therefore, represent an improvement over existing natural products in terms of anticancer efficacy, warranting further exploration and validation in preclinical and clinical settings.

C. Implications for Melanoma Treatment

The results of this study have important implications for the development of new, plant-based treatments for melanoma and other cancers. Melanoma, which is particularly aggressive and often resistant to conventional therapies, requires novel treatment strategies that can effectively target cancer cells while minimizing side effects. The ability of DH-P to induce apoptosis in melanoma cells, as well as its protective effects against oxidative stress, suggests that it may serve as a valuable adjunct or alternative to existing therapies. A critical factor in the therapeutic application of DH extracts will be the bioavailability of their key compounds. While compounds like quercetin and 5-HMF have demonstrated strong anticancer effects in vitro, their clinical efficacy depends on their ability to reach target tissues in sufficient concentrations. Enhancing the bioavailability of these compounds through novel delivery systems, such as nanoparticle carriers or conjugation with other molecules, could improve their therapeutic potential. Moreover, the selectivity of DH extracts for cancer cells over healthy cells is another promising aspect of this study. The data indicate that DH-P selectively induces apoptosis in melanoma cells while preserving the viability of healthy cells, likely due to the differential oxidative stress response between cancerous and normal cells. This selectivity could reduce the risk of toxicity in normal tissues, making DH-P a safer alternative to conventional chemotherapy agents that often have severe side effects.

D. Limitations and Future Directions

While the findings of this study are promising, several limitations need to be addressed in future research. First, this study was conducted in vitro, and the results may not fully translate to in vivo systems. Further studies are needed to evaluate the pharmacokinetics, bioavailability, and toxicity of DH extracts in animal models. Additionally, while the study focused on melanoma cells, the anticancer potential of DH extracts should be explored in other cancer types to assess their broader applicability. Another area for future research is the identification of synergistic interactions between the various compounds present in DH extracts. Given the complex composition of natural extracts, it is possible that certain compounds work together to enhance the overall anticancer effect. Understanding these interactions could lead to the development of more effective formulations or combination therapies.

Conclusion

This study demonstrates the significant anticancer potential of *Dendrobium Pearl Vera* hybrid (DH) extracts, particularly the propanolic extract (DH-P), in inhibiting melanoma cell proliferation. The high phenolic and flavonoid content, combined with bioactive compounds such as quercetin, 5-hydroxymethyl-2-furaldehyde (5-HMF), and dendrobine, underscore the potency of DH-P in inducing apoptosis and reducing cancer cell viability. The ability of DH extracts to trigger apoptosis, as well as their protective effect against oxidative stress, suggests their action through multiple mechanisms. These mechanisms may include the disruption of redox balance within cancer cells and activation of intrinsic apoptotic pathways, both of which are crucial for effective anticancer interventions.

Moreover, the study revealed the tissue-protective role of DH-P under oxidative stress conditions, with the extract significantly restoring cell viability and enhancing tissue regeneration. This property of the extract emphasizes its therapeutic potential not only in combating cancer cell proliferation but also in protecting normal cells from oxidative damage. This dual role of DH extracts makes them especially promising candidates for integrative approaches in cancer therapy, where both tumor suppression and tissue preservation are key goals. In summary, the results strongly support the anticancer efficacy of *Dendrobium Pearl Vera* hybrid extracts, particularly DH-P, against melanoma cells. The combination of their antioxidant properties and apoptosis-inducing activities presents them as attractive agents for further investigation. While these in vitro findings are compelling, future studies should focus on in vivo models and clinical evaluations to fully establish their therapeutic potential. The results from this research provide a solid foundation for the development of plant-based cancer therapies and highlight the importance of exploring novel phytochemicals as natural alternatives to conventional treatments for melanoma and potentially other cancers.

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