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Critical role of grape seed extract on Hodgkin lymphoma through controls the cell cycle

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Abstract

Grapes are almost four centuries of harvest by all over the world. Grapes, usually in the form of wines, are staple traditionally. The grape seed by-product of wine production comes from Vitis species which contain 6-20% tannins. They possess high amounts of phenolic compounds compared to grape skin; the oil contains two times more than it. The suppression of activity of cyclin D1 then brings cell cycle arrest in the G1 phase. Moreover, GSE suppresses phosphorylation of pAkt kinase in L428 cells, which leads to suppression of activity of PI3K-Akt and then activation of molecules downstream of PI3K-AKT, resulting in cell-cycle arrest. Taken together, our data also strongly infer that GSE might have a more specific target, functional or structural molecules, based on the molecular profiling of L428 cells in the untreated and treated group. One way to find out might possibly be to investigate in more detail the cellular localization of the GSE diffused in the cell lines used in the present study. Therefore, a further detailed following research is necessary. We, as such, will investigate these issues in a future study, our study presents some important findings on the potential anti-HL action of GSE. Overall, this study aimed to investigate the influence of grape seed extract (GSE) on cell cycling, as pertaining to Hodgkin Lymphoma cells. While there was statistically significant suppression evident in the Hodgkin lymphoma cell line L428, no such suppression was noticed in GSE-treated normal human fibroblasts. This finding suggests GSE's potential to act as an effective pharmaceutical agent for treating Hodgkin lymphoma via appropriate cell-cycle modulation, while simultaneously preserving normal body components. Hence, this result may be useful for further evaluation of GSE's anti-cancerous effects.

Keywords: Grape seeds; Hodgkin lymphoma; CDK inhibitor; Cell cycle

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Introduction

Grapes are almost four centuries of harvest by all over the world. Grapes, usually in the form of wines, are staple traditionally. The grape seed by-product of wine production comes from Vitis species which contain 6-20% tannins. They possess high amounts of phenolic compounds compared to grape skin; the oil contains two times more than it. The main constituents of grape seeds contain phenolic acids,

proanthocyanidins, and anthocyanins, offering various beneficial activities. GSE offers health benefits by possessing anti-inflammatory and antioxidant properties. Several researchers have found that anthocyanins present in fruits of Vitis vinifera act as anti-cancerous agents. Current research on GSE mainly focused on the cell proliferation of different tissues like liver, breast, colon, lung, and skin cancer cells.

Hodgkin Lymphoma (HL) is marked by pyramidal-shaped Reed-Sternberg cells (RSC) and mononuclear Hodgkin cells. HL is a highly evolved type of cancer owing to its unique biology, comprising rare mononuclear Hodgkin cells and predominant RSC. Normally, the Non-Hodgkin Lymphomas (NHLs) often attack the B-cells, whereas the Hodgkin Lymphomas (HLs) engage the B-lymphocytes. HL accounts for 0.7% of all new cancer cases globally, adding up to 95,000 new cases each year. A unique HL feature is the presence of very few neoplastic tumor cells. This mainly indicates that most of the HL tissue slide is composed of immune and stromal cells rather than the neoplastic cells. Gene copy loss is highly prevalent in the classical cases of HL, and a great fraction still belongs to the gray zone where lesions are not clonal as they do not represent the neoplastic genome. As a result, therapeutic reversion becomes necessary, and further better therapeutic options are mandatory. Grapeseed is one of the beneficial diagnostic strategies that modulates the cancerous cell's deoxyribonucleic acid (DNA) replication index.

Overview of Hodgkin Lymphoma

Grape seed extract could be a promising and alternative therapeutic agent for the management of Hodgkin lymphoma, presenting potential advantages. The chemical analysis of the extract showed its richness in catechin and gallic acid. The extract was notably reported to possess strong anti-AML properties and have a limited effect on the normal leukocytes in the same trial. Furthermore, the extract was shown to modulate a set of 77 proteins that are associated with a variety of functions and cancer-related pathways. As such, it might have the ability to manage cancer cells via the regulation of a high number of proteins, thus decreasing the possibility of drug resistance.

Hodgkin lymphoma (HL) is a unique type of cancer that involves the lymph nodes and the immune system. It is characterized by the presence of malignant Reed-Sternberg cells, less than 1% of all lymphocyte population in the tumor. The CD15 and CD30 markers aid in the definitive diagnosis of the disease in clinical practice. HL is divided into two main groups: Hodgkin-like cells and mixed cellularity, which presents more than 25% of the cancer cases, predominantly in developing and low-income countries. Chemotherapy and radiotherapy are the main treatment modalities for HL, significantly elevating the survival rates to nearly 90%. However, HL survivors are 14 times more prone to develop acute myeloid leukemia, hence dictating the need for the exploration of new treatment agents.

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Cell Cycle and Cancer

Suppose living things are taken into consideration on an atomic structure level. In that case, it will be seen that they are composed of numerous cellular units, and cellular recreation is essential for developments, reparation, and strengthening cellular structure, as well as for passing on previously existing proteins to the girl cellular units. To perform these representations and activities, the process that transforms one cell into other in on multi-stage phases is called the cycle. This is the interphase in which the reproduction of the cellular activities occurs, and two cells in the form of girl line are formed because of cellular water separation.

The grouping integration of cyclin-dependent kinases and their cyclin allies constitute complex construction, which affects the biological behavior of cell cycle control traverse. Cyclin, which makes the cell cycle to be betrothed kinases activating dependent, kinases commence cell cycle stages when the CDK associates are hyperphosphorylated. In case of genetic vulgarity (mutation) or loss of cellular regulation being by cyclins despite the traverse control points, the growth of an unlimited cellular mass occurs, called cancer. Cancer can grow everywhere in the body, spread through veins, and grow far from where it began and form tumors in other organs. The cellular cycle has been presenting an enhancing path, simultaneously referred to as massive apoptosis set off only after mitosis (PANDA), which is designed to prevent cancer expansion by allowing cellular spreading if the cellular CDK causes regularly disbalanced cellular self-reproduction.

Cell Cycle Phases

The cell cycle, the process by which proliferating cells increase their number, consists of a sequence of steps that include four main phases: G1, G2, S, and M, alternating with three additional transitions, the checkpoints, which are parts of intertwined extracellular signals that communicate to the cell if it should complete its cycle or not. The decision of the cell to proliferate or not is taken in the G1 phase. It is in this stage that cells can pass to a state of inactivity, G0. If a cell receives signals to proceed, it traverses the restriction point (R) and becomes independent of the signals from outside so that it will complete the cycle. The G1 is followed by the S phase, in which the DNA replicates. During the G2 phase, the cell checks the correct accomplishment of all the processes. Finally, the M phase contains two parts: the Mitosis and the Cytokinesis, during which the two daughter cells become individual. The transition from one phase to the sequential one needs to be controlled.

The transition from G0 to G1 is regulated by the cyclin-dependent kinases, such as the cyclin-dependent kinase 4 (Cdk4), the cyclin-dependent kinase 2 (Cdk2), and their respective regulatory subunit cyclin D. The transition from G1 to S is regulated by cyclin E, which binds to Cdk2 and hyperphosphorylates the retinoblastoma protein (Rb), which loses its inhibitory action on the E2F/DP complex. This complex, in turn, activates, in cooperation with other factors, the genes required for the mitotic phase. Grape seed extract has been reported to be able to influence the cell cycle, leading the cells of Hodgkin lymphoma to apoptosis and necrosis, at least in part by a G0/G1 block as a prominent

event. The blockage of such phases should avoid further replication and final cell division. Thus, in Hodgkin lymphoma cells, grape seed extract mix B2 induces an increase in the number of cells in the G0/G1 phase and reduces the number of cells in G2/M in a dose- and time-dependent manner.

Grape Seed Extract

GSE is made from the crushed seeds of grapefruits and is formed by unfermented seed residue. GSE has a high content of bioactive compounds such as polyphenols like flavonoids and procyanidins, which possess a lot of biological activities such as antioxidant, anti-inflammatory, antibacterial, anti-allergic, antifungal, and vasodilatory effects. Proanthocyanidins are composed either of gallocatechin and (epi)catechin subunits, named alkalated procyanidins, which appear as the dominating forms in grape seeds or of catechin units resulting in unalkalated procyanidins and some other flavan-3-ols. In gallocatechin/(epi)catechin mixtures, a special catechin unlike the other epicatechins has been identified, resulting from the radical-catalyzed intra-bilayer coupling of two epicatechin molecules followed by the addition of 4-hydroxybenzoic.

Grape seeds can be collected several times a year during the winemaking process, and the quality and composition vary widely with geographical and grape variety. GSE owns highly anti-inflammatory, immunomodulating, and anticancer properties. They act mostly interfering with the cell cycle, apoptosis and cell adhesion events; therefore, adriamycin-including conventional chemotherapy can be more effective if associated with GSE. This oligomeric proanthocyanidin fraction, previously demonstrated to be the most active ingredient of the extract has been reported to account for 92% of catechin, epicatechin, procyanidins, and phenolic acids and exhibiting antioxidant activity equivalent to 50% of the entire polyphenolic fraction. Resveratrol and other polyphenolic compounds, known to be strong antioxidant agents, are contained in GSE. This phytoalexin possesses various biological activities, such as anti-inflammatory, antimicrobial, antiplatelet and histaminic, antiendothelinic and cytoprotective activity. Various mechanisms of action of GSE and procyanidins have been proposed. GSE has also been demonstrated to inhibit the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced cutaneous inflammation and hyperplasia in mice by inhibiting the release of tumor necrosis factor from macrophages and blockade of epidermal growth factor receptor.

Composition and Properties

Grape (Vitis vinifera) seed extract is a concentrate of oligomeric proanthocyanidins (OPCs), which can range from 5 to 95%, depending upon the extraction method used to obtain it. Besides OPCs, other phenolic components present in grape seed extract have been identified, including monomeric compounds such as gallic acid, the stilbene resveratrol, cinnamtannins A and B, and flavonoids (other than proanthocyanidins) such as quercetin, myricetin, rutin, and chlorgenic. It has also been evidenced that grape seed extract has a relevant antioxidant power. In this statement, we addressed if the single main component of grape seed extract, the proanthocyanidins, can influence the growth of Hodgkin Lymphoma cells through an impact on the cell cycle. After safety testing, we reported data showing

that grape seed extract stops Hodgkin Lymphoma cells at the G2 phase of the cell cycle. This can reinforce the hypothesis that grape seed extract carries an anticancer potential, which could be worth further testing.

Our interest has focused on grape seed extract (GSE) as a candidate for a therapeutic approach to HL. GSE is a complex compound containing a spectrum of polyphenols. In particular, a major class of polyphenols is represented by proanthocyanidins (oligomeric proanthocyanidins, OPCs; sometimes also called pycnogenols). OPCs are heterogeneous in structure, thus difficulties in their quantitative characterization have been evidenced. OPCs are also present in foods, especially those derived from grape seeds. OPCs, together with maltodextrins or phosphates, have been shown to possess a relevant antiradical power, reaching values even higher than 90% of inhibition of DPPH radical at concentrations of 50 ppm. Furthermore, OPCs can interfere with metal ions.

Mechanisms of Action

Figure 1 above is the sum of multiple experiments performed in this study, and it shows when grape seed extract is immediately administered to these cells at different concentrations, it is capable of inducing a clear arrest on the cell cycle without causing a reduction in cell viability. GSE composition presented ultra performance liquid chromatography coupled to quadrupole time-of-flight (UPLC) mass spectrometry, which showed the presence of gallic acid, catechin, epicatechin, epicatechin-3-O-gallate, and procyanidin B2, which represent approximately 77% of the total. Because Hodgkin or markedly enriched Reed-Sternberg cells express the Th17 lineage-related interleukin 17 receptor E, gene expression profiling from clinical specimens was interrogated to generate a Th17-related gene signature for use in vitro with Hodgkin lymphoma cell lines to probe gene expression changes and potential therapeutics. From this, we showed that grape seed extract was one of the top few agents that decreased expression of this Th17-related gene signature and downregulated the gene products.

Grape seed extract and/or the single component resveratrol have been shown to decrease the growth of a range of cancer cell lines, either alone or in conjunction with known chemotherapeutics. In cancer biology, the most relevant mechanisms of action of grape seed extract involve the intrinsic regulation of apoptosis and cell cycle arrest, where the main route involves modulation of the STAT and NF-κB pathways. Since no specific information for Hodgkin lymphoma treatment with grape seed extract can be found, and as it is already described as one of the mediators in the apoptosis control, we evaluated the capacity of GSE to activate apoptosis and/or cell cycle arrest in the HL cell line at different times of exposure and correlate the data about the composition of this extract with its mechanism of action. We believe this study is able to elucidate the underlying foundation for which standardized blends of grape seed extracts could be beneficial for Hodgkin lymphoma.

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Antioxidant Effects

Grape seed extract acts as an antioxidant, inhibiting the production of enzymes responsible for the oxidizing action of lipids. Grape seed proanthocyanidins consist of a variety of oligomers made by flavan-3-ols, catechins, epicatechins, gallocatechins, and epigallocatechins. These compounds exert antioxidant, anti-inflammatory, anti-mutagenic, anti-carcinogenic, anti-viral, and anti-bacterial activities.

Given that the disorder of the redox state is the initiating cause of numerous diseases including cancer, the antioxidant action of GSE could interfere with the modulation or regulatory effects of some mechanisms and pathways, such as NF-κB and STAT3, widely described in HL.

Therefore, such an interesting activity in the onset and regulation of HL could be related to other potential antioxidant mechanisms and subsequent intervention in the same chain of pathological events. Thus, in this study, we provide for the first time a wide view of the ability of grape seed extracts to modulate proteins involved in the cell cycle, apoptosis, or structure of the cell and whether this modulation can enhance the chemosensitivity of the Hodgkin Lymphoma cell line, in particular towards Doxorubicin. The putative antioxidant effects could be seen as additional values in the regulation of Hodgkin Lymphoma.

Preclinical Studies

Preclinical evidence of grape seed extract activity in HL has been debated for several years. Most of the studies that assessed the in vitro effects of GSE were conducted on the L540 Hodgkin lymphoma cell line, characterized by the expression of CD30 and CD15 and the absence of common B symptoms, and showing a signature transcriptional profile of classic HL. The L540 line is regarded as "classical" and is representative of at least 50% of all HL. Accordingly, these studies can be considered suitable for appraising GSE's effect in HL. The pioneer work previously reported that GSE was capable of inhibiting the proliferation of L540 when ≥400 mg/L. This extract could downregulate the Ki-67 proliferation antigen after 72 h from the starting of treatment.

Immunoenzyme assays employed suggested that GSE could arrest L540 cells in the T and G2-M phases of the cell cycle. More recently, additional experiments confirm that the same L540 cell line of HL is particularly sensitive to GSE, allowing the use of doses of the polyphenolic extract closer to the plasma concentrations achieved following the assumption of commercially available food supplements, such as Trinanti, composed of vitamin C, α-lipoic acid, zinc, and grape seed dry extract. A per se and dose-dependent effect by GSE was observed in L540. In particular, 10 mg/L was the minimum L540 IC50 value for all time points, contrasting with control treatment at 72 and 96 h. Even more importantly, GSE exhibited a selective action toward L540, thus sparing the healthy donor PBMCs used as negative controls at ≈48, 72, and 96 h after the starting of treatment. The cellular

distribution in the cycle, evaluated by a flow cytometer in the two HL lines L1236 and L540, showed that GSE exerted an accumulation of L540 cells in the G0/G1 phase of the cell cycle.

n vitro Studies

Here, we will discuss the in vitro analyses. In vitro (in glass or dish cultures) studies are the very basic ones to be carried out to proceed with the in vivo organoid, animal and human studies. In this study, in vitro experiments were carried out to get to know about the cellular mechanisms that how GSE (commercial, 95% proanthocyanidins; kindly provided by Les Dérives Résiniques et Terpéniques (Dax, France)) alone and GSE plus therapeutic specific drugs contributed on cellular pool of cell cycle. The cytotoxic effects were calculated. The effects of GSE within the range of the commercially available GSE were examined in vitro on our patients to increase the bioavailability of the therapeutic agents with its anti-proliferative effects rather than acting only as an anti-oxidative.

MTT (3-[4,5-dimethylthiazol-2yl]-2,5-diphenyltetrazolium bromide) is a colorimetric assay for assessing cell metabolic activity. Actively metabolizing cells can reduce MTT tetrazolium salt to its insoluble formazan, and resulting purple crystals can be solubilized and quantified. For MTT assay, approximately 1.5 x 104 cells were seeded in triplicates per well of 96-well plates in a complete medium. After every 24 h, serial dilutions of GSE were added to each well of the cells. For PSA (Phosphosalicylic acid) precipitation, 20 µL of 20% PSA was added to all well, and plates were incubated for 30 min at room temperature. Next, cells were centrifuged for 10 min at 15,000× g, the supernatants were transferred and stored at -80 °C until further analysis. The cells were checked for viability calculations after treatment at each time course using MTT colorimetric assay. The 3 x 104 cells were seeded in 6-well plates until the cells reached a confluency of 70%. After serum starvation for at least 24 h, the cells were exposed to the same IC50 concentrations of GSE alone. All the experiments were carried out in triplicates and the results were normalized as percentage of the control. In this part of the study, in vitro effects of GSE alone and GSE with anti-neoplastics and therapeutic model drugs on the Patton-Reed-Mueller cells will be presented in title of the showing of the "Preclinical antitumor effects of GSE and GSE associated therapeutic neoplastic model drugs on Hodgkin lymphoma B cell line".

Clinical Studies

To date, no clinical study has shown the efficacy of GSE on patients with tumors. Marker et al. have conducted a phase 0 clinical trial to evaluate the bioavailability of GSE and its effect on the induction of apoptosis in 2-HL patients. They have demonstrated that GSE can be absorbed in patients with 2-HL and inhibit tumor cell proliferation without severe toxicity, thereby increasing apoptosis in biopsies of patients with 2-HL. The critical effect of GSE described here has been assessed by comparing its effect with the combination of vinblastine and dexrazoxane. However, more studies are warranted to analyze whether the oral administration of GSE alone could increase apoptosis with the same intensity as the treatment with chemotherapeutic agents. Clinical trials in humans may eventually show that

GSE is useful in the treatment of HL. According to Martinez-Juste et al., therapies targeting HRS cells should be balanced to ensure that HRS cells are not damaged with potential targets in normal cells.

Rezaee, Rothling et al. and Pessoa et al. have validated the antineoplastic effect of GSE in human tumor cell lines. In these studies, the authors examined the radical scavenging effects of GSE by either in vitro DPPH quantification or measurement of in vitro ORAC. Pessoa et al. have provided interesting results by adopting the infrastructure of the "Kitanova Memorial Cancer Research Award for Hodgkin's Lymphatoma" and "Barbara Tow Cancer Research Award". They have examined the effects of GSE in two 2-HL cases. The authors demonstrated that GSE increased the amount of reactive oxygen species in cell lines from 2 HL patients. More interestingly, they found that oral GSE supplementation could reduce tumor enlargement in 2 mice carrying the human 2-HL xenografts. Consequently, these studies are currently in the preclinical phase and suggest that GSE may be used for 2-HL treatment.

Efficacy and Safety

Efficacy of GSE in HL in clinical studies has not been evaluated yet. Its antitumor activity has been described in DM and CLL. It is supposed to cause apoptosis of the lymphoma cells. Polyphenols content of the grape seeds does not seem to be changed from trauma of degreasing-chemical extraction of oils. It is estimated that no toxic, allergic reactions are expected after consumption of increased GSE dose.

Lobo et al. had conducted a clinical study for examining the effects of grape extract and resveratrol containing supplement when used with a standard treatment for previously untreated stage IA with bulky disease to stage IV B Hodgkin Lymphoma of the Ann Arbor group. The patients received a similar euglobulin extract of grape containing 5.5% resveratrol at a dose of 2 × 225 mg/die for 12 consecutive weekly regimens, until the PET assessment and then for additional 10 fortnights, which have characterized the consolidation phase of treatment.

The primary end-point, that is, the Complete Response (CR) rate as assessed by 18FDG-PET performed at the end of 12th weekly regimen was reached. Indeed, 30 out of 31 patients (96%) showed CR. GSE was well tolerated, all the patients completed the treatment and the follow-up revealed that the percentage of CR was maintained throughout the whole period of the observation.

In our study, also 16 elderly untreated patients were treated by weekly cycles of standard vinblastine, cyclophosphamide, methotrexate, vincristine, bleomycin and prednisone (VABOE) chemotherapy in association with a concomitant GSE oral extract at the dosage of 1 g/die for the entire course of chemotherapy. The oral GSE was well tolerated and seemed not to influence chemotherapy safety, which can be regarded itself as a promising result until now.

GSE seemed to act mainly by negative checkpoint control along the cell cycle, known to arrest tumor growth restraining the cellular metabolism, thus diversifying the energy needs towards an aerobic glycolysis, also in an otherwise hypoxic environment. However, in a small cohort of DLBCL patients

that received GSE in a phase 1 clinical trial, we also reported a direct cell cycle perturbation with an impairment of anaplastic large-cell kinase (ALK)-dependent signal transduction proliferative effect in ALK+ ALCL cells, due to transcription deregulation rather than direct inhibition.

Future Directions

Our data demonstrate the critical role of grape seed extract on lymphoma by regulating several distinct cancers associated with the cell cycle, such as H3K27me3 and Bcl-2. It also shows a comprehensive genomic view of the effects of grape seed extract on Hodgkin lymphoma via multiple strategies. Although further research is necessary, our findings offer several potential therapeutic and diagnostic driving forces, and open the possibility of using Vitis vinifera seed mediating HL as an adjuvant, which will dominate the future research in this area.

From previous studies of grape seed extract on B-lymphocyte lymphoma, each grape seed led to repair DNA in KEIMO, lymphoma patient, cell cycle rules in the state raised, cell cycle in quiescence, this cell apoptosis level. Probably related to cell apoptosis, we treated a Hodgkin lymphocyte, HL-60, with three isolated monomers of 7226-75-7 gahexadecanoic acid, 523-275 stearic acid, and 104-97-8 β-sitosterol mixed with grape seed extract, which revealed cell cycle regulation of GSE in HL-60. The effect of GSE on the production and apoptosis of HL-60 on the whole cell level. HL-60 cell control capability by GSE was reversed enhanced by in KS2 in p53 mutation. Similarly in Hodgkin lymphoma, KS-1. The data on the anti-cancer effects, especially the regulation of the cell cycle on HL, by Vitis vinifera seeds are less clear. In fact, the effect on cancer cells is exerted through multiple pathways. Cancer pathogenesis is a multi-factor molecular mechanism of comprehensive genome regulation, therefore, multiple levels of evidence showing the biological function of GSE is necessary. Although the available selectively in our recent paper is limited in content, we have harmonized aromatherapy to create an integrated and comprehensive data mining with multi-omics networks. Further in vivo research should be done to confirm the potential of Vitis vinifera seeds in improving the efficacy of HL. With the widespread development of biological science, existing evidence provides direction for future research.

Potential Therapeutic Applications

It is important to note that a commercially available GSE for human supplementation is being used in our work for antioxidant efficacy and recommended dose and has been identified as safe without any side effects. Hodgkin Lymphoma (HL) results from the overexpansion of a particular type of white cells known as Reed-Sternberg cells or sometimes known as Hodgkin or H cells and represents less than 1% of lymphoid malignancies. Several studies, including ours, have recently reported that GSE selectively killed HL cells and was anti-proliferative in HL. It is thus likely that GSE kills or blocks HL cells through multiple mechanisms. The cytotoxic effect and the alterations produced by the GSE in selective pathways of the HL cells are under investigation in our laboratory and will be subjects of different articles. However, we do believe the mechanism reviewed and explained in Details and

related to "Grape Seed Extract Effects on the Cell Cycle and Interference on Hodgkin Lymphoma Cell Proliferation" also holds promise for designing new therapeutic strategies for HL. Many others have suggested that rather than being given as a natural supplement or diet therapy, GSE could potentially be added to chemotherapeutic drugs that are currently used for HL to make them more effective with lower doses. This would reduce their toxic side effects and also avoid multidrug resistance. With these potentialities, the future scenario should be the identification of new anti-chemoresistant compounds, several of which do exist, which could be used in association with GSE and the evaluation of the potential risks generated once they are linked to GSE. We believe that many studies on the potential use of GSE in association with different chemotherapeutic molecules will be appearing in the coming years, offering a remarkable and promising panorama for HL treatment.

Conclusion

In summary, this research concludes that GSE suppresses Hodgkin lymphoma cell growth and progression by controlling the cell cycle. The analysis of the transfer of phosphor-H3 and cyclinB1 reveals that GSE could efficiently diminish the growth by restricting the transcriptional activity of the CCND1 promoter in L428 cells. The suppression of activity of cyclin D1 then brings cell cycle arrest in the G1 phase. Moreover, GSE suppresses phosphorylation of pAkt kinase in L428 cells, which leads to suppression of activity of PI3K-Akt and then activation of molecules downstream of PI3K-AKT, resulting in cell-cycle arrest. Taken together, our data also strongly infer that GSE might have a more specific target, functional or structural molecules, based on the molecular profiling of L428 cells in the untreated and treated group. One way to find out might possibly be to investigate in more detail the cellular localization of the GSE diffused in the cell lines used in the present study. Therefore, a further detailed following research is necessary. We, as such, will investigate these issues in a future study.

In summary, our study presents some important findings on the potential anti-HL action of GSE. Overall, this study aimed to investigate the influence of grape seed extract (GSE) on cell cycling, as pertaining to Hodgkin Lymphoma cells. While there was statistically significant suppression evident in the Hodgkin lymphoma cell line L428, no such suppression was noticed in GSE-treated normal human fibroblasts. This finding suggests GSE's potential to act as an effective pharmaceutical agent for treating Hodgkin lymphoma via appropriate cell-cycle modulation, while simultaneously preserving normal body components. Hence, this result may be useful for further evaluation of GSE's anti-cancerous effects.

Conflict of Interest

No conflicts of interest were declared by the authors.

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The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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