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Grape Seed Chemical Composition and Its Activity on Different Leukemia Cell Lines: A Review

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ABSTRACT:

Recent researches on natural chemicals as potential cancer drugs has been focused on grape seeds, a plant-derived extract with a complex chemical structure and health benefits. Grape seeds are rich in bioactive compounds that have potential health-promoting effects. The combination of polyphenols, flavonoids, and procyanidins in grape seeds results in a powerful collection of antioxidants. Polyphenols, particularly proanthocyanidins, have significant potential in cancer research. Flavonoid compounds, such as catechin and epicatechin, exhibit significant antioxidant activity and are considered promising candidates for both the prevention and treatment of cancer.

Leukemia, a blood cancer characterized by the uncontrolled proliferation of white blood cells, presents significant problems due to the limited availability of effective therapeutic interventions. Grape seed extracts have been investigated for their potential in combating various cancer cell lines, including leukemia. The study of grape seed extracts has revealed intricate mechanisms of action, such as apoptosis induction, which acts as a protective mechanism against cancer cell proliferation. The complex interaction between bioactive compounds found in grape seeds and specific molecular targets within JURKAT cells presents opportunities for the development of novel drugs for treating leukemia. This review gives insight the potential effects of grape seed components on cancer cell lines, specifically leukemia, focusing on K562, HL60, and JURKAT cell lines.

INTRODUCTION

Research on grape seeds has received considerable attention as a prospective contender within the realm of natural sources, primarily owing to their multifaceted chemical composition and the consequential health advantages they offer.[1] Grape seeds, which are commonly regarded as a secondary output of the wine production sector, contain a diverse array of bioactive chemicals that have been associated with various biological functionalities.[2] The purpose of this introduction is to offer a comprehensive examination of the complex chemical makeup of grape seeds and their possible effects on various leukemia cell lines, including K562, HL60, and JURKAT[3].

The presence of a diverse array of bioactive chemicals within grape seeds is well documented, and the main components found in grape seeds consist of polyphenols, flavonoids, procyanidins, and a variety of other antioxidant compounds.[4-8] Polyphenols, which are a heterogeneous collection of phytochemicals, are highly prevalent in grape seeds and have been linked to a range of biological functions, such as anti-inflammatory, antioxidant, and anticancer properties. [9] Within the group of polyphenols, one prominent class known as proanthocyanidins, or procyanidins, has exhibited considerable potential in the field of cancer research. Procyanidins are a class of flavonoids that exist in oligomeric and polymeric forms .[10] These compounds are comprised of monomers of catechin and epicatechin, which are connected by both C-C and O-C bonds. The distinctive antioxidant and free radical scavenging activities of these compounds are attributed to their polymerization degree, rendering them very promising candidates for the prevention and treatment of cancer.

Leukemia is a diverse collection of hematological malignancies distinguished by the unregulated

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proliferation of immature or atypical white blood cells .[11] Chronic lymphocytic leukemia (CLL) and T-cell leukemia, the JURKAT cell lines, represent distinct forms of leukemia that present notable difficulties in therapy because of their aggressive and resistant characteristics. The K562 and HL60 cell lines are used as models for myeloid leukemia, contributing to the breadth of leukemia subtypes being studied. Researchers have been motivated to investigate natural substances, including those present in grape seeds, in order to discover innovative therapeutic strategies that could offer more precise and less harmful alternatives to traditional treatments.

Several studies have provided evidence of the possible anticancer properties of grape seed extracts against several types of cancer cells; including those related to leukemia .[12-14]. The induction of apoptosis, a crucial process for maintaining tissue homeostasis, is one of the primary ways through which grape seed extracts exert their effects. The initiation of apoptosis hinders the viability of cancer cells that manage to resist the regulatory mechanisms of normal cellular processes. The K562 and HL60 cell lines, which are commonly used to study myeloid leukemia, have been the focus of research regarding the potential effects of grape seed extract.

GSE Chemical Composition

Grape seed extract (GSE) is comprised of a wide range of chemical compounds, primarily polyphenols and phenolic acids(60-70%). Polyphenols have been identified as the predominant and diverse metabolites found in grape seeds. Flavan-3-ols, broad classes of polyphenols that includes monomeric catechins and procyanidins (also known as condensed tannins), are the main constituents that accumulates in grape seeds. In addition, the presence of different grape varieties can result in the occurrence of diverse additional constituents, including phenolic acids, stilbenes, flavanols, water-hydrolysable tannins, and organic acids. In the following section, we will explore the extensive range of chemical components found in grape seeds.

The positive characteristics of wine, as well as its physiological and health benefits, can largely be linked to the polar chemicals present in grape seed extracts, particularly flavan-3-ols. The chemical composition of grape seed oil has been extensively studied and reported by various researchers .[15-17]

The anti-tumoral actions attributed to grapes involve a diverse range of biological pathways and cellular targets. Consequently, this phenomenon finally results in the suppression of cellular proliferation and a concurrent elevation in programmed cell death (apoptosis) in a wide range of cancer cell types, encompassing lung, colon, breast, bladder, leukemia, and prostate cancers. The present study aims to investigate the effectiveness of anti-tumor agents in different types of leukemia cell lines.

Flavan-3-Ols

The term "phenol" denotes the presence of an aromatic ring that is substituted with one or more hydroxyl groups. Moreover, the use of the prefix "poly" indicates the existence of several rings inside the molecular configuration. Phenolic substances can be classified into four primary categories: stilbenes, lignans, phenolic acids, and flavonoids.[18] Flavonoids exhibit a characteristic tricyclic structure, with a central pyran ring (C ring) containing oxygen, which is fused to an aromatic ring (A ring) through a singular bond. Furthermore, the C ring is connected to the B ring, which is also an aromatic ring, by a single bond (Figure 1). A comprehensive compendium comprising more than 6,000 unique flavonoids has been meticulously recorded and documented.

Flavonoids can be categorized into distinct groupings based on their chemical structure, which notably encompasses changes in the quantity and arrangement of substitution groups such as hydroxyl, hydrogen, methyl, glycosyl, malonyl, and sulphate groups. The main subgroups of flavonoids are flavanols, flavones, flavanones, anthocyanidins, isoflavones, dihydroflavonols, and chalcones. Flavanols, also known as flavan-3-ols because of the hydroxyl group located at the 3-position of the C ring, are considered the most chemically reduced category of flavonoids. The structural variety of flavan-3-ols is determined by the stereochemistry and hydroxylation patterns of the C ring, along with the quantity of hydroxyl groups on the B ring. A flavan-3-ol molecule possesses four different configurations due to the presence of two chiral centers located at C2 and C3. As a result, four diastereoisomers are obtained.[19] Flavan-3-ols, which

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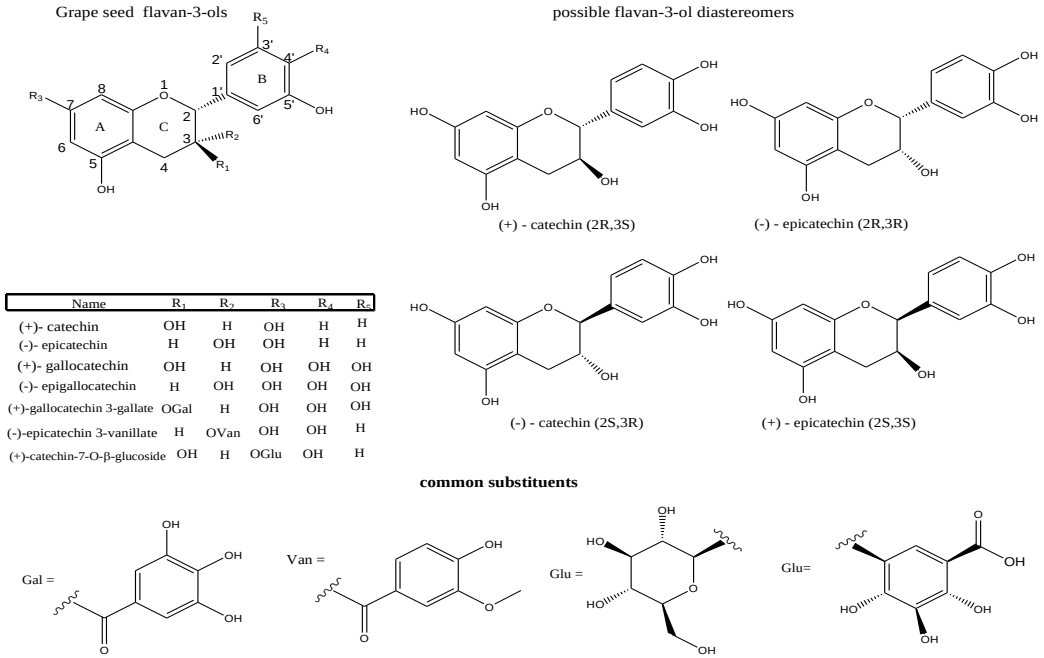
can be found in different molecular configurations, including monomers, dimers, oligomers (3 to 10 units of flavan-3-ols), and polymers (more than 10 units of flavan-3-ols). Proanthocyanidins are composed of oligomers and polymers of polyhydroxyflavan-3-ol units, namely (+)-catechin and (-)-epicatechin in the context of procyanidins. The most common type of procyanidins consists of dimers, with the predominant dimers being the four C4→C8 linked dimers (B1-4). The identification and characterization of these dimers have been reported in previous studies conducted on grapes.[20-27]



Name	R_1	R_2	R_3	R_4	R_5
(+)- catechin	OH	H	OH	H	H
(-)- epicatechin	H	OH	OH	H	H
(+)- gallocatechin	OH	H	OH	OH	OH
(-)- epigallocatechin	H	OH	OH	OH	OH
(+)-gallocatechin 3-gallate	OGal	H	OH	OH	OH
(-)-epicatechin 3-vanillate	H	OVan	OH	OH	H
(+)-catechin-7-O-β-glucoside	OH	H	OGlu	OH	H

Fig.1. Flavan-3-ol monomers reported in grape seed (upper left) including possible flavan-3-ol epimers and enantiomers (upper right). Common O- or COO-linked substituents of flavan-3-ols and other phenols are included in the lower panel.

The flavan-3-ol is the fundamental structure within the flavonoid class. It is distinguished by its 2-phenyl-3, 4-dihydro-2H-chromene framework, with a hydroxyl group attached to the 3-position of ring C (Figure 1). The existence of two chiral centers at positions 2 and 3 in flavan-3-ols gives rise to four potential configurations, leading to the formation of chiral diastereomers. Two enantiomers are present for each epimer. The two enantiomers, specifically referred to as (+)- or (-)-catechin in the trans conformation and (+)- or (-)-epicatechin in the cis conformation (as shown in Figure 1) result in the corresponding epimers of (+)-catechin (2R, 3S) and (-)-epicatechin (2R, 3R), respectively.[28-31] Nevertheless, comprehensive documentation of their absolute configurations is frequently lacking in the published literature, primarily because these configurations are determined using methodologies such as mass spectrometry or nuclear magnetic resonance (NMR)analysis. The monomers known as (+)-gallocatechin and (-)-epigallocatechin are synthesized by introducing an additional hydroxyl group to the B rings of the epimers (+)-catechin and (-)-epicatechin, respectively. The presence of these metabolites has been commonly seen in grape skin .[32-33] The process of galloylation involves the conversion of gallic acid into a molecule known as a "gallate," which is produced as a byproduct during this particular activity. As of now, a total of eleven unique flavan-3-ols have been discovered in grape seeds, and their chemical compositions have been comprehensively described in scholarly publications .[34-35] The monomers that are most prevalent and often seen are (+)-catechin, (-)-epicatechin, and (-)-epicatechin 3-O-gallate .[36-37] Additional monomers that are not as commonly found include (+)-catechin-3-O-gallate, (+)-Gallo catechin, (+)-epigallocatechin, (+)-gallocatechin-3-O-gallate, (+)-epigallocatechin-3-O-gallate, and (+)-epigallocatechin-3-O-vanillate .[38]

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The two main glycosylated flavan-3-ols identified in previous research are (+)-catechin-4'-O-glucoside and (+)-catechin-7-O-glucoside.[42].The presence of (+)-Gallo catechin, (+)-epigallocatechin, and their O-gallate derivatives in grape berry skins necessitates careful examination in certain studies using grape seeds .[43-46] Several investigations have indicated that the fragrance profile and biological activity of wine can be influenced by the presence of galloylated metabolites.[39-42]

The detection of glycosylated catechins in grape seeds has been reported in a recent study.[51] Delcambre and Saucier *et al* demonstrated that a comprehensive set of 14 flavan-3-ol mono glycosides may be produced through the synthesis of four different aglycone units, namely (+)-catechin, (-)-epicatechin, (-)-epigallocatechin, and (-)-epicatechin gallate. Nevertheless, a comprehensive understanding of their structures is still awaited. Focused MS/MS fragmentation patterns have been utilized to acquire partial structural information. The exact placement of the hexoside substituent in the initial investigation remains uncertain. Furthermore, these molecules have the potential to function as fundamental units for the formation of oligomers. Zerbib et al., also identified glycosylated procyanidines in grape seed, but, the stereochemistry and glycosylation of these molecule is not reported. Conducted a recent study wherein they identified the existence of flavan-3-ol mono glycosides in different grape seed kinds, including merlot, cabernet sauvignon, and syrah.

Procyanidins

A diverse range of compounds can be found in grape seed, including monomers, dimers, oligomers (composed of 3 to 10 units), and polymers (consisting of more than 10 units, commonly known as condensed tannins) . Procyanidins are formed through the condensation of (+)-catechin and/or (-)-epicatechin units. In contrast, the formation of prodelphinidins occurs through the condensation of gallocatechins. Based on authoritative references, it has been shown that prodelphinidins are predominantly located in the skins of grapes, whereas procyanidins are primarily found in the seeds of grapes. The lack of prodelphinidins in grape seeds raises questions regarding claims that gallocatechins, which are considered its essential monomer constituents, are present in these seeds. Procyanidins are frequently classified into two types, B-type and A-type, based on their interflavanic connections. The connection in question encompasses either a solitary bond connecting carbon atoms C4→C8 or a bond connecting carbon atoms 4 and 6 (C4→C6), as depicted in Figure 2. Certain procyanidins may possess an extra ether bond connecting carbon atoms 2 and 7. The existence of B-type procyanidins in grape seeds has been well acknowledged. However, a solitary investigation utilizing tandem mass spectrometry identified the presence of A-type procyanidins in a particular white Vitis vinifera cultivar, namely chardonnay .

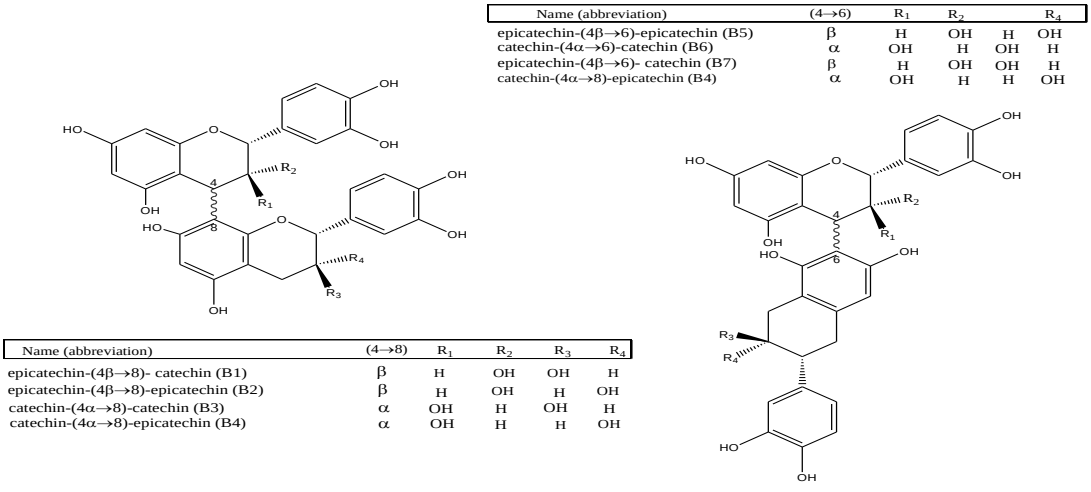

Fig.2. Procyanidin dimers reported in grape seeds

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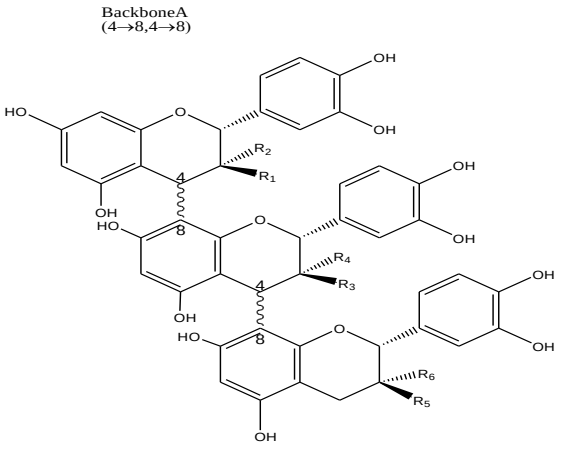
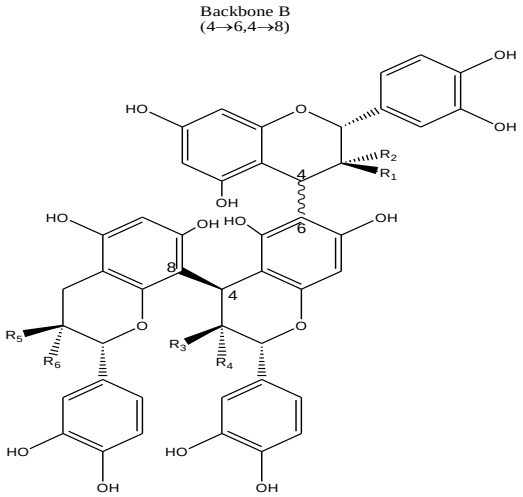
The composition of procyanidins in grape seeds consists of 17 dimers, 16 trimers, and 1 tetramer. The majority of gallic acid esterifications are associated with units of (-)-epicatechin. Nine of these procyanidins exhibit esterification of gallic acid with one or two moieties. Enzymatic esterification processes are implicated in the formation of esters, namely those involving procyanidins B1 to B4, which exhibit the highest levels of abundance. These procyanidins are linked together through carbon 4 to 8 carbon connections.[43-47]

Procyanidin B2 (epicatechin-(4β→8)-epicatechin) is the most abundant dimer among the many procyanidins present in grape seeds. Nevertheless, the documentation of procyanidins B3- and B6-3-O-gallates in grape seeds is limited to a solitary article. The study undertaken by De Freitas et al. aimed to investigate the occurrence and properties of procyanidins B3 and B6 gallates in V. vinifera seeds through the utilization of several analytical techniques. The unsolved issue is the shortage or likely lack of procyanidins B3 and B6 O-gallates in grape seeds. cyanidin C1 and epicatechin-(4β→8)-epicatechin-(4β→8)-catechin (Figure 3) are commonly observed as the predominant trimers within the set of 16 trimeric procyanidins that have been found in grape seeds. The diversity of C-type procyanidins is derived from four distinct backbones (A–D), which exhibit variations in the organization of their constituent monomer units. Backbone A demonstrates the utmost level of structural diversity as it displays the coupling of the three-monomer units at locations C4→C6through alpha or beta bonds. De Freitas et al. have provisionally provided a description of a solitary trimer containing the C4→C6 linkage inside the C-type procyanidins, specifically pertaining to backbone D.(Fig.4.)

Procyanidins can be synthesized by employing catechin and epicatechin as initiation, extension, or terminal subunits to form various types of backbones.[52] While several studies indicate for particular flavan-3-ols as terminal and extension subunits, conflicting findings have been reported by other investigations. In general, (-)-epicatechin seems to function as the primary extension unit, despite the extract containing a higher abundance of (+)-catechin. As the concentration of epicatechin increases, its occurrence as a monomer in other places likewise exhibits an upward trend. According to Santos-Buelga, seeds with elevated levels of (-)-epicatechin demonstrate increased relative proportions of procyanidins that incorporate this particular chemical in both the initiation and terminal units .[53-55] This association is frequently linked to elevated concentrations of the aforementioned monomer.





Name	Backbone	R1	R2	R3	R4	R5	R6
epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin-(C1)	A	H	OH	H	OH	H	OH
epicatechin-(4β→8)-epicatechin(4β→8)-catechin	A	H	OH	H	OH	OH	H
epicatechin(4β→6)-epicatechin(4β→8)-epicatechin	B	H	OH	H	OH	H	OH
epicatechin(4β→6)-epicatechin(4β→8)-catechin	B	H	OH	H	OH	H	OH

Fig. 3. Procyanidin trimers (backbones A and B) reported in grape seeds

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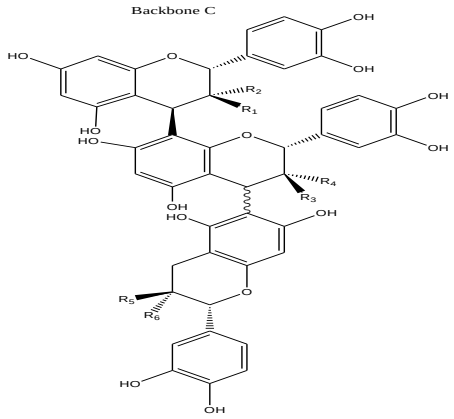

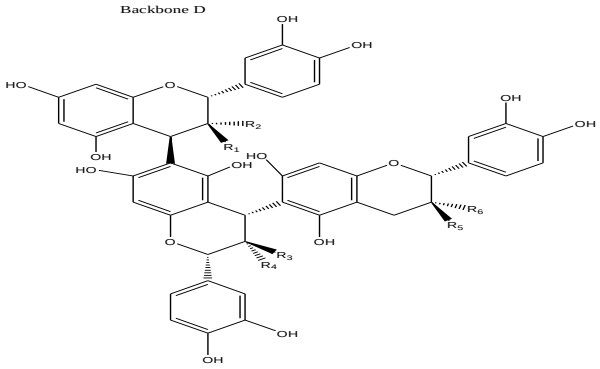

Name	Backbone	R1	R2	R3	R4	R5	R6
epicatechin-(4β→8)-epicatechin-(4β→6)-epicatechin	C	H	OH	H	OH	H	OH
epicatechin-(4β→8)-epicatechin(4β→6)-catechin	C	H	OH	H	OH	OH	H
epicatechin-(4β→8)-epicatechin-(4α→6)-catechin-3-O-gallate	C	H	OH	H	OH	Gal	H
epicatechin-(4β→6)-catechin-(4α→6)-epicatechin 3-O-gallate	D	H	OH	OH	H	H	Gal

Fig. 4. Procyanidin trimers (backbones C and D) reported in grape seeds

The presence of 16 procyanidin trimers has been identified in grape seeds, with 10 of these trimers including (-)-epicatechin as the extension unit. The aforementioned trimers account for 75% of the total initiation units, whereas (+)-catechin contributes to merely 25% of them. The process of galloylation has a higher frequency in the (+)-catechin compound in comparison to the (-)-epicatechin compound. Out of the 33 identified dimeric and trimeric procyanidins, it has been observed that only three of them possess galloylation on units of (+)-catechin, whereas twelve of them exhibit galloylation on units of (-)-epicatechin. According to Santos-Buelga, the observed phenomenon could potentially arise due to steric hindrance occurring within the active site of esterifying enzymes. Out of the total of 16 procyanidin trimers, six of them exhibit (+)-catechin as their terminal unit, followed by five trimers with (-)-epicatechin and four trimers with (-)-epicatechin-3-O-gallate. This observation suggests that the origin of initiation units is separate from that of extension units, as they come from distinct metabolic pools.

Nonetheless, it is important to exercise caution in drawing firm conclusions regarding the feasibility of this hypothesis, as our understanding of procyanidin oligomerization remains limited.
In addition to widely recognized trimers and dimers, polymerizations with significantly greater degrees of polymerization are also observed. Previous investigations have indicated that procyanidins display a range of galloylation levels, often falling between 8 and 15. Additionally, these compounds have been found to have degrees of polymerization ranging from 28 to 37 units.[56,57] In a study conducted by Sica et al. 2018, it was observed that certain tannins found in grape seeds possess molecular weights that surpass 100,000 Daltons . In order to characterize the extensive polymers, it is important to ascertain both the binding sites and identities of each extension unit. Additional mass spectrometry investigations are required in order to achieve a thorough characterization of these polymers. Based on the limited available information, it appears that there is a tendency for galloylation to decrease as the levels of polymerization increase. Nevertheless, there remains a dearth of full biological elucidation for this occurrence. The strong selectivity of esterifying enzymes is expected to arise from their preference for galloylation on (-)-epicatechin in polymeric procyanidins, possibly because of steric hindrance caused by the polymer.

The current advancements in the field of flavan-3-ols derived from grape seeds have brought attention to significant information gaps. These gaps pertain to the identification of galloylated monomers, comprehensive structural analysis of glycosylated flavan-3-ols, and the study of oligomeric procyanidins. Comprehending these biosynthetic processes is of utmost importance, as both monomeric and polymeric flavan-3-ols play a substantial role in the biological and nutritional characteristics of grape seed extracts.

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Grape Seed Chemical Composition Activities on Different Leukemia Cell Lines

Grape seed activity on K562 cell line

The challenge of multidrug resistance (MDR) poses a substantial barrier in the field of cancer therapy, particularly in the context of treating acute myeloid leukemia (AML). The effectiveness of grape seed proanthocyanidin extract (GSPE) in addressing multidrug resistance (MDR) among individuals diagnosed with acute myeloid leukemia (AML) has yet to be established. The main aim of this study was to investigate the capacity of GSPE to counteract multidrug resistance (MDR) in an in vitro environment as well as elucidate the underlying processes involved in this reversal process .

The objective of this research was to investigate the cytotoxic properties of GSPE on K562 human chronic myelogenous leukemia cells, with a specific emphasis on analyzing the correlation between concentration and duration of exposure. The growth inhibition effect of GSPE on these cells was shown to be contingent upon both the concentration of GSPE and the duration of exposure. A progressive augmentation in the proliferation of the cultivated cells was seen throughout the duration of incubation, spanning from 0 to 72 hours. However, there were no significant alterations seen in cellular proliferation at comparable times after the administration of GSPE doses of 25 or 50 mg/l.

Grape seed activity on HL60 cell line

The study utilized human leukemia cell lines, specifically HL-60 cells and HL-ADR cells. The MTT assay was employed to assess the cytotoxic impacts of different chemotherapeutic drugs and to investigate the potential of GSPE to counteract these effects. Flow cytometry tests were performed to verify the occurrence of cellular death resulting from GSPE. The evaluation of gene expression related to multidrug resistance (MDR) was conducted using the real-time polymerase chain reaction (Q-PCR) method. The use of Western blot analysis , a widely used laboratory technique, was employed in order to assess the expression of proteins relevant to multidrug resistance (MDR) at both the genetic and protein levels. The research investigation centered on three crucial proteins, namely multidrug resistance protein 1 (MRP1), MDR1, and lung resistance-related protein (LRP).

The study's findings indicated that HL-60/ADR cells showed resistance to multiple chemotherapeutic drugs, such as cytarabine (Ara-C), Adriamycin (ADR), vincristine (VCR), daunorubicin (DNR), mitoxantrone (MTZ), pirarubicin (THP), homoharringtonine (HHT), and etoposide (VP16). The simultaneous delivery of GSPE resulted in a notable reduction in IC50 values for Ara-C and ADR in HL-60/ADR cells, with statistical significance ($P < 0.01$) . Significantly, the levels of both mRNA and protein expression of MRP1 and MDR1 were significantly greater in HL-60/ADR cells in comparison to HL-60 cells ($P < 0.01$). Nevertheless, the protein expression of LRP demonstrated a noteworthy augmentation in HL-60/ADR cells ($P < 0.05$). Furthermore, the treatment of GSPE has shown the capacity to augment the concentration of intracellular ADR in HL-60/ADR cells. Additionally, it demonstrated the ability to hinder the phosphorylation of Akt, leading to the inhibition of MRP1, MDR1, and LRP, triggering cellular apoptosis . At a dosage of 25.0 grammes per milliliter (g/mL), GSPE exhibited a strong inhibitory effect on Akt phosphorylation ($P < 0.05$).

In summary, the observed reversal of multidrug resistance (MDR) in HL-60/ADR cells following treatment with grape seed proanthocyanidin extract (GSPE) can potentially be due to the suppression of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, resulting in reduced expression levels of multidrug resistance-associated protein 1 (MRP1), P-glycoprotein (MDR1), and lung resistance-related protein (LRP) . The results of this study indicate that GSPE may have the potential to be used as an adjunctive therapy in the treatment of acute myeloid leukemia (AML), therefore justifying the need for additional investigation

Grape seed activity on JURKAT cell line

The primary objective of this work was to conduct an analysis and provide a comprehensive understanding of the functional role of c-Jun NH_2-terminal kinase (JNK) and its associated variables. The present study explores the apoptotic pathways induced by grape seed extract (GSE) in human leukemia cells, utilizing a combination of pharmacological and genomic

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methodologies. The experimental design involved exposing JURKAT cells to different concentrations of GSE treatment over a period of 12 hours. Two distinct methodologies were employed in this study: one involved subjecting the samples to a 24-hour exposure to GSE, while the other involved subjecting the samples to a concentration of 50 μg/mL of GSE for different durations. Additional measurements were performed in order to assess apoptosis and the activation of caspases, which are essential components of cellular death signaling pathways. Additionally, the investigation entailed the examination of cellular signaling networks.

The investigation conducted on human leukemia cells revealed that the administration of GSE (grape seed extract) led to a gradual and proportional rise in apoptosis, which is a controlled mechanism of cell death. Additionally, the treatment induced caspase activation, which is a crucial enzymatic activity involved in signaling cell death. It is worth mentioning that there was a substantial increase in the expression of Cip1/p21, a protein that is known to be involved in the regulation of the cell cycle . Moreover, the use of GSE on Jurkat cells demonstrated a significant increase in phospho-JNK levels, which is a subject of great significance in our study. In contrast, notable outcomes were observed when the JNK pathway was inhibited using pharmacological agents such as SP600125 or genetic techniques such as short interfering RNA. The findings of this study provide evidence for the possible protective effects of this method against GSE-induced mortality in Jurkat cells.[48-50]

CONCLUSION

This review article described the grape seed extract, chemical composition and its structure and backbone framework, which are useful for its pharmacological activity particularly flovon-3-ol and proanthocyanidines activity on K562, HL60, and JURKAT cell lines. Grape seed extract does not show any activity on the K562 cell line. In the HL60 cell line, grape seed extract showed induced apoptosis in cells, and it significantly reduced multidrug resistance in the HL60 cell line. The standard grape seed extract increases apoptosis in JURKAT cells. The apoptosis process is encompassed by a series of events, including the activation of JNK and the overexpression of Cip1/p21. The grape seed extract demonstrated significant activity on different cell lines, but there are no standard studies available for which chemical ingredient or molecule responsible for showing different activity on leukemia cell lines. Hence, studying the grape seed at molecular and cellular level may pave the way to obtain a safe therapeutic drug candidate, which can save the millions from cancer.

Conflicts of Interest

All authors report no financial or any other conflicts of interest related to this work.

REFERENCES

1. Flowers CR, Glover R, Lonial S, Brawley OW. Racial differences in the incidence and outcomes for patients with hematological malignancies. Current Problems in Cancer 2007; 31:182-201.
2. IARC. Direct estimates of cancer mortality due to low doses of ionizing radiation: an international study. IARC Study Group on Cancer Risk among Nuclear Industry Workers. Lancet 1994; 344:1039-43.
3. Pyatt DW, Aylward LL, Hays SM. Is age an independent risk factor for chemically induced acute myelogenous leukemia in children? Journal of Toxicology and Environmental Health 2007; 10:379 - 400.
4. Hayes RB, Songnian Y, Dosemeci M, Linet M. Benzene and lymphohematopoietic malignancies in humans. American Journal of Industrial Medicine 2001; 40: 117-6.
5. La Vecchia C. Mediterranean diet and cancer. Public Health Nutrition 2004; 7: 965-8.
6. Agarwal C, Singh RP, Agarwal R. Grape seed extract induces apoptotic death of human prostate carcinoma DU145 cells via caspases activation accompanied by dissipation of mitochondrial membrane potential and cytochrome c release. Carcinogenesis 2002;23: 1869- 76.
7. Tyagi A, Agarwal R, Agarwal C. Grape seed extract inhibits EGF-induced and constitutively active mitogenic signaling but activates JNK in human prostate carcinoma DU145 cells: possible role in antiproliferation and apoptosis. Oncogene 2003 ; 22: 1302-16.

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www.jchr.org

JCHR (2023) 13(6), 2771-2780 | ISSN:2251-6727

8. Singletary KW, Meline B. Effect of grape seed proanthocyanidins on colon aberrant crypts and breast tumors in a rat dual-organ tumor model. Nutrition and Cancer 2001; 139: 252- 258.
9. Sundarrajan T, Velmurugan V, Jothieswari D. Hepatoprotective Activity of Ethanol Extracts of Amaranthus viridis Linn on Aflatoxcin B^ sub 1^ Induced Rats. Journal of Pharmaceutical Sciences and Research. 2017 Oct 1;9(10):1899-902.
10. Meeran SM, Katiyar SK. Grape seed proanthocyanidins promote apoptosis in human epidermoid carcinoma A431 cells through alterations in Cdki-Cdk-cyclin cascade, and caspase-3 activation via loss of mitochondrial membrane potential. Experimental Dermatology 2007; 16(5):405-15.
11. Kaur M, Agarwal R, Agarwal C. Grape seed extract induces anoikis and caspase-mediated apoptosis in human prostate carcinoma LNCaP cells: possible role of ataxia telangiectasia mutated-p53 activation. Molecular Cancer Therapeutics 2005; 5(5): 1265 -74.
12. Sundar-Rajan T, Vijey-Anandhi M. Molecular docking studies of isolated flavonoids compounds from Amaranthus tristis linn. As alpha-amylase and alpha-glucosidase activators. Asian J Pharm Clin Res. 2018.
13. J Shi, J Yu, J E Pohorly, Y Kakuda. "Polyphenolics in Grape Seeds-Biochemistry and Functionality," Journal of Medicinal Food 2003;6(4) 291-299.
14. Garavaglia J, Markoski MM, Oliveira A, Marcadenti A. Grape Seed Oil Compounds: Biological and Chemical Actions for Health. Nutrition and Metabolic Insights 2016; 9:59–64
15. Martin M.E, Grao-Cruces E, Millan-Linares MC, Montserrat-de la Paz S. Grape (Vitis vinifera L.) Seed Oil: A Functional Food from the Winemaking Industry. Foods 2020;9:1360.
16. Shinagawa FB, de Santana FC, Torres LRO, Mancini-Filho J. Grape seed oil: A potential functional food? Food Science and Technology (Campinas) 2015; 35: 399-406.
17. Freitas VPD, Glories Y, Monique AA. Developmental Changes of Procyanidins in Grapes of Red Vitis vinifera Varieties and Their Composition in Respective Wines. American Journal of Enology and Viticulture 200; 51: 397–403.
18. Ricardo da Silva J, Bourzeix M, Cheynier V, Moutounet M. Procyanidin composition of Chardonnay, Mauzac and Grenache blanc grapes. Vitis- Geilweilerhof 1991; 30: 245–252.
19. Silva RC, Rigaud J, Cheynier V, Chemina A. Procyanidin Dimers and Trimers from Grape Seeds. Phytochemistry 1991;30, 1259-1264
20. Santos-Buelga C, Francia-Aricha EM, Escribano-Bailón MT. Comparative flavan-3-ol composition of seeds from different grape varieties. Food Chemistry 1995; 53:197–201.
21. Aron PM, Kennedy JA. Flavan-3-ols: Nature, occurrence and biological activity. Molecular Nutrition and Food Research 2008; 52: 79-104.
22. Unusan, N. Proanthocyanidins in grape seeds: An updated review of their health benefits and potential uses in the food industry. Journal of Functional Foods 2020;67:103861.
23. Mattivi F ,Vrhovsek U, Masuero D, Trainotti D. Differences in the amount and structure of extractable skin and seed tannins amongst red grape varieties. Australian Journal of Grape and Wine Research 2009;15: 27-35.
24. Kim, S Y Jeong, S M Park, W P Nam, K C Ahn, D.U Lee, S C. Effect of heating conditions of grape seeds on the antioxidant activity of grape seed extracts Food Chemistry. 2006; 97: 472-479.
25. T sai Su, C Singleton, V.L. Identification of three flavan-3-ols from grapes Phytochemistry 1969; 8:1553-1558.
26. Zerbib M, Mazauric JP, Meudec E, Le Guernevé C, Lepak A, Nidetzky B , Cheynier V, Terrier N, et al . New flavanol O-glycosides in grape and wine. Food Chemistry 2018; 266: 441-448.
27. Yilmaz Y, Toledo RT. Major Flavonoids in Grape Seeds and Skins: Antioxidant Capacity of Catechin, Epicatechin, and Gallic Acid. Journal of Agriculture and Food Chemistry 2004;52: 255-260.
28. Ma W, Waffo-Téguo P, Jourdes M, Li H, Teissedre PL. First evidence of epicatechin vanillate in grape seed and red wine. Food Chemistry 2018;259: 304-310.
29. Popov M, Hejtmánková A, Kotíková Z, Sťralková R, Lachmann J. Content of flavan-3-ol monomers and gallic acid in grape seeds by variety and year. Vitis 2017; 56: 45-48.
30. Sica VP, Mahony C, Baker TR. Multi-Detector Characterization of Grape Seed Extract to Enable

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JCHR (2023) 13(6), 2771-2780 | ISSN:2251-6727

in silico Safety Assessment. Frontiers in Chemistry 2018; 6:334

31. Rinaldi A, Jourdes M, Teissedre PL, Moio L. A preliminary characterization of Aglianico (Vitis vinifera L. cv.) grape proanthocyanidins and evaluation of their reactivity towards salivary proteins. Food Chemistry 2014;164: 142-149
32. Braicu C, Pilecki V, Balacescu O, Irimie A, Berindan Neagoe I. The Relationships between Biological Activities and Structure of Flavan-3-Ols. International Journal of Molecular Sciences 201; 12: 9342-9353.
33. Huaman-Castilla LN, Mariotti-Celis SM, Perez-Correa RJ. Polyphenols of Carménère Grapes. Mini Reviews in Organic Chemistry 2017; 14:176–186.
34. Suriano S, Alba V, Di Gennaro D, Basile T, Tamborra M, Tarricone L. Major phenolic and volatile compounds and their influence on sensorial aspects in stem-contact fermentation winemaking of Primitivo red wines. Journal of Food Science and Technology 2016; 53: 3329-3339.
35. Delcambre A, Saucier C. Identification of new flavan-3-ol monoglycosides by UHPLC-ESI-Q-TOF in grapes and wine. Journal of Mass Spectrometry 2012; 47: 727-736.
36. Pérez-Navarro J, Cazals G, Enjalbal C, Izquierdo-Cañas PM, Gómez-Alonso S, Saucier C. Flavanol Glycoside Content of Grape Seeds and Skins of Vitis vinifera Varieties Grown in Castilla-La Mancha, Spain. Molecules 2019; 24:4001.
37. Rousseri P, Rabot A, Geny-Denis L. From Flavanols Biosynthesis to Wine Tannins: What Place for Grape Seeds? Journal of Agriculture and Food Chemistry 2019; 67:1325–1343.
38. Escribano-Bailón MT, Guerra MT, Rivas-Gonzalo JC, Santos-Buelga C. Proanthocyanidins in skins from different grape varieties. Z. Lebensm.-Unters. European Food Research and Technology 1995; 200:221–224.
39. Passos CP, Cardoso SM, Domingues MRM, Domingues P, Silva CM, Coimbra MA. Evidence for galloylated type-A procyanidins in grape seeds. Food Chemistry 2007;105: 1457–1467.
40. Boukharta, M. Study of Vitis vinifera Flavonoids: Structures of the Procyanidins of Grape Seeds, Canes and Leaves. Ph.D. Thesis, Institut National Polytechnique de Lorraine, Nancy, France, 1988.
41. Malik S, Kishore S, Sundarrajan T, Nargund SL, Ghosh A, Emran TB, Chaicumpa W, Dhama K. Yellow fever virus, a mosquito-borne flavivirus posing high public health concerns and imminent threats to travellers–an update. International Journal of Surgery. 2023 Feb 1;109(2):134-7.
42. Fuleki T, Ricardo da Silva JM. Catechin and Procyanidin Composition of Seeds from Grape Cultivars Grown in Ontario.Journal of Agriculture and Food Chemistry 1997; 45:1156–1160.
43. Lea AGH, Bridle P, Timberlake CF, Singleton VL. The Procyanidins of White Grapes and Wines. American Journal of Enology and Viticulture 1979; 30:289
44. Zhao J, Wang J, Chen Y, Agarwal R. Anti-tumor-promoting activity of a polyphenolic fraction isolated from grape seeds in the mouse skin two-stage initiation–promotion protocol and identification of procyanidin B5-3′ -gallate as the most effective antioxidant constituent. Carcinogenesis1999; 20:1737–1745.
45. Romeyer FM, Macheix JJ, Sapis JC. Changes and importance of oligomeric procyanidins during maturation of grape seeds. Phytochemistry 1985; 22: 219–221.
46. Downey M.O, Harvey JS, Robinson SP. Analysis of tannins in seeds and skins of Shiraz grapes throughout berry development. Australian Journal of Grape and Wine Research 2003;9: 15–27.
47. Spranger I, Sun B, Mateus AM, Freitas VD, Ricardo-da-Silva JM. Chemical characterization and antioxidant activities of oligomeric and polymeric procyanidin fractions from grape seeds. Food Chemistry 2008; 108:519–532.
48. Prieur C, Rigaud J, Cheynier V, Moutounet M. Oligomeric and polymeric procyanidins from grape seeds. Phytochemistry 1994; 36: 781–784.
49. Haslam E, Opie CT, Porter LJ. Procyanidin metabolism—A hypothesis Phytochemistry 1977; 16:99–102.
50. Stafford H.A., Shimamoto M, Lester HH. Incorporation of [14C]Phenylalanine into Flavan-3-ols and Procyanidins in Cell Suspension Cultures of Douglas Fir 1. Plant Physiology 1982; 69:1055–1059.