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Role of Diallyl Disulfide (DADS) in Apoptosis in Acute Myeloid Leukemia (AML): A Comprehensive Analysis

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Abstract:

Acute Myeloid Leukemia (AML) is a highly aggressive hematologic malignancy characterized by uncontrolled proliferation and impaired differentiation of myeloid progenitors. Diallyl Disulfide (DADS), a bioactive organosulfur compound derived from garlic (Allium sativum), has emerged as a potent anti-leukemic agent due to its ability to induce apoptosis in AML cells. This review comprehensively examines the molecular mechanisms underlying DADS-mediated cell death, including reactive oxygen species (ROS) generation, activation of intrinsic caspase cascades, inhibition of survival pathways such as EGFR/ERK/PKM2 and mTOR, and induction of autophagy. In addition, DADS demonstrates synergistic apoptotic effects when combined with bioactive compounds and chemotherapeutic agents, while selectively sparing normal hematopoietic cells. Beyond apoptosis, DADS promotes differentiation and inhibits proliferation in leukemic cells, further contributing to its anti-leukemic potential. Collectively, these findings highlight DADS as a multifaceted therapeutic candidate capable of targeting chemoresistant and stem-like AML cells. Further investigation is warranted to optimize its clinical application and develop effective combination strategies.

Keywords: *Diallyl Disulfide, Apoptosis, Acute Myeloid Leukemia, Reactive Oxygen Species, Leukemic Stem Cells.*

Introduction:

Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy characterized by the clonal expansion of immature myeloid progenitor cells, resulting in bone marrow failure, impaired hematopoiesis, and high morbidity and mortality (Döhner et al., 2015). Despite advances in conventional chemotherapy, targeted therapies, and hematopoietic stem cell transplantation, relapse and chemoresistance remain significant clinical challenges, particularly in elderly patients or those with high-risk cytogenetic and molecular profiles (Estey & Döhner, 2006). These limitations highlight the urgent need for novel therapeutic agents capable of selectively inducing apoptosis in leukemic cells while sparing normal hematopoietic populations.

Diallyl disulfide (DADS), a major oil-soluble organosulfur compound derived from garlic (Allium sativum), has been historically associated with reduced cancer incidence in epidemiological studies, including hematological and solid malignancies (Amagase et al., 2001). DADS exhibits a broad spectrum of biological

activities, such as anti-proliferative effects, induction of apoptosis, cell cycle arrest, inhibition of metastasis, and promotion of differentiation in various cancer cell types (Suangtamai & Tanyong, 2016; Ling et al., 2017). In AML, emerging studies have demonstrated that DADS engages multiple cellular signaling pathways to trigger programmed cell death, including the generation of reactive oxygen species (ROS), activation of caspase cascades, modulation of kinase-mediated survival pathways (e.g., EGFR/ERK/PKM2), and inhibition of mTOR-dependent autophagy signaling (Bae & Park, 2024; Ling et al., 2017).

Given its multifaceted mechanisms of action, DADS represents a promising candidate for adjunctive therapy in AML, with the potential to overcome chemoresistance and target leukemic stem cells. Understanding the molecular underpinnings of DADS-induced apoptosis is critical to harnessing its therapeutic potential and may inform the development of combination strategies that enhance efficacy while minimizing toxicity.

Objectives: This review comprehensively examines the molecular mechanisms underlying DADS-mediated cell death, including reactive oxygen species (ROS) generation, activation of intrinsic caspase cascades, inhibition of survival pathways such as EGFR/ERK/PKM2 and mTOR, and induction of autophagy.

DADS Induces Apoptosis in Myeloid Leukemia Cells

Diallyl Disulfide (DADS), a biologically active organosulfur compound derived from garlic, has been widely recognized for its potent pro-apoptotic effects in myeloid leukemia cells. Experimental studies using AML cell lines such as HL-60 demonstrate that DADS induces apoptosis in a clear dose- and time-dependent manner, indicating that both concentration and exposure duration significantly influence the extent of leukemic cell death (Suangtamai & Tanyong, 2016). Morphological observations reveal hallmark features of apoptosis, including chromatin condensation, nuclear fragmentation, and membrane blebbing, confirming the cytotoxic action of DADS at the cellular level.

At the molecular level, DADS activates key components of the apoptotic machinery, particularly caspase-3, an executioner enzyme responsible for orchestrating cellular dismantling. This activation leads to the cleavage of poly(ADP-ribose) polymerase (PARP), a critical DNA repair enzyme, thereby marking irreversible commitment to programmed cell death (Bae & Park, 2024). Notably, this caspase activation is closely linked to upstream oxidative and mitochondrial events, suggesting that DADS triggers apoptosis through a coordinated intracellular signaling network.

A crucial initiating factor in this process is the generation of reactive oxygen species (ROS), especially hydrogen peroxide (H_2O_2). The accumulation of ROS disrupts cellular redox balance and acts as a primary signal for activating apoptotic pathways. This oxidative stress induces mitochondrial membrane depolarization, leading to the release of cytochrome c into the cytoplasm and subsequent activation of the intrinsic apoptotic pathway. The central role of ROS is further supported by evidence showing that antioxidants significantly reduce DADS-induced apoptosis, emphasizing oxidative stress as a key mediator (Ling et al., 2017). Thus, DADS effectively integrates oxidative stress, mitochondrial dysfunction, and caspase activation to induce apoptosis in AML cells.

Molecular Mechanisms Underlying DADS-Mediated Apoptosis

ROS Generation and Stress-Activated Signaling: A central initiating event in Diallyl Disulfide (DADS)-mediated apoptosis is the rapid and sustained generation of reactive oxygen species (ROS) within leukemic cells. Upon exposure to DADS, intracellular ROS—particularly hydrogen peroxide (H_2O_2)—accumulate beyond physiological thresholds, leading to a profound disruption of cellular redox homeostasis. This oxidative imbalance functions as a primary upstream signal that activates multiple stress-responsive signaling cascades.

Among these, the c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38 MAPK) pathways play pivotal roles. These kinases regulate a network of transcription factors, including c-Jun and ATF-2, which in turn modulate the expression of pro-apoptotic genes such as *Bax*, *Bad*, and *Fas ligand*. In AML models like HL-60 cells, elevated ROS levels show a strong correlation with enhanced JNK phosphorylation and activation, and pharmacological inhibition of JNK markedly attenuates apoptosis, underscoring its essential contribution (Bae & Park, 2024).

Beyond signaling, ROS directly impacts mitochondrial integrity by inducing lipid peroxidation, protein oxidation, and mitochondrial membrane depolarization. This leads to the release of cytochrome c into the cytosol, thereby linking oxidative stress to activation of the intrinsic apoptotic pathway. Thus, ROS serves as a critical molecular bridge connecting extracellular stress stimuli with intracellular apoptotic machinery, orchestrating a coordinated cell death response.

Caspase Activation Cascade and Apoptotic Execution: The execution phase of DADS-induced apoptosis is mediated through a highly coordinated activation of the intrinsic caspase cascade, ensuring efficient and irreversible cell death. Following mitochondrial disruption, the release of cytochrome c facilitates the formation of the apoptosome complex, which activates initiator caspase-9. This, in turn, triggers the activation of executioner caspase-3, the central effector enzyme responsible for dismantling cellular architecture.

Activated caspase-3 cleaves several critical substrates, most notably poly(ADP-ribose) polymerase (PARP), a key enzyme involved in DNA repair. PARP cleavage not only inhibits DNA repair mechanisms but also serves as a biochemical hallmark of apoptosis. These molecular events culminate in classical apoptotic features such as DNA fragmentation, chromatin condensation, nuclear shrinkage, and formation of apoptotic bodies.

Importantly, the caspase cascade is tightly interlinked with ROS-mediated mitochondrial damage. The release of additional pro-apoptotic factors such as Smac/DIABLO further enhances caspase activation by neutralizing inhibitor of apoptosis proteins (IAPs). This creates a self-amplifying loop, ensuring that once initiated, apoptosis proceeds in a rapid and irreversible manner. The synergistic interplay between ROS generation and caspase activation underscores the potency of DADS as an inducer of leukemic cell death (Ling et al., 2017).

Modulation of Survival Pathways: EGFR/ERK/PKM2 Axis: In addition to activating apoptotic machinery, DADS exerts profound effects on cellular survival and metabolic pathways, particularly the EGFR/ERK/PKM2 signaling axis, which is crucial for leukemic cell proliferation and metabolic adaptation.

DADS inhibits the activation of the epidermal growth factor receptor (EGFR), thereby suppressing downstream extracellular signal-regulated kinase (ERK) signaling. This inhibition disrupts transcriptional programs that promote cell survival, proliferation, and resistance to apoptosis. A key downstream target of this pathway is pyruvate kinase M2 (PKM2), a metabolic enzyme that plays a central role in the Warburg effect, enabling cancer cells to sustain high rates of glycolysis even in oxygen-rich conditions.

By preventing the nuclear translocation of PKM2, DADS interferes with its non-metabolic functions, including transcriptional regulation of genes involved in cell cycle progression and survival. This results in metabolic reprogramming, reduced ATP production, and increased metabolic stress, ultimately sensitizing leukemic cells to apoptosis (Bae & Park, 2024).

This dual targeting of metabolic and survival pathways highlights the unique ability of DADS to integrate metabolic disruption with apoptotic signaling, thereby attacking leukemic cells on multiple fronts.

Autophagy-Linked Apoptotic Events via mTOR Regulation: Another critical dimension of DADS-mediated cytotoxicity is its ability to regulate autophagy through inhibition of the mTOR (mechanistic target of rapamycin) pathway, a master regulator of cell growth, protein synthesis, and cellular metabolism.

In AML cell lines such as K562 and NB4, DADS suppresses mTOR signaling, leading to decreased phosphorylation of its downstream effectors, including p70S6 kinase (p70S6K) and 4E-binding protein 1 (4E-BP1). This inhibition initiates autophagic flux, promoting the degradation of damaged organelles, misfolded proteins, and other cellular debris.

Initially, autophagy may function as a cytoprotective mechanism, allowing cells to survive under stress conditions. However, with prolonged DADS exposure, autophagy transitions into a pro-death process, often referred to as autophagic cell death. This shift amplifies apoptotic signaling by increasing cellular stress and depleting essential survival components.

Moreover, mTOR inhibition enhances cellular sensitivity to ROS-induced damage and caspase activation, creating a tightly interconnected network between autophagy and apoptosis. This crosstalk results in a synergistic cytotoxic effect, ensuring comprehensive elimination of leukemic cells (Suangtamai & Tanyong, 2016; Ling et al., 2017).

Synergistic and Enhanced Pro-Apoptotic Effects

Recent advances in leukemia research have highlighted the ability of Diallyl Disulfide (DADS) to function not only as an independent pro-apoptotic agent but also as a potent enhancer of apoptosis when combined with other bioactive compounds and chemotherapeutic drugs. This synergistic potential significantly broadens its therapeutic relevance in acute myeloid leukemia (AML), particularly in overcoming drug resistance and improving treatment efficacy.

A notable example of such synergy is observed in the combination of DADS with the oolong tea–derived polyphenol oolonghomobisflavan B (OHBFB). This combination has been shown to induce a markedly enhanced apoptotic response in AML cells through activation of a novel signaling cascade involving the 67 kDa laminin receptor (67LR), cyclic guanosine monophosphate (cGMP), protein kinase C delta (PKCδ), and acid sphingomyelinase (ASM) (Bae & Park, 2024). Activation of this pathway leads to robust cleavage of caspase-3, amplifying the apoptotic signal and resulting in efficient leukemic cell death. Importantly, this combinatorial approach demonstrates selective cytotoxicity, effectively targeting leukemic cells while sparing normal peripheral blood mononuclear cells, thereby suggesting a favorable therapeutic index.

Beyond natural compounds, DADS also exhibits synergistic interactions with conventional chemotherapeutic agents such as cytarabine and daunorubicin. These combinations enhance apoptosis through mechanisms including increased reactive oxygen species (ROS) generation, mitochondrial membrane depolarization, and activation of intrinsic apoptotic pathways (Ling et al., 2017). By sensitizing leukemic cells to these drugs, DADS may help overcome intrinsic and acquired chemoresistance, allowing for improved therapeutic outcomes even at lower drug concentrations.

Furthermore, combinatorial strategies involving DADS have been shown to amplify stress-activated signaling pathways, particularly c-Jun N-terminal kinase (JNK) and p38 MAPK, which play crucial roles in mediating apoptosis (Suangtamai & Tanyong, 2016). The simultaneous activation of these pathways results in a more pronounced apoptotic response than that achieved by individual agents alone. This suggests that DADS acts as a molecular amplifier of cytotoxic signaling, enhancing the overall efficacy of therapeutic interventions while potentially reducing the required doses of toxic chemotherapeutic agents and minimizing adverse side effects.

Alternative Mechanisms Beyond Apoptosis

In addition to its well-established role in inducing apoptosis, DADS exerts significant anti-leukemic effects through non-apoptotic mechanisms, particularly by promoting cellular differentiation and inhibiting proliferation. These alternative pathways further enhance its therapeutic potential in AML.

One of the key effects of DADS is the induction of differentiation in leukemic cells. In HL-60 cells, DADS treatment has been shown to increase the expression of differentiation markers such as CD11b, indicating a shift from an immature blast phenotype to a more mature myeloid state (Ling et al., 2017). This process of differentiation reduces the proliferative capacity of leukemic cells and limits their ability to sustain malignant growth.

Mechanistically, DADS-mediated differentiation is associated with the downregulation of cofilin-1, an actin-binding protein involved in cytoskeletal dynamics, cell motility, and invasion. By inhibiting cofilin-1, DADS disrupts cytoskeletal organization, thereby reducing the invasive and migratory potential of leukemic cells. This not only suppresses disease progression but also contributes to the containment of leukemic spread (Ling et al., 2017).

The induction of differentiation represents a crucial therapeutic strategy in AML, as it drives leukemic blasts toward a non-proliferative and functionally mature state. Although differentiation does not directly induce apoptosis, it sensitizes cells to apoptotic signals and enhances the effectiveness of other therapeutic interventions (Suangtamai & Tanyong, 2016). Moreover, differentiation therapy is associated with reduced stemness, which is particularly important for targeting leukemic stem cells that are often responsible for relapse and treatment resistance.

Additionally, DADS-mediated differentiation may complement its pro-apoptotic effects by modulating gene expression patterns, restoring normal cellular functions, and disrupting oncogenic signaling networks (Bae & Park, 2024). This dual action—combining apoptosis induction with differentiation—provides a comprehensive approach to reducing leukemic burden.

Potential Clinical and Therapeutic Implications

Diallyl Disulfide (DADS), a naturally occurring organosulfur compound derived from garlic, has emerged as a promising therapeutic candidate in acute myeloid leukemia (AML) due to its ability to target multiple cellular pathways that sustain leukemic survival and proliferation. Unlike conventional agents that often act on a single molecular target, DADS exerts a multidimensional mode of action, integrating oxidative stress induction, apoptotic activation, metabolic disruption, and autophagic regulation.

At the core of its anti-leukemic activity is the generation of reactive oxygen species (ROS), which disturbs intracellular redox balance and initiates a cascade of stress responses. This oxidative stress triggers mitochondrial dysfunction, leading to cytochrome c release and subsequent activation of the intrinsic caspase cascade, particularly caspase-9 and caspase-3, culminating in programmed cell death. Simultaneously, DADS suppresses key pro-survival signaling pathways such as the EGFR/ERK/PKM2 axis, thereby disrupting cellular proliferation and metabolic reprogramming that are essential for leukemic cell maintenance (Ling et al., 2017; Suangtamai & Tanyong, 2016). Its ability to inhibit the mTOR pathway further promotes autophagy, which, under sustained stress conditions, transitions into a pro-death mechanism that complements apoptosis.

The clinical relevance of DADS becomes particularly evident in the context of chemoresistant AML, a major challenge in current treatment strategies. Resistance is often driven by aberrant activation of survival pathways such as PI3K/AKT/mTOR and NF-κB, which enhance cell survival, inhibit apoptosis, and maintain leukemic stem cell (LSC) populations (Martelli et al., 2010; Julien et al., 2007). DADS has

demonstrated the capacity to downregulate these signaling networks, destabilize survival-promoting proteins, and restore apoptotic sensitivity in resistant leukemic cells. This suggests that DADS could function as a potent adjunct to conventional chemotherapy and targeted therapies, improving treatment responsiveness and reducing the likelihood of relapse.

In addition, DADS modulates stress-activated signaling pathways, including c-Jun N-terminal kinase (JNK) and p38 MAPK, which play pivotal roles in amplifying apoptotic signals. Activation of these pathways enhances the cytotoxic efficacy of co-administered therapeutic agents, providing a strong rationale for combination therapy approaches that exploit synergistic mechanisms. Such strategies may enable dose reduction of standard chemotherapeutics, thereby minimizing toxicity while maintaining or even enhancing therapeutic outcomes (Suangtamai & Tanyong, 2016).

Selectivity and Cytotoxicity

A particularly compelling feature of DADS is its selective cytotoxicity, which distinguishes it from many conventional anti-cancer agents. Experimental evidence indicates that DADS preferentially induces apoptosis in leukemic cells while exerting minimal effects on normal hematopoietic cells and peripheral blood mononuclear cells. For instance, combinatorial treatments involving DADS and bioactive polyphenols such as oolonghomobisflavan B (OHBFB) have demonstrated robust apoptotic induction in AML cells with negligible toxicity in normal cells (Bae & Park, 2024).

This selectivity is largely attributed to differences in cellular redox status and signaling dynamics between malignant and normal cells. Leukemic cells typically exhibit elevated basal ROS levels and heightened metabolic activity, rendering them more vulnerable to further oxidative stress. DADS exploits this vulnerability by amplifying ROS production beyond the threshold of cellular tolerance, thereby selectively triggering apoptosis in cancerous cells while sparing normal cells that possess more efficient antioxidant defenses (Ling et al., 2017).

The presence of such a favorable therapeutic window has significant clinical implications. It suggests that DADS-based therapies may reduce the systemic toxicity commonly associated with chemotherapy, improving patient tolerance and quality of life. Furthermore, its compatibility with combination regimens enhances its potential as a safe and effective adjuvant, capable of maximizing anti-leukemic efficacy while minimizing adverse effects (Suangtamai & Tanyong, 2016).

Conclusion

Diallyl Disulfide (DADS) exerts multifaceted pro-apoptotic actions in acute myeloid leukemia models through mechanisms involving ROS accumulation, caspase activation, inhibition of survival pathways (e.g., EGFR/ERK/PKM2, mTOR), induction of autophagy, and enhancement of combination therapy effects. Its ability to trigger programmed cell death and alter key leukemic signaling pathways underscores its potential as a therapeutic agent or adjuvant in AML treatment. Continued investigation into optimized combinations and mechanistic nuances will be crucial for translating DADS into clinical utility.

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