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The Progress of Diallyl Disulfide in Anti-Cancer

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Abstract

Considerable evidence in recent years suggests that garlic has anti-proliferative effects on various types of cancer. Garlic contains water-soluble and oil-soluble sulfur compounds. Oil-soluble compounds (OSCs), such as diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS) and ajoene are more effective than water-soluble compounds in protection against cancer. DADS, a major organosulfur compound derived from garlic, can reduce carcinogen-induced cancers in experimental animals and inhibit the proliferation of various types of cancer cells. The mechanisms of these action of DADS include activation of metabolic enzymes that detoxify carcinogens, suppression of the formation of DNA adducts, antioxidant effects, regulation of cell-cycle progression, induction of apoptosis, and inhibition of angiogenesis and metastasis. These topics are discussed in depth in this review.

Keywords: DADS; Cell-cycle; Apoptosis; Angiogenesis; Invasion; Organosulfur compounds; iNOS; COX-2

Introduction

Cancer is one of the most severe health problems that human beings are facing now. Epidemiological and experimental studies have shown that natural or synthetic ingredients in diet may affect the development of tumors. The daily diets made up of resveratrol, curcumin, genistein, garlic, and capsaicin can greatly reduce the risk of cancer or slower down the tumor progression [1]. As far back as ancient times, Egyptians realized that eating garlic could improve human health. In recent years, the anti-tumor effects of garlic and its active constituents have attracted extensive attention [2]. Garlic, commonly used as a food ingredient in cook, has been found to be associated with lower risk of certain cancers, such as lung, colorectal, and prostate cancers [3-5]. The organosulfur compounds in garlic can inhibit the development of cancer cell through targeting multiple signaling pathways that mediate the cell cycle arrest, apoptosis and antioxidants of cancer cells and the metabolism of carcinogens [6-9]. The intake of garlic is negatively associated with the occurrence and development of tumors, including oropharyngeal, esophageal, colorectal, laryngeal, breast, ovarian and prostate cancer and renal cell carcinoma [5,10].

As the main component of garlic oil-soluble compounds (OSCs), the antitumor and immunomodulatory functions of diallyl disulfide (DADS) have attracted attention of researchers [3]. More and more studies showed that DADS inhibits the development and progression of tumors, and the mechanism of action may be closely related to induction of cell cycle arrest and apoptosis, inhibition of oncogenic pathways and elimination of free radicals and oxidants [11]. This article updates the progression in DADS studies.

The anti-tumor effects of DADS

DADS, as one of the OSCs of garlic, has the potential of inhibiting tumor cell proliferation, promoting tumor cell apoptosis and inhibiting tumor cell metastasis in addition to the anti-inflammatory [12] and antibacterial activity [13]. Importantly, as a food ingredient, DADS has low toxicity and could be used as alternative chemotherapeutic agents for carcinomas [14]. DADS exerts anti-cancer effects *via* activating antioxidant enzymes to degrade carcinogens, inhibiting formation of carcinogen-DNA adducts [15,16], inducing cell cycle arrest and apoptosis [17-19], and inhibiting differentiation [20], angiogenesis, migration and invasion [21-23], etc. For instance, DADS can reduce 35% to 60% of DNA damage induced by N-nitrosodimethylamine in liver as assessed by the comet assay [24]. In liver cancer cells exposed to cytotoxic chemicals, DADS can accumulate intracellular ROS and induce the dysregulation of mitochondrial membrane potential, triggering DNA damage-induced G2/M phase arrest and mitochondrial apoptotic pathway [19]. Similarly, DADS can suppress apoptosis resistance induced by DCA through inhibiting the DCA-induced ROS production, inflammatory factors, IκBα phosphorylation, and expression of p50 in the nucleus in a dose-dependent manner in human barrett's epithelial cells [25,26]. On the other hand, an *in vitro* study reported that the oil-soluble compound diallyl disulfide were more potent inhibitor of human esophageal squamous cell carcinoma by inducing p53/p21-mediated G2/M phase arrest and apoptosis *via* p53/p21 and MEK-ERK pathway [27]. Recently, DADS was reported to inhibit the invasion and metastasis of MCF-7 cells *in vitro* by down-regulating p38 activity [28]. The anti-tumor effect of DADS is achieved by regulating many complex signaling pathways. Additional studies on DADS are still needed.

The anti-tumor mechanisms of DADS

Garlic organosulfur compounds were tested for their anticancer potential in many isolated cell systems. However, the mechanisms underlying the anticancer effects of this class of compounds are not

fully understood [29]. Several mechanisms have been proposed, including antioxidant activity, cell growth inhibition, effective stimulation of the immune response, and induction of apoptosis, which coincides with an increase in the percentage of cells blocked in the G2/M phase of the cell cycle [30]. In recent years, the studies have shown that DADS can suppress inflammation and apoptosis by inhibiting the ROS and NF-κB signaling pathways [10].

Modulation of cytochrome p450-dependent monooxygenase by DADS

Cytochrome p450-dependent monooxygenase plays an important role in the metabolism of drugs, steroids, fat soluble vitamins, carcinogens, pesticides and other chemicals [31]. Carcinogenesis is a multistage and complex process that requires binding of a chemical carcinogen to DNA and formation of DNA adduct. Blockage of DNA adducts is an essential and important early step in prevention of carcinogenesis [32]. It's well-known that chemical carcinogens are often required to modulate metabolic activity through cytochrome p450-dependent monooxygenase and acceleration of carcinogen detoxification *via* induction of phase-I enzymes [33,34]. Animal experiments have also confirmed that DADS can promote the degradation of carcinogens by regulating the activity of cytochrome p450-dependent monooxygenase or activating the metabolism of phase-II enzymes [35]. For instance, Nkrumah-Elie and his colleagues had found that DADS can inhibit the carcinogenesis of BP which required metabolic activation to display its full carcinogenic potential by the cytochrome p450 pathway [36], *via* modulating the activation of multiple phases I and II enzymes, including CYP1A1, CYP1A2, CYP1B1, and epoxide enzymes in HepG2 cells [37-39]. Many studies have indicated that inhibition of CYP2E1 (cytochrome p450 2E1) with DADS leads to significant decrease in the single strand DNA damage, which can result in significant reduction in the DNA adduct level [16,40,41]. Not all of the subunits of cytochrome p450-dependent monooxygenase are inhibited by DADS, but DADS can degrade the substance closely associated with cyclophosphamide-induced progressive toxicity and oxidative stress by significantly up-regulation of CYP2B1/2 and CYP3A1 [42,43]. Therefore, the role of DADS in cytochrome p450 is also needed to be confirmed by a large number of studies.

Promotion of the antioxidant response by DADS

The term ROS encompasses a wide range of molecules, including superoxide (O2-), hydrogen peroxide (H2O2), hydroxyl radical, and peroxynitrite [44]. Redox control is achieved through the cooperative and coordinated action of antioxidant enzymes, such as catalase and low-molecular-weight antioxidant compounds, such as glutathione (GSH) [45]. Apart from being directly implicated in carcinogenesis, ROS are strongly involved in tumor proliferation, survival, and resistance to chemotherapeutic agents [46]. On the one hand, the constitutive high level of ROS in some cancer cells appears to promote their proliferation. Additional amounts of ROS above a certain threshold may further cause cell-cycle arrest and/or apoptosis [47]. Recent studies have shown that DADS achieves anti-tumor effects by activating antioxidant responses *via* inhibiting the expression of ROS [15]. The progressive toxicity and oxidative stress induced by DADS play an important role in the pathogenesis of cancer through changing the structure of chromosomes [48,49]. Accordingly, it was observed that NADPH oxidase and ROS play a pivotal role in DADS-induced apoptosis [50]. DADS caused pronounced intracellular ROS accumulation, phosphorylation, and expression of Bcl-2 to cause apoptosis through the activation of JNK and inactivation of ERK1/2 and Akt.

The effects of DADS on IL-1β-induced intracellular ROS production and lipid peroxidation were detected and the proteins expression of Nrf2, Bax, Bcl-2, caspase-3, total and phosphorylated JNK, and p38 MAPKs were evaluated [26]. Nuclear transcriptional factor 2 (Nrf2) is an activator of the antioxidant responsive element (ARE) [51]. In DMBA/TPA-induced cancer cells, the nuclear localization of Nrf2 is reduced, leading to the inhibition of the activation of ARE, resulting in decreased activity of the antioxidant enzymes which activity is essential to antioxidant responses [52]. However, DADS is capable to inhibit the tumorigenesis and progression of TPA-induced tumor *via* promoting the localization of Nrf2 by up-regulating the expression of p21, or inhibiting the degradation of Nrf2 [15]. Therefore, Nrf2 is critical for the inhibition of mouse skin cancer by DADS and can become a promisinglytherapeutic target. However, the mechanisms that DADS inhibit the activation of oncogenic factors and the expression of proto-oncogenes activated by carcinogenic factors are still not very clear, which requires a large number of studies to clarify.

Induction of G2/M phase arrest by DADS

Studies have confirmed that the anti-proliferative activity of DADS is associated with a decrease in the percentage of cells in the G1 phase and a phase G2/M arrest in many human cancer cells [53], but the mechanisms are not very clear. Previous studies indicated that DADS induces G2/M phase arrest in MGC803 cells [54]. High phosphorylation of checkpoint kinase 1(Chk1), low phosphorylation of Chk2 and the low expression of Cdc25c, 14-3-3 and cyclin B1 are closely associated with the inactivation of G2/M checkpoint [55]. However, some researchers found that the overexpression of Chk1, but not Chk2, exhibited increased accumulation in G2/M phase [56]. In addition, DADS can cause high phosphorylation of Cdc2 and decrease the expression of Cdc25c protein that is critical in G2/M arrest [57]. Actually, Cdc2 activation depends on the dephosphorylation of Tyr15 by Cdc25c [27]. However, p53 and the p53-responsive gene, p21, can decrease cyclin B1 and Cdc2 expression by inhibiting either Cdc2 kinase activity or blocking the interaction of cyclin B1-Cdc2 complexes with their substrates, leading to G2/M-phase cell cycle arrest, which indicated that p53/p21 signaling pathway may be the mechanism underlying G2/M phase arrest [58-60]. In addition, DADS can induce G2/M phase cell cycle arrest by activating p38 [57], and suppressing the ATR/Chk1/Cdc25C/cyclinB1 signaling pathway by specifically activating Chk1 [61].

DNA damage has been reported to induce activation of cell cycle arrest to enhance cellular DNA repair capacity [62]. Yang and other researchers found that DADS could induce the DNA damage through up-regulating ROS protein levels in skin cancer cells, and then activate p21, one of the downstream genes of p53, to affect G2/M regulators, including Wee l kinase, Cdc25c and Cdc2 (p34), etc. Simultaneously, p53 can also activate the mitochondrial apoptotic pathway by activating caspase-9, caspase-3 and PARP, thereby promoting apoptosis in skin cancer cells [62]. Recent studies have verified that DADS-induced DNA damage can cause specific phosphorylation of the Ser345 site of the Chk1 protein and interact with the downstream effectors that induce G2/M phase arrest in PaCa-2 MIA cancer cells [19]. The phosphorylation of Chk1 is able to induce the phosphorylation of Ser216 site of the Cdc25c that ultimately results in the proteasome degradation of Cdc25c [63]. The degradation of

Cdc25c protein significantly inhibits the formation of the complex of cell protein dependent kinase, including Cdc2/cyclin B1 (a crucial driver of phase G2/M transitions), etc [64]. Ling et al. found that DADS could increase the rate of phase G0/G1 cells and accordingly reduce the rate of phase S cells in leukemiacells HL-60 treated with different concentrations of DADS [20]. But the mechanisms need to be further elucidated.

Activation of the apoptotic pathways by DADS

Apoptosis is a phenomenon of programmed cell death in normal cells. Apoptosis pathways contain the death receptor-mediated extrinsic pathway [65], the intrinsicmitochondrial pathway [65], granzyme B-mediated pathway [66], and the endoplasmic reticulum stress-mediated pathway [67]. The protein closely associated with apoptosis mainly contains four important protein molecules involved in apoptotic pathways: caspases (the proteases which execute cell death), adapter proteins (caspase activators), Bcl-2 family proteins and inhibitors of apoptosis proteins (IAPs) [68]. In the experiment of apoptotic cell models established by pretreatment of 10 μM DADS in HeLa cells with 2Gy high-LET carbon beams, some researchers found that DADS can obviously promote the activation of apoptosis signal pathway *via* up-regulating the balance between Tap73 (transcriptionally active p73 isoforms) and ΔNp73 (N-terminally truncated anti-apoptotic p73 isoforms). At the same time, DADS can deregulate important molecules involved in internal and external apoptotic pathways, such as apoptotic protease-activating factor-1(APAF1), IL10 and FASLG [69]. Among them, APAF1 plays a key role in the mechanism of apoptosis and can activate the caspase cascade reaction responsible for the apoptotic effector phase [70]. In addition, IL-10 in serum induces apoptosis of T cells by activating the caspase-8 pathway by Fas signaling [71]. New research confirms that receptor for advanced glycation endproduct (RAGE) can specifically deliver DADS into three negative breast cancer cells and significantly enhance the cytotoxicity of DADS by reducing anti-apoptotic proteins and upregulation of pro-apoptotic protein [72]. The researchers have found that DADS-RAGE-SLN can be obviously absorbed by MDA-MB231 and upregulate the expression of pro-apoptotic proteins (Bax, caspase-3, and caspase-9) and downregulate the expression of anti-apoptotic proteins, such as Bcl-2 family (Bcl-2, Bcl-xl, Mcl-1) and survivin through the experiment of establishing the model of solid lipid nanoparticles with DADS-loaded solid lipid location nanoparticles (DADS-SLN), and DADS-loaded solid lipid location nanoparticles with the RAGE positioning (DADS-RAGE-SLN) [72]. In fact, caspase-3 plays an important role as the central effector for initiation of apoptosis [73]. DADS promoted the apoptosis of ECA109 cells by downregulating Bcl-2 mRNA expression and upregulating the Bax expression in a dose-dependent manner, thus increasing the Bax/Bcl-2 ratio, leading to a pro-apoptotic process *via* caspase-3 pathway. In one word, DADS controls cell apoptosis by activating caspase-3, upregulating Bax/Bcl-2 ratio and downregulating the MEK-ERK signaling pathway [19,27,41,74].

Regulation of the miRNAs by DADS

MicroRNAs (miRNAs) are a class of post-transcriptional regulators that negatively regulate plant development, signal transduction, and response to abiotic stresses and pathogen invasions [75-77]. Recently, numerous studies found that DADS could activate/or inhibit the expression of some miRNAs to regulate cell growth, cell cycle progression and apoptosis of human cancer cells [32,78]. For example, miR-200b and miR-22 synergistically induces apoptosis of human GCs (gastric cancer cells) by enhancing theeffects of DADS *in vitro* and *in vivo via* the Wnt-1 signaling pathway [79]. However, different miRNAs in different contexts are aberrantly expressed in various cancers, such as prostatic cancer, esophageal squamous cell carcinoma, breast cancer, and gastric cancer. For example, the miR-22 shows different effects in these cancers [80-83]. DADS can silence HIF-1α (hypoxia inducible factor 1α) *via* increasing expression of miR-22 to repress VEGF (vascular endothelial growth factor) expression to block angiogenesis, leading to the disruption of cancer progression [79,84]. The up-regulation of miR-22 induced by DADS may post-transcriptionally target cyclin A2 and CDKN1A (cyclin-dependent kinase inhibitor 1A) to arrest the cell cycle in G0/G1 phage in CRC and liver cancer cells, respectively [85,86]. The recent researches have confirmed that DADS induces apoptosis of SGC-7901 cells by upregulation of miR-34a, *via* inhibition of the PI3K-Akt signaling pathway [87]. In addition, DADS induced neovasculogenesis through the modulation of crucial signaling pathways and the suppression of miR 221 *via* mediating the upregulation of c-kit expression and the phosphorylation (activation) of the Akt signaling cascade in human EPCs (endothelial progenitor cells) [32]. However, the role of DADS on miRNAs is still in infancy and needs to be studied by researchers.

Inhibition of tumor metastasis by DADS

Epithelial-mesenchymal transition (EMT) is an important phenomenon in the development of tumorigenesis, and is also an important mechanism for the invasion of tumor cells and secondary metastasis [88]. The cells with EMT are present certain anti-apoptotic activity and drug resistance [89]. The signaling pathways involved in EMT include TGF-β, Wnt, Hedgehog, Notch, ILK, and uPAR (urokinase-type plasminogen activator receptor) [90-95]. A recent study has revealed that DADS induces the reversal of the EMT and inhibits cell growth by inactivating the β-catenin signaling pathway in breast cancer cells [96]. Interestingly, DADS inhibits the occurrence of EMT in tumor cells by inhibiting multiple EMT-related signaling pathways.

Previous researches demonstrated that the DADS-induced downregulation of uPAR results in the inhibition of the ERK/Fra-1 pathway in addition to gastric cancer cell migration and invasion [97]. DADS downregulates LIM kinase-1 (LIMK1), vimentin and EMT-related proteins (Slug, Snail), and upregulates E-cadherin and TIMP-3 (tissue inhibitor of metalloproteinase-3) expression which are the signs of the occurrence of EMT, suggesting that DADS may reverse EMT by downregulating LIMK1 [97,98]. DADS suppresses actin cytoskeletal remodeling and cell pseudopodia formation, and the occurrence of EMT *via* down regulating LIMK1 expression to decrease the expression of vimentin, CD34, and Ki-67; increase E-cadherin expression; and impede cancer cell proliferation, angiogenesis, and EMT alteration, thereby inhibiting invasion and metastasis [98-100]. Actually, the effects of DADS on E-cadherin and vimentin expression may result in blockage of the ERK/Fra-1 pathway by inhibition of LIMK1 expression and activity.

MMPs (matrix metalloprotease) have many physiological functions in tumor metastasis, *via* degrading extracellular matrix and basement membrane, which then caused the integrity of basement membrane to be localized for infiltration and distant metastasis [101]. Thus inhibition of MMPs activity could prevent or suppress the tumor metastasis [102,103]. Park et al. have found that DADS significantly inhibited cell motility and invasive activity by decreasing MMP activity

and tightening TJs (tight junctions) [104]. The anti-invasive activity of DADS was associated with inhibition of MMP-2 and MMP-9 activities through elevation of TIMPs expression, and increased TIMPs/MMPs ratio is a key factor in regulation of the anti-metastatic process [104]. Recently, the DADS was confirmed that it could inhibit the invasion and migration of MCF-7 cells in a dose-dependent manner by down-regulated the expression of vimentin and MMP-9 and up-regulated E-cadherin expression in the cells *via* down-regulating the activity of p38 which activates the TGF-β signaling pathway [15]. The recent research found that DADS dose-dependently inhibited HIF-1α transcriptional activity and hypoxia-induced hematogenous metastasis of MDA-MB-231 cells rather than inhibition of HIF-1α mRNA expression or ubiquitin proteasome degradation [23]. In addition, DADS can alter cell morphology and cell motility *via* inhibiting the activation of PI3K/Akt signal pathway, and then inhibited the tumor migration and invasion [105]. However, the inhibition by DADS on tumor metastasis is a complex process, and it is not limited to affecting one key molecule related to tumor metastasis, more studies are needed.

The inhibition of angiogenesis by DADS

Angiogenesis is essential for proper tissue development, but neovascularization can facilitate the progression of pathological conditions, such as tumor growth and survival. Aberrant neovascularization is an essential pathogenic mechanism in many human diseases, including tumor growth and survival [106,107]. Tumor angiogenesis results in abnormally formed, tortuous, and poorly organized vessels that exhibit altered permeability [108,109]. Previous researches have confirmed that the aberrant activated TNF-α receptor signaling is associated with coordination of tumor angiogenesis and metastasis [110]. DADS can inhibit the CCL2 (CC chemokine-2) releasing induced by TNF-α to play an anti-angiogenesis role in MDA-MB-231 cells. The decreasing level of CCL2 attenuates the phosphorylation of ERK which is a key molecule of the MAPK signaling pathway, leading to the weakening of angiogenesis in tumor cells [111]. Activation of ERK and Akt signaling can promote the angiogenesis of HCC (hepatocellular carcinoma) [112]. Recently, DADS has been shown to reduce migration, invasion, and angiogenesis of human colon cancer in part mediated by NF-κB, ERK1/2, JNK1/2, and p38 signaling [113]. Xiao et al. found that the p-Akt protein expression decreased with the increasing DADS concentration[114], and led to attenuating the pro-angiogenesis effect of VEGF. The effect of DADS on angiogenesis may be related to the regulation of metalloproteinase activation which is essential for the pro-angiogenic growth factors available to their receptors [115].

However, pervious study found that DADS and DATS dose-dependently enhance the neovasculogenesis of human EPCs (endothelial progenitor cells), in part through the up-regulation of c-kit protein as well as the activation of the PI3K/Akt/NF-κB cascades and MAPK/ERK pathway [32]. DADS significantly induces the phosphorylation of the Akt, and I-κBα proteins in human EPCs thus activating the PI3K/Akt and NF-κB signaling pathways. Meanwhile, DADS also augment the phosphorylation of the GSK-3β protein and stabilize its downstream target β-catenin protein through the suppression of the phosphorylated β-catenin level, resulting in the inactivation of β-catenin signaling pathway [40,114]. Based on the pro-angiogenic effects of DADS in human EPCs, whether or not the DADS has the same effect in tumor still needs further researches.

The inhibition of inflammation by DADS

Inflammation is a main component of the host immune response to infection, and can have both protective and pathogenic roles. Some pro-inflammatory cytokines play pathogenic roles during tumorigenesis [116]. Particularly, chronic inflammation creates and maintains a tumor microenvironment where there is migration and a relative abundance of immune inflammatory cells and cytokines [117]. For example, studies have shown that tumor necrosis factor α (TNF-α), IL-8 and IL-10 levels are higher in patients with inflammation-associated cancer [118]. DADS has been shown to have both immunomodulatory and anti-inflammatory effects in several types of cancer [7,119].

Although a recent research paper reported that the anti-inflammatory activity of garlic OSCs help reduce TNF-α, IL-6, and iNOS [120], whether DADS can suppress inflammatory bowel disease and the molecular mechanisms haven't been investigated yet [116]. Many studies has been shown that DADS could suppress nitric oxide production through inhibiting the activation of NF-κB (nuclear factor kappa B), and attenuating expression of inducible nitric oxide synthase (iNOS) and blocking the nuclear translocation of NF-κB [121]. Interestingly, ROS are recognized as an important link between inflammation and cancer, who can induce tumor cell proliferation and mutagenesis and inhibits apoptosis *via* activating various signaling pathways, such as NF-κB signaling pathway. Constitutive NF-κB activation in inflammatory bowel disease is associated with an increased risk of developing colorectal cancer [122]. The recent research indicated that DADS exerted its protective effects against colorectal tumors by suppressing inflammation in the colitis-induced colorectal cancer AOM/DSS mouse model [123]. The suppressive effect of DADS on NF-κB activity is likely due to its ability to inhibit the nuclear translocation of the phosphorylated NF-κB heterodimeric Rel-A (P65S536)-p50 complex. Meanwhile, DADS can induce the inactivation of GSK-3(α/β) that can activate the NF-κB signaling cascade by enhancing the transcriptional activity of NF-κB in the nucleus by blocking its phosphorylation of serine residue 21/9 [124,125] . Previous studies have confirmed that DADS can obviously decrease ROS production as a natural antioxidant both *in vivo* and *in vitro* and pro-inflammatory cytokines levels by inhibiting the phosphorylation of IκBα and the nuclear translocation of p65 and p50 to inactivate the NF-κB signaling pathways [126]. Subsequent researches have verified that DADS can inhibit the expression of iNOS and cyclooxygenase (COX-2) in activated RAW 264.7 cells. Due to the inhibition of signal transduction for the iNOS and COX-2 gene expression and the direct inhibition of iNOS and COX-2, the production of NO and PGE2 (prostaglandin E2) is significantly inhibited. NO, PGE2, and related enzymes have been implicated as important mediators in the inflammation process. DADS has anti-inflammatory activity, including the reduction of pro-inflammatory cytokines, such as TNF-α, a key player in the development of tumors. The concrete anti-inflammatory mechanism of DADS does not elucidate very clearly, which need to further study.

Conclusions

As a major component of garlic, more and more evidence indicates that DADS could have broad-spectrum anti-tumor effects, but has no toxic effects in healthy cells. The mechanism of action of DADS is closely related with antioxidants, regulation of cell-cycle arrest, induction of apoptosis and inhibition of angiogenesis and invasion (Figure 1).

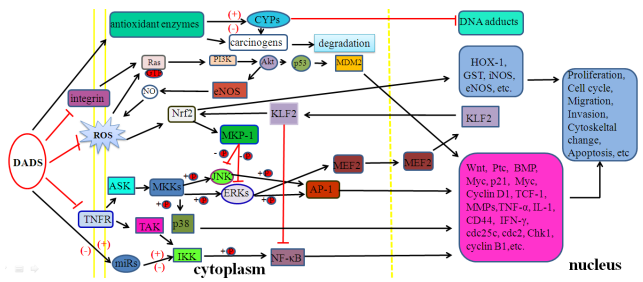

Figure 1: Schema pattern of molecular mechanisms of DADS on anti-cancer effects; DADS inhibits the development and progression of tumors, and the mechanism of action may be closely related to induction of cell cycle arrest and apoptosis, inhibition of oncogenic pathways and elimination of free radicals and oxidants, which achieved by regulating many complex signaling pathways, such as inhibiting the ROS, PI3K/Akt, MAPK and NF-κB signaling pathways.

However, the applications of DADS are only demonstrated *in vitro* and *in vivo* experiments on cancer cell lines and animals. It is implemented into clinical practice thus far because the potential use of DADS in the clinical treatment of cancer has not been excavated. The high concentrations of DADS used in animal studies are unlikely to be physiologically achievable in humans if such compounds are considered for clinical applications, and how to modify the DADS construction to get the clinical effects of cancer treatment is a challenge. Nevertheless, base on the existing studies, it indicates that DADS may be a prospective agent for multi-targeted prevention and/or treatment against human cancer.

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