

# Deguelin, a novel anti-tumorigenic agent targeting apoptosis, cell cycle arrest and anti-angiogenesis for cancer chemoprevention (Review)

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**Abstract.** Deguelin is a natural compound of the flavonoid family products isolated from *Derris trifoliata* Lour. or *Mundulea sericea* (Leguminosae). It exhibited significant anti-tumorigenesis and anti-proliferative activity in various types of cancer both *in vitro* and *in vivo*. Deguelin induced cell apoptosis by blocking anti-apoptotic pathways, such as PI3K-Akt, IKK-I $\kappa$ B $\alpha$ -NF- $\kappa$ B and AMPK-mTOR-survivin, while inhibiting tumor cell propagation and malignant transformation through p27-cyclinE-pRb-E2F1 cell cycle control and HIF-1 $\alpha$ -VEGF anti-angiogenic pathways. In pre-clinical trials, deguelin markedly decreased the tumor incidence. These biological findings identified deguelin as a novel anti-tumorigenic agent targeting apoptosis, cell cycle arrest and anti-angiogenesis for cancer chemoprevention and chemotherapy.

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## 1. Introduction

Growing attention has been focused on the application of natural flavonoids in the chemoprevention and chemotherapy

of malignant diseases. Several plant rotenoid compounds, such as rotenone, deguelin and tephrosin, have previously been reported to be effective against tumorigenesis, metastasis and invasion (1-3). Deguelin [(7aS, BaS)-13, 13a-dihydro-9, 10-dimethoxy-3, 3-dimethyl-3H-bis [1] benzo-prano [3, 4-b: 6', 5'-e] pyran-7 (7aH)-one] is a natural rotenoid extracted from several plants, including *Derris trifoliata* Lour. (Leguminosae), *Mundulea sericea* (Leguminosae) and *Tephrosia vogelii* Hook.f. (Leguminosae) (Fig. 1). In pre-clinical and clinical trials, deguelin has shown effective anti-tumorigenic and anti-angiogenic activities in various types of cancers.

Rotenone is a highly-toxic deguelin-analogue, utilized as an insecticide and inducer of Parkinson's disease (4). As the old inhibitor of mitochondrial complex I (NADH), rotenone contributes to electron transport chain-blocking and ATP depletion, as well as cell toxicity. Despite their similar structure, the differences in the way deguelin and rotenone function are notable. Numerous studies confirmed that deguelin activated the virus signaling pathway for inhibiting tumor cell proliferation with no or less toxicity (5-8), while demonstrating the highest activity in inhibiting DMBA-induced tumorigenesis compared with tephrosin, 13 $\alpha$ -hydroxytephrosin and 13 $\alpha$ -hydroxydeguelin. No sign of overt toxicity has been observed at the dose of 2-4 mg/kg (5).

Deguelin is a well-known PI3K/Akt inhibitor, capable of specifically binding to the ATP pocket of heat-shock protein 90 $\alpha$  (Hsp90 $\alpha$ ), thus suppressing the function of a variety of Hsp90 client proteins. In the comprehensive signaling network of tumorigenesis, metastasis, apoptosis and angiogenesis, deguelin is pivotal in inducing apoptotic cell death and prohibiting their malignant transformation. Deguelin has been reported to kill cancer cells or inhibit tumor growth through targeting apoptosis, cell cycle arrest and anti-angiogenesis, including PI3K-Akt, IKK-I $\kappa$ B $\alpha$ -NF- $\kappa$ B and AMPK-mTOR-survivin pathways. These findings suggest deguelin to be a novel anti-tumorigenic agent for cancer therapeutic intervention.

## 2. Deguelin induced tumor cell death by targeting apoptosis

*Targeting of the PI3K-Akt anti-apoptotic signaling pathway.* Apoptosis is a crucial step in cancer therapy and prevention, whereby cells undergo programmed death to eliminate the

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damaged and harmful cells and restrict cell proliferation. Since dysregulated apoptosis is considered to be necessary for tumor development, apoptosis, a pivotal mechanism for normal homeostasis, is crucial in the therapy of various tumors. Therefore, key regulatory components involved in apoptotic or anti-apoptotic pathways are necessary with a view to developing new targeting agents, with fewer side effects, eliminating cancer cells (9).

Deguelin is known to induce apoptosis by disrupting anti-apoptosis signaling, such as the PI3K/Akt pathway in lung and breast cancer. The PI3K/Akt pathway and its downstream targets are both important for cell survival and proliferation. In 2003, Chun *et al* (10) reported that subsequent to deguelin treatment ( $10^{-7}$  M) premalignant and malignant human bronchial epithelial (HBE) cells showed morphologic changes typical of apoptosis, in contrast to healthy HBE cells. Furthermore, deguelin was confirmed to have induced apoptosis by inhibiting PI3K activity and downregulating the pAkt-level, with no effects on MAPK pathways (10). Subsequent studies have demonstrated that deguelin induced apoptosis by inhibiting the PI3K/Akt pathway in human leukaemia HL-60, U937 and human breast cancer MCF-7 cells (11-13).

In the PI3K-Akt pathway, deguelin treatment resulted in a reduced pAkt level, inhibiting the activity of the pro-apoptotic proteins Bad and Bax by phosphorylation. Bad and Bax are crucial for activating caspase-3, as well as apoptotic downstream targets. Deguelin treatment offsets pAkt inhibition of Bad and Bax, and the caspase cascade of apoptosis is initiated (10,14).

*Targeting of the IKK-I $\kappa$ B $\alpha$ -NF- $\kappa$ B anti-apoptotic signaling pathway.* Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is a family of well-known transcription factors involved in key signaling pathways, such as acquired immunity, inflammation, stress and carcinogenesis. One pivotal function of NF- $\kappa$ B is its ability to block cell apoptosis (15). Several studies showed that in deguelin-induced apoptosis, NF- $\kappa$ B activation was suppressed (16-20). In 2006, Nair *et al* (16) demonstrated that deguelin inhibited IKK activation to protect I $\kappa$ B $\alpha$  from degradation in a variety of cell types. IKK was necessary for I $\kappa$ B $\alpha$  phosphorylation as well as for ubiquitination. I $\kappa$ B $\alpha$  is a known NF- $\kappa$ B inhibitor. After deguelin-incubation, increasingly active I $\kappa$ B $\alpha$  masked the nuclear localization signals of NF- $\kappa$ B. I $\kappa$ B $\alpha$  was kept outside the nucleus and deprived of the ability to bind to DNA (16). Further investigation suggested that deguelin also suppressed the expression of the downstream targets of NF- $\kappa$ B, including numerous anti-apoptotic proteins, such as Bcl-2, Bcl-x1, Bfl-1, IAP1/2 and TRAF-1 (17).

Nair *et al* (16) also suggested that the upstream molecules of NF- $\kappa$ B might be modulated by deguelin. Those authors transiently transfected NF- $\kappa$ B-regulated reporter plasmid, TNFR1, TRAF2, TRADD, NIK and p65 expression plasmids into cancer cells and examined NF- $\kappa$ B-dependent SEAP expression after deguelin treatment. Deguelin was found to have blocked NF- $\kappa$ B activation induced by TNFR1, TRAF2, TRADD and NIK, although not by p65, compared to the control group. The results demonstrated that deguelin acted upstream of p65 in the NF- $\kappa$ B signaling pathway (16).

In contrast to Nair *et al* (16), Geeraerts *et al* (18) demonstrated that deguelin promoted I $\kappa$ B $\alpha$  degradation in B-chronic lympho-

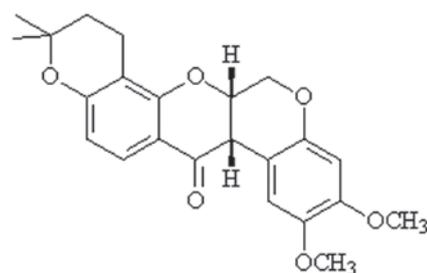


Figure 1. The structure of deguelin.

cytic leukemia (B-CLL) cells. Nevertheless, Chen *et al* (19) demonstrated that deguelin inhibited the I $\kappa$ B $\alpha$  expression and induced apoptosis by interacting with the NF- $\kappa$ B pathway in leukemia cells. Despite these results, the precise mechanism underlying the I $\kappa$ B $\alpha$  downregulation and the subsequent NF- $\kappa$ B-inactivation-related apoptosis has yet to be determined. The studies conducted, however, confirmed the efficacy of deguelin on apoptotic cell death through the NF- $\kappa$ B signaling pathway.

*Targeting of the AMPK-mTOR-survivin anti-apoptotic signaling pathway.* Apart from the PI3K-Akt and IKK-I $\kappa$ B $\alpha$ -NF- $\kappa$ B pathways, deguelin also blocked cell survival through AMPK/mTOR/survivin signaling in HBE cells (21). In this pathway, the first target of deguelin was the AMP-activated protein kinase (AMPK), an enzyme for maintaining cellular energy homeostasis. AMPK activation is correlated with the increase of the ADP/ATP ratio. Various studies have confirmed that sustained activation of AMPK inhibited cell proliferation and induced apoptosis (22-24), since cell growth and mitosis are major consumers of ATP. Recent studies have also demonstrated that activated AMPK-mediated chemotherapy-induced cell apoptosis in bladder cancer or melanoma cells (25,26). These data shed light on the precise mechanism of deguelin induced apoptosis. In HBE cells, deguelin activated AMPK by ATP depletion and inhibited Akt activation. Conversely, the suppressed Akt promoted the function of AMPK, causing the activation of tuberous sclerosis complex 2 (TSC2), a major tumor suppressor, which in turn inhibited mTOR and its upstream protein, p70S6, and activated 4E-BP1. The latter two events suppressed survivin expression. Survivin is another important molecule regulating cell division and protecting cells from normal death. Survivin plays a key role in tumor immune escape and anti-apoptosis. Taken together, deguelin inhibits mTOR-mediated survivin expression. The ultimate chemopreventive effect of deguelin is owed to its blocking malignant transformation and inducing apoptosis in lung cancer cells.

### 3. Deguelin inhibited tumor cell growth by targeting cell cycle arrest

Cell cycle regulator abnormalities are important characteristics of the progression of human cancers. The loss of control over cell cycle checkpoints contributed significantly to cell proliferation. These checkpoints maintain gene expression in a coordinated manner. Thus, several studies conducted on chemoprevention agents focus on rescuing the cell cycle

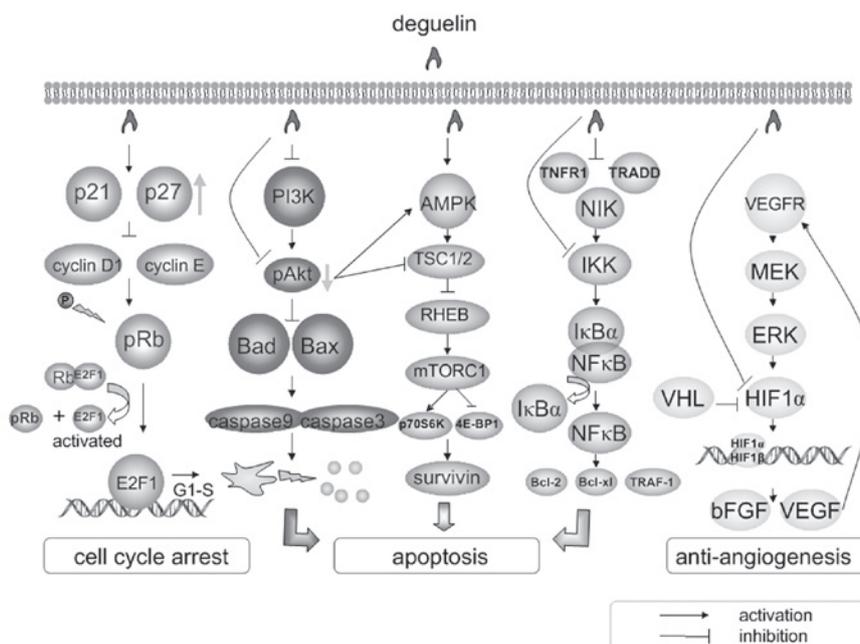


Figure 2. Schematic model of deguelin, a novel anti-tumorigenic agent targeting cell cycle arrest, apoptosis and anti-angiogenic pathways.

regulators, by targeting the p27-cyclin E-pRb-E2F1 cell cycle control signaling pathway.

Deguelin has been found to regulate cell cycle in colon cancer cells by stimulating p27 expression. p27 is a cyclin-dependent kinase (CDK) inhibitor, identified as a crucial factor in the cell cycle regulatory cascade, and found to be involved in the prognosis of several types of cancer. Western blot analysis demonstrated that deguelin mediated p27 overexpression resulting in cyclin E inactivation and consequently, pRb dephosphorylation. pRb acts as a tumor suppressor, while hypophosphorylated pRb is able to bind to E2F1 and inhibit its action. Therefore, deguelin increased the p27 expression and arrested the E2F1 release, contributing to a G1-S phase cell cycle arrest at the end (27). In pre-malignant HBE cells, deguelin treatment also increased the expression of p21 and p27, in a dose-dependent manner (28). According to Murillo *et al* (29) and Liu *et al* (30), deguelin induced cyclinD1/pRb decrease as well as subsequent G1-S phase arrest in breast cancer MDA-MB-231 and lymphoma Daudi cells. These data support the cell cycle blocking effects of deguelin on cancer cells. Nevertheless, additional studies examining the precise mechanism of deguelin modulating the cell cycle are needed.

#### 4. Deguelin induced tumor cell death by targeting anti-angiogenesis

To examine the anti-angiogenic efficacy of deguelin in cancer cells, micro-vessel density was measured in xenograft tumors obtained from control or deguelin-treated mice by targeting of the HIF-1 $\alpha$ -VEGF signaling pathway. The administration of deguelin evidently decreased tumor vascularization, as reflected by the tumor vessel number/high-power field from 100 to 58% (31). The chick aortic arch ring assay showed that deguelin at a concentration of 5 nmol significantly reduced

the number of endothelial cell sprouts. The chorioallantoic membrane and Matrigel plug assays also confirmed the anti-angiogenic activity of deguelin. The treatment of deguelin (1 nmol/egg) suppressed new vessel formation to 46.7 $\pm$ 3.33% (n=20) in chick embryos. Subsequent experiments were carried out to investigate the inner machinery between deguelin and vessel development in the tumor. It is well-known that VEGF and bFGF are crucial elements in new vessel generation. Western blot analysis suggested that deguelin treatment (100 nmol) arrested HIF-1 $\alpha$  protein synthesis and initiated ubiquitin-mediated protein degradation, resulting in the down-regulation of its target, VEGF and bFGF. Further evidence indicated that HIF-1 $\alpha$  degradation was correlated with Hsp90 binding (32,33). The HIF-1 $\alpha$ -driven expression of VEGF is significant in vascular endothelial cancer cell growth, while deguelin appears to block tumor angiogenesis by breaking down the HIF-1 $\alpha$ -driven, VEGF-induced autocrine/paracrine loops.

Deguelin-induced apoptosis, cell cycle arrest and anti-angiogenesis provide novel mechanisms to retinoid research, while preclinical/clinical trials of deguelin are promoted to explore its antitumor efficacy in practice.

A schematic model of deguelin as a novel anti-tumorigenic agent targeting the cell cycle arrest, apoptosis and angiogenic pathways is shown in Fig. 2.

#### 5. Deguelin was applied in pre-clinical and clinical trials

In early 1997, animal experiments confirmed that deguelin decreased tumor incidence from 60% in the control group to 10% in the deguelin-treated group at a dose of 33  $\mu$ g/rat, while tumor multiplicity was reduced from 4.2 to 0.1. At an elevated (330  $\mu$ g/rat) dose, no tumors were observed in the treatment group (5). Topically-administered deguelin significantly suppressed the multiplicity of skin tumors with

UVB-induction, indicating its effect as a potential cancer chemopreventive agent (6). In A/J mice, deguelin clearly reduced the tumor multiplicity and volume, as well as the overall tumor burden with exposure to the tobacco-specific carcinogen benzo(a)pyrene (Bap) and other carcinogens, with no detectable toxicity (7,8). Nevertheless, the toxicity of deguelin over a certain dose should not be neglected. Treatment with deguelin, a potential mitochondria complex I inhibitor (34), reduced tyrosine hydroxylase-positive neurons, leading to Parkinson's disease (PD). Kim *et al* (35) showed that deguelin promoted a PD-like syndrome, mainly by Src/STAT signaling, since  $\alpha$ -synuclein (a key protein function in the pathogenesis of PD) was phosphorylated by deguelin-activated Src (35).

Numerous studies conducted on pre-clinical trials have focused on deguelin modification, because of its antitumor activity and some cell toxicity. Through the hydroxylation of 7 $\alpha$  carbon or the functional group substitution of 7 carbon of deguelin, several derivatives have been synthesized and their biochemical features, such as solubility and anti-proliferative effects, evaluated. Candidate SH-14 showed the highest apoptotic activity with no detectable effect on PD evoking for clinical use (35). Thus, the modified derivatives successfully reduced the side-effects of deguelin, while maintaining its potential antitumor activity, which is crucial for the systemic clinical evaluation of these novel derivative drugs.

## 6. Conclusion

Generally, the essential changes in tumors are alterations in the genome and protein expression levels that contributed to the biological events involved in tumor malignant phenotype: dysregulated growth stimuli, apoptosis control deletion, cell cycle checkpoint turning off, limitless angiogenesis, immune escape, tissue infiltration and metastasis, as well as insensitivity to chemoradiation.

Deguelin is potentially superior as a natural antitumor agent for various types of cancer cells: Colo 16 and SRB-12 skin cancer cells, normal HBE and BEAS-2B HBE cells, as well as MKN-28 and SNU-484 gastric cancer cells. At times, however, it is highly toxic, being closely correlated with the pathogenesis of Parkinson's disease. However, whether deguelin is an excellent antitumor agent or a poisonous drug depends solely on its dose. For example, deguelin (4 mg/kg) significantly inhibits the growth of H1299 xenograft tumors [(115.9 mm<sup>3</sup> (treatment group) vs. 798 mm<sup>3</sup> (control group)] without detectable toxic effects (32), whereas a long-term and high-dose deguelin or rotenone administration resulted in a PD-like syndrome in rats (34,36). Despite these findings, deguelin is beneficial. 17-Allylamino-17-demethoxygeldanamycin (17-AAG), a small-molecular inhibitor of Hsp90 currently in phase II clinical trials, demonstrated various side-effects with clinical symptoms (37,38), whereas deguelin demonstrated antitumor activity at a certain dose with no toxicity to healthy cells. Additionally, new derivatives were found to be promising in overcoming the probable toxicity of deguelin in the future.

As mentioned previously, deguelin has been shown to induce cancer cell death or suppress tumor growth by PI3K-Akt, IKK- $\kappa$ B $\alpha$ -NF- $\kappa$ B, MAPK-mTOR-survivin-mediated apoptosis, p27-cyclinE-pRb-E2F1-mediated cell cycle arrest

and HIF1 $\alpha$ -VEGF-mediated anti-angiogenesis. Deguelin is essential in such signaling pathways, mainly due to its being a special inhibitor of Hsp90 chaperon function. Its binding to Hsp90 leads to a decreased expression of numerous oncogenic proteins, including MEK1/2, Akt, HIF1 $\alpha$ , COX-2 and NF- $\kappa$ B.

The aim of future studies is to investigate the precise mechanism of deguelin-induced apoptosis and anti-angiogenesis, which are likely to provide a guide for further clinical trials and the development of new derivatives. The clarification of the molecular mechanism of deguelin-induced cell death and the pre-clinical and clinical trials indicate that deguelin has a marked potential for cancer chemoprevention and chemotherapy. Thus, further clinical experiments should be conducted for novel agent development.

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