

# Modulation of Apoptosis by Natural Products for Cancer Therapy

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## Key words

- natural products
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## Abstract

Natural products can exhibit many beneficial effects on human health. As far as cancer is concerned, naturally occurring compounds have been reported to prevent tumorigenesis and also to suppress the growth of established tumors. As cancer cells have evolved multiple mechanisms to

resist the induction of programmed cell death (apoptosis), the modulation of apoptosis signaling pathways by natural compounds has been demonstrated to constitute a key event in these anti-tumor activities. This review presents some examples of how apoptosis pathways are targeted by selected naturally occurring agents and how these events can be exploited for cancer therapy.

## Introduction

Over the last decades, natural compounds have attracted considerable attention as cancer chemopreventive agents and also as cancer therapeutics [1]. Among their various biological activities, natural products can modulate apoptosis signaling pathways. Apoptosis or programmed cell death is an evolutionary highly conserved intrinsic death program that plays a key role in maintaining tissue homeostasis during development and in adult life [2]. Consequently, too little apoptosis can promote tumorigenesis even without an increase in proliferation [3]. Evasion of apoptosis is a characteristic feature of human cancers that promotes tumor formation and progression [3,4]. Additionally, the inability of most cancers to undergo apoptosis in response to appropriate stimuli is a key cause of treatment failure and presents one of the major, yet unsolved problems in oncology [3,4]. Therefore, new concepts are required to overcome cancer resistance to conventional treatment approaches. Since natural compounds can modulate apoptosis pathways that are frequently blocked in human cancers, these compounds may provide novel opportunities for cancer drug development.

## Core Apoptosis Signal Transduction Pathways

Two major apoptosis pathways, i.e., the receptor (extrinsic) pathway and the mitochondrial (intrinsic) pathway, eventually result in the activation of caspases, a family of enzymes that act as death effector molecules in various forms of cell death [5,6]. In the receptor pathway, ligation of death receptors of the tumor necrosis factor (TNF) receptor superfamily, for example, CD95 (APO-1/Fas) or TNF-related apoptosis inducing ligand (TRAIL) receptors, by their cognate natural ligands or by agonistic antibodies initiates receptor oligomerization followed by the recruitment of adaptor molecules such as FADD and caspase-8 to the activated death receptors leading to the activation of caspase-8 [7]. Once activated, caspase-8 either directly cleaves and thereby activates effector caspase-3 or alternatively, cleaves Bid into tBid [8,9]. Bid is a BH3-only protein of the Bcl-2 family, which upon cleavage translocates as tBid to mitochondria to stimulate mitochondrial outer membrane permeabilization [9]. Thus, Bid links the receptor to the mitochondrial pathway and can initiate a mitochondrial amplification loop upon its caspase-mediated proteolytic processing [9]. Initiation of the mitochondrial (intrinsic) pathway of apoptosis constitutes a point of no return in various models of apoptosis, eventually resulting in the activation of caspases [10]. In the mitochondrial pathway, the release of mi-

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tochondrial intermembrane space proteins such as cytochrome c or second mitochondria-derived activator of caspase (Smac)/direct IAP binding protein with low pI (DIABLO) into the cytosol triggers a common prefinal stage of apoptosis that is characterized by the activation of effector caspases [11]. To this end, cytochrome c promotes caspase-3 activation via the formation of the apoptosome complex that contains besides cytochrome c also Apaf-1 and caspase-9 and results in the activation of caspase-9 and subsequently caspase-3 [11]. Smac/DIABLO promotes activation of caspases-3, -7 and -9 by binding to and antagonizing “inhibitor of apoptosis” (IAP) proteins [11]. IAP proteins are a family of endogenous caspase inhibitors and comprise eight human analogues, including XIAP, c-IAP1, c-IAP2, survivin and livin/melanoma-IAP (ML-IAP) [12].

There are various intervention points that control cell death pathways, since inappropriate induction of apoptosis may have detrimental effects on the cell's survival [3]. For example, pro- and anti-apoptotic proteins of the Bcl-2 family play an important role in the regulation of the mitochondrial pathway [9]. The anti-apoptotic Bcl-2 family members comprise, e.g., Bcl-2, Bcl-XL and Mcl-1, while the multidomain proteins Bax and Bak and BH3 domain-only proteins such as Bid, Bim, Noxa and Puma belong to the pro-apoptotic molecules [9]. The ratio of anti-apoptotic versus pro-apoptotic Bcl-2 family proteins rather than the expression of one single family member is considered to control apoptosis sensitivity. These anti-apoptotic control points that prevent accidental cell death under physiological conditions are often deregulated in cancers and may confer drug resistance. Besides apoptosis, several non-apoptotic modes of cell death have also been identified in recent years, including necrosis, autophagy or mitotic catastrophe [13].

### Examples of Natural Compounds that Induce Apoptosis in Cancer Cells (Table 1, Fig. 2)

#### Betulinic acid

Betulinic acid [3 $\beta$ -hydroxy-lup-20(29)-en-28-oic acid] is a pentacyclic triterpenoid, which naturally occurs, for example, in the bark of white birch trees and has been identified to stimulate the mitochondrial apoptosis pathway preferentially in cancer cells [14–16]. In a cell-free system, betulinic acid has been demonstrated to directly cause mitochondrial outer membrane permeabilization and cytochrome c release in a Bcl-2 or Bcl-X<sub>L</sub>-dependent manner, yet independently of caspases [14, 15, 17, 18]. Betu-

linic acid was also reported in various models to induce apoptosis in a p53-independent fashion, including chemotherapy-refractory cases [15, 19–24], indicating that betulinic acid may bypass some types of drug resistance.

#### Resveratrol

Resveratrol (Fig. 1) is another natural compound that is present in several dietary items, e.g., in grapes and red wine [25]. Chemically, resveratrol belongs to the group of polyphenolic phytoalexins [25]. Resveratrol has been described to interfere with mitochondrial functions by inhibiting mitochondrial ATP synthesis through its binding to F<sub>1</sub>-ATPase [25]. In addition, resveratrol can antagonize anti-apoptotic proteins that prevent the induction of apoptosis in cancer cells. For example, resveratrol has been reported to induce p53-independent upregulation of p21, p21-triggered cell cycle arrest and subsequently cell cycle-dependent depletion of the anti-apoptotic protein survivin, thereby sensitizing cancer cells to TRAIL-induced apoptosis [26]. Besides survivin, resveratrol has also been demonstrated to suppress expression levels of additional anti-apoptotic proteins, for example, Bcl-X<sub>L</sub> and Mcl-1 [27]. The antitumor activities of resveratrol have also been linked to its ability to interfere with the phosphatidylinositol-3 kinase (PI-3K)/AKT and the MAPK pathways [28–31], two key survival cascades that are frequently aberrantly activated in human cancers [32]. To improve the targeting to mitochondria, resveratrol has been coupled to the membrane-permeant lipophilic TPP cation [33]. Compared to the parent compound, mitochondria-targeted resveratrol derivatives, i.e., 4-triphenylphosphoniumbutyl-4'-O-resveratrol iodide, accumulate in mitochondria and may provide the basis for the design of more selective and potent resveratrol derivatives [33].

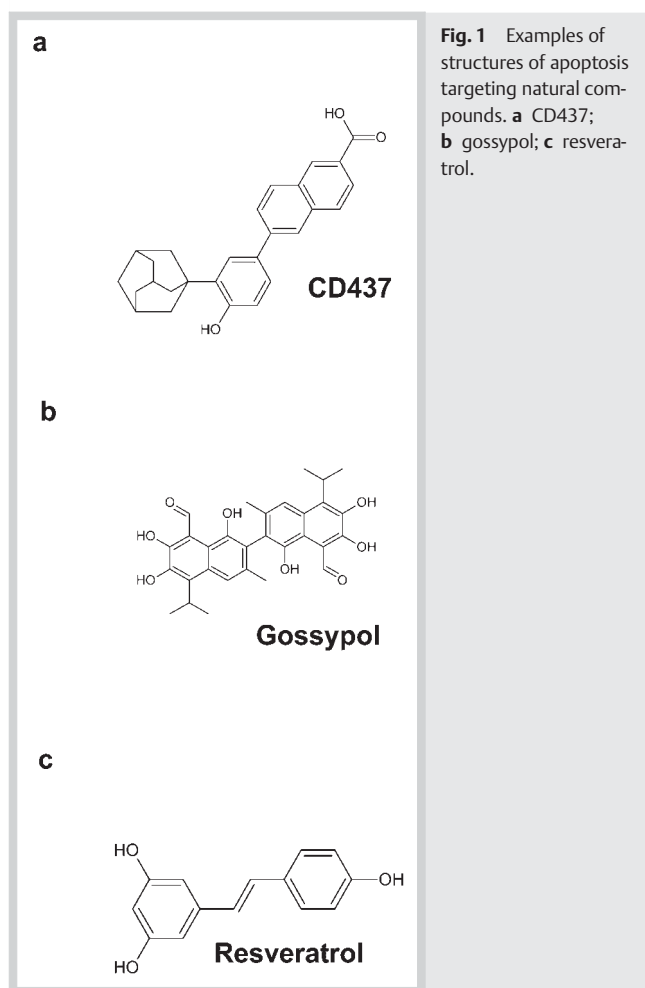
#### Vitamin E analogues

Vitamin E analogues, for example,  $\alpha$ -tocopheryl succinate ( $\alpha$ -TOS), have also been reported to selectively trigger mitochondrial apoptosis in tumor cells [34]. Recently, evidence has been provided that  $\alpha$ -TOS directly interacts with both ubiquinone-binding sites of the respiratory complex II, leading to the displacement of ubiquinone from complex II and subsequently to ROS generation [35].  $\alpha$ -TOS not only targets cancer cells but also endothelial cells [36], which may contribute to its potent antitumor activity. Experiments performed in endothelial cells that were depleted of mitochondrial DNA confirmed the key role of the intrinsic apoptosis pathway to  $\alpha$ -TOS-mediated cytotoxicity [36]. In addition to  $\alpha$ -TOS, a series of vitamin E analogues has

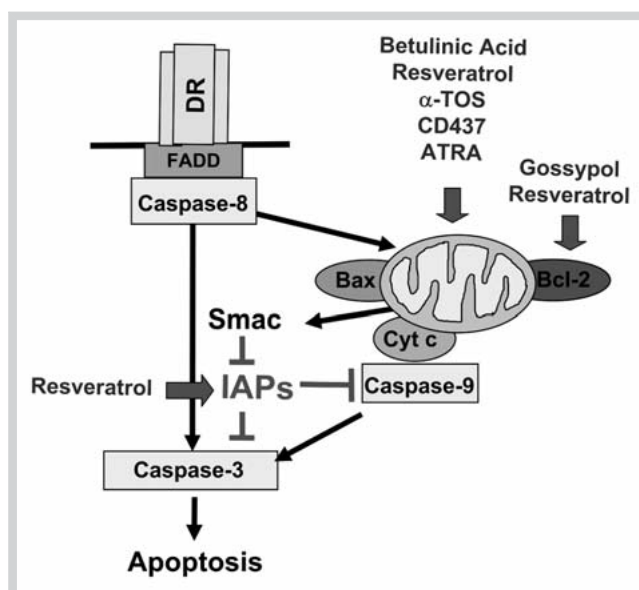
Compound	Target/Mode of action	References
$\alpha$ -TOS	Ubiquinone-binding sites in respiratory complex II	[35]
ATRA	ANT ligand	[47]
Betulinic acid	PTPC	[15]
CD437	PTPC	[45, 46]
Gossypol (AT-101)	Inhibitor of Bcl-2, Bcl-X <sub>L</sub> , Bcl-W, Mcl-1	[41, 44, 57]
2-Methoxyestradiol	SOD inhibition	[50]
Methyl jasmonate	Interferes with HK2/VDAC interaction	[56]
PEITCs	ROS regulator (GSH depletion, GPX inhibition)	[48]
Resveratrol	F <sub>1</sub> -ATPase	[25]

Abbreviations:  $\alpha$ -TOS,  $\alpha$ -tocopheryl succinate; ANT, adenine nucleotide translocase; ATRA, all-*trans*-retinoic acid; CD437, 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid; GPX, glutathione peroxidase; GSH, reduced glutathione; HK, hexokinase; PBR, peripheral benzodiazepine receptor; PEITCs, phenyl ethyl isothiocyanates; PTPC, permeability transition pore complex; ROS, reactive oxygen species; SOD, superoxide dismutase; VDAC, voltage-dependent anion channel

**Table 1** Examples of apoptosis targeting natural compounds.



**Fig. 1** Examples of structures of apoptosis targeting natural compounds. **a** CD437; **b** gossypol; **c** resveratrol.



**Fig. 2** Modulation of apoptosis pathways by natural compounds. The extrinsic (death receptor) pathway is stimulated by ligation of death receptors (DR) by their respective ligands, which leads to receptor trimerization, recruitment of adaptor molecules (FADD) and activation of caspase-8. The intrinsic (mitochondrial) pathway is initiated by the release of mitochondrial proteins such as cytochrome c or Smac into the cytosol. Natural compounds modulate apoptosis signaling at various points, e.g., at mitochondria by targeting the permeability transition pore complex (e.g., CD437, betulinic acid), by interacting with the ubiquinone-binding sites in respiratory complex II ( $\alpha$ -TOS), as ANT ligand (ATRA), by suppression of IAP proteins (resveratrol) or by inhibition of anti-apoptotic Bcl-2 proteins (gossypol, resveratrol). See text for more details.

been synthesized, e.g., a non-hydrolyzable ether-linked acetic acid derivative of  $\alpha$ -TOH (i.e.,  $\alpha$ -TEA) [37–39]. These derivatives proved to harbor improved antitumor activity in some (but not all) cancers compared to the parent compound [37–39]. Of special interest is also the reported tumor selectivity of  $\alpha$ -TOS [40], which has been linked to its ester structure.

### BH3 mimetics

Gossypol (AT-101) (● Fig. 1), a polyphenolic aldehyde that naturally occurs in the cotton plant [41], has been demonstrated to simultaneously antagonize several anti-apoptotic Bcl-2 proteins, which interfere with mitochondrial outer membrane permeabilization, including Bcl-2, Bcl-X<sub>L</sub>, Bcl-W and Mcl-1 [42]. The derivative apogossypol has been described to exhibit superior antitumor activity combined with reduced toxicity compared to gossypol [43]. It is interesting to note that gossypol showed clinical activity as monotherapy in a phase I trial for the treatment of prostate cancer [44] and is currently being evaluated as mono- or combination therapy in several malignancies.

### Compounds targeting permeability transition pore complex (PTPC)

The permeability transition pore complex (PTPC) is a highly dynamic supramolecular structure, which comprises the voltage-dependent anion channel (VDAC) in the outer membrane, the peripheral benzodiazepine receptor (PBR, also known as TSPO, translocator protein of 18 kDa) in the outer membrane, the ad-

enine nucleotide translocase (ANT) in the mitochondrial inner membrane, hexokinase (HK), which interacts with the mitochondrial outer surface from the cytosol, and cyclophilin D, which is localized in the mitochondrial matrix [10]. The sustained opening of the PTPC coupled with the loss of interactions with HK favors the loss of the mitochondrial membrane potential leading to an osmotic imbalance and swelling of the mitochondrial matrix, a phenomenon called mitochondrial permeability transition (MPT) [10]. This causes the physical rupture of the outer mitochondrial membrane, since the surface area of the inner membrane exceeds by far the surface area of the outer membrane [10]. Components of the PTPC can be targeted by natural products, for example by retinoid-related compounds such as 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalenecarboxylic acid (CD437) (● Fig. 1) and all-trans-retinoic acid (ATRA). Of note, these retinoids trigger ANT-dependent MPT and subsequently apoptosis independent from their ability to bind to nuclear receptors [45–47].

### ROS regulators

Agents that produce reactive oxygen species (ROS) can trigger mitochondrial outer membrane permeabilization and apoptosis by overwhelming the antioxidant defense of mitochondria and hence causing excessive oxidative damage of mitochondria. One such class of compounds are the dietary phenylethyl isothiocyanates (PEITCs), which inhibit the GSH antioxidant system by conjugating GSH and by inhibiting glutathione peroxidase, lead-

ing to the production of ROS and subsequently to oxidative damage-mediated mitochondrial apoptosis [48,49]. Some estrogen derivatives, e.g., 2-methoxyestradiol, have been described to induce cell death in cancer cells by blocking superoxide dismutase (SOD), an enzyme of the antioxidant defense, thereby increasing ROS generation [50,51].

### Agents targeting aberrant metabolism

Deregulation of mitochondrial functions lies at the intersection between the regulation of cell death events and metabolism [52]. Indeed, metabolic reprogramming is increasingly being recognized as one of the hallmarks of human cancers [52]. Therefore, molecules that are involved in the control of metabolic pathways represent potential targets for the development of new anticancer strategies. Despite high oxygen tension, cancer cells characteristically have an increased glycolytic rate flow, which results in enhanced production of lactate [53]. This phenomenon of aerobic glycolysis is also referred to as the “Warburg effect”, as it was first described by Otto Warburg [54]. Hexokinase (HK), the rate-limiting enzyme of glycolysis that catalyzes the conversion of glucose to glucose 6-phosphate, is frequently overexpressed in human cancers and its two isoforms HK1 and HK2 are more tightly bound to VDAC at the outer mitochondrial membrane in cancer cells than in nonmalignant cells [52]. This couples residual ATP production from mitochondria to the rate-limiting step of glycolysis and further promotes the Warburg effect. HK has also been described to exert anti-apoptotic functions by blocking the opening of the permeability transition pore complex (PTPC) due to its ability to bind VDAC [55].

Methyl jasmonate is a plant hormone that has been reported to detach HK from mitochondria via direct interaction, thereby triggering mitochondrial apoptosis [56]. Since HK is expressed at high levels in many human malignancies, targeting HK by methyl jasmonate may provide a means to tackle abnormal metabolism in cancer cells.

### Conclusions

Natural products of various chemical classes can exert many beneficial effects on human health including the prevention of cancer as well as suppression of tumor growth. These chemopreventive and antitumor activities are mediated, at least to a large extent, via the modulation of cell death pathways including apoptosis in cancer cells. There are multiple intervention points within the apoptotic machinery that have been identified to mediate the antitumor effects of natural compounds, depending on the specific agents. Natural products often exert pleiotropic effects, a feature that may prove to be especially advantageous, as distinct mechanisms of cell death evasion can be simultaneously targeted in cancer cells. Further insights into the molecular mechanisms that mediate the antitumor activities of natural products are expected to promote their development as chemopreventive agents and cancer therapeutics in the ongoing battle against cancer.

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