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Chapter

Apoptotic Inhibitors as Therapeutic Targets for Cell Survival

El-Shimaa Mohamed Naguib Abdelhafez, Sara Mohamed Naguib Abdelhafez Ali, Mohamed Ramadan Eisa Hassan and Adel Mohammed Abdel-Hakem

Abstract

Apoptosis has revealed an essential function in the development or prevention of oncogenic transformation in the body; however, programmed cell death (PCD) must be tightly controlled since deregulated cell death is involved in the development of a large number of different pathologies. Apoptosis can be decreased in pathological states such as in cancer and autoimmunity or elevated such as in stroke, neurodegeneration, retinal cell death, myocardial and liver ischemia, inflammatory diseases such as sepsis, osteoarthritis (OA), rheumatoid arthritis (RA), and asthma. Different types of apoptotic inhibitors will be discussed in this chapter displaying their mechanism of action, which have been reported to be therapeutic targets for cell survival or at least limiting cell death. These inhibitors are classified according to their nature into natural antiapoptotic proteins that present mainly in the cell and synthetic small molecule inhibitors that are widely used to protect against overexpression of apoptosis mediators and, in turn, to prevent corresponding diseases.

Keywords: antiapoptosis, mechanism, apoptotic inhibitors, endogenous, synthetic, cell survival

1. Introduction

Apoptosis is a crucial normal biological process that occurs in the cell as a component of animal development, tissue hemostasis, and immune response. In pathological state, it can be abrogated as in cancer and autoimmune diseases, or over-expressed as in case of stroke, ischemia, psoriasis, and inflammatory diseases.

The apoptotic mechanism occurs through either extrinsic pathway or intrinsic pathway, which leads to cell death through different apoptotic cascades, according to the type of stimuli [1].

These cell survival strategies involve a myriad of coordinated and systematic physiological and genetic changes that serve to ward off death [2].

There are various inhibitors of these pathways, which have been reported to be helpful in inhibition of the cell death or limiting it. These inhibitors are classified

according to their nature into endogenous antiapoptotic proteins that present mainly in the cell to regulate the apoptosis process and synthetic inhibitors that are synthesized to be used in case of overexpression of apoptosis mediators as in some diseases.

1.1 Endogenous antiapoptotic inhibitors

1.1.1 Reduction in the number of apoptotic cells

It was reported that *Ginkgo biloba* extract (EGb 761) exhibited antiapoptotic effect on different cell types [3], and it particularly inhibits death in human lymphocytes when exposed to gossypol, a toxin that causes cell death via apoptosis. Similar results have been observed in thymus cells pretreated with EGb 761 and then exposed to ferrous sulfate in hydrogen peroxide (H_2O_2) [4]. Lymphocytes that are isolated from spleen of aged mice and treated with EGb 761 were less susceptible to reactive oxygen species (ROS)-induced apoptosis [5]. Scientists revealed that the posttreatment with EGb 761 in the peripheral nervous system decreased efficiently the number of apoptotic cells in injured rat spinal cord [6]. Moreover, it helps in treatment of the central nervous system reduced neuronal death in the *substantia nigra pars compacta* from an experimental model of Parkinson's disease [7].

1.1.2 Maintaining the mitochondrial integrity

Rhodiola crenulata extract (RCE) is an edible alcohol extract, conserving greatly the mitochondrial integrity and in turn prohibiting the release of cytochrome C, which leads to cell death. The effective concentration of the most important component, salidroside, was ~4% (w/w).

Other herbals mediate its antiapoptotic effect through the same mechanism as they possess a potent reactive oxygen species scavenging function; however, they restore the mitochondrial membrane potential [8, 9].

Some drugs were tested in sympathoadrenal cells that showed obviously another antiapoptotic pathway through inducing the antiapoptotic protein B-cell lymphoma 2 (Bcl-2) transcription rate and B-cell lymphoma-extra-large (Bcl-xL) proteins. The role of these proteins appears crucial, because inhibition of their production by antisense oligonucleotides (directed toward the translation initiation site of the Bcl-2 transcript) resulted in aboliting protective effect. The prosurvival pathway also included activation of the transcription nuclear factors NF-κB (a protein complex that controls transcription of DNA, cytokine production, and cell survival) and CREB (cellular transcription factor). It binds to certain DNA sequences and the antiapoptotic kinase PKCα/β such as dehydroepiandrosterone (DHEAS) and Allo [10].

1.1.3 Decrease in caspase transcription rate and DNA fragmentation

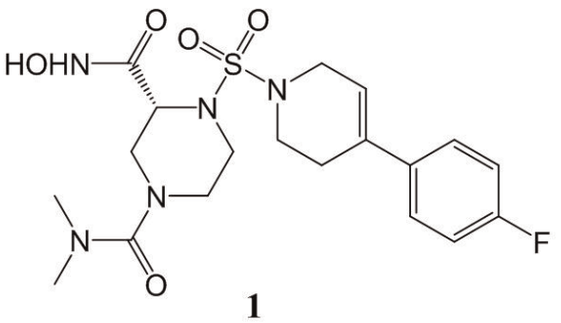
Some natural component reverse such as diosmin induces Bad and Bax, pro-apoptotic members of the Bcl-2 family, to react with the mitochondrial membrane and prevent the release of apoptotic-inducing factor (AIF) and cytochrome-C. Cytochrome-C in turn inhibits initiator caspase-9, which prevents sequential cascade of activation of caspase-3, and conserves DNA fragment along with no apoptotic cell death [11].

1.2 Synthetic apoptotic inhibitors

1.2.1 Tumor necrotic factor (TNF) inhibitors

Infliximab (IFX) [12], etanercept (ETN) [13], Adalimumab (ADA), golimumab (GOLI) [14], and certolizumab pegol (CZP) [15] are clinical biologic drugs that act as necrotic factor (TNF)-α inhibitors that were approved by the U.S. Food and Drug Administration (FDA). Other synthetic TNF inhibitors were designed such as:

Compound (1) inhibited the release of TNF in cells and in animals. It was active in a chronic rheumatoid arthritis model (MCIA) when administrated orally and it was advanced for further preclinical evaluation [16]. A novel thalidomide analog was synthesized and characterized for anti-TNF-α activity with up to a 38% inhibition for compound (2) with no obvious concentration dependence [17].



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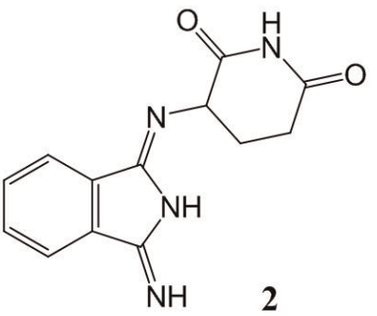
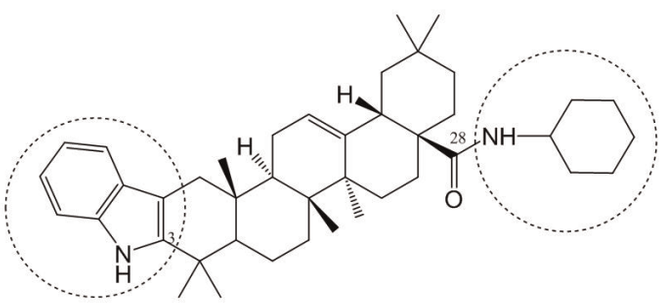


2

Compound (3) is an oleanolic acid analog, characterized by structural modifications at position C-3 and C-28 of oleanane skeleton and tested for anti-inflammatory potential, when C-3 became Indole, and C-28 = cyclohexamine, gave mild inhibition by 51.9% [18]. Compound (4) suppressed serum TNF-α levels by 2.45 ng/ml compared to the control group 5.61 ng/ml [19].



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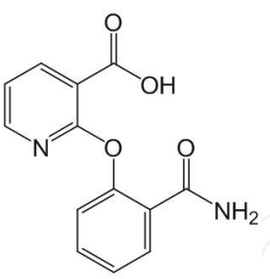

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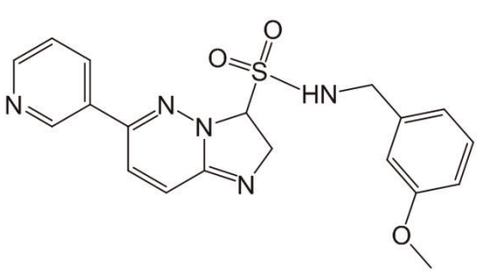
Compound (5) possessed TNF inhibition with half-maximal inhibitory concentration (IC50) = 0.5 μm [19]. Besides, Compound (6) decreased the level of the pro-inflammatory cytokine TNF-α by (39.19%) [20].



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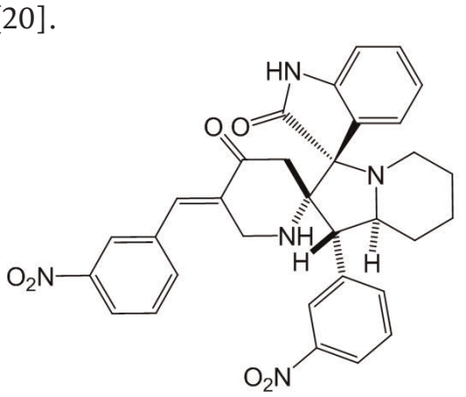

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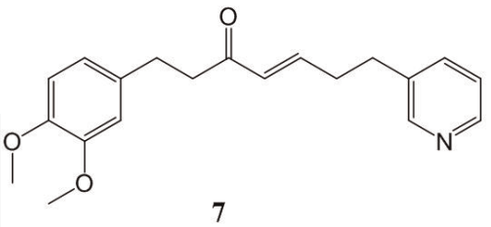
Compound (7) had 56% inhibition of TNF-α at 10 μm [21]. Betulinic acid (8) had a significant decrease in IL1β, IL6, and TNFα in the neuronal tissues [22].



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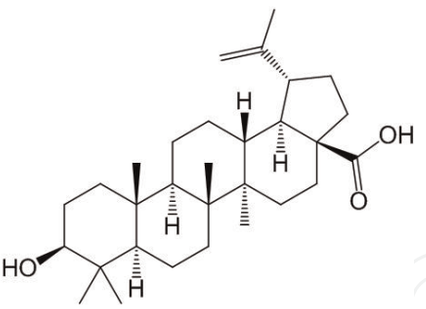

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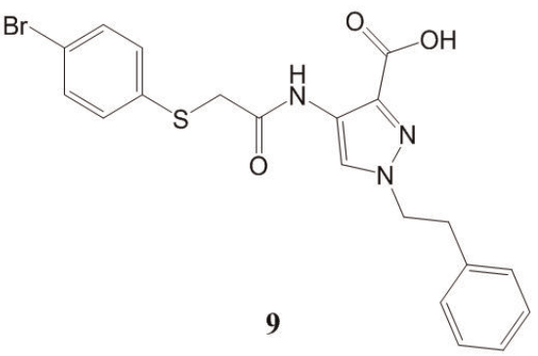
1.2.2 Fatty acid synthase (Fas) inhibitors

KR-33493 (9) was used as a potent inhibitor for ischemia Fas-mediated cell death 68 [23]. Compound (10a, b) RKTS-33,34 with 10 μm ED50 value (concentration causing 50% of maximum effect) selectively inhibited apoptosis induced by FasL as well as ECH (epoxycyclohexenone derivative) (11), which is produced by fungus [24].



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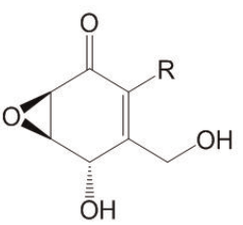
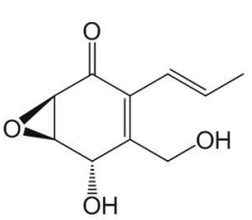


a= RKTS-33 R = H
b= RKTS-34 R = -C(CH3)=CH-CH3

10

Glycine (12) was tested as a cytoprotector against ischemic damage by downregulation of FasL/Fas and caspase3 and upregulation of Bcl2 and Bcl2-bax (apoptosis regulator BAX) [25]. Compound (13) was designed as a novel class of ischemic cell death inhibitors targeting Fas-mediated cell death pathway with EC50 = 0.557 μm (the concentration of a drug that gives half-maximal response), and cell survival = 92.98% at 10 μm [26]. It was found that (dichlorovinyl dimethyl phosphate) DDVP (14) significantly decreased the expression of Fas antigen on YAC-1S target cells and the expression of FasL (Fas ligand) on LAK cells (lymphokine-activated killer cell). These findings provided direct evidences that DDVP impaired the FasL/Fas pathway via downregulating the expression of both Fas and FasL [27]. Geldanamycin (15), which was originally discovered in Streptomyces hygroscopicus [28], inhibited Fas signaling pathway and protected neurons against ischemia [29].



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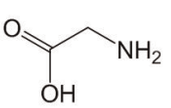

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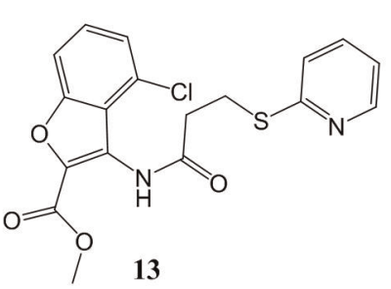

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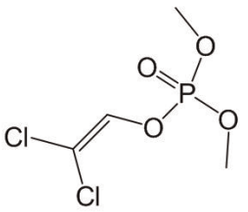
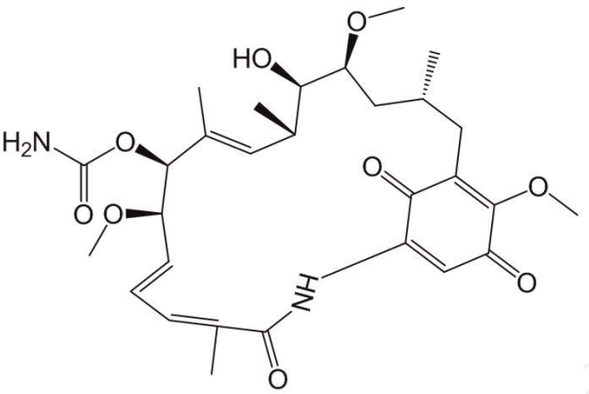


DDVP

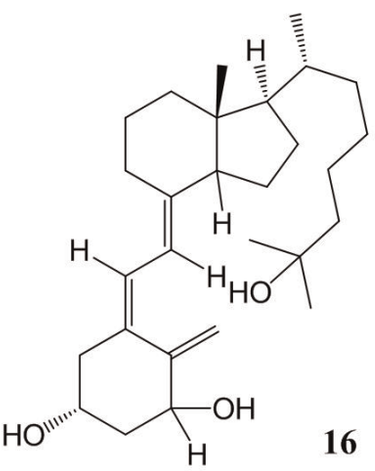
14



Geldanamycin

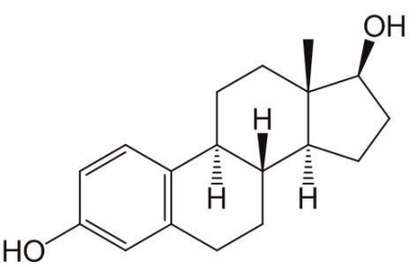
15

Compound (16) is the active form of vitamin D that inhibited Fas ligand-induced apoptosis in human osteoblasts by regulating components of both the mitochondrial and Fas-related pathways [30]. Estrogen (17) also inhibited Fas-mediated apoptosis in experimental stroke [31].



VIt. D3 (active form)

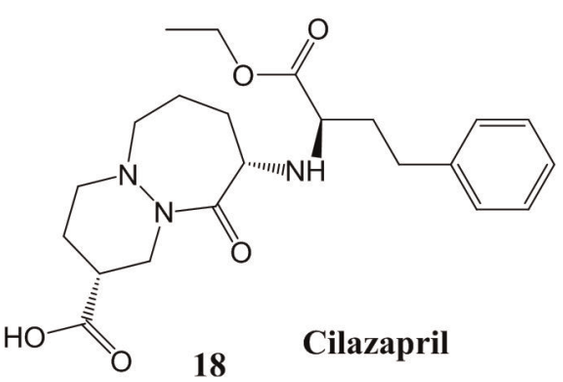
16



Estrogen

17

Cilazapril (18) acts as an angiotensin-converting enzyme inhibitor along with protection against apoptosis through downregulating Fas protein during the induction of apoptosis in cardiomyocytes in rat hearts when subjected to reperfusion after ischemia [32]. M50054 (19) (cell-permeable inhibitor of the activation of caspase-3) inhibited apoptosis induced by a variety of apoptotic stimuli such as the Fas/Fas ligand system and etoposide. Thus, it might be effective for hepatitis when administered orally and chemotherapy-induced alopecia when administered topically [33].



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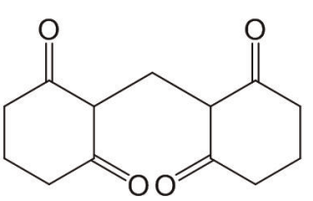
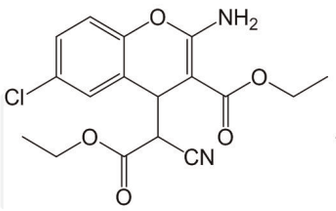
Cilazapril



M50054

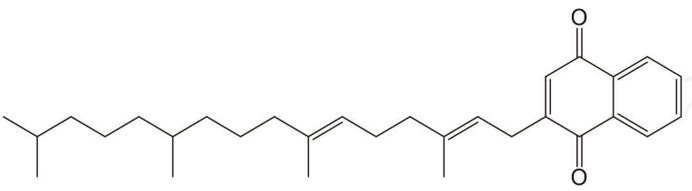
19

SC79 (20) (AKT activator) prevented acute hepatic failure induced by Fas-mediated apoptosis of hepatocytes [34]. Vit K2 (21) significantly suppressed both Fas expression and Fas-mediated apoptosis of the cells in a dose-dependent fashion. The maximum effect was observed when 6–10 mol/L of vitamin K2 was added to the culture, a concentration comparable to that attained during therapy with vitamin K2 [35].



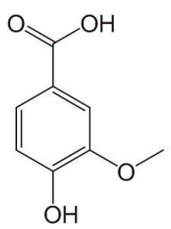
SC79

20



Vit.K2 21

Vanillic acid (22) inhibited Fas-receptor and caspase-mediated apoptosis signaling pathway and so acted as cardioprotective [36]. NCX-1000 (NO-releasing derivative of ursodeoxycholic acid) (23) is a nitric oxide (NO) derivative of ursodeoxycholic acid (UDCA). When an NO-releasing moiety is added to UDCA, the effectiveness in preventing Fas-mediated liver injury increased [37].



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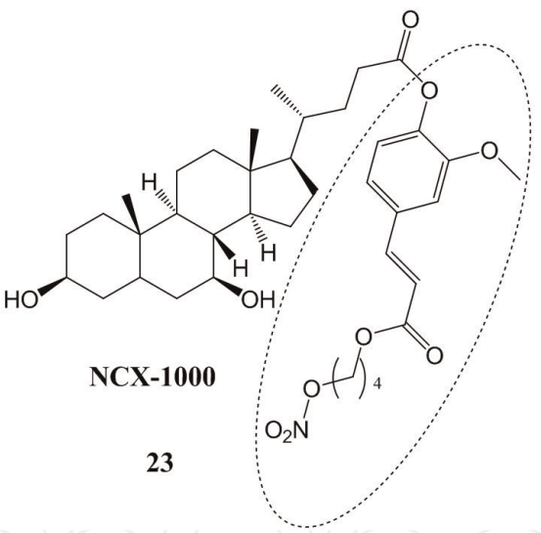


NCX-1000

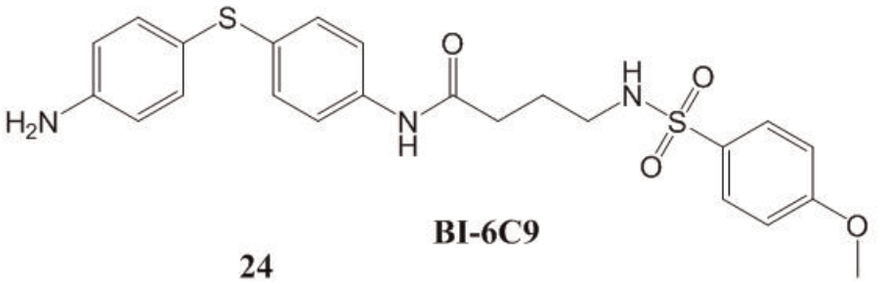
23

1.2.3 BH3 interacting-domain death agonist (BID) inhibitors

BID plays a central role in the apoptotic machinery mediating cytochrome C and SMAC/DIABLO (mitochondrial protein that potentiates some forms of apoptosis) released from mitochondria, a crucial event for caspase activation and cell death [38]. Pharmacological inhibition of BID could therefore provide a protective benefit against pathological cell death, occurring in cerebral ischemia [39], neurodegenerative diseases [40, 41], liver inflammation [42], or other illnesses where BID has been implicated [43].

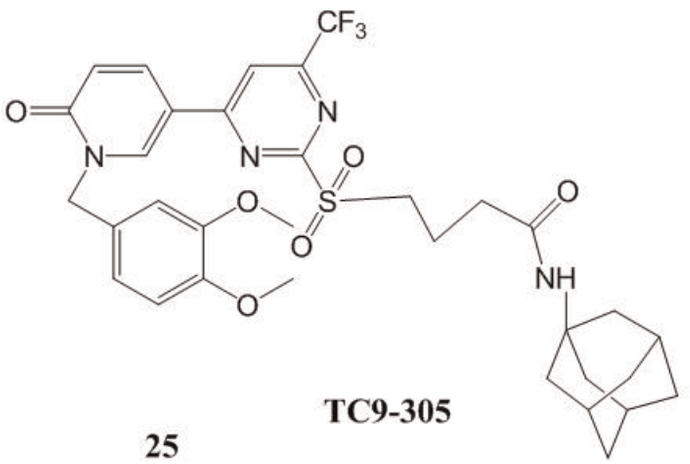
BI-6C9 (24) was effective in inhibiting the carboxyl-terminal fragment (tBid) (truncated protein) association with isolated mitochondria at 20 μm [39]. TC9-305 (2-sulfonyl-pyrimidinyl derivatives) (25) had an EC50 = 0.23 nm [44]. BI-11A7 (26) was much more effective in this assay when compared with BI-6C9 (24) but showed some toxicity at higher concentrations (20 μm) [45]. 3-o-tolylthiazolidine-

2,4-dione (27) protected neural cells against glutamate- and tBid-induced toxicity with an EC50 = 6.78 μm [46].



BI-6C9

24



TC9-305

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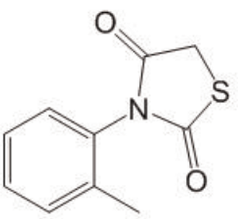

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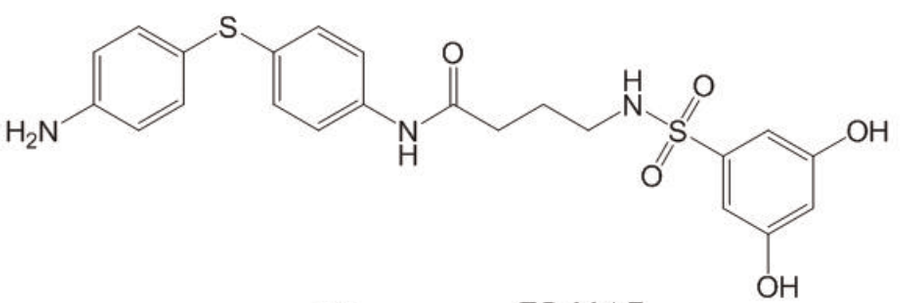
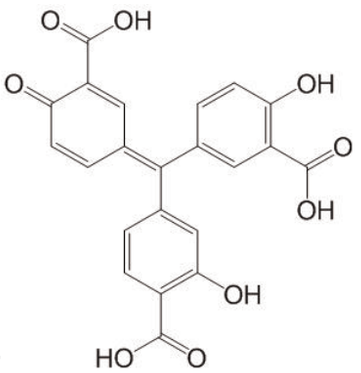


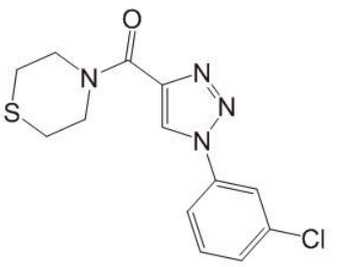
26 **BI-11A7**

1.2.4 Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) inhibitors

TWEAK also known as (Apo3L or TNFSF12) was first described as an inducer of apoptosis in transformed cell lines [47]. It is a member of the tumor necrosis factor (TNF) receptor family that is induced in a variety of cell types in situations of tissue injury. It is a crucial player in muscle atrophy, cerebral ischemia, kidney injury, atherosclerosis, and infarction, as well as in various autoimmune scenarios including experimental autoimmune encephalitis, rheumatoid arthritis, and inflammatory bowel disease [48]. Aurintricarboxylic acid (ATA) (28) was a potent inhibitor of the TWEAK-Fn14 signaling axis and could potentially be utilized to enhance the therapeutic response in glioblastoma (GBM) [49]. L524-0366 (29) was a specific dose-dependent inhibitor of TWEAK-Fn14 interaction [50] and it was found to be a complete suppressor for TWEAK-induced T98G cell migration at dose equal to 10 μm [51].



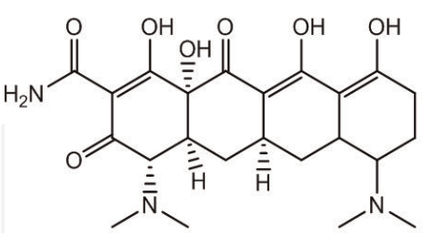
ATA 28



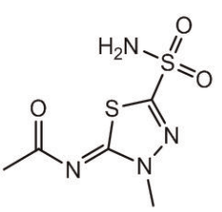
L524-0366 29

1.2.5 Cytochrome C inhibitors

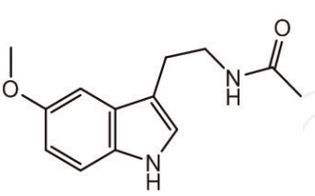
Cytochrome C is the specific and efficient electron transfer mediator between the two last redox complexes of the mitochondrial respiratory chain [52]. The release of cytochrome C from the mitochondria into the cytoplasm results in caspase-9 activation leading to cell death [43]. Minocycline (30) directly inhibited the release of cytochrome C from mitochondria. Therefore, it was beneficial in experimental models of stroke, traumatic brain and spinal cord injury, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Parkinson's disease, and multiple sclerosis [53, 54]. Methazolamide (31) was FDA approved for the treatment of glaucoma, while melatonin (32) inhibited oxygen/glucose deprivation—induced cell death, loss of mitochondrial membrane potential, release of mitochondrial factors, pro-IL-1β processing, and activation of caspase-1 and -3 in primary cerebrocortical neurons. Furthermore, compounds (32, 33) decreased infarct size and improved neurological scores after middle cerebral artery occlusion in mice [54–56]. Gamma-tocotrienol (GTT) (33) had the antiapoptotic effects by preventing the activation of caspase-3 and caspase-9, reducing the release of cytochrome C from the mitochondria and preventing H_2O_2-induced apoptosis in human diploid fibroblasts (HDFs), and delayed cellular aging [57].



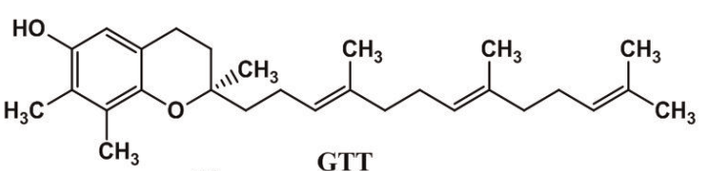
Minocycline 30



Methazolamide 31



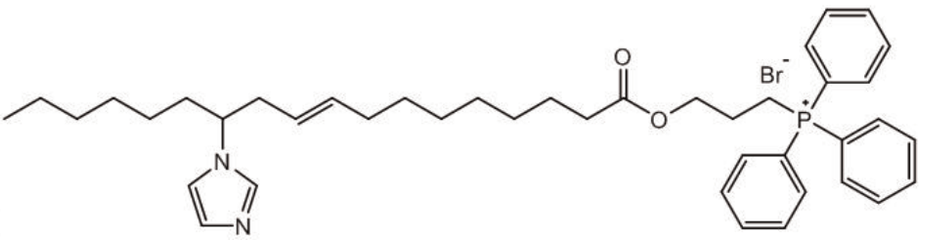
melatonin 32



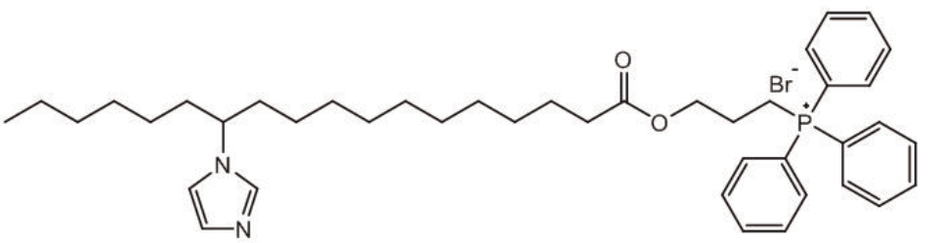
GTT 33

3-hydroxypropyl-triphenylphosphonium (TPP)-conjugated imidazole-substituted oleic acid (TPP-IOA(34a)) and stearic acid (TPP-ISA(34b)) exerted strong specific liganding of heme-iron in cytochrome C/cardiolipin (CL) complex and effectively suppressed its peroxidase activity and CL peroxidation, thus preventing cytochrome C release and cell death, and protecting mice against lethal

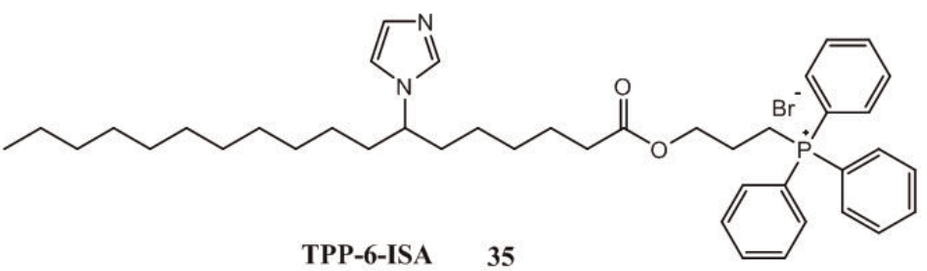
doses of irradiation [58, 59]. TPP-6-ISA (35) was an effective inhibitor of the peroxidase function of cyt c/CL complexes with a significant antiapoptotic activity that realized in mouse embryonic cells exposed to ionizing irradiation [60, 61].



Tpp-IOA 34a



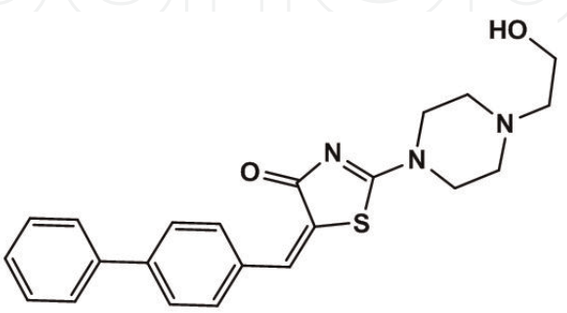
TPP-ISA 34b



TPP-6-ISA 35

1.2.6 P53 upregulated modulator of apoptosis (PUMA) inhibitors

It is a Bcl-2 homology 3 (BH3)-only Bcl-2 family member and a key mediator of apoptosis induced by a wide variety of stimuli 106. PUMA inhibitors may provide radiation protection and mitigation, there were three compounds that had a strong PUMA inhibition and that were designed by Gabriela Mustata et al., and data were not published due to intellectual property protection [62].

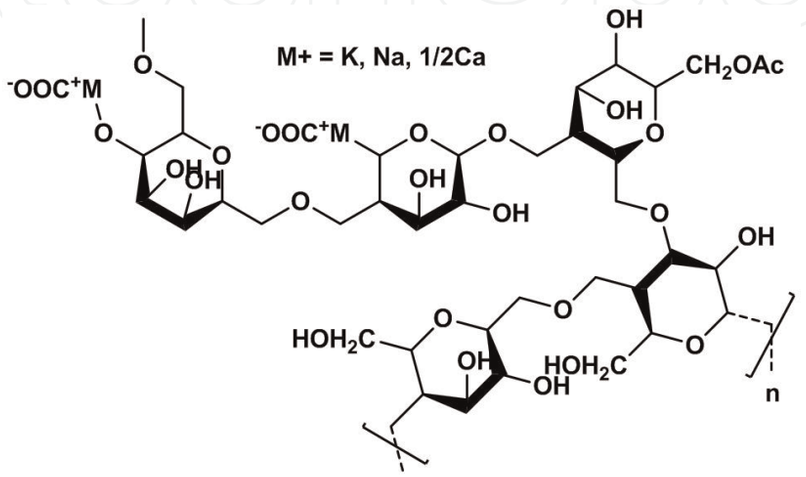


CLZ-8 36

CLZ-8 (36) was capable of targeting a PUMA protein and has very good physicochemical properties, very good apoptosis resistance, and radiation protection effects. It was found to protect cells from DNA damage under the concentration of 1 μm [63].

1.2.7 Bax inhibitors

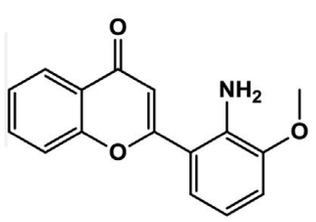
Xanthan gum (XG) (37) is an extracellular polysaccharide secreted by microorganisms and was first discovered during fermentation process using Xanthomonas campestris. It could protect subchondral trabecular in bone subchondral, decrease the apoptosis of chondrocytes, downregulate the expressions of active caspase-9, active caspase-3 and bax, and upregulate the expression of bcl-2. Lower range of molecular weight of xanthan gum (LRWXG) could upregulate the expression of cytochrome C in mitochondria while downregulating the expression of cytochrome C in cytoplasm. These findings showed that LRWXG could inhibit cartilage degradation via an intrinsic bax-mitochondria cytochrome C-caspase pathway [64].



LRWXG **37**

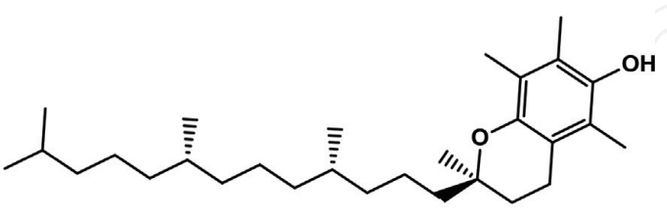
PD98059 (38) showed inhibition of staurosporine-, UV-, anticancer drug-induced apoptosis in vitro and protected brain against cell death through inhibition of BAX and other factors [65, 66]. Vitamin E (39) significantly reduced the effects of gentamicin on BAX and BCL-2 expression levels [67].

Tanshinone (40) could inhibit the expression of Bax and stimulated the expression of Bcl-2 in cardiomyocytes in the ischemia-reperfusion rat model [68].

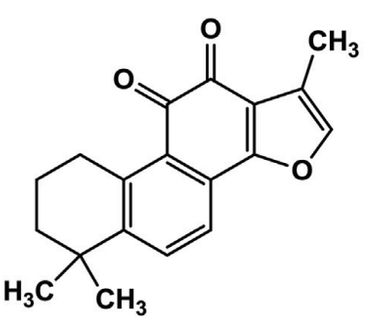


PD98059

38



Vit.E **39**



Tanshinone **40**

2. Conclusion

Apoptotic inhibitors regulate cell proliferation by promoting cell survival. One promising area of research that has been covered extensively in this review is displaying the recent developed apoptotic inhibitors and their significance to functional therapies for a number of diseases and pathophysiologies. These inhibitors are working through numerous built-in avenues' mechanisms, including inhibition of pro-apoptotic and apoptotic factors. Our perspectives are to develop new therapeutic strategies aiming to participate in treatment of serious diseases such as stroke, neurodegeneration, retinal cell death, myocardial and liver ischemia, sepsis, osteoarthritis (OA), rheumatoid arthritis (RA), and asthma or to reduce the adverse effects accompanied with long-term therapy of cancer and autoimmunity. Hopefully, scientists will soon be able to provide every patient suffering from imbalanced apoptotic disease with a more specified and suitable therapy.

Conflict of interest

No financial or commercial conflicts of interest were declared by all authors.

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