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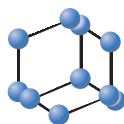
Restoring TRAIL Induced Apoptosis Using Naturopathy. Hercules Joins Hand with Nature to Triumph Over Lernaean Hydra

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Abstract: Cancer is a multifaceted disease. Our deepened knowledge about genetic and biological mechanisms of cancer cells presents an opportunity to explore the inter-individual differences in the body's ability to metabolize and respond to different nutrients. It is becoming progressively more understandable that the deregulation of several signaling pathways and the alterations in apoptotic response are some of the major determinants that underpin carcinogenesis. Tumor necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL)-mediated signaling has gained a remarkable appreciation because of its ability to selectively induce apoptosis in cancer cells leaving normal cells intact. However, technological advances have started to shed light on underlying mechanisms of resistance against TRAIL-induced apoptosis in cancer cells. The impairment of TRAIL-mediated apoptosis includes various factors ranging from the loss or down regulation of TRAIL receptors or pro-apoptotic proteins to the up regulation of anti-apoptotic proteins. Intriguingly to mention that there is an ever-increasing number of natural herbal extracts (phytometabolites), which have been explored to date for their potential action in restoring apoptosis TRAIL-mediated in cancer cells. In this review, we will highlight the progress in understanding the mechanisms opted by phenolic compounds in overcoming TRAIL resistance.

PRESENT OBSERVATIONS:

➢ Tumor necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL)-mediated signaling induces apoptosis selectively in cancer cells leaving normal cells intact.

➢ Several herbal extracts have a potential ability in restoring TRAIL-mediated apoptosis in cancer cells by re-balancing pro-apoptotic proteins, functionalizing intrinsic and/or extrinsic pathways.

➢ Accumulating evidence emphasizes mechanistic insights and novel approaches to overcome a resistance of cancer cells to TRAIL-mediated apoptosis. A number of phytometabolites have shown promising results in enhancing TRAIL-induced apoptosis.

➢ Curcumin has been shown to effectively inhibit cancer progression in TRAIL-resistant LNCaP prostate cancer xenografts *in vivo*.

OPEN QUESTIONS AND FUTURE STUDIES:

➢ Are the mechanisms of intrinsic or acquired resistance against TRAIL-mediated apoptosis different depending on the type of cancer?

➢ Therefore, further pre-clinical studies are necessary to clarify intrinsic or acquired resistance mechanisms against TRAIL and the regulatory functions of different proteins so that phytochemicals mediated targeting of different proteins can be improved and TRAIL-mediated apoptosis can be restored in resistant cancer cells.

➢ Pro-survival signaling in TRAIL-treated cells has added another layer of intricacy to puzzle of effective therapeutic approaches. Recently emerging clues of microRNA regulation by NF-κB in TRAIL treated cells and death receptor-mediated modulation of microRNA biogenesis has started to scratch the surface of new paradigms in TRAIL-induced signaling.

➢ Combinatorial approach largely depends on the cancer type, and on the signaling pathways engaged in modulation of cell resistance to apoptosis. Therefore, combinatorial treatments with effective synergy and minimal off target effects in pre-clinical settings need to be identified.

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➢ It needs to be determined which strategy will be used (intravenous administration or oral intake) for evaluation of efficacy of phenols in cancer models.

➢ Low bioavailability of phenols is another stumbling block that requires detailed research.

INTRODUCTION

Tumor necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL) is a type II membrane protein belonged to Tumor Necrosis Factor (TNF) family acting as mediator of the immune system and the inflammatory response, and inducing apoptosis in some cell types [1]. There is a progressive expansion in the proteome involved in TRAIL-mediated apoptosis due to its death induction selectively in cancer cells [2-6]. Potential of TRAIL in inducing apoptosis in cancer cells was a major breakthrough in molecular oncology [2-4]. It is noted that the death receptors, which are members of the TNF receptor superfamily, trigger apoptotic signaling via TRAIL to induce apoptotic death in cancer cells [5, 7, 8]. Upon apoptosis stimuli, the death-inducing signaling complex (DISC) is formed [5, 8]. DISC is composed of the various death receptors, an adaptor protein that bridges members of the TNF receptor superfamily (TNFRSF), Fas-associated protein with death domain (FADD), and caspase-8, as reviewed in [5, 8]. DISC acts as protein assembly platform for recruitment of caspase-8 while transducing a downstream signal cascade resulting in apoptosis [5, 8]. Rapidly accumulating data suggests that TRAIL-mediated signals can be transduced within a cell through two distinct molecular signaling pathways, such as extrinsic (receptor-mediated) and intrinsic (mitochondrial) pathways [5]. Both pathways are essentially leading to activation of caspase cascade pathway [5, 7, 8]. Biologically, caspases are categorized into two initiator caspases and executioner caspases [5].

In the upcoming sections, we will give an overview of how TRAIL-induced signals intracellularly trigger apoptosis starting from an exploration of TRAIL-mediated signaling pathway and its regulation. We will further discuss the bioactive ingredients, which have shown a potential treatment use in targeting protein network to restore TRAIL-mediated apoptosis in resistant cancer cells. We finally discuss potential effects of natural phytometabolites on the cancer cell survival and the TRAIL-mediated pathway as a potential anticancer therapeutic approach.

TRAIL-MEDIATED SIGNALING NETWORK

Human *TRAIL* gene (3q26) encodes a 32.5 kDa protein consisting of 281 amino acid residues, which is composed of the N-terminal cytoplasmic, transmembrane and C-terminal extracellular, domains [1, 9]. TRAIL is a cytokine produced and secreted by most normal tissue cells functioning as a ligand that induces the apoptotic cell death pathway by binding to specific members of the TNF receptor superfamily that contain a death domain motif (death receptors)[1-3]. Four distinct high-affinity membrane death receptors were designated, as TRAILR1 (death receptor 4, TNFRSF10A), TRAILR2 (death receptor 5, TNFRSF10B), TRAILR3 (decoy receptor 1, TNFRSF10C), TRAILR4 (decoy receptor 2, TNFRSF10D) [5, 7, 8]. Death receptors 4 and 5 transduce an apoptotic signal upon TRAIL binding. However, decoy receptor 1 and 2 have a regulatory function modulating the TRAIL binding to death receptors in response to a tumor protein p53 accumulation, thus interfering with the TRAIL binding to death receptors 4 and 5 [5, 7, 8].

TRAIL induces apoptosis through interacting with its receptors [5, 7, 8]. TRAIL protein induces apoptosis in several tumor cell lines *in vitro* and *in vivo*, while exhibiting a minimal toxicity to normal cells [2-6]. This is because death receptors, TRAILR1 and TRAILR2, are mainly expressed in transformed cells, and its decoy receptors are expressed in normal cells, as reviewed elsewhere [5, 8]. Binding of TRAIL to death receptor (4 and 5) results in the Death Inducing Signaling Complex (DISC) formation [5, 7, 8]. The death receptors recruit the adapter molecule Fas-Associated Death Domain (FADD, also known as MORT1), whose absence triggers a resistance to the TRAIL-induced apoptosis in tumor cells [5, 7, 8]. Upon stimulation by the FAS ligand (FASL or CD95L), the FAS receptor (also known as apoptosis antigen 1 [APO-1], cluster of differentiation 95 [CD95], or TNFRSF6) forms homotrimeric complex [7, 8]. Similarly, when FADD binds to the death domains of other death receptors, they trimerize, too [7, 8]. This molecular event leads to an unmasking of the FADD's death-effector domain and subsequent recruitment of initiator caspases 8, 9 and 10 leading to formation of DISC [7, 8]. The initiator caspases activated by autoproteolysis can then cleave and activate executioner caspases 3, 6, and 7, thereby initiating the caspase cascade [7, 8]. Binding of TRAIL to death receptors 4 and 5 can lead to apoptosis by the same mechanism [7, 8]. Cellular FLICE-like inhibitory protein (cFLIP) negatively regulates TRAIL induced signaling by interfering with the activation of caspase-8. Caspase-8 activates its downstream effector caspase-3 thus functionalizing extrinsic pathway. Intrinsic pathway is activated via Caspase-8 mediated processing of BH3 Interacting Death Domain (BID) into truncated BID. Truncated BID moves into mitochondria to promote release of cytochrome C, SMAC/DIABLO, serine protease Omi/Htra. Cytochrome C co-operates with Apoptotic Protease Activating Factor 1(APAF1) to form apoptosome resultimng in activation of caspase-9 [5, 7-9].

TRAIL protein has a strong ability to induce apoptosis [2-4] in several tumor cell lines both *in vivo* and *in vitro* while it exhibits minimal toxicity to normal tissues [2-6]. In fact, not only recombinant human TRAIL (dulanermin), but also agonistic antibodies for TRAIL receptors have been developed as anti-cancer agents including TRAIL-R1 (mapatumumab) or TRAIL-R2 (conatumumab ,drozitumab , lexatumumab, LBY135 and tigatuzumab [10-15]. Currently, phase I/II clinical trials are assessing TRAIL or agonistic TRAIL-receptor antibodies therapy in non-Hodgkin lymphomas and non-small cell lung cancer patients (Cinical-Trials.gov. NCT00094848; NCT00508625).

TRAIL SIGNALING AND MECHANISMS OF TUMOR RESISTANCE TO TRAIL

Experimental data is rapidly improving existing concept regarding negative regulators of TRAIL-mediated signaling. Among negative regulators of TRAIL-mediated signaling, c-FLIP, is the most extensively studied protein existing as a catalytically inactive paralogue of caspase-8 lacking intrinsic

caspase activity because it differs in the C-terminal enzymatic region of caspase-8 [16]. In fact, c-FLIP is involved in caspase-8 inhibition by interfering with binding sites on the DISC (Fig. **1**) [16]. Its controversial role in apoptosis reported as an inhibitor of caspase-8 activation by death receptor (*e.g.* Fas, CD95), and cell death process, as well as an enhancer of caspase activity and cell death [16]. In any case, structural studies show that c-FLIP could form heterodimer with caspase-8 [16]. The structural findings revealed that c-FLIP contains in its C-terminus a loop that actually activates the enzymatic pocket of caspase-8 and stabilizes its activity in a full-length form [17]. Hence, in addition to its function as an inhibitor of caspase-8 activation by competitive binding to FADD, c-FLIP has now emerged as an activator of caspase-8 [16-18].

Heat shock protein (HSP)-27 is another negative regulator of TRAIL-mediated signaling and is overexpressed in TRAIL-resistant human lung adenocarcinoma cell line A549 [18]. SiRNA-mediated silencing of HSP27 considerably improved TRAIL-mediated apoptosis in resistant cancer cells [19]. NF-κB is also activated in TRAIL-treated cancer cells, while Inhibitors of Kappa B Kinases (IKK) are activated with the phosphorylated Inhibitor of Kappa B (IκB), thereby sequestering NF-κB away [19, 20]. IKK interacts with various kinases including Aurora kinase to activate NF-κB [18]. Furthermore, the pre-treatment of melanoma cells with pan-Aurora kinase inhibitors notably inhibited NF-κB activation in TRAIL-treated cancer cells [20].

Numerous signaling cascades can influence TRAIL signaling via modulation of pro- and anti-apoptotic genes expression. TRAIL is an endogenous key mediator that has central role in killing neoplastic cells. However, TRAIL undergoes a down regulation in prostate cancer cells [21]. Silencing of the E3 ubiquitin-protein ligases, NEDD4 and SMURF2, in LNCaP prostate cancer cells co-treated with transforming growth factor-β results in a remarkable up regulation of TRAIL expression, which subsequently leads to an apoptosis [21]. Wingless (WNT) and Sonic Hedgehog (SHH) signaling cascades were shown to participate in cross talk with TRAIL pathway in prostate cancer cells [22]. Ataxia Telangiectasia Mutated protein kinase (ATM), a member of phosphatidyl-inositol 3-kinase-related kinase family, known to trigger cell death response to DNA damage, has been shown to regulate TRAIL-mediated signaling [23]. The ATM/p53 signaling axis controls the transcriptional regulation of death receptors [23].

However, in addition to ability of TRAIL to induce apoptosis, there are some protein networks that trigger pro-survival anti-apoptotic signals upon TRAIL exposure [24]. For example, Receptor-Interacting Kinase (RIPK) was shown to stimulate apoptosis through activation of Stress-Activated Protein Kinase (SAPK)/JNK pathway, and NF-κB *in vitro*. However, *Rip* null mice were displaying extensive apoptosis in both the lymphoid and adipose tissue and were highly sensitive to TNF-α induced cell death. Sensitivity to TNF-α mediated cell death in *Rip*-/- cells is accompanied by a failure to activate the transcription factor NF-κB. These observations suggest that RIP kinase is able to act as an inhibitor of apoptosis *in vivo* [25]. In this regard, anti-apoptotic signals are generated because of TRAIL induces the assembly of TRADD, regulation of RIPK1 and 3 and TRAF2 essentially leading to alternative mechanism of cell death, necroptosis [26].
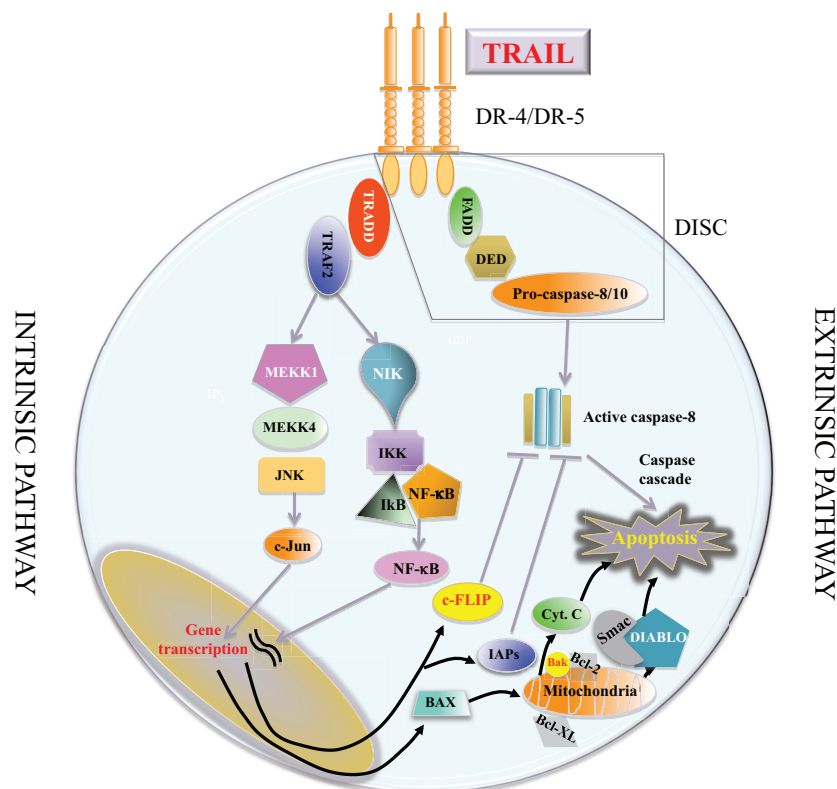

Fig. (1). TRAIL-mediated signaling network and its crucial role in apoptosis regulation.

TRADD activation in cancer cells results in TRADD inhibition, which leads to a phenotype reversal, TRAIL-resistant cancer cells are becoming TRAIL-sensitive ones [19, 27]. TRAIL failed to induce NF-κB activation in TRADD$^{-/-}$ Mouse Embryonic Fibroblasts (MEFs), however, functionally active NF-κB was noted in wild type MEFs [27]. Similarly, impaired TRAIL induced apoptotic cell death was observed in cells ectopically expressing either p65 or IKKβ [28]. MEFs reconstructed with TRADD developed resistance against TRAIL induced apoptosis [28]. Moreover, in-vitro assays revealed that TRADD competed with RIP1 and/or FADD for positioning at DISC, therefore depletion of TRADD promoted additional FADD recruitment in TRADD$^{-/-}$ MEFs was contributory in enhancing sensitivity to TRAIL induced apoptosis [28].

SH3 domains of SH3 domain-containing kinase-binding protein 1 (SH3KBP1 or CIN85) were shown to interact with 3 PxxxPR motifs in the mitogen-activated protein kinase/extracellular signal-related kinase kinase 4 (MEKK4) [19]. MEKK4 directly phosphorylates p38 MAPK as evidenced by notably enhanced levels of phosphorylated p38 MAPK in the wild type MEKK4 expressing cells and non-detectable phosphorylated p38 levels in the MEKK4 kinase mutant (K1361R) expressing cells [19]. MEKK4 also interacts with CIN85 and TRAIL was shown to enhance these protein-protein interactions [19]. In turn CIN85/MEKK4 protein complex promotes the MEKK4/MEK/p38/HSP27 cascade protecting cells from apoptotic stress [19]. However, the CIN85 down regulation was observed to promote p38 MAPK phosphorylation in TRAIL-treated cells [19].

Casitas B-lineage Lymphoma (CBL, E3 ubiquitin-protein ligase) protein, a CIN85-binding protein also stabilizes a protein-protein association between of MEKK4 with CIN85 in TRAIL-treated cells [19]. SRC protein kinase is also activated in cancer cells upon TRAIL exposure [29]. Activation of SRC then resulted in the phosphorylation of CBL protein and p85 subunit of PhosphatidylInositol-4, 5-bisphosphate 3-Kinase (PI3K) [19]. CBL acts as a connecting protein between SRC and PI3K, while CBL silencing using siRNA leads to inhibition of SRC/PI3K protein-protein interaction [19, 30]. SRC inhibition completely blocked phosphorylation of AKT and CBL and increased p38/HSP27 phosphorylation to effectively transduce TRAIL induced signals [19, 30].

There is a direct evidence suggesting that TRAIL is unable to induce apoptosis by promoting DISC formation in lipid rafts in CBL-β competent gastric cancer cells. Silencing of CBL-β failed to alter formation of DISC, however EGFR was shown to move into lipid rafts and EGFR-mediated intracellular signaling was noted in TRAIL-treated cancer cells [19, 31, 32]. Additionally, siRNA-mediated silencing of MEKK4 leads to abrogation of phosphorylation of p38 MAPK11 and 14, as well as c-Jun N-terminal kinases (JNK) in cancer cells treated with TRAIL [19, 33, 34].

Targeting the RING-finger containing E3 ligase, Seven In Absentia Homolog (SIAH)-2, as well as the signaling platform molecule POSH (SH3RF1) confers robust caspase-8 activation in response to TRAIL stimulus [35]. Silencing SIAH2 or POSH in prostate cancer cells leads to increased caspase activity and apoptosis in response to both TRAIL and Fas ligand [35]. The E3 activity of SIAH2 was responsi-

ble for mediating apoptosis resistance; while POSH protein levels were critical for maintaining cell viability [35]. The observed apoptosis resistance provides one biological explanation for the induction of SIAH2 and POSH reported in lung and prostate cancer, respectively [35]. Therefore, both POSH and SIAH2 can play a role of important mediators of death receptor-mediated apoptosis suggesting that targeting the interaction of these two E3 ligases is a promising cancer therapeutic strategy [35].

Internalization of death receptors 4 and 5 is compromised in galectin-3 overexpressing cancer cells [36]. Since death receptors 4 and 5 contain several O-linked oligosaccharides in their ectodomains, galectin-3 forms clusters with these receptors, thus abrogating their internalization upon TRAIL treatment [36]. However, galectin-3 silenced cancer cells had a higher rate of endocytosis of death receptor 4 and 5 [36]. TRAIL resistant cancer cells have activated MADD that interacts with death receptor 4 thus interfering with the recruitment of FADD to form DISC [29]. In TRAIL-resistant cancer cells AKT was reported to phosphorylate MADD [29].

HOW TO RESTORE THE TRAIL-MEDIATED APOPTOSIS IN RESISTANT CANCER CELLS?

In this section of review we will discuss restoration of TRAIL-mediated apoptosis by phenolic compounds in resistant cancer cells. (Table **1** and Table **2**) summarize phytochemicals that affect the expression of pro-apoptotic and anti-apoptotic markers in TRAIL-resistant cancer cells, displayed as up regulated and down regulated, respectively.

Table 1.   **Shows the list of phytochemicals that regulate expression of death receptors.**

Phytochemicals	DR4	DR5
Parviflorene		↑
Dihydroartemisinin		↑
Resveratrol	↑	↑
Gomisin N	↑	↑
Plumbagin	↑	↑
Methyanthraquinone	↑	

SESQUITERPENES

Sesquiterpenes belong to the class of terpenes consisting of three isoprene units. These phytometabolites, including eupatolide, zerumbone, artemisinin and parviflorene, have emerged as potential agents reported to overcome TRAIL resistance. Eupatolide is sesquiterpene lactone isolated from the medicinal plant *Inula Britannica* has been shown to be effective in inducing apoptosis in breast cancer cells [37]. Breast cancer cells treated with eupatolide displayed a considerable decrease in phosphorylated AKT levels and a down-regulation of its target gene c-FLIP (Fig. **2**). Forced expression of c-FLIP in silenced breast cancer cells abrogated eupatolide mediated apoptosis in breast cancer cells

Table 2.   **Shows the list of phytochemicals that regulate protein network of TRAIL resistant cancer cells.**

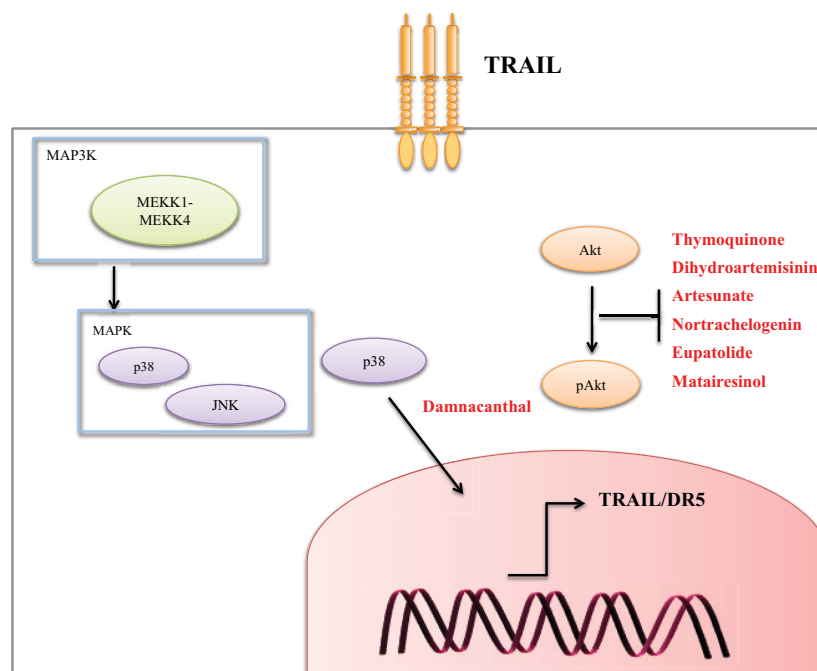| Phytochemicals	Caspase-8	Caspase-3	Caspase-9	Cytochrome-c	Bax/Bak	SMAC/DIABLO
Sesquiterpene isointermedeol			↑	↑		
Parviflorene	↑	↑	↑			
Resveratrol				↑	↑	↑
Gomisin N	↑	↑				
Plumbagin		↑				
Methyanthraquinone	↑					

Fig. (2). MAPKs including p38 and JNK are activated in TRAIL treated cancer cells. It is also surprising to note that Damnacanthal mediated upregulation of TRAIL and DR5 is triggered *via* p38 MAPK. Akt is also activated in TRAIL treated cancer cells. *In vitro* studies have shown targeted inhibition of Akt through different herbal extracts. TRAIL, Tumor necrosis factor-Related Apoptosis-Inducing Ligand; DR5, Death Receptor 5; MEKK1/4, Mitogen-activated protein Kinase 1/4; JNK, c-Jun N-terminal kinase; MAPK, Mitogen Activated Kinase-like Protein; MAP3K, Mitogen Activated 3 Kinase-like Protein; Akt, serine/threonine protein kinase Akt; p-Akt, phosphorylated serine/threonine protein kinase Akt.

[37]. Zerumbone is a sesquiterpene from tropical ginger *Zingiber zerumbet (L) Smith* and it is effective in inducing apoptosis in colon cancer cells [38]. Detailed mechanistic insights suggest that cancer cells treated with zerumbone displayed a decrease in c-FLIP expression and a marked increase in kinase activity of ERK1/2 and p38 MAPK [38]. Moreover, there was an increase in expression of death receptors 4 and 5 [39]. Sesquiterpene isointermedeol is an important constituent of *Cymbopogon flexuosus* has been shown to activate caspase 9 by promoting release of cytochrome c from mitochondria [39].

Artemisinin is a sesquiterpene lactone isolated from *Artemisia annua* and dihydroartemisinin is a derivative of artemisinin (Fig. **2**). Interestingly, prostate cancer and pancreatic cancer cells treated with dihydroartemisinin show an increase in the expression of death receptor 5 [40]. Moreover, there was a suppression of cell survival pathways including PI3K/AKT and ERK pathways [41]. Cervical cancer cells treated with artesunate displayed a decrease in the expression of anti-apoptotic proteins including survivin, XIAP and BCL-xL (Fig. **2**). Artesunate interfered with negative regulators of TRAIL-mediated signaling through inactivation NF-κB and AKT [42]. Parviflorene is a novel sesquiterpenoid dimer isolated from *Curcuma parviflora* wall has been observed effectively inducing apoptosis in cancer cells [43]. In human leukemic MOLT-4 cells it was shown to activate caspase 3, 8, and 9 and induce death receptors' expression and the down-regulate c-FLIP levels [43]. Furthermore, there was an increase in expression of TRAILR2 (death receptor 5), as described in [44].

PROCYANIDINS

Procyanidins are oligomeric and polymeric polyphenols involved in inducing apoptosis in colon cancer-derived metastatic SW620 cells [45]. These polyphenols induce expression of death receptor 4 through NF-κB and p53-dependent transcription [45]. Moreover, inactivation of tumor protein p53 and NF-κB with chemical inhibitors severely compromised the expression of death receptor 4 (Fig. **3**) [45]. Certain herbal extracts have been shown to induce TRAIL-mediated apoptosis by facilitating the accumulation of death receptors in lipid rafts; however, procyanidins induced apoptosis in cancer cells through a mechanism independent of lipid-raft formation [46]. Moreover, the treatment of cells with inhibitors of polyamine catabolism was shown to considerably enhance apoptotic effects of procyanidins [47].

STILBENOIDS

Structural analysis of stilbenoids indicates that these are hydroxylated derivatives of stilbene. The most important studied stilbenoids are resveratrol and piceatannol. Human promyeloblastic leukemia KG-1a cells pretreated with resveratrol displayed an increase in expression of death receptor 5 [48]. Interestingly, there were remarkably enhanced expressions of death receptors 4 and 5, BAX, and down regulated BCL-2 and cyclin D1 (CCND1) [49]. There are different pro-apoptotic proteins, which are up regulated in cancer cells in response to resveratrol treatment, including BAK, PUMA, NOXA, and BIM [50]. In addition, there was a notable increase in release of cytochrome c and SMAC/DIABLO from mitochondria [50]. Piceatannol has also been shown to trigger the expression of death receptor 5 via SP1 transcription factor in human leukemia THP-1 cells [51]. Intriguingly, resveratrol was shown to decrease in expression of c-FLIP and simultaneous activation of JNK-c-JUN pathway in various cancer cells via inhibition of NF-κB and STAT3-dependent transcriptional mechanism (Fig. **3**) [51, 52]. Although, a treatment of cancer cells with resveratrol is beneficial in overcoming the TRAIL-dependent resistance, there are some negative regulators (BCL-2, N-terminally

cleaved FADD), whose high expression levels might impair the resveratrol-induced sensitization to TRAIL [53].

LIGNANS

Lignans are one of the major classes of phytoestrogens, which have an estrogen-like chemical structure. Principal lignans are: gomisin N, matairesinol and nortrachelogenin. Gomisin N is a lignan extracted from *Schisandra chinensis* and potent enough to restore apoptosis in TRAIL-resistant cancer cells through generation of reactive oxygen species (ROS) [54]. Notably, gomisin N was shown to trigger the expression of TRAILR1 and 2 (death receptors 4 and 5), as described in [54]. Surprisingly, the death receptor 4 and 5 transcription induced by gomisin N was drastically reduced upon treatment with antioxidant [54]. Androgen-dependent LNCaP prostate cancer cells had shown the activation of AKT upon treatment with TRAIL [55]. A lignan matairesinol was reported to inhibit AKT expression and phosphorylation in LNCaP cells upon TRAIL treatment leading to sensitization of prostate cancer cells to TRAIL-induced apoptosis [55] (Fig. **2**). However, the forced expression of AKT in LNCaP cells reverted their phenotype to become more resistant to TRAIL exposure supporting the AKT involvement in tumor cell response [56]. Nortrachelogenin is another lignin that is reported to be effective in inhibition of AKT in prostate cancer cells [56] (Fig. **2**).

QUINONS

Quinones are heterocyclic compounds, some of which (various naphthoquinone derivatives) markedly enhance a TRAIL-mediated apoptosis [57]. They include: plumbagin, phenazine alkaloid, pyranonaphthoquinones, thymoquinone, 2-hydroxy-3-methylanthraquinone, and damnacanthal. Plumbagin, a naphthoquinone derivative, has been shown to effectively upregulate mRNA and protein levels of death receptor 5 in human melanoma A375 cells [58]. Moreover, there was a notable increase in activation of caspase-3 [58]. Interestingly, plumbagin was able to induce ROS levels, which in turn trigger the expression of death receptors 4 and 5 in human K562 leukemia cells [58, 59]. Whereas, the
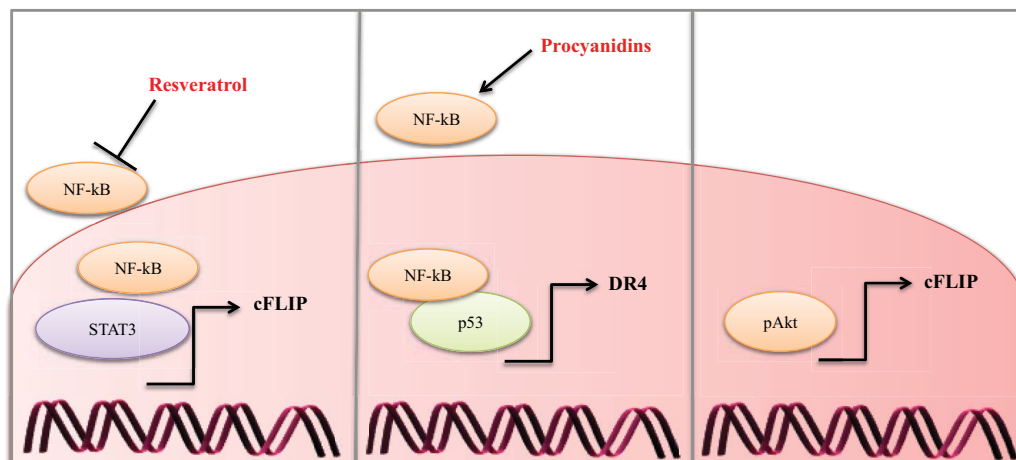

Fig. (3). Diametrically opposed roles of NF-kB in regulation of TRAIL-mediated apoptosis. P-Akt is also involved in transcriptional upregulation of cFLIP in TRAIL treated cancer cells. NF-κB, Nuclear Factor-kappa B; STAT3, Signal Transducer and Activator of Transcription 3; p-Akt, phosphorylated serine/threonine protein kinase; DR4, Death Receptor 4; cFLIP, cellular FLICE inhibitory protein.

treatment of leukemic cells with antioxidant dramatically reduced plumbagin-induced up-regulation of death receptor 4 and 5 levels [59].

Interestingly to note that phenazine alkaloid and pyranonaphthoquinones from *Streptomyces sp.* are effective in overcoming resistance against TRAIL in gastric adenocarcinoma cells [60]. Thymoquinone from *Nigella sativa* (Fig. **2**) is reported to be involved in inhibition of AKT and concomitant activation of intrinsic apoptotic pathway [61]. Thymoquinone-mediated inhibition of AKT is likely to be regulated by ROS, because the treatment of cells with antioxidant drastically reduced an inhibitory effect of thymoquinone on AKT in cancer cells [61]. *Hedyotis diffusa* is a source of 2-hydroxy-3-methylanthraquinone showing the ability to induce expression of TRAIL and death receptor 4, as well as caspase-8 activation, and subsequently apoptosis in leukemic THP-1 cells [62]. *Morinda citrifolia* is a rich source of damnacanthal, an apoptotic inducer in cancer cells through p38 MAPK pathway [63]. *In vitro* studies indicated that exposure of cancer cells to damnacanthal resulted in activation of p38 MAPK and subsequently up-regulation of levels of TRAIL, death receptor 5 and TNFR1 and finally to apoptotic phenotype [63].

CHALCONES

Chalcones are precursor compounds in flavonoid biosynthesis in which two aromatic rings are joined by a three-carbon α, β -unsaturated carbonyl system. They include: isoliquiritigenin, licochalcone-A, isobavachalcone, xanthohumol, butein and flavokawain B. Isoliquiritigenin is the most explored compound among chalcones due to its higher anti-proliferative activity mainly via apoptosis induction in various cancer cell lines [64], breast and skin cancer [65-67], prostate lung and gastrointestinal colon cancer [64, 68-72], multiple myeloma [73, 74], hepatoma [72], melanoma [75], and also in a mouse model of renal cell carcinoma *in vivo* [76]. Xanthohumol, desethylxanthohumol, isobavachalcone, and cryptocaryone were reported to inhibit proliferation in prostate cancer cell lines [77-79], chalcone was shown to promote apoptosis in bladder and breast cancer cells blocking cell cycle [72, 80], and flavokawain B - to cause apoptosis in human squamous carcinoma cell lines [81].

All five different types of chalcones (isoliquiritigenin, licochalcone-A, isobavachalcone, xanthohumol and butein) in combination with TRAIL increased apoptosis in LNCaP prostate cancer cell lines resistant to TRAIL exposure [82]. Intriguingly, xanthohumol showed the most potent compound to induce apoptosis in cancer cells due to its chemical structure (the presence of the methoxy group in xanthohumol at the 6' position) [82]. Chalcones alone or in association with TRAIL were found to induce a TRAIL-mediated apoptosis via induction of death receptor 5 [83-85]. In particular, Kim observed that butein treatment augmented the activation of death receptor 5 and caspase-3 in U937 human leukemia cells [86]. Isoliquiritigenin in combination with a recombinant human TRAIL protein strongly induced the apoptosis in HT29 colon cancer cell line through the increase of death receptor 5 and caspases-3, 8, 9 and 10 levels [84]. Co-treatment of PC3 resistant prostate cancer cells with TRAIL and flavokawain B increased the expression of death receptor 5, BIM and PUMA resulting in an increase of apoptotic cells [83, 86]. In addition, flavokawain B potently induced apoptosis in SYO-I and HS-SY-II synovial sarcomas cell lines through an increase of caspase-3, 7, 8, and 9, death receptor 5, BIM, PUMA, BAX, and decreased expression of survivin and BCL-2 [86].

CURCUMIN

Curcumin, isolated from *Curcuma longa*, is a phenolic compound in which the aromatic ring is connected by two α, β-unsaturated carbonyl groups [87]. Curcumin was reported to induce apoptosis in prostate cancer cells, as well as in glioma cells through intrinsic and extrinsic pathways [87-92]. *In vitro* assays have provided a sufficient evidence for induction of extrinsic apoptotic pathway through activation of caspase-3 and -8. Intrinsic pathway is also triggered by curcumin via processing of BID by caspase-8. Truncated BID was shown to translocate into mitochondria and promote the release of cytochrome c from mitochondria to cytoplasm [87].

NF-κB was also shown to be up regulated in prostate cancer cells, however was effectively targeted by curcumin [89, 90]. Curcumin repressed NF-κB -dependent transcriptional expression of anti-apoptotic genes (*BCL-2, BCL-xL, and XIAP*), however AKT overexpression rescued cells from the effect of curcumin [90]. Curcumin is also effective in stimulating the expression of death receptors via generation of ROS [91]. Treatment of cells with antioxidants severely reduced curcumin-triggered up regulation of death receptor 5 [91]. Intriguingly, curcumin-treated cancer cells displayed an increase in mRNA and protein expression of DNA damage inducible transcript (DDIT3), also known as C/EBP homologous protein (CHOP) at its mRNA and protein levels. CHOP is likely to be involved in stimulating the expression of death receptor 5 [93]. Additional information about the role for curcumins in modulation TRAIL-induced apoptotic signaling can be found elsewhere [93].

COUMARINS

Coumarins are fragrant organic chemical compounds in the benzopyrone chemical class that include: esculetin and psoralidin. Esculetin is a 6,7-dihydroxycoumarin and has previously been shown to overcome resistance against TRAIL in oral cancer SAS cells. [94] Esculetin-treated cancer cells displayed a substantially enhanced caspase-8 activation and a notably increased expression of death receptor 5 [94]. Psoralidin is a furanocoumarin extracted from *Psoralea corylifolia* and has remarkable apoptosis-inducing efficacy in prostate cancer cells [95]. Subsequent study in HeLa cancer cells revealed that psoralidin triggers the expression of death receptor 5 [96]. Additional information about the role for coumarins in modulation TRAIL-induced apoptotic signaling can be found elsewhere [93].

ZYFLAMEND

Zyflamend® is a preparation consisting of a combination of extracts from multiple herbs, each with reported anticancer properties. They include but not limited to the following phytometabolites: Berberine, wogonin, baicalein, baicalin, Rosemary leaf, Turmeric, (rhizome), Ginger, (rhizome),

Holy Basil leaf extract, Green Tea (leaf), Hu Zhang, (Polyganum cuspidatum) (root & rhizome), Chinese Goldthread, (root), extract, Barberry, (root), extract, Oregano, (leaf) extract, Scutellaria baicalensis (root), as reviewed elsewhere [97-101].

Zyflamend was reported to potentiate a TRAIL-induced apoptosis in human cancer cells *in vitro* and *in vivo* through several mechanisms [97]. They include up regulation of proapoptotic protein BAX expression, as well as death receptors for TRAIL [97]. Silencing of death receptor 5 expression leads to a significantly reduced effect of Zyflamend on TRAIL-induced apoptosis [97]. Up regulation of the death receptor 5 was dependent on CCAAT/enhancer-binding protein-homologous protein (CHOP) [97]. Zyflamend was shown to induce CHOP expression, while CHOP silencing abolished the increase in the TRAILR2 (death receptor 5) expression [97].

Zyflamend®, a combination of extracts from multiple herbs, each with reported anticancer properties, can inhibit growth of various prostate cancer cell lines *in vitro* and *in vivo* [98, 99]. Zyflamend down regulated the expression of all class I and II histone deacetylases in castrate-resistant prostate cancer CWR22Rv1 cells [98]. The Zylfamend components, Chinese goldthread and baikal skullcap, appear to be primarily responsible for these results [98]. In addition, Zyflamend up regulated the histone acetyl transferase complex CBP/p300, potentially contributing to the increase in the histone H3 acetylation [98]. Expression of the tumor suppressor gene p21 (CDKN1A), a known downstream target of histone deacetylases and CBP/p300, was increased by Zyflamend treatment and the effect on p21 (CDKN1A) was, in part, mediated through ERK1/2 [98]. Knockdown of p21 (CDKN1A) with siRNA attenuated Zyflamend-induced growth inhibition. Over expression of p21 (CDKN1A) inhibited cell growth, and concomitant treatment with Zyflamend enhanced this effect [98].

Zyflamend was shown to reduce the phosphorylation of AKT, expression of prostate specific antigen, histone deacetylases, and androgen receptor [99]. Zyflamend is suggested to regulate multiple pathways in cancer progression, and its ingredients can suppress tumor cell proliferation, invasion, angiogenesis, and metastasis through regulation of inflammatory pathway products [100]. Zyflamend was observed to inhibit melanoma growth by regulating the autophagy-apoptosis switch [100].

Finally, Zyflamend was shown to repress NF-κB activation, and subsequently the expression of NF-κB regulated gene products involved in cell survival (inhibitor of apoptosis protein [IAP]-1 and 2, BCL-2, BCL-xL, FADD-like interleukin-1β converting enzyme/caspase-8 inhibitory protein [FLIP], TNF receptor-associated factor [TRAF]-1, and survivin) and angiogenesis (vascular endothelial growth factor [VEGF], cyclooxygenase [COX]-2, intercellular adhesion molecule [ICAM], and matrix metalloproteinase [MMP]-9), as reviewed elsewhere [101].

CONCLUDING REMARKS

Intrinsic or acquired resistance against TRAIL in different cancer types is a rapidly emerging challenge in transla-

tional oncology. There is a progressive increase in the list of natural agents reportedly involved in overcoming resistance against TRAIL based therapeutics [93]. Accordingly, degradation of death receptors is an outstanding question that is currently under investigation. There are still unexplored mechanisms, which might trigger degradation of death receptors, such as mislocalization or enhance internalization. Intriguingly, a recent report provides evidence that basal autophagosomes are high in TRAIL-resistant breast cancer cells [102]. In contrast, TRAIL- sensitive breast cancer cells have low levels of basal autophagosomes [102]. Concordantly with this concept, another report has previously revealed that death receptors 4 and 5 re-appeared on cell surface of breast cancer cells deficient for adaptor protein-2 (AP-2) and clathrin [103]. Moreover, repeated treatment of breast cancer cells (MDA-MB-231) with subtoxic doses of TRAIL induced resistance to TRAIL [104].

The standardization of therapy is additionally confounded because of diametrically opposed roles of different proteins in regulation of TRAIL-mediated apoptosis. NF-κB is surprisingly found to function as a positive and negative regulator of TRAIL-mediated signaling [105, 106]. In cancer cells there is evidence of NF-κB-mediated regulation of c-FLIP and DR4. In accordance with this notion, AKT modulates the expression of c-FLIP [105, 106].

However, PI3K/AKT/FOrkhead boX O3A (FOXO3A) signaling axis is also involved in the transcriptional up regulation of death receptors 4 and 5 in colon cancer cells [107]. In addition, despite various herbal extracts have shown efficacy in restoration of TRAIL induced apoptosis in resistant cancer cells, a pro-apoptotic role of AKT cannot be overlooked. Therefore, these aspects of divergent functionality of NF-κB and AKT need detailed investigation in different cancer types. Currently, phase I/II clinical trials are assessing TRAIL or agonistic TRAIL-receptor antibodies therapy in non-Hodgkin lymphomas and non-small cell lung cancer patients [108-112].

LIST OF ABBREVIATIONS

ATM	=	Ataxia Telangiectasia Mutated protein
BAK	=	BCL-2 Antagonist/Killer 1
BAX	=	Bcl-2-Associated X protein
BCL-2	=	B Cell Leukemia/lymphoma 2
CBL	=	Casitas B-lineage Lymphoma
DDIT3	=	DNA-Damage-Inducible Transcript 3
CHOP	=	C/EBP homologous protein
CYCS	=	Cytochrome C
DAXX	=	Death-domain associated protein 6
DD	=	Death Domain
DED	=	Death Effector Domain
DIABLO	=	Direct IAP binding protein with low pH
DISC	=	Death-Inducing Signaling Complex
FADD	=	Fas (TNFRSF6)-Associated via Death Domain
ERK 1/2,	=	Elk-Related tyrosine Kinase 1/2

EGFR = Epidermal Growth Factor Receptor

MADD = Mitogen-Activated kinase-activating Death Domain protein

FADD = Fas (TNFRSF6)-associated via death domain

c-FLIP = Cellular FLICE-Inhibitory Protein

HSP27 = Heat Shock Protein 27

IAPs = Inhibitors of Apoptosis Proteins

IkB = Inhibitor of kappa B

IKK = IkB kinases

JNK = c-Jun N-terminal kinase

MADD = Mitogen-Activated kinase-activating Death Domain protein

MAPK = Mitogen Activated Kinase-like Protein

MAP kinase kinase kinase (or MAP3K or MEKK, NIK, NF-κB- inducing kinase)

NF-κB = Nuclear Factor-kappa B

PI3K = Phosphatidylinositol-4,5-bisphosphate 3-kinase

ROS = Reactive Oxygen Species

RTK = Receptor Tyrosine Kinase

S; SMAC, = Second Mitochondrial derived Activator of Caspase

STAT = Signal Transducer and Activator of Transcription

TNF = Tumor Necrosis Factor

TRADD = TNFRSF1A-Associated via Death Domain

TRAF2 = TNF Receptor-Associated Factor 2

TRAIL = Tumor necrosis factor-Related Apoptosis-Inducing Ligand

XIAP = X-linked Inhibitor of APoptosis

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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