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REVIEW

# The role of oxidative stress in anticancer activity of sesquiterpene lactones

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**Abstract** Sesquiterpene lactones (SLs) are plant-derived compounds that are abundant in plants of the Asteraceae family and posses a broad spectrum of biological activities, ranging from anti-inflammatory, phytotoxic, antibacterial, and antifungal to cytotoxic/anticancer. In recent years, anticancer properties of these compounds and molecular mechanisms of their action have been studied extensively on numerous cell lines and also on experimental animals. SLs have been shown to disrupt cellular redox balance and induce oxidative stress in cancer cells. Oxidative stress is associated with increased production of reactive oxygen species (ROS) which in turn can promote many aspects of cancer development and progression. On the other hand, ROS, which initiate apoptosis via the mitochondrial-dependent pathway, can also be used to kill cancer cells, if they can be generated in cancer. One of the most important regulators of the redox equilibrium in the cells is reduced glutathione (GSH). In cancer cells, GSH levels are higher than in normal cells. Therefore, SL can induce apoptosis of cancer cells by decreasing intracellular GSH levels. The use of SL which can affect intracellular redox signaling pathways can be considered an interesting approach for cancer treatment. In this review, we give a brief description of the mechanisms and pathways involved in oxidative stress-induced anticancer activity of SL.

**Keywords** Alkylating agents · Apoptosis · GSH · α-Methylene-γ-lactones · Oxidative stress · ROS · Sesquiterpene lactones

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## Introduction

Natural products isolated from plants have for centuries been and still are an important source of pharmaceutical agents with diverse chemical structures and bioactivities. Today, natural products and their derivatives or analogs still represent over 50 % of all drugs in clinical use. With cancer being the second leading cause of death worldwide, it is no wonder that new therapeutic agents to fight cancer are often being sought in the kingdom of plants.

In the past, organized collection of plants for evaluation as potential sources of new drugs resulted in the development of several important anticancer agents. One of the well-known examples of such screening programs resulted in the discovery of taxol in the bark of the Pacific Jew tree. Taxol and related compounds enhance the polymerization of tubulin to microtubules stabilizing them against depolymerization and thus interfere with the ability of cancer cells to divide. Generally, plant-derived anticancer drugs can be classified on the basis of their mechanism of action as compounds interfering with the process of mitosis (Taxol, vinca alkaloids), antioxidant agents (thymoquinone, vincristine), inhibitors of DNA modifying agents (camptothecin), and angiogenesis-inhibiting agents (flavopiridol, epigallocatechin gallate).

A new group of compounds, named sesquiterpene lactones (SLs), is emerging as a promising alternative to already known anticancer therapies. In the recent years, the anticancer potential of SLs has drawn attention of chemists and pharmacologists to this interesting group of natural compounds. Several studies have provided convincing evidence of the anticancer properties of SLs on numerous human cancer cell lines (Merfort 2011; Kreuger et al. 2012; Zhang et al. 2005) and also on experimental animals. But so far, only one compound in this group, arglabin, is already used as a drug in oncological clinics in Kazakhstan (Zhangabylov et al. 2004); others are in various stages of clinical or pre-clinical trials.

In this review, we concentrated on one aspect of SL anticancer activity which is their involvement in the induction of oxidative stress triggering the apoptosis process. We also discussed the differences in the sensitivity of normal versus cancer cells to SLs that may be caused by their different oxidative states.

## Origin and structure of SLs

SLs constitute a large and diverse group of over 5000 biologically active compounds of plant origin that have been identified in several families of flowering plants, such as Cactaceae, Solanaceae, and Araceae, but are most abundant in Asteraceae (Chadwick et al. 2013). SLs were used in traditional medicine, especially for the treatment of inflammatory diseases. However, they possess a broad spectrum of other biological activities, including cytotoxic, antibacterial, antifungal, and antiviral.

SLs are 15-carbon terpenoids, consisting of three isoprene (5C) units and a lactone ring. Most, but not all of them, are characterized by an α-methylene-γ-lactone motif with an exocyclic double bond conjugated with a carbonyl function (Zhang et al. 2005) (Fig. 1). The major categories of SLs and the examples of their important representatives are given in Table 1. The well-known examples of SLs lacking an exocyclic double bond are artemisinin (currently used as an antimalarial drug) and thapsigargin (Janecka et al. 2012).

## Mode of action of SLs

Although the exact mechanisms of action of SLs are not well understood, it is believed that α-methylene-γ-lactone group is the one responsible for their biological effects, especially for their anticancer activity. The exocyclic double bond conjugated with a carbonyl function is a strong alkylating agent and can act on transcription factors and enzymes in the human body causing steric and chemical changes that affect the ability of the targets to function appropriately. Accordingly, the methylene group of SLs reacts by the Michael-type addition with various bionucleophiles (Fig. 2), especially mercaptyl groups of cysteine residues in proteins and in the free intracellular glutathione (GSH), leading to reduction of enzyme activity and the disruption of GSH metabolism and intracellular redox balance (Pati et al. 2007; Lee et al. 1977). Such alkylation of cellular thiols disrupts the key biological processes (Zhang et al. 2004, 2005; Heilmann et al. 2001; Knight 1995) resulting in the controlled cell death, apoptosis. SLs were shown in vitro to induce apoptosis, inhibit cell cycle and proliferation, and diminish metastasis in various cancer cell lines (Zhang et al. 2005; Janecka et al. 2012). Conducted research showed that cytotoxic activity of SLs involves different signaling pathways and affects multiple targets in cancer cells (Janecka et al. 2012; Kreuger et al. 2012). Emerging data suggest that the underlying mechanism for anti-tumor effects of SLs seems to be mediated by oxidative stress (Wen et al. 2002). The SL-induced apoptosis, described in many cancer cell lines, was found to be associated with reduced glutathione (GSH) depletion, reactive oxygen species (ROS) generation, mitochondrial transmembrane potential dissipation, cytochrome c release, and activation of caspases (caspase 9 and 3) (Wen et al. 2002; Khan et al. 2012).

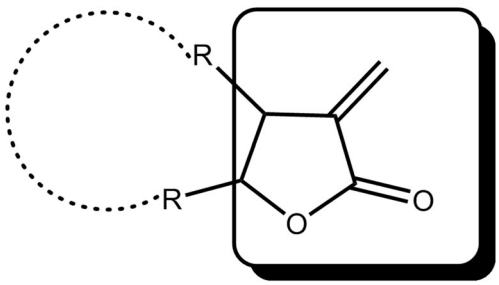



**Fig. 1** The general structure of α-methylene-γ-lactones

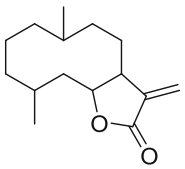
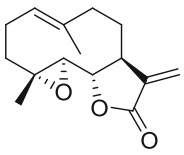
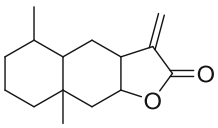
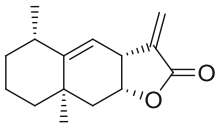
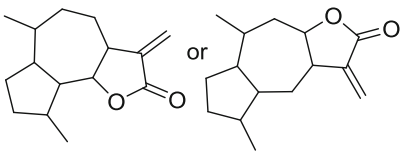
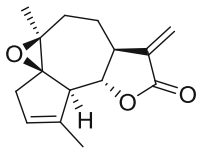
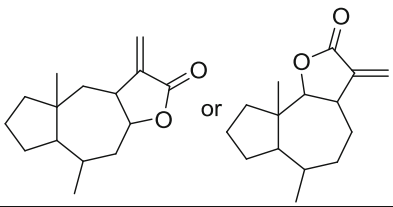
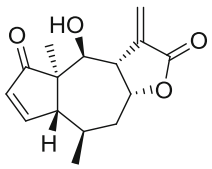
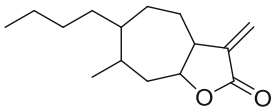
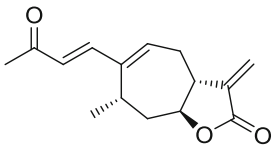
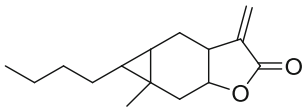
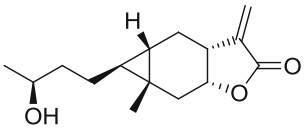
It seems that the exo-methylene group conjugated with a carbonyl in a lactone ring is essential for the cytotoxic function of SLs. However, other factors, such as lipophilicity, molecular geometry, and the chemical environment of the target sulfhydryl group can also influence the activity of SLs (Beekman et al. 1997; Scotti et al. 2007). The differences in activity can be also explained by different numbers of alkylating structural elements. Compounds with two alkylating centers are termed "bifunctional." Parthenolide (PTL), which in addition to its α-methylene-γ-lactone moiety also contains an epoxide, is an example of such bifunctional structure, with two sites for potential nucleophilic attack. Another example is helenalin, with an additional endocyclic α,β-unsaturated ketone (Lee and Furukawa 1972). In general, compounds with two alkylating centers are more potent inhibitors of tumor cell proliferation but sometimes are also more toxic.

The exocyclic double bond is also responsible for such effects as regulation of gene expression by activating and deactivating transcription (Wong and Menendez 1999; Mazor et al. 2000; Schomburg et al. 2013).

## Parthenolide—the most studied sesquiterpene lactone

Parthenolide (PTL) is the major SL found in feverfew (*Tanacetum parthenium*), a herbal plant used in traditional medicine. For centuries, PTL was known for its anti-inflammatory activity (Mathema et al. 2012), but the more recent evidence points at its potential as a novel anti-tumor agent. PTL was shown to induce cytotoxicity in various

**Table 1** Sesquiterpene lactones with anticancer potential

| Group/skeleton | Ring size | Representative example | Origin |
|---|---|---|---|
| Germacranolides  | 10-membered | Parthenolide  | *Tanacetum parthenium* |
| Eudesmanolides  | 6/6-fused bicyclic | Alantolactone  | *Inula helenium* |
| Guaianolides  | 5/7-fused bicyclic | Arglabin  | *Artemisia myriantha* |
| Pseudoguaianolides  | 5/7-fused bicyclic | Helenalin  | *Arnica montana* |
| Xanthanolides  | 7-membered | Xanthiatin  | Xanthium family |
| Carabranolide  | 6/3-tricyclic | Carabrol  | *Carpesium faberi* |

cancer cell types, including prostate (Hayashi et al. 2011), pancreatic (Liu et al. 2010), breast (Nakshatri et al. 2004) and colorectal cancers (Zhang et al. 2004), multiple myeloma (Suvannasankha et al. 2008), and leukemia (Zunino et al. 2007). More recently, it has been demonstrated in in vivo studies using mice xenografts of childhood acute lymphoblastic leukemia that PTL eliminates leukemia-initiating cell populations (LICs) and improves survival and restoration of normal murine hemopoiesis (Diamanti et al. 2013).

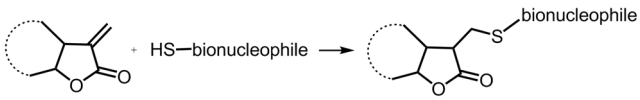



**Fig. 2** The mode of action of sesquiterpene lactones with the exocyclic methylene group conjugated with carbonyl function

Anticancer effect of PTL involves inhibition of proliferation, induction of apoptosis, cell cycle arrest, and inhibition of metastasis (Janecka et al. 2012; Koprowska and Czyz 2010;

Zhang et al. 2005). The broad array of biological activities exerted by PTL is due to its ability to bind proteins that are overexpressed in various pathophysiological states, including cancer. The molecular mechanisms of PTL action are strongly associated with DNA-binding inhibition of two transcription factors, the nuclear factor κB (NF-κB) (Rüngeler et al. 1999; Steele et al. 2006) and the signal transducer and activator of transcription 3 (STAT3), as well as the proapoptotic activation of p53, together with reduced glutathione (GSH) depletion (D'Anneo et al. 2013), reactive oxygen species (ROS) generation (Wen et al. 2002; Zunino et al. 2007; Guzman et al. 2005), and c-Jun N-terminal kinase (JNK) activation (Nakshatri et al. 2004). PTL decreases also the activity of histone deacetylase (HDAC) (Gopal et al. 2007) and DNA methyltranspherase 1 (DNMT1) (Liu et al. 2009). Furthermore, PTL can interfere with microtubule function through tubulin binding (Fonrose et al. 2007). However, the main mechanism of PTL action is linked to the inhibition of NF-κB (Rüngeler et al. 1999). NF-κB is an extracellular signal-activated transcription factor that governs the expression of various important genes involved in cytokine production, cell proliferation and differentiation, cellular adhesion, inflammatory processes and apoptosis (Karin and Lin 2002). Constitutive activation of NF-κB is a relatively common feature of many cancers, including leukemias (Guzman et al. 2001) and mediates the cellular transformation, proliferation, invasion, angiogenesis, and metastasis of cancer (Fujioka et al. 2003). Antiapoptotic activity of NF-κB is one of the major mechanisms of cancer cell resistance to chemotherapy and radiation (Montagut et al. 2006). NF-κB is localized in the cytoplasm and consists of two subunits, p50 and p65, which are inactive due to their association with the inhibitory protein IκB-α. PTL inhibits NF-κB activity by preventing IκB-α degradation and p50 and p65 NF-κB subunit modification. Blocking NF-κB can cause tumor cells to stop proliferating, to die, or to become more sensitive to the action of anti-tumor agents. Thus, a very important new direction in PTL-based studies is sensitization tumor cells to antineoplastic agents (Wyrebska et al. 2014).

However, the major drawback that restricts efficacy of PTL as a drug is its poor solubility in water. To overcome the solubility problem, a series of PTL derivatives was obtained through the diastereoselective addition of several primary and secondary amines to the exocyclic double bond (Nasim and Crooks 2008; Neelakantan et al. 2009). Based on the favorable pharmacokinetic and pharmacodynamic properties, *N*,*N*-dimethylaminoparthenolide (DMAPT) (Fig. 3) with improved solubility and bioavailability was selected as a lead compound (Neelakantan et al. 2009; Guzman et al. 2007). When formulated as a fumarate salt, DMAPT demonstrated more than 1000-fold greater solubility in water than PTL and maintained the anticancer activity of the parent compound because in body fluids, DMAPT is rapidly converted back to PTL. In vitro studies on cancer cells confirmed that DMAPT maintains basic characteristics of its parent compound with the ability to generate ROS, activate p53 protein as well as inhibit NF-κB DNA binding and proliferation of cancer cells. Recently, inhibition of STAT3 signaling pathway was also highlighted in anticancer activity of DMAPT (Song et al. 2014). DMAPT was shown to eradicate in vitro stem and progenitor cells of acute myeloid leukemia (AML). Pharmacologic experiments using both mouse xenograft models and spontaneous acute canine leukemias demonstrated its high in vivo bioactivity (Guzman et al. 2007). Further in vivo studies demonstrated that DMAPT significantly suppressed the growth of prostate (Shanmugam et al. 2010), lung, bladder (Shanmugam et al. 2011), and breast cancers (D'Anneo et al. 2013). Moreover, it inhibited metastasis in mouse xenograft model of breast cancer and enhanced survival of the treated mice.

## Reactive oxygen species

ROS are chemically reactive molecules containing oxygen. It is a collective term used for oxygen-derived free radicals such as superoxide anion, hydroxyl, peroxyl, and alkoxyl, as well as $O_2$-derived non-radical species such as hydrogen peroxide, singlet oxygen, alkyl peroxide, etc. (Fig. 4) (Halliwell and Cross 1994). ROS are produced intracellularly by eukaryotic cells during normal oxidative metabolism through multiple mechanisms. Depending on the cell and tissue type, the major sources of ROS are NADPH oxidase (NOX) complexes in the cell membranes, mitochondria, peroxisomes, and endoplasmic reticulum.

At physiological low levels, ROS function as "redox messengers" for normal signaling transduction. Recently, the role of ROS in regulation of different cellular processes, such as gene expression, metabolism, cell differentiation, proliferation, and apoptosis, has been emphasized. However, at higher concentrations, ROS become toxic and induce cell depth by various signaling pathway.

## Oxidative stress

Oxidative stress reflects an imbalance between the intracellular production of ROS and a cell ability to readily detoxify the reactive intermediates or to repair the resulting damage (Betteridge 2000; Sharma et al. 2007). The balance between ROS formation and anti-oxidative defense is crucial for normal cellular function and determines the fate of the cell. Cellular redox balance is maintained by a powerful cell's endogenous antioxidant systems, including glutathione and thioredoxin and antioxidant enzymes such as superoxide dismutase, catalase, etc., which are able to eliminate ROS. Disturbance in the redox balance and excess ROS induce lipid

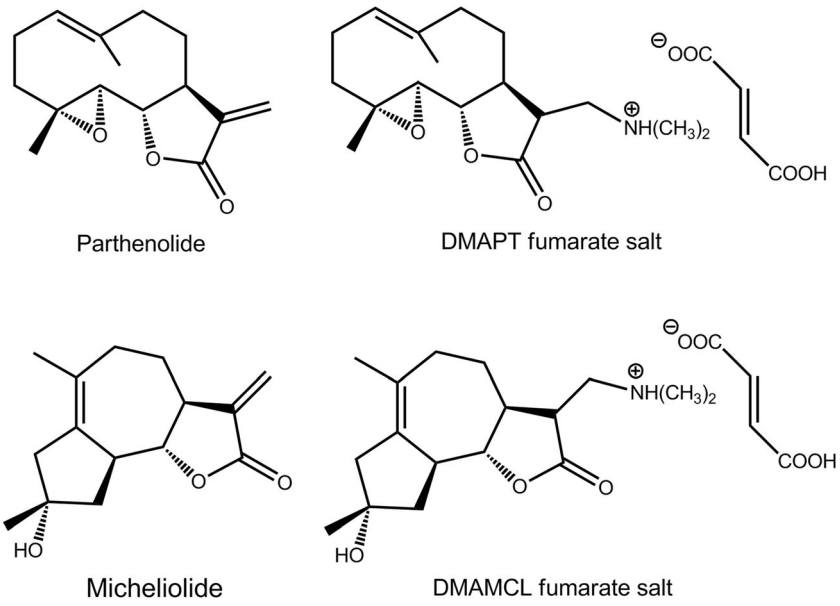



**Fig. 3** The structure of parthenolide and micheliolide and their water-soluble derivatives—DMAPT and DMAMCL, respectively

and protein oxidative modifications and DNA damage, leading to apoptotic cell death or cancerogenic cell transformation (Valko et al. 2007). Therefore, oxidative stress is involved in most of pathological states and diseases, including cancer. Recent evidence has demonstrated that enhanced ROS generation and oxidative stress may trigger cell transformation and contribute to cancer progression by increasing DNA mutations or inducing DNA damage and amplifying genomic instability (Reuter et al. 2010; Visconti and Grieco 2009).

It is well documented that cancer cells contain higher level of endogenous ROS than normal cells. Increased generation of ROS in cancer cells is caused largely by the products of their highly metabolic nature. When compared with the normal cells, cancer cells are in a persistent prooxidative state that can lead to intrinsic oxidative stress (Szatrowski and Nathan 1991; Toyokuni et al. 1995). The higher levels of endogenous ROS in cancer cells increase their susceptibility to oxidative stress-induced cell death and could be exploited for cancer therapy (Nogueira and Hay 2013). Chemotherapeutic agents

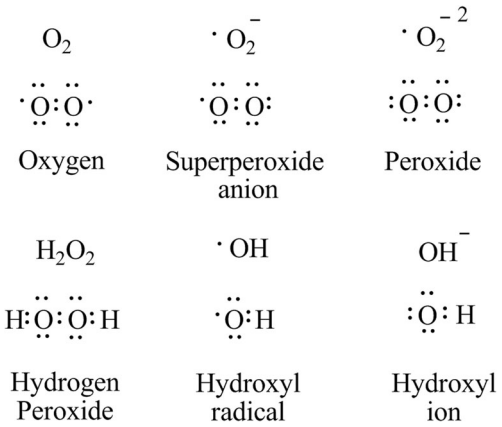



**Fig. 4** Electron structures of common reactive oxygen species

that specifically increase ROS production or inhibit ROS elimination by scavenging systems can favor the accumulation of ROS in cancer cells and hence push these already stressed cells beyond their threshold of "tolerance" that will induce cell death (Schumacker 2006; Fang et al. 2009). Therefore, compounds targeting intracellular redox signaling pathways and ROS metabolism in cancer cells seem to be a new interesting approach for cancer treatment.

## Cellular redox system

Cellular redox balance is maintained by a powerful antioxidant system that includes enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, or glutathione reductase, and non-enzymatic scavengers, such as glutathione, flavonoids, and minerals (Se, Mn, Cu, and Zn) (Irshad and Chaudhuri 2002). The tripeptide glutathione (γ-glutamyl-cysteinyl-glycine, GSH) is the most abundant intracellular free thiol in eukaryotic

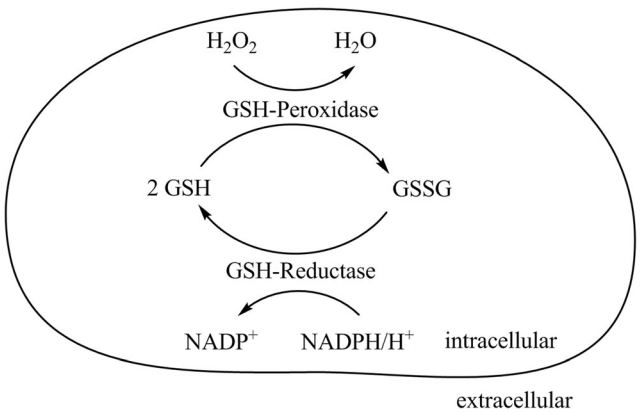



**Fig. 5** Mechanism of enzymatic GSH oxidation and GSSG reduction

**Table 2** Mechanism of sesquiterpene lactones anticancer activity

| Sesquiterpene lactone | Mode of action | Cell line | Refs |
|---|---|---|---|
| Parthenolide (PTL) | Induction of apoptosis (through ROS generation) | Primary human AML cells, blast crisis CML (bcCML) | Guzman et al. 2005 |
| | Induction of apoptosis (through ROS generation, mitochondrial cytochrome c release, and caspase activation) | Chronic lymphocytic leukemia (CLL) | Steele et al. 2006 |
| | Induction of apoptosis (through *GADD153* overexpression (an oxidative stress or anticancer agent inducible gene) and tumor cells sensitization to apoptosis) | Chang liver and SH-J1 cells | Wen et al. 2002 |
| | Induction of apoptosis (through ROS generation, nitric oxide and superoxide anion radical increased, and mitochondrial membrane potential disruption) | Pre-B acute lymphoblastic leukemia (ALL) lines | Zunino et al. 2007 |
| | Modification of the redox state of critical exofacial thiols | Large B cell lymphoma lines | Skalska et al. 2009 |
| | ROS generation with subsequent JNK activation | Non-small lung cancer (NSCLC) cell lines (A549 and H522) | Shanmugam et al. 2011 |
| | Induction of apoptosis (through ROS generation) | Multiple myeloma (MM) cell lines: KMM-1, MM1S, KMS-5, NCI-H929 | Wang et al. 2006 |
| | Induction of autophagy (through ROS generation, GSH depletion, JNK activation and inhibition of NF-kB activity) | Human breast cancer cell line MDA-MB231 | D'Anneo et al. 2013 |
| | Induction of necrosis (through ROS generation and mitochondrial dysfunction) | | |
| Costunolide | Induction of apoptosis (through ROS generation, mitochondrial permeability transition (MPT) induction, and cytochrome c release) | Human promyelocytic leukemia cell line HL-60 | Lee et al. 2001 |
| | Induction of apoptosis (ROS generation and mitochondrial membrane potential disruption) | Human bladder cancer T24 cells | Rasul et al. 2013 |
| | Induction of apoptosis (through ROS-mediated JNK activation) | Human promonocytic leukemia U937 | Choi and Lee 2009 |
| Helenalin | Induction of apoptosis (through ROS generation and mitochondrial membrane potential disruption) | Activated $CD4^+$ T cells | Berges et al. 2009 |
| Alantolactone | Induction of apoptosis (GSH depletion, ROS generation, and mitochondrial dysfunction) | Human glioblastoma cell lines U87 | Khan et al. 2012 |
| | Induction of apoptosis (through GSH depletion, inhibition of STAT3 activation, and mitochondrial dysfunction) | HepG2 | Khan et al. 2013 |
| | Induction of apoptosis (through ROS generation, and mitochondrial membrane potential disruption) | RKO human colon cancer | Zhang et al. 2013 |
| Eupalinin A | Mainly, induction of autophagic cell death (ACD) (through ROS generation, and mitochondrial membrane potential reduction) | Human promyelocytic leukemia HL-60 | Itoh et al. 2008 |
| | Induction of ACD (through ROS generation and intracellular GSH reduction) | Human M2-type leukemia cell line<br>Human promyelocytic leukemia HL-60 | Itoh et al. 2009 |
| Telekin | Induction of apoptosis (through ROS generation and loss of mitochondrial membrane potential) | Human hepatocellular carcinoma cells: HepG2, Smmc-7721 | Zheng et al. 2013 |
| Salograviolide A (Sal A)<br>Iso-seco-tanapartholide (TNP) | Induction of apoptosis (through ROS generation, and mitochondrial membrane potential disruption) | Human colon cancer cell lines: HT-29, HCT-116, DLD-1 | Salla et al. 2013 |

cells that plays the major role in maintaining the intracellular redox status and defense against oxidative stress (Circu and Aw 2008). Reduced GSH is the biologically active form which is oxidized to glutathione disulfide (GSSG) during oxidative stress. Typically, cells exhibit a high ratio of GSH to GSSG and more than 90 % of total GSH is maintained in a reduced

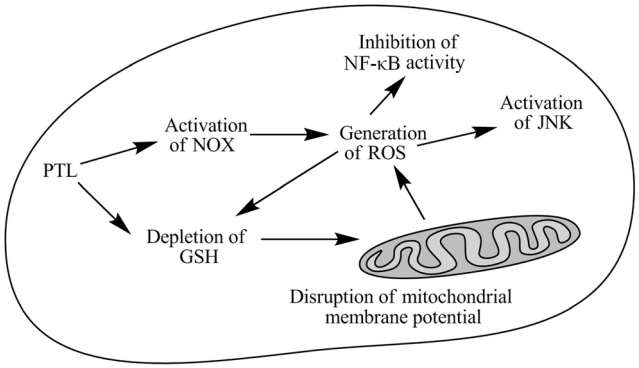



**Fig. 6** Schematic mechanism of PTL action in the cell

form through de novo GSH synthesis, enzymatic reduction of GSSG, or exogenous GSH uptake (Circu and Aw 2010) (Fig. 5). A shift in the cellular GSH/GSSG ratio constitutes an important signal that could decide the fate of a cell. Depletion of intracellular GSH concentration results in oxidative stress and increased formation of ROS which initiate apoptosis via the mitochondria-dependent pathway (Circu and Aw 2008). On the contrary, elevated GSH levels afford protection against stress-induced apoptosis (Friesen et al. 2004) and have been associated with drug resistance to chemotherapy.

## Sesquiterpene lactones as oxidative stress inducers

It has been shown in several studies that anticancer activity of PTL and other SLs is associated with their ability to induce oxidative stress in cancer cells. Numerous cellular factors and signaling pathways linked to oxidative stress were already described in various cancer cell lines (Table 2). Even though many of them were discussed in detail, the overall molecular mechanism of oxidative stress-induced cell death is still under investigation.

Recently, D'Anneo and co-workers (D'Anneo et al. 2013) described the possible mechanism of the oxidative stress-induced effects of PTL in MDA-MB231 cells. In the time course experiment of ROS generation, they showed that the level of ROS rapidly increased in the first hours (1–3 h) of the treatment with PTL, when the drug induced the production of superoxide anion by stimulation of NOX activity. In this phase, the increased ROS generation caused activation of JNK and inhibition of NF-κB activity. During the prolonged PTL treatment (5–20 h), ROS generation led to the dissipation of mitochondrial membrane potential and the appearance of necrotic events (Fig. 6).

Agents targeting the redox state of cancer cells by GSH depletion may be considered for the development of specific anticancer therapies. In tumor cells exposed to SLs, reduction of intracellular GSH levels has been observed both in vitro and in vivo (Woerdenbag et al. 1989). In the study of Wen (Wen et al. 2002), it was shown that intracellular GSH depletion in hepatoma cell lines is crucial for triggering the oxidative stress-mediated apoptosis after PTL treatment. The authors suggested also that the tumor cell sensitivity to PTL seemed to correlate well with GSH metabolism.

Although most attention has been focused on the intracellular redox state as a target for cancer therapy, the recent studies suggest that extracellular redox-related proteins may be potential therapeutic targets for cancer treatment (Chaiswing and Oberley 2010). Extracellular redox state is an important factor that affects cell behavior and plays an important role in the regulation of critical cellular functions and microenvironmental cell interactions (Chaiswing and Oberley 2010; Skalska et al. 2009). For example, the redox status of exofacial thiols on T cells regulates their activation and proliferation (Gelderman et al. 2006). Extracellular redox environment is a dynamic state determined by several known variables, including redox-modulating proteins and extracellular protein thiol groups (i.e., exofacial thiols), and is sculpted by intracellular metabolism. Under physiological conditions, the extracellular space is relatively more oxidized than the interior

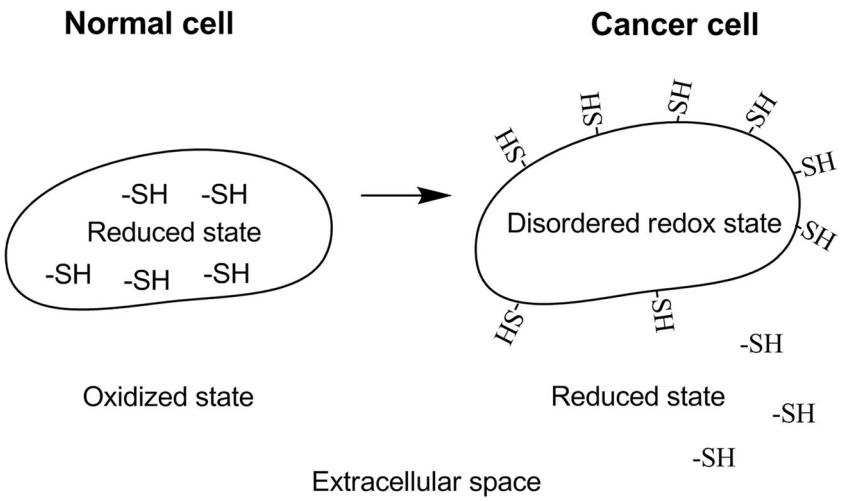



**Fig. 7** Redox state alternations during cancer progression

of the cell. During pathologic conditions, such as cancer, the extracellular redox state may be altered (Chaiswing and Oberley 2010) (Fig. 7). Recent evidence suggests that in contrast to the oxidized extracellular state of normal cells, malignant cells exist in a reduced environment (Nogueira and Hay 2013). Different cancer cell types or stages may demonstrate different and unique extracellular redox states. Therefore, the redox state of the extracellular micro-environment may be important in terms of the response of cancer cells to chemotherapy. It has been shown that PTL can modulate the redox state of cancer cell exofacial thiols and induce selective apoptosis in acute myelogenous leukemia (AML) and chronic lymphocytic leukemia (CLL) cells without affecting normal hematopoietic stem cells or T cells (Steele et al. 2006; Guzman et al. 2005). It seems that the selectivity of PTL against cancer cells might be due to the difference in extracellular redox state between normal and cancer cells. Exofacial thiols are reduced on cancer cells and can readily interact with PTL but are oxidized on normal cells thus unavailable for interaction with PTL (Skalska et al. 2009).

Detailed in vitro investigations of the anti-leukemic activity of PTL and its water-soluble analog DMAPT have been carried out against cultured primary AML, CML, and CLL cells and demonstrated potent eradication of leukemic stem and progenitor cells, as well as the overall blast population of both myeloid and lymphoid leukemias. It has also been shown that DMAPT specifically ablated the primitive human leukemia cells without impairing their normal counterparts (Neelakantan et al. 2009; Guzman et al. 2007; Zhang et al. 2012). Similar selectivity in anticancer action was observed with another representative of SLs, micheliolide (Fig. 3) and its water-soluble derivative dimethylaminomicheliolide (DMAMCL) (Zhang et al. 2012).

It seems that reduction of cell surface protein free thiols on cancer cells is emerging as a novel mechanism of SL action. DMAPT has already entered clinical trials in the UK for the treatment of AML, ALL, and CLL (Kevin 2010).

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