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REVIEW ARTICLE

Natural sesquiterpene lactones in prostate cancer therapy: mechanisms and sources

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Abstract

Prostate cancer is a condition characterized by the uncontrolled proliferation of abnormal cells inside the prostate gland, part of the male reproductive system. Prostate cancer is the most common cancer among men and the second largest cause of cancer-related mortality in the United States. A novel approach to treating advanced Prostate cancer has emerged, attributable to the enhanced effectiveness of new pharmacological agents sourced from natural origins and this has led to increased rates of global existence and progression-free survival. Sesquiterpene lactones and their derivatives are now used worldwide to create and manufacture innovative cancer therapeutics. A thorough search was performed according to PRISMA guidelines in SciMed, PubMed, and Google Scholar, focusing on publications published from 1999 to 2024. The safety, efficacy, and bioactivity of sesquiterpene lactones must be evaluated via clinical trials, *in vitro* studies, and *in vivo* research and data was rigorously gathered and validated to verify its accuracy and usefulness. Prostate cancer may be treated far more effectively using naturally occurring sesquiterpene lactone molecules. The most prominent sesquiterpene lactones identified were artemisinin, alantolactone, costunolide, helenalin, cynaropicrin, parthenolide, and inuviscolide, which are originated from botanical sources like *Ferula penninervis, Tanacetum argenteum, Artemisia kopetdaghensis, Cichorium intybus, Carpesium divaricatum, and Leptocarpha rivularis.* Numerous studies indicated that sesquiterpene lactones may treat cancer by modifying many cellular signaling pathways, including PI3K/AKT, MAPK, JNK, NF-κB, TNF-α, and STAT3. Sesquiterpene lactones were shown to be significant in suppressing the proliferation of prostate cancer cell lines (DU-145, PC-3, LNCaP, MR49F, and BPH-1) in both laboratory and clinical settings.

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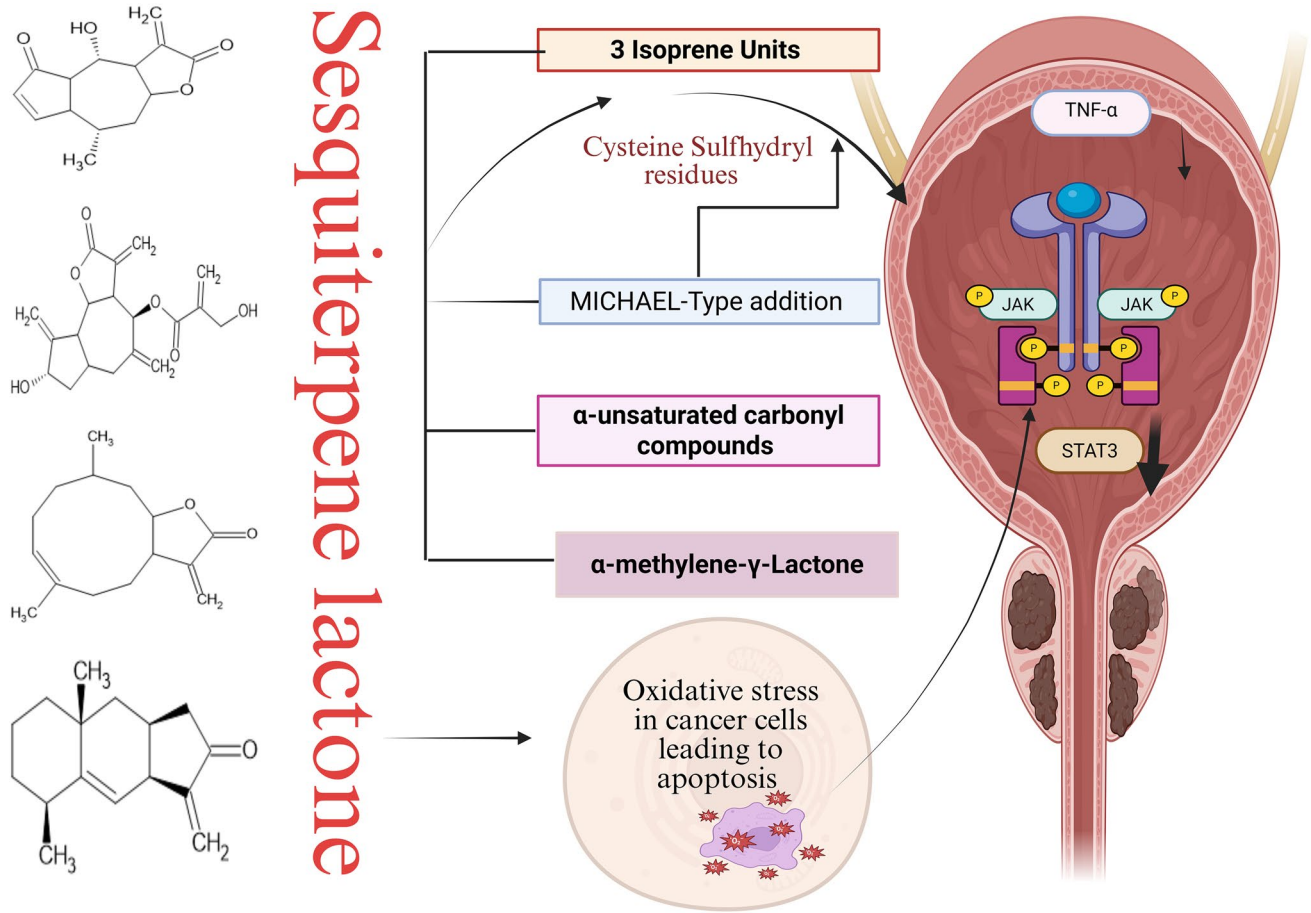
Graphical abstract



Keywords Prostate cancer · Sesquiterpene lactone · MAPK · STAT3 · NF-κβ · Natural products

Abbreviations

A-375	Cell line exhibiting epithelial morphology that was isolated from the skin of a 54-year-old, female patient with malignant melanoma.
AP-1	Activator protein-1
ART-Tf	Artemisinin-transferrin conjugate
ADHA	Anhydrodihydroartemisinin
BM-MSCs	Bone marrow mesenchymal stromal cells
BRCA1 and BRCA2	Breast Cancer gene 1 and Breast Cancer gene 2
Bax/Bcl-2 ratio	Measure of the expression levels of the Bax and Bcl-2 proteins, which determines how sensitive cells are to apoptosis
CAMs	Cell adhesion molecules
DMAPT	Dimethylamino Parthenolide
DNMT1	DNA methyltransferase 1
DU-145	Cell line with epithelial morphology that was isolated from the brain of a 69-year-old, White, male with prostate cancer.
EGFR	Epidermal growth factor receptor
GSH-γ	Glutamyl-cysteinyl-glycine
HaCaT	A spontaneously immortalized, aneuploid human keratinocyte cell line derived from the adult human skin of a 62-year-old male
HDAC	Histone deacetylases
HTB140	Human melanoma cell line
Holo-transferrin (Tf)	An iron-bound protein that can be added to cell culture media to help cells grow. It's used in cell culture because it's required for optimal growth of all types of cells
IGF-1	Insulin-like growth factor-1

IKKβ	A serine/threonine kinase that phosphorylates the IκB protein
IκBα	Member of a family of cellular proteins that function to inhibit the NF-κB transcription factor
IFN-γ gene	Protein interferon gamma (IFN-γ)
IGF-1	Insulin-like growth factor-1
IL-2	Interleukin 2
IL-1 beta	Interleukin-1 beta
JAK	Janus kinase
JNK	C-Jun N-terminal kinase
LNCaP	Lymph node carcinoma of the prostate
LTB4	Leukotriene B4
MMPs	Matrix metalloproteinases
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
NP'	Natural Product
PC	Prostate cancer
PC-3	Human prostate cancer cell line
PI3 K-AKT pathway	Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)
Phospho-p38 MAPK	A synthetic phosphorylated peptide around T180 & Y182 of human MAPK(NP_002742.3)
Phospho-ERK1/2	Extracellular signal-regulated kinase (ERK1/2)
Phospho-IGF-1R	Phosphorylation of the insulin-like growth factor (IGF-1) receptor and insulin receptor (IR)
PBMC	Peripheral blood mononuclear cells
PNT2	Immortalisation of normal adult prostatic epithelial cells
PSA	Prostate-specific antigen
p65/RelA	Transcription factor that regulates gene expression by binding to DNA
Si-TrxR1	A small interfering RNA (siRNA) that targets the thioredoxin reductase 1 (TrxR1) gene
SL's	Sesquiterpene lactones
STAT1	Signal transducer and activator of transcription 1
STAT3	Signal transducer and activator of transcription 3
TIC	Tumor-initiating cells
TNF-α	Tumor necrosis factor alpha
TrxR1	Thioredoxin reductase 1
IL-8	Interleukin 8
CCL2	C–C motif chemokine ligand 2
VCAP	Epithelial cell that was isolated from a White, 59-year-old, male patient with prostate cancer
VCaP-CR	Castration-resistant subline of the VCaP human prostate cancer cell line
Wnt/β-catenin	Wnt/β-catenin pathway

Introduction

Prostate cancer (PC) is a substantial global health concern for men, representing the most prevalent malignancy within this population and the 2nd leading cause of cancer-associated mortality. The prevalence of this pervasive disease typically occurs in middle-aged men, with an increase in prevalence between the ages of 45 and 60 [1]. The diversity of PC is extensively recognized, with notable alterations in its epidemiological and genetic features. There is a constant pattern of racial differences in the occurrence and death rates of PC, with African American men having a greater probability of attaining and suffering to this condition compared to Caucasian men [2].

These differences are driven by an intricate interplay of social, environmental, and genetic factors, highlighting the importance of personalized approaches to management of PC and responsible for about 7.3% of all cancer diagnoses worldwide. Each year, approximately 1.41 million newly identified cases of PC are reported, making it the fourth-most frequently detected cancer in all populations [3].

Prostate cancer (PC) risk is highly influenced by genetic predisposition; one of the most significant risk factors is familial inheritance. Twin and family investigations have given convincing proof that PC sensitivity is much influenced by genetic elements [4]. Men having a first-degree relative with PC are 2–3 times more probable to progress it. The identification of BRCA1 and BRCA2 gene abnormalities has improved the comprehension of PC dissemination within families. This allows for focused therapies [5].

Because of medication resistance and the limited effectiveness of current treatments, PC is still difficult to control, even though there have been great advancements in PC therapy. Unfortunately, treatment-resistant variants of the illness do emerge, even after early success with conventional chemotherapeutic meds and androgen-deprived treatments. Treatment results are worsened by medication absorption and toxicity concerns, which calls for new therapeutic approaches [6, 7].

Accordingly, the development of novel cancer treatments that are safe, effective, and generally well-received is a major goal for a great number of pharmaceutical and research companies. These medications should target cancer cells in a specific manner. When it comes to PC treatment, natural

substances have been the subject of a significant amount of research in this particular instance. In recent times, there has been a significant amount of coverage on the potent anticancer properties that sesquiterpene lactones possess. Plants that are members of the Asteraceae family are the ones that are mostly responsible for producing this category of secondary metabolites. Sesquiterpene lactones, also known as SLs, are terpenoid compounds that are believed to comprise an important component for their biological activity, which is an α-methylene-γ-lactone group [8].

The tenth Over the last 5000 years, researchers have discovered sesquiterpene lactones in a wide range of plant species. The Asteraceae family has the most of these compounds, however they are also common in the Euphorbiaceae, Solanaceae, Cactaceae, and more the eleventh A large body of literature suggests that sesquiterpene lactones may have anticancer properties. Their potential to cause cell death, limit cell proliferation, and slow down spread has been highlighted in in vitro and in vivo investigations of many malignancies, including Prostate cancer. NF-κB, STAT3, and Wnt/β-catenin are among the significant signaling pathways influenced by these chemicals, which contribute to the progression of cancer [6–11].

STAT3 inhibition of sesquiterpene lactones

Animal models and cancer cell lines have revealed numerous natural SLs in recent years that could block STAT3 signaling and cause cell death. ROS generation, GSH levels, and the GSH/GSSG ratio were all demonstrated to be changeable to cause cell death. Though the ultimate biological impact of all SLs is well-known, the molecular mechanism of their anti-STAT3 action has not been disclosed by all of them [12]. Cheng et al., demonstrated that 6-O-angeloylplenolin directly interacts with the SH2 domain of STAT3 to decrease both the constitutive and IL-6-induced STAT3 activity in lung cancer cells [13]. Studies have shown that the STAT3 SH2 domain is directly interacted with by alantolactone. Liu et al. claimed that parthenolide binds covalently to Cys residues of JAKs, which subsequently downmodulates the STAT3 pathway and lowers its kinase activity [14].

NF-κB inhibition of sesquiterpene lactones

SL's have a substantial anti-inflammatory impact by specifically alkylating the p65 subunit of the transcription factor NF-κB. Comprising two reactive centers, these SLs have been shown to influence several inflammatory processes, including oxidative phosphorylation, platelet aggregation, and the release of histamine and serotonin. The molecular mechanism behind their anti-inflammatory activity remains incompletely known. Recent study discovered that at μM concentrations, nine pseudoguaianolide-type sesquiterpenes from the flowerheads of Arnica species and germacranolide-type sesquiterpenes from the leaves of *Tithonia diversifolia* effectively inhibit the transcription factor NF-κB. NF-kB, a crucial regulator of the human immune response, is liberated from the cytoplasmic complex upon binding to its inhibitory component, IκB. The activated factor then translocates to the nucleus to initiate the transcription of its target genes. For example,compounds like helenalin and SL helenalin were examined for their ability to inhibit NF-κB activation. They were categorized into three groups: germacrolides, melampolides, and heliangolides. The compounds differed in molecular geometry and the number of alkylating structural components. The study indicated a molecular mechanism involving bifunctional compounds that crosslink cysteine residues in the p65 subunit, hence inhibiting DNA binding. Two SL molecules were required to alkylate the cysteine residues for the formation of monofunctional SL's [15].

In addition, research has shown that SLs may enhance the effectiveness of conventional chemotherapy medications, offering a potential paradigm for cancer treatment that utilizes a combination and mutually reinforcing approach. This study aims to explore the potential of SL's as a new class of therapies for battling prostate cancer, a worldwide burden; the epidemiology of this disease has been reviewed below. Numerous research support the anticancer properties of SL's [16].

Epidemiology of prostate cancer

According to information provided by the World Health Organization (WHO), it was anticipated that cancer will be responsible for roughly one fatality out of every six deaths in the year 2020, which would result in a total of nearly 10 million persons losing their lives. Within the same year, the Global Cancer Observatory (GCO) documented a total of 1,414,259 recent instances of pancreatic cancer around the globe, which led to 375,304 fatalities that were related with this particular kind of cancer. In terms of the death rate, it is ranked among the eight most lethal forms of cancer in the world. In spite of the fact that it is the most prevalent form of cancer in Latin America and ranks ninth in Asia, the data concerning prostate cancer are similar throughout a wide range of regions [17–19].

Consequently, this gives rise to the question of whether or not there are racial, ethnic, and socioeconomic distinctions in the biology of the development of PC, as well as whether or not some groups are more likely to be affected by more severe forms of the illness. Black men continue to have a greater incidence of prostate cancer and a poorer prognosis for the disease, even when demographically varied groups with equivalent treatment options are taken into account.

The death rate from prostate cancer was nearly twice as high for men of African American, Caribbean American, and European heritage as it was for white men. This was the case despite the fact that the incidence rate was greater for these groups of men. An increased risk of prostate cancer seems to have a genetic component, according to the findings, which show that this is the case. Furthermore, owing to the significance of racial disparities in PC, there has been a considerable decrease in the proportion of males in the nation that was investigated who had equitable access to healthcare [22–24].

Racial disparities in prostate cancer treatment lead to a decrease in equal access for males in the examined nation. Current cancer chemotherapy regimens pose significant health risks due to potential side effects, lack of efficacy, and multidrug resistance. Novel anticancer drugs could lead to more efficient therapies. Natural products and their semi-synthetic derivatives have been successful in treating cancer for decades. SLs, a class of NPs with 15 carbon atoms and three isoprenyl groups, have been identified as secondary metabolites in plant species, particularly in the Asteraceae family. These NPs have significant bioactivities, including antibacterial, anticancer, antiulcer, insect-feeding deterrent, phytotoxic, and schistosomicidal properties [20–23]

Sesquiterpene lactones

Plants contain a number of useful secondary metabolites, including sesquiterpenoids and SLs, which are good for people and other animals. Parthenolide (a sesquiterpene lactone) and Artemisinin (a sesquiterpene lactone) are two examples; various semi-synthetic derivatives of these two compounds are also present. The Asteraceae family produced the greatest quantity of these colorless, bitter, lipophilic components, which were also highly stable. Genera Tanacetum, Vernonia, Arnica, Ambrosia, Artemesia, and Helenium are all part of the Asteraceae family and are studied in chemotaxonomic investigations. C-15 terpenoids are abundant in several plant families, including Angiosperms, Winteraceae, Acanthaceae, Bombacaceae, Polygonaceae, Amaranthaceae, Lauraceae, Apiaceae, Lamiaceae, and Bombacaceae. The sesquiterpene lactone family, which includes more than 5,000 known chemicals, is an important class of secondary metabolites found in many plant species. Because of their high concentration of these chemicals, Asteraceae plants have been the subject of substantial research into their possible medicinal uses, leading to the identification of promising new pharmacological ingredients. Because of their many beneficial medicinal properties, including anticancer agents, antimicrobials, anti-inflammatory, and viral inhibitors, SLs have attracted a lot of attention [20, 24, 25].

Chemistry of SL

Among plant phytochemicals, SL are by far the most common. A family of plant natural compounds known as terpenoids includes essential oils, gibberellins, carotenoids, iridoids, saponins, steroids, abscisic acid, cardiac glycosides, and gibberellins. Terpenoid molecules known as sesquiterpene lactones have 15 carbon atoms and are identified by the presence of a lactone ring connected to an exomethylene group, abbreviated as α-methylene-γ-lactone. Three isoprene units, each with five carbon atoms, make up these compounds. The rings are organized in various ways, and these compounds commonly include one or more lactone rings that give them their special qualities. One reason these compounds have biological effects is because they contain the α–β unsaturated carbonyl group. The α–β unsaturated carbonyl group is an effective alkylating agent that may form Michael-type additions with nucleophiles inside cells, such as cysteine sulfhydryl residues in proteins, which weakens their biological activity [26, 27].

The interaction between the sulfhydryl groups of cysteine residues, glutathione (GSH), and the α–β unsaturated carbonyl group has the potential to generate oxidative stress and alter the equilibrium of the cellular redox system. In the process of sesquiterpene lactone production, sesquiterpene synthases, which play a crucial role, make use of farnesyl phosphate. Farnesyl phosphate is derived from the mevalonate and 2-C-methyl-D-erythritol-4-phosphate pathways, and it is used by sesquiterpene synthases, which play a crucial role in the manufacture of sesquiterpene lactones (SL's). SL's represent a diverse group of biologically active plant molecules classified into germacranolides, xanthanolides, eudesmanolides, guaianolides, and pseudoguaianolides as illustrated in Fig. 1, [27, 28, 29, 30, 31].

Structural requirements for antitumor activity

New research has identified key structural components for fighting cancers in living things. An α-epoxy cyclopentenone structure, an α-unsaturated cyclopentenone ring, or an α-methylene-γ lactone group must be present for this to be true. If a compound just has one of these functional groups, it must have other properties that make it active. Chemistry shows that carcinogenic sesquiterpene lactones form a Michael-type addition with thiols, such as cysteine, very quickly. Sesquiterpene lactones, which are known to inhibit tumor growth, cause this reaction, which in turn renders sulphydryl enzymes like phosphofructokinase and glycogen synthase inactive. Based on the results, sesquiterpene lactones may inhibit tumor development by targeting certain biological macromolecules that control cell division and other growth-related processes in the text [32, 33].

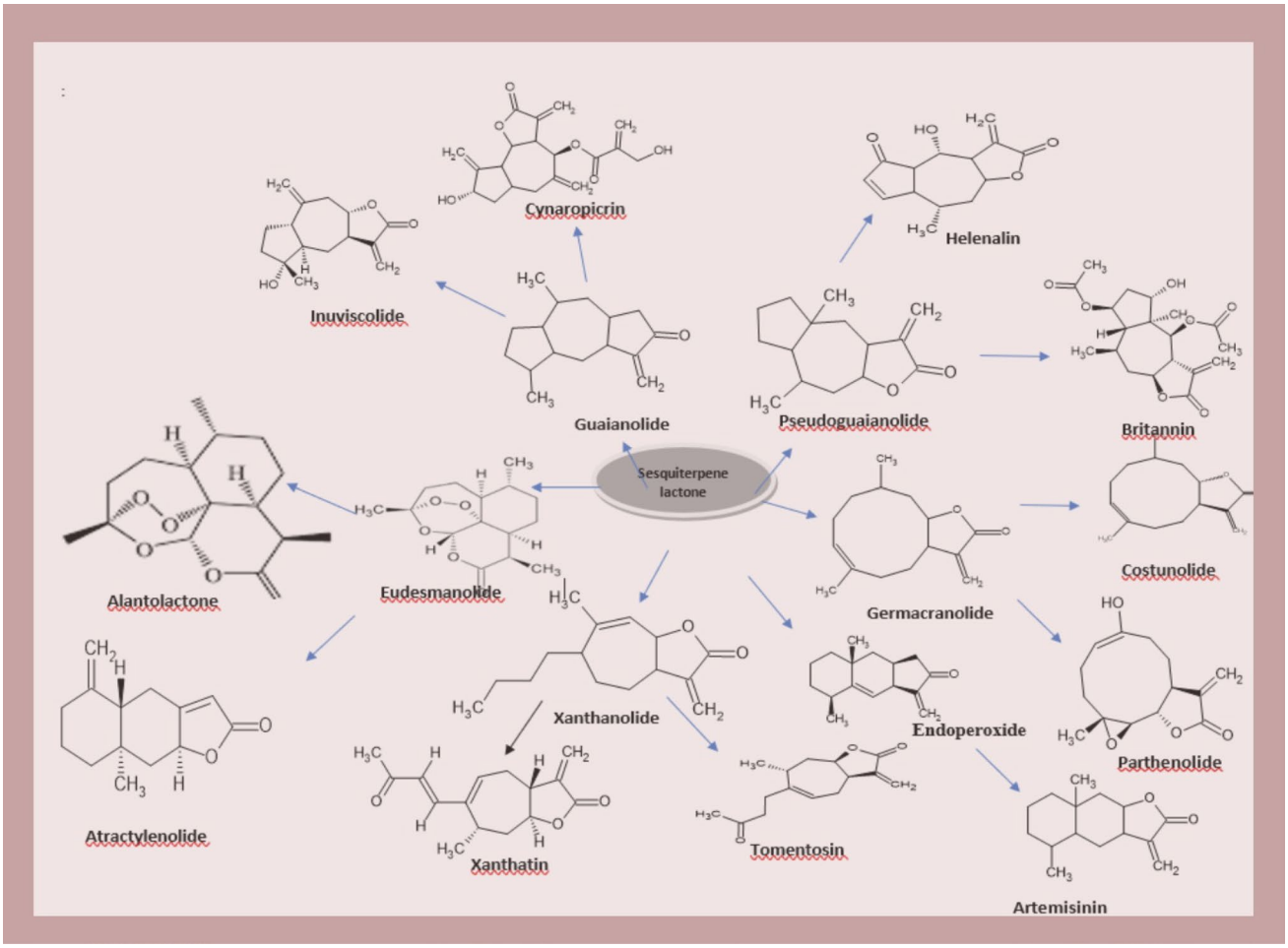


Fig. 1 Classification and structural diversity of sesquiterpene lactones (SL's):The figure shows the structural diversity of sesquiterpene lactones, a class of bioactive secondary metabolites found in the Asteraceae family. The central core, "Sesquiterpene lactone," is divided into major subtypes like guaianolide, pseudoguaianolide, germacranolide, eudesmanolide, and xanthanolide. Key molecules include Alantolactone, Costunolide, Parthenolide, Helenalin, Britannin, Cynaropicrin, Inuviscolide, Tomentosin, Eudesmanolide, Xanthatin, and Artemisinin

Antitumor activity of sesquiterpene lactones

Recent global research has extensively documented the potential anticancer activity of SLs. A majority of active sesquiterpene lactones exhibit cytotoxic effects against P388 as well as KB leukemia in laboratory conditions, and they also demonstrate effectiveness against P388 leukemia in living organisms [34]. Over 50 sesquiterpenes were assessed for growth inhibition against various tumor models, revealing that all cytotoxic sesquiterpenes contain a lactone function, mostly α–β-unsaturated with an exocyclic α-ethylenic linkage. Sesquiterpene lactones notably inhibit nuclear DNA synthesis, particularly the enzymatic activities of thymidylate synthetase as well as DNA polymerase, within tumor cells. These compounds interfere with glycolytic and mitochondrial energy processes, contributing to their antitumor effects [35].

Apoptosis is a programmed cell death process that involves two signaling cascades: intrinsic and extrinsic. It is involved in the treatment response of various cancer types and is a target for cancer treatment. Cancer cells have six hallmarks, including continuous growth signals, unlimited proliferation, resistance to proliferation inhibitors, apoptosis escaping, active angiogenesis, and metastasis. Sesquiterpene lactones, a diverse group of phytochemicals, can be used as sources for various drugs, including anti-inflammatory, anti-viral, antimicrobial, antimalarial, anticancer, antidiabetic, and analgesic activities. This review article briefly overviews the intrinsic and extrinsic pathways of apoptosis and the interactions between modulators of both pathways. It also summarizes the potential effects of sesquiterpene lactones on different modulators of apoptosis in various cancer cell lines and animal models. The main purpose is to provide future direction in cancer therapeutics [36].

Sesquiterpene lactones and their molecular mechanisms in prostate cancer (PC)

Cancer metastasis is a significant issue in cancer therapy, accounting for over 90% of global cancer-associated deaths. This process involves cancer cells spreading to distant tissues and organs, regulated by cellular signaling pathways. Plant-derived phytochemicals, including sesquiterpene lactones, have been shown to target molecular factors in cancer cells to combat metastasis. These phytochemicals have been shown to suppress the promotion and progression of different cancer types by acting on multiple cell-signaling pathways. This review article provides a brief overview of metastasis, its components, and the molecular mechanisms of their effects on different cancers. The review article provides a comprehensive understanding of the process of metastasis and its components [37].

SL's have the potential to specifically focus on and cure cancer stem cells and tumors without harming healthy cells. They demonstrate cytotoxic effects on prostate tumor-initiating cells (TICs) obtained from prostate cell lines including VCaP, DU-145, LNCaP, and PC-3, as well as from actual prostate tumor-initiating cells [36]. There were several distinct SLs molecules, each with its own method by which they exert their influence on prostate cancer. Prostate cancer inhibition was achieved by many signaling pathways, such as NF-κB and STAT3. The various molecular mechanisms of SL and their various targets have been discussed below [38].

SLs and STAT3

Several endogenous SLs have the potential to induce apoptosis. One of these pathways is the STAT3 signaling pathway, which has been discovered in recent years in many animal and cellular cancer models. Studies have demonstrated that induction leads to a reduction of glutathione (GSH), an elevated generation of reactive oxygen species (ROS), and an altered ratio of condensed glutathione (GSH) to oxidized glutathione (GSSG). While the ultimate biological outcome of each SL is well-documented, not all of them have revealed their molecular mechanism of anti-STAT3 activity. The signaling function of STAT3 in cancer cells has been demonstrated to be inhibited by 6-O-Angeloylplenolin, both in its intrinsic state and when activated by IL-6.

This inhibition is accomplished by specifically targeting the SH2 domain of STAT3. For example, Alantolactone has been shown to directly bind to the STAT3 SH2 domain, inhibiting JAK kinase activity and subsequently downregulating the STAT3 signaling pathway. The researchers noted that SL hinder the STAT3 signaling pathway by facilitating S-glutathionylation of certain cysteine residues in the STAT3 protein. Compounds with an α, β-unsaturated carbonyl group immediately interlink with glutathione (GSH) via a process called Michael addition. This interaction continues until the level of GSH is exhausted, at which point STAT3 undergoes S-glutathionylation. By blocking STAT3 phosphorylation, the whole signaling pathway is halted [39–42] The numerous SL's and their molecular mechanism of action were represented in the following Table 1.

SLs and NF-κB

Several naturally occurring sesquiterpene lactones trigger apoptosis in PC cells by specifically targeting the NF-κB pathway. This action entails the suppression of the P50/P65/IκBα kinase complex. Sesquiterpene lactones inhibit the interaction between the NF-κB p65 subunit and DNA [40]. Sesquiterpene lactones hinder the interaction between the NF-κB p65 subunit and DNA. Furthermore, they decrease the phosphorylation of IκB kinase (IKK), which in turn hinders the breakdown of IκB and therefore prevents the stimulation of the NF-κB transcription factor. The suppression of IKKβ kinase activity and NF-κB expression leads to apoptotic cell death in PC cells. Additionally, the inhibition of matrix metalloproteinases (MMPs) and cell adhesion molecules (CAMs), which are measured by NF-κB, also hinders cell growth [39, 55, 56].

SLs and TNF-*α*

TNF-α, a cytokine occupied in the expansion of PC, stimulates certain signaling pathways that are vital for promoting the persistence of tumor cells and the role of NF-κB in supporting cell survival has been recognized as crucial. NF-κB has been identified as pivotal in promoting cell survival [57]. Research has established that Parthenolide, a SL compound, inhibits NF-κB stimulation by targeting TNF-α. This inhibition occurs through the prevention of the IκB kinase (IKK) complex from associating with the TNF receptor, thereby obstructing signaling pathways including p65 nuclear translocation, transactivation, DNA binding, and IκBα degradation [58].

SLs and PI3 K/AKT and MAPK

The PI3 K signaling pathway is important for both cell survival and proliferation, and abnormal expression is frequently seen in the development of Prostate cancer[58]. Research investigated the levels of expression of IGFR-1 and other molecules associated with the PI3 K/MAPK pathway. The research found a substantial reduction in the

Table 1 Important Sesquiterpene molecules and their molecular mechanisms

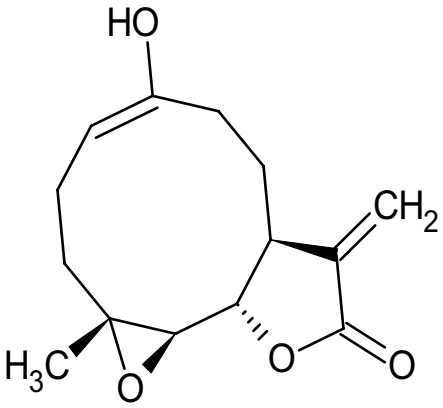
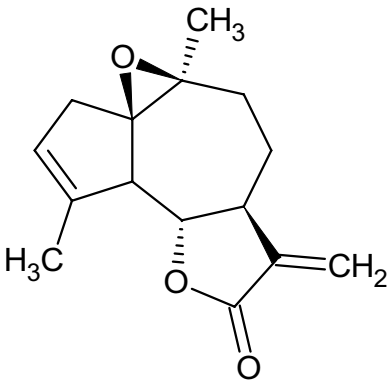
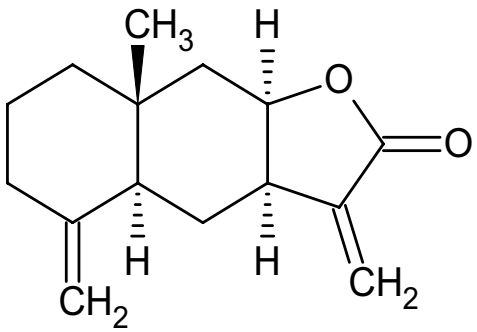
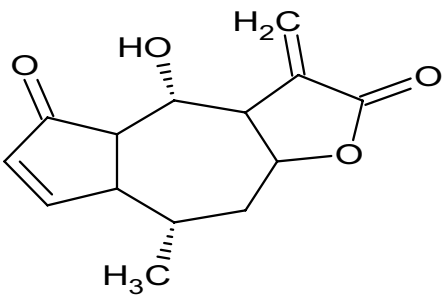
Molecules	Chemical structure	Biological source	Mechanism	References
Parthenolide		*Tanacetum parthenium and T. vulgare*	Inhibition of NFκB pathway and stimulation of phosphatidylinositol-3-kinase/Akt in prostate cancer cell	[43]
Arglabin		*Artemisia glabella*	Suppression of farnesyl transferase activates the RAS proto-oncogene, which reduces proliferation and induces apoptosis	[44]
Isoalantolactone		*Inula helenium,*	ROS induced ER stress by inactivating STAT3 and trigger death in DU-145 and PC-3 cells	[45]
Helenalin		*Arnica montana,*	It suppressed the thioredoxin reductase (TrxR1) and accelerate cell cycle arrest and ROS-mediated apoptosis	[46]

Table 1 (continued)

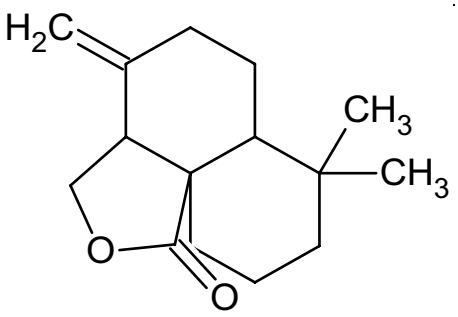
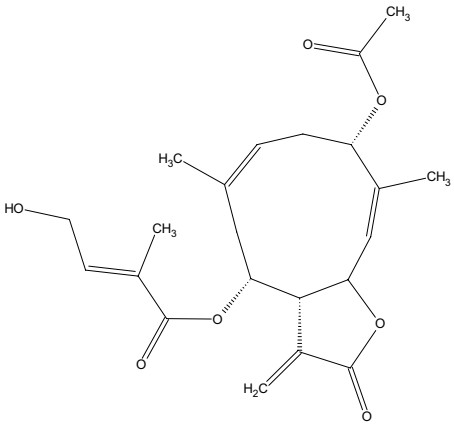
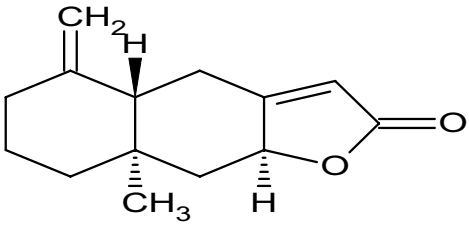
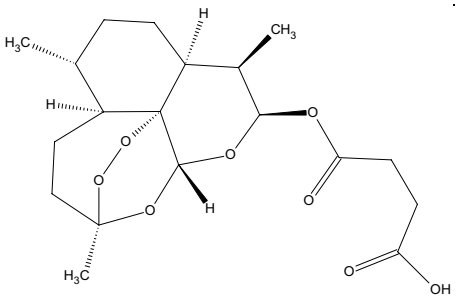
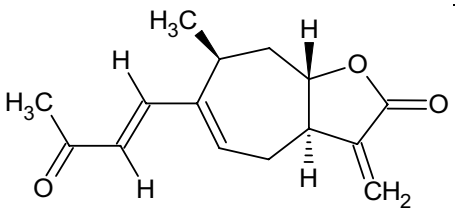
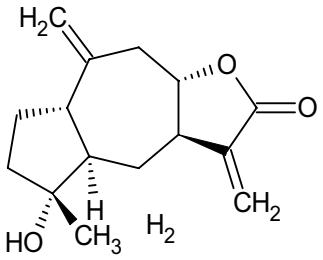
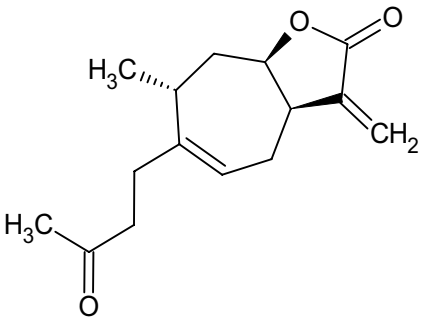
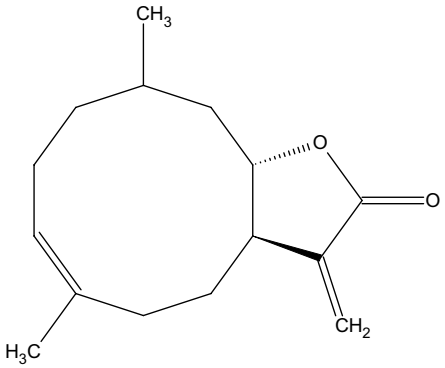
Molecules	Chemical structure	Biological source	Mechanism	References
Antrocin		*Antrodia camphorate*	Inhibition of PI3 K/AKT and MAPK signaling pathways and sensitize prostate cancer cell	[47]
Eupalinolide J		*Eupatorium lindleyanum*	It showed their effect by cell apoptosis, cell cycle arrest, MMP (Matrix metalloproteinases) disruption and DNA damage	[48]
Atractylenolide II		*Andrgraphis paniculate*	Inhibition of JAK2/STAT3 pathway	[49]
Artesunate		*Artemisia annua,*	Suppression of UCA1(Urothelial Cancer Associated 1) and in another study it suppressed AR (Androgen receptor) expression	[50]
Xanthatin		*Xanthium strumarium,*	Suppression of the signal transducer and activator of STAT3	[51]

Table 1 (continued)

Molecules	Chemical structure	Biological source	Mechanism	References
Inuviscolide		*Inula viscosa*	Stimulation of ATM/ATR kinase and contribution of NF-kB	[52]
Tomentosin		*Inula viscosa,*	Stimulation of ATM/ATR kinase and participation of NF-kB	[53]
Costunolide		*Saussuera lappa*,	Induce PC cell via activating MAPK and generation of ROS	[54]

levels of phospho-p38, phospho-Erk1/2, phospho-IGF-1R, and phospho-JNK in cells exposed to IR and sesquiterpene lactone compared to cells that were not treated. Furthermore, the simultaneous exposure to infrared radiation (IR) and sesquiterpene lactone resulted in a reduction in the levels of phospho-GSK3-β, phospho-AKT, and PI3 K, while the levels of phospho-β-catenin rose [59]. Previous studies have shown a connection between the initiation of the β-catenin signaling pathway via AKT phosphorylation and the onset of apoptosis. To summarize, a compound called sesquiterpene lactone specifically inhibits the signaling pathways known as MAPK and PI3 K-AKT, which ultimately leads to the promotion of apoptosis in the presence of IR radiation [60].

Sesquiterpene lactones on JNK pathway

Sesquiterpene lactones has the capacity to trigger the JNK pathway in prostate cancer cells. This route is a member of the MAPK (mitogen-activated protein kinase) family, which regulates a range of cellular functions, including apoptosis. When activated, JNK translocate from the cytoplasm to the nucleus of cancer cells [61]. Within the nucleus, JNK catalyzes the addition of a phosphate group to many transcription factors, hence triggering their activation. One such transcription factor that is affected by this process is c-Jun. Activation of c-Jun, in combination with other transcription factors, initiates the transcription of genes that stimulate apoptosis [62].

Various sources of sesquiterpene lactones

SL's are a diverse array of physiologically active chemicals mostly located in plants, especially within the Asteraceae family (as represented in the Fig. 2), however they are also present in other plant groups [63]. Carabrone, carabrol, and

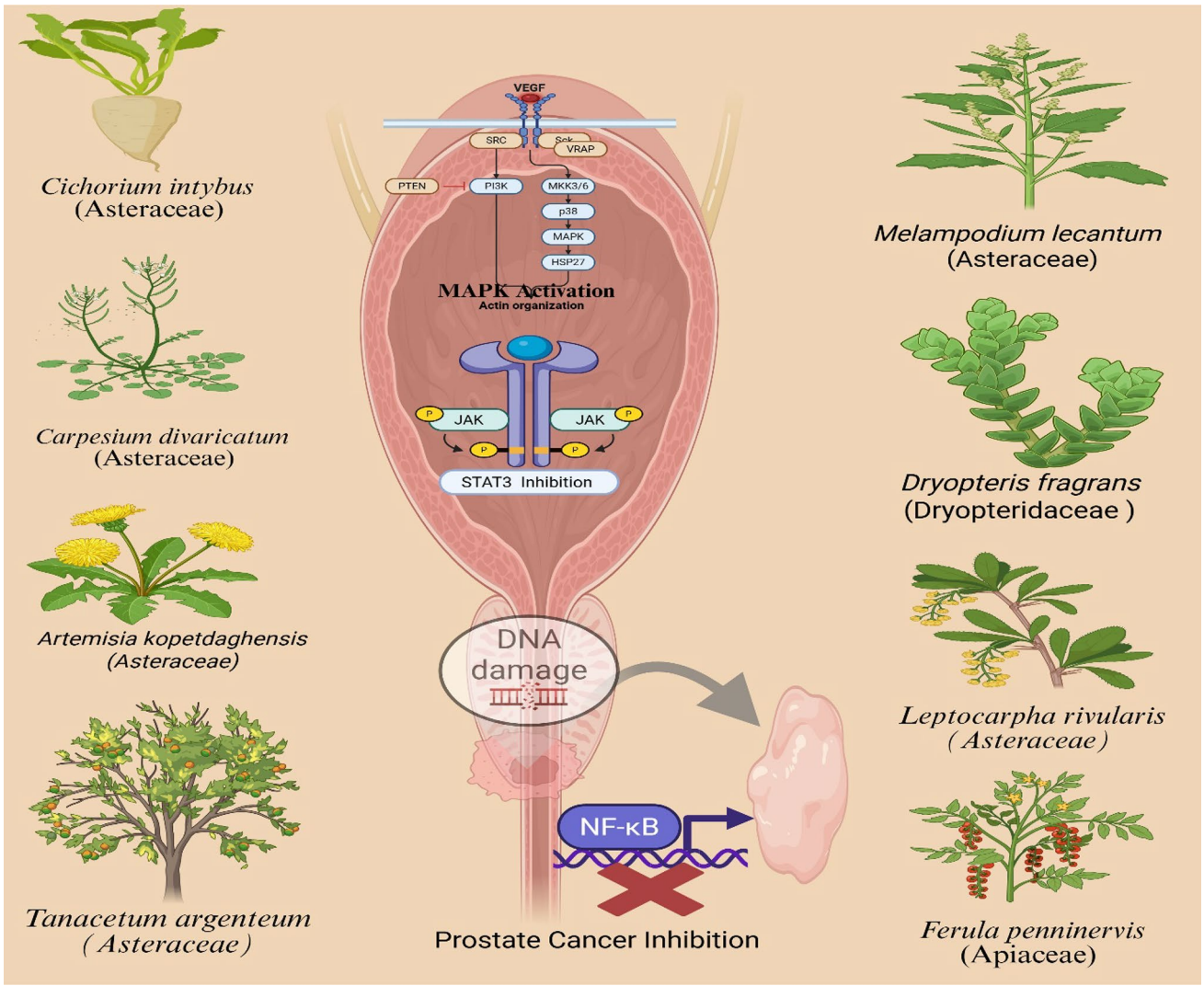


Fig. 2 Prostate cancer inhibition by sesquiterpene lactone–producing medicinal plants and associated molecular targets: The figure shows the inhibitory mechanisms of various medicinal plants, primarily from the Asteraceae family, against prostate cancer progression. These plants inhibit tumor suppression through central signaling pathways like MAPK activation, STAT3 inhibition, and NF-κB suppression, leading to DNA damage-induced apoptosis and reduced cancer cell proliferation. The phytoconstituents from these plants modulate upstream molecular targets like VEGF, JAK, PI3 K, and SRC, offering promising leads for prostate cancer therapeutics

carpesiolin, among other chemicals derived from *Carpesium divaricatum*, have shown substantial anticancer activity, especially for breast, lung, and liver malignancies. In a similar way *Cichorium intybus* possesses lactucin, lactucopicrin, and 8-deoxylactucin, each of which have sedative characteristics and have been shown to suppress leukemia and colon cancer cells [64]. In *Artemisia kopetdaghensis*, artemisinin, arteannuin B, and artemisinic acid have been extensively studied, with artemisinin being particularly effective against malaria and also showing promising activity against breast and ovarian cancers [65].

Tanacetum argenteum produces parthenolide, santamarine, and arglabin, all of which have demonstrated anti-inflammatory and anticancer properties, particularly in the treatment of melanoma, pancreatic cancer, and glioblastoma [66]. *Dryopteris fragrans* contains filicinic acid, albicanol, and fragransin, which are known for their anthelmintic properties and emerging anticancer potential, particularly against colorectal and gastric cancers [67].

Additionally, Leptocarpin, rivularin, and leptocarpanolide are the byproducts of the *Leptocarpha rivularis* plant, which has been shown in research to have cytotoxic effects on breast and lung malignancies[68]. *Ferula penninervis* contains ferutinin, jaeschkeanadiol, and lapidol, which are SLs with estrogenic properties. These compounds have potential in the treatment of osteoporosis and show its potential in fighting prostate and breast cancers [69].

Melampodium leucanthum is known for its production of melampodin, leucanthin-B, and diversifolin. These complexes have been found to suppress inflammation, have antimicrobial, and anticancer characteristics, specifically targeting skin, breast, and colon cancers. These SL's have significant roles in plant defense mechanisms and also show promise for human health, especially in treating different types of cancers [70].

The subsequent part provides an in-depth analysis of the biological activities of each SL, their specific molecular targets, and the most recent discoveries on their effectiveness in cancer treatment.

Carpesium divaricatum (CD)

CD belonging to the Asteraceae family, is commonly employed in conventional treatments across various countries in the Far East. It is recognized for its antipyretic, analgesic, antiparasitic, and anti-inflammatory characteristics. In Japan, China, and Korea, it is furthermore used for treating UTIs, sore throat, common cold, fever, and diarrhea [71].

In the 1990's, a phytochemical investigation was conducted on *carpesium divaricatum*, resulting in the isolation of a specific kind of sesquiterpene lactone called germacanolide. Subsequently, an additional 40 germacrane-type sesquiterpene lactones were identified from plants of the same species [72, 73]. In an investigation conducted by Kłeczek et al., 2021 explored the cytotoxicity and anti-inflammatory activity of *Carpesium divaricatum*. Cardivarolide H and incaspitolide A were two sesquiterpene lactone isolated from *Carpesium divaricatum*.

As sesquiterpene lactone was less known for its cytotoxic and anti-inflammatory effects. In this study researcher's motive is to assess the cytotoxicity of a novel compound (4,5,8,9-tetrahydroxy-3-oxo-germacran-6,12-olide) from *Carpesium divaricatum* on both normal cells and cancerous [72].

The researchers tested these compounds on different types of cells: skin cells, gastrointestinal cells, and prostate cells. They also looked at how these compounds affected inflammation by measuring TNF-α, IL-1β, IL-8, and CCL2 in human neutrophils triggered with lipopolysaccharide using ELISA. The sesquiterpene lactones under investigation exhibited non-selective activity against A-375 and HTB140 (melanoma cells), PC-3, DU-145, PNT2, and HaCaT [72].

Cichorium intybus (CI)

Perennial CI, a member of the Asteraceae family, is innate to the Americas, Europe, and Western Asia. It has been used for medicinal plants, vegetable crops, and coffee alternatives. Ancient Rome, Egypt, and Greece used it for these purposes, as does Uyghur folk medicine in China [77]. Many studies and experiments performed on CI proved its potency and health benefits such as immunoregulatory, antimicrobial, anti-hyperuricemia, antidiabetic, anti-inflammatory, anticancer, and antioxidant [75].

Additionally, many phytochemical studies performed on CI revealed various constituents in which sesquiterpene lactones mainly lactucin-like guaianolides, being recognized as one of the most distinctive and primary active constituents present in it [76]. Lactucin-like guaianolides have been found to impede the DNA-binding activity of the NF-κB transcription factor and decrease the levels of IL-6, IL-1, and TNF-α [77].

Research performed by Meg et al., 2022 on CI to know its cytotoxic as well as anti-inflammatory properties. To perform the study researchers isolated 21 sesquiterpene lactones of which five were unreported (one 12,8-guaianolides and four 12,6-guaianolides) and 16 known analogs. Among the total of 21 sesquiterpene lactones examined, four displayed notable inhibitory effects on the generation of inflammatory cytokines, alongside undergoing cytotoxic study showed that five sesquiterpene lactones showed antitumor activities against four tumor cell proliferation [78].

Artemisia kopetdaghensis (AK)

There are more than 500 species of Artemisia, making it one of the major genera in the Asteraceae family. AK is a member of the Artemisia family and can only be found in the wild in the northeastern regions of Iran, Turcomania, and Afghanistan [79]. In addition, this species is abundant in novel components and has received very little attention from scientists. Furthermore, studies revealed that sesquiterpene lactone can also be used as an antimalarial, antibacterial, antifungal, antioxidant, and cytotoxic effect. In addition to its antioxidant properties, sesquiterpene lactone has been revealed to have a cytotoxic impact, antifungal activity, antibacterial action, and antimalarial action, according to research [80].

A phytochemical experiment was conducted by Fattahian et al., 2022, whereby three novel sesquiterpene lactones of the eudesmanolide type were isolated from the apical portions of Artemisia kopetdaghensis. These lactones were identified as 3α,4-epoxypersianolide A, 4-epi-persianolide A, and persianolide A—three of which had not been reported before. In addition to these, three more sesquiterpene lactones of the eudesmane type are being investigated for their potential to have a cytotoxic effect on prostate cancer cells, particularly those of the DU-145 and LNCaP strains, for the purpose of the MTT experiment that is now being carried out. Following that, following research concentrated on the development of apoptosis using techniques such as western blotting, ELISA, and biochemical assays from the laboratory. It has been discovered via research that 11-epi-artapshin is

capable of inhibiting the growth of DU-145 cells and initiating apoptosis that is assisted by mitochondria. Inducing an excessive amount of reactive oxygen species (ROS), regulating the ratio of Bax to Bcl-2, and activating caspase-3 are all components of this mechanism [79, 81].

Tanacetum argenteum (TA)

The genus Tanacetum comprises approximately 160 species worldwide, of which 60 are present in Turkey in which 26 are endemic. This genus was found in Turkey, West Asia, and Europe belongs to family Asteraceae and it is used as an anthelmintic, diuretic, stimulant, antipyretic, and antimigraine [82]. Sesquiterpenoids and flavonoids are the main components of TA, by the isolation from these β-amyrin, β-sitosterol, 8α-angeloyloxycostunolide, spiciformin, 10αepoxide, desacetyl-β-cylclopyrethrosin, tatridin-A, desacetyltulipinolide-1β, tatridin-B, and desacetyllaurenobiolide were found in this genus [83, 84].

Out of all the Tanacetum subspecies, Orhan et al., 2015 conducted research to determine which subspecies of Tanacetum have the greatest levels of parthenolide. Parthenolide is the most significant molecule of sesquiterpene lactone, and it has anti-inflammatory and anticancer characteristics. has the greatest levels of parthenolide. *Tanacetum argenteum* extracts were treated with n-hexane, ethyl acetate, and methanol in a study that was conducted in 2017 by Albayrak and colleagues. The researchers investigated the cytotoxic and anti-inflammatory properties of these chemical compounds. In order to analyze the anti-inflammatory effects, they used the NF-κB and induced nitric oxide production (iNOS) assays. Additionally, the MTT test was utilized to evaluate the cytotoxic impact of the substance. The research showed that the n-hexane extract of *Tanacetum argenteum* exhibited anti-inflammatory activities in addition to cytotoxic effects on PC-3, MPANC-96, MDA-MB 231, HEK293, and CaCo-2cell lines. These results were uncovered by the researchers [84, 85].

Dryopteris fragrans (DF)

DF is a perennial herb, belongs to the Dryopteridaceae family. It is dispersed widely across Europe, Asia-temperate, and North America. It gains attention in North China due to its traditional use in treating rheumatoid arthritis and dermatological conditions [86]. It was found that many phytoconstituents from DF demonstrated various activities, including antibacterial, anticancer, antioxidant activities, antifungal, and anti-inflammatory. Zhong et al. (2017) investigated DF for its potential anticancer effects. In addition, scientists have discovered two previously identified chemicals and one novel sesquiterpene lactone, Dryofraterpene A. Researchers examined the anticancer efficacy of Dryofraterpene -A on PC-3, MCF-7, HeLa, HepG2, and A549 to confirm its biological activity. The outcomes presented that the novel chemical effectively reserved the proliferation of cancer cells [87–89].

Leptocarpha rivularis (LR)

Among the Asteraceae family, LR stands out as a distinct species. Its endemicity, monotypy, and dioeciousness are its most notable features. The Mapuche people of Chile call this perennial plant palonegro. You may find it all across the southern part of the country. Its setting is the woods of Valdivia. Historically, the Mapuche people have used this compound for its antioxidant, hypoglycemic, and anticancer properties; it contains sesquiterpene lactones, essential oils, flavonoids, and triterpene contents [90, 91].

Research conducted by Bosia et al., 2015 on Leptocarpin, a sesquiterpene lactone derived from LR, aimed at elucidating its impact on the apoptosis mechanism. For this researcher took different cell lines including PC-3, DU-145, HT-29, MCF-7, and MDA-MB-231. Their findings unveiled that the stimulation of the mitochondrial pathway inhibited NF-κB [92].

Ferula penninervis (FP)

FP belongs to the Apiaceae family, containing around 180 species. It is a perennial herb that spreads over mountains of Iran, North India, and Northwest China. FP, belonging to the genus Ferula, and its natural habitat is limited to the hot and dry region of Central Asia. The roots of FP are used as a traditional folk medicine in Kazakhstan for rheumatism, neurosis, epilepsy, and inflammatory diseases like wounds, dyspepsia, tumors, and gastroduodenal ulcers [93, 94].

An investigation done by Luca et al., 2021 intended to examine the cytotoxic properties of *Ferula penninervis*. The work included isolating SLs from a raw methanolic root extract by liquid–liquid chromatography. Through this extraction technique, a total of seven sesquiterpene lactones were obtained. In this study, two novel compounds were identified and named penninervins P and Q [94].

Additionally, five previously known guaiane-type sesquiterpene lactones like olgin, oferin, olgoferin, laferin, and daucoguainolactone-F were detected. Cytotoxicity assays were performed using various cell lines, revealing that olgin and laferin exhibited cytotoxic activity against androgen-dependent LNCaP prostate cancer cells [95].

Melampodium lecantum(ML)

ML is a herbaceous plant that is a member of the Asteraceae family and has an extended lifespan. It is indigenous to Colombia, Africa, Central America, the Caribbean, and

Southern America. This plant is widely used as an indigenous remedy for a variety of purposes, such as the treatment of fever, wound healing, infection, discomfort, antipyretic, antiulcer, and embolism. Additionally, its leaves are employed to alleviate diuretics and stomachaches. ML is a subspecies of the Melampodium species. It is prevalent in Texas and the southwestern region of the United States. The cytotoxic activity of the sesquiterpene lactone isolated from ML has been demonstrated by research [70].

A study was performed, on ML to know its cytotoxic activity. Researchers isolated Sesquiterpene lactone molecules from ML using bioassay-guided fraction. The extract underwent separation via flash column chromatography and reversed-phase HPLC, and five sesquiterpene lactones were isolated. Among these compounds, one new sesquiterpene named meleucanthin was identified, along with four compounds known as melampodinA, leucanthin-A, leucanthin-B, and 3α-hydroxyenhydrin [96]. To check and evaluate the cytotoxic activities of isolated compounds, they were screened against PC-3 and DU-145 prostate cell lines and results showed that the newly isolated compound meleucanthin is more potent [97].

Important SLs and their molecular mechanisms

Among their numerous useful characteristics of SLs, are compounds that inhibit inflammation, cancer, bacteria, and parasites. Their therapeutic potential is further improved by their ability to adapt, enabling them to engage with a diverse range of biological targets and regulate important cellular processes as represented in the Fig. 3**.**

The following section is a discussion of some of the most notable isolated SL's, including their anticancer mechanisms, pharmacological activity, and reported occurrences.

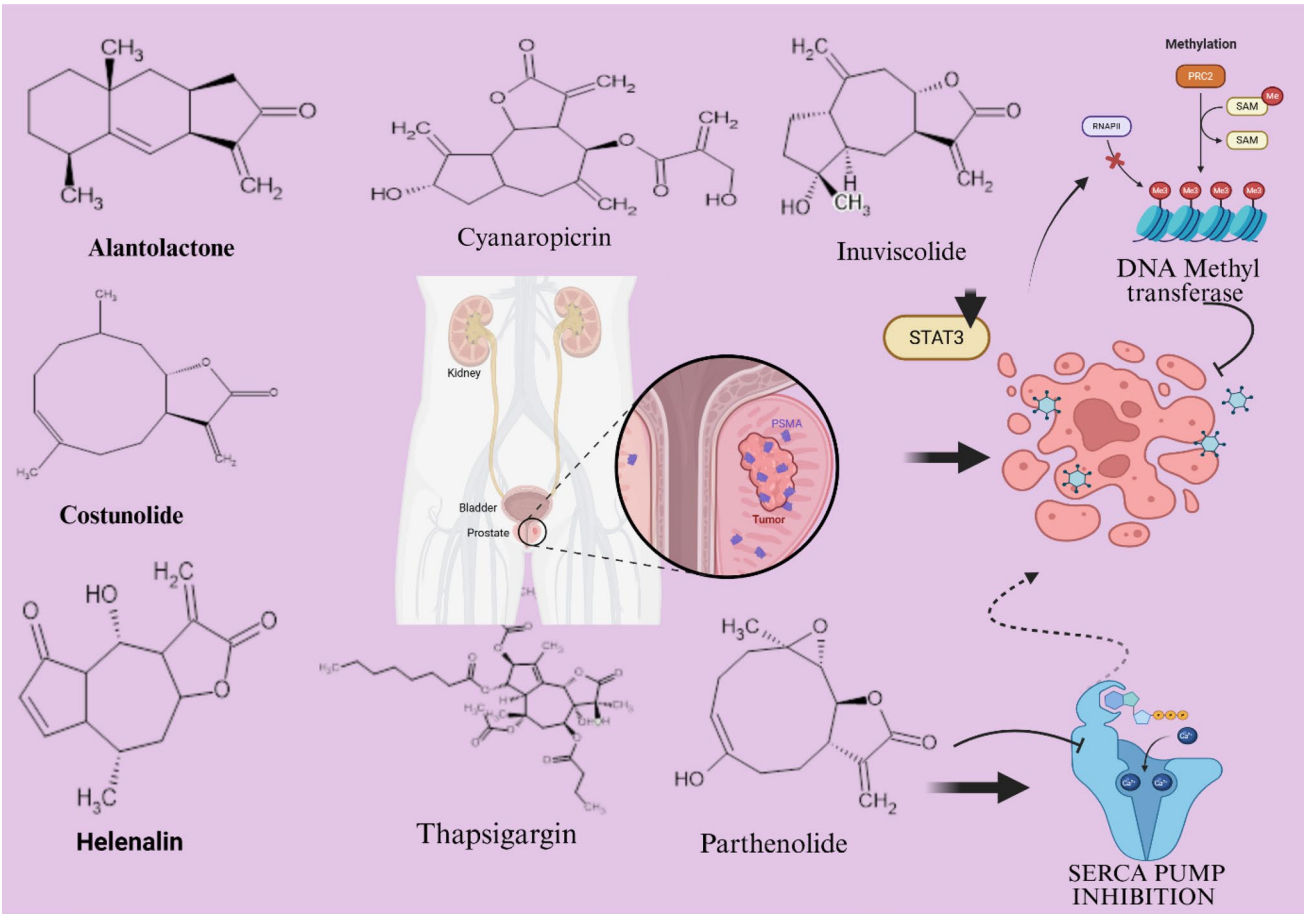


Fig. 3 Mechanistic insights into the anticancer activities of sesquiterpene lactones in prostate cancer: The figure shows the anticancer activities of key sesquiterpene lactones, including Antanolactone, Cynaropicrin, Inuviscolide, Costunolide, Helenalin, Thapsigargin, and Parthenolide, against prostate cancer. These compounds act through multiple pathways, including STAT3 inhibition, epigenetic modulation via DNA methyltransferase suppression, and SERCA pump inhibition, disrupting calcium homeostasis and causing endoplasmic reticulum stress and cancer cell death. These multimodal activities offer a promising approach for prostate cancer therapy

Alantolactone

The eudesmanolide alantolactone($C_{15}H_2O_2$) was isolated from *Inula helenium* roots and, in the course of time, it was also discovered in other Inula species and non Inula. Species [98]. For e.g., both *Saussurea lappa and Aucklandia lappa* [99].

Alantolactone is also used as the component causing allergic dermatitis of the contact type, with the species of genus Inula, it was first reported as antihelminthic [100] with consequent studies proving its peculiar beneficial properties, mainly the antitumor, the anti-inflammatory, and the antioxidant effect [101].

Babaei et al., 2020, set out to examine the effects of alantolactone on cancer cells as it pertains to the treatment of prostate cancer. The treatment of prostate cancer is a significant difficulty due to stem cells. In order to determine alantolactone's effects, PC-3 cells were subjected to the MTT assay. Then, three experiments were performed to measure chemoresistance, cell migration, and colony formation proficiency: the wound-healing assay, the chemosensitization assay, and the colony-formation assay, respectively. The results of gene and protein expression were also examined using western blotting and real-time PCR. The results demonstrated that STAT3 phosphorylation and signaling pathways were inhibited when nontoxic amounts of alantolactone (0.01 and 0.1 μM) were administered for 72 h. Additionally, alantolactone might control PC cell stemness by boosting p53 expression and decreasing Oct-4, Nanog, CD133, CD44, and SOX2 expression [102].

Costunolide

Costunolide ($C_{15}H_{20}O_2$) and evidence suggests that this chemical is derived from the mevalonate pathway. Separated from *Saussurea costus* in 1960, it is categorized as a germacranolide. For instance, costunolide is found in plant genera belonging to Asteraceae, such as *Inula, Helianthus, and Lactuca*, as well as in the Magnoliaceae [103].

In a study focusing on Costunolide's effective antiproliferative action against LNCaP, PC-3, and DU-145 cancer cell lines attained from ATCC®, researchers employed the clonogenic test, sulforhodamine B assay, and flow cytometric analysis using carboxyfluorescein. For PC-3 cells, it was found that Costunolide caused an initial rise in nuclear Ca2 + levels and activated a DNA damage response, leading to the phosphorylation of ATR proteins and this led to cell cycle arrest in the G1 phase, which was supported by elevated levels of p21.

Furthermore, this impact was characterized by the inhibition of the cyclin E complex as well as the activity of cyclin-dependent kinase 2 (CDK2), which ultimately resulted in the suppression of phosphorylated Rb that was produced. At the time that these experiments were carried out, the effects of costunolide were significantly mitigated by GSH, acetylcysteine, a ROS scavenger, the GSH precursor, and a Ca2 + chelator (BAPTA-AM), with the exception of the effect that was enhanced by Trolox®, which is a reactive oxygen species (ROS) scavenger. This led researchers to hypothesize that apoptosis is caused by a combination of oxidation–reduction process and cellular Ca2 + transport, with reactive oxygen species (ROS) serving as DNA modifiers [104].

Helenalin

Helenalin ($C_{15}H_{18}O_4$), is the most constant terpene in *Arnica Montana* [105]. Helenalin is recognized for its ability to prevent the nuclear transcriptive activity of NF-κB, a transcription factor crucial for stimulating inflammatory cytokine. This function is significant as it contributes to regulating immune-driven inflammation and the development of certain cancers [106]. It also reflects specific mechanistic pathways that impede the process of cellular proliferation, thereby offering the potential for cancer cell reversal through various means, such as telomerase blocking, stimulation of ROS generation DNA, apoptosis, and inhibit the protein synthesis [107].

The main discovery is a tendency to stop the stimulation of NF-κB, which was established in T-cells, epithelial cells, and B-cells, after being exposed to several stimuli, particularly sesquiterpene helenin. This inhibition effectively nullifies the expression of downstream genes via the κB promoter. Importantly, this inhibition appears to be selective, as it does not interfere with transcription factors like TDP, Sp1, or STAT 5, the NF-κB [108].

Research of helenalin in an in vitro model, conducted with PC cells, revealed an upregulation of ROS-associated apoptosis. Additionally, it has been shown to enhance the G0/G1 phase of the cell cycle. showed. The Selective killing of TrRx1 in prostate cancer indicates such an effect of helenalin. The findings revealed that helenalin has the ability to cause apoptosis in prostate cells which are cancerous and to likewise involve the cells in a new cycle positioned somewhere at the G-phase [109].

TrxR1, a particular isoform, is directly linked to aggressive types of PC. In addition, investigations have shown that statin medicines might cause a substantial increase in the expression of the p27 protein in PC-3 prostate cancer cells, beyond the levels seen in normal cells. Blocking TrxR1 might potentially slow down the transition to an androgen-independent stage in prostate tumors [110]. Based on study, it was found that helenalin treatment of DU-145 and PC-3 cell lines lowered TRXR1 levels.

This was achieved by inhibition of the enzyme and through decreased production of splice variants.

Significantly, following the insertion of a TrxR1 plasmid through transfection, helenin effectively suppressed the excessive production of proteins in these PC cells. This suggests that helenin actively acts on the TrxR1 enzyme [110]. This study replicates previous findings that TrxR1 inactivation raises ROS levels in gastric cancer cells, and it also finds that knocking down TrxR1 in prostate cancer cells has the same effects [111]. On the other hand, helenalin was found to hinder the stimulation of NF-κB via impeding the breakdown of IκBα. However, data also suggested that helenalin could prevent the reduction of IκBα caused by CD437, indicating a potential mechanism where CD437 might facilitate the degradation of IκBα [108].

Yang et al. explored the mechanisms behind helenalin's anti-prostate cancer effects in vitro. The researchers employed three siRNAs targeting TrxR1 were transfected into DU-145 and PC-3 cells, and RT-qPCR confirmed effective silencing of TrxR1 expression in both cell lines, by Si-TrxR1 showed the most effective knockout, making it the choice for subsequent experiments. TrxR1 was notably overexpressed in DU-145) and PC-3 cells following transfection with the TrxR1 plasmid, as confirmed by RT-qPCR (represented in the Fig. 4).

It was observed that helenalin notably intensified the reduction in TrxR1 mRNA expression caused by si-TrxR1. The rise in TrxR1 mRNA expression caused by the TrxR1 plasmid was reduced following co-treatment with helenalin. Western blot analysis revealed that helenalin treatment further decreased TrxR1 protein expression in DU-145 and PC-3 cells transfected with si-TrxR1. Si-TrxR1 is a small

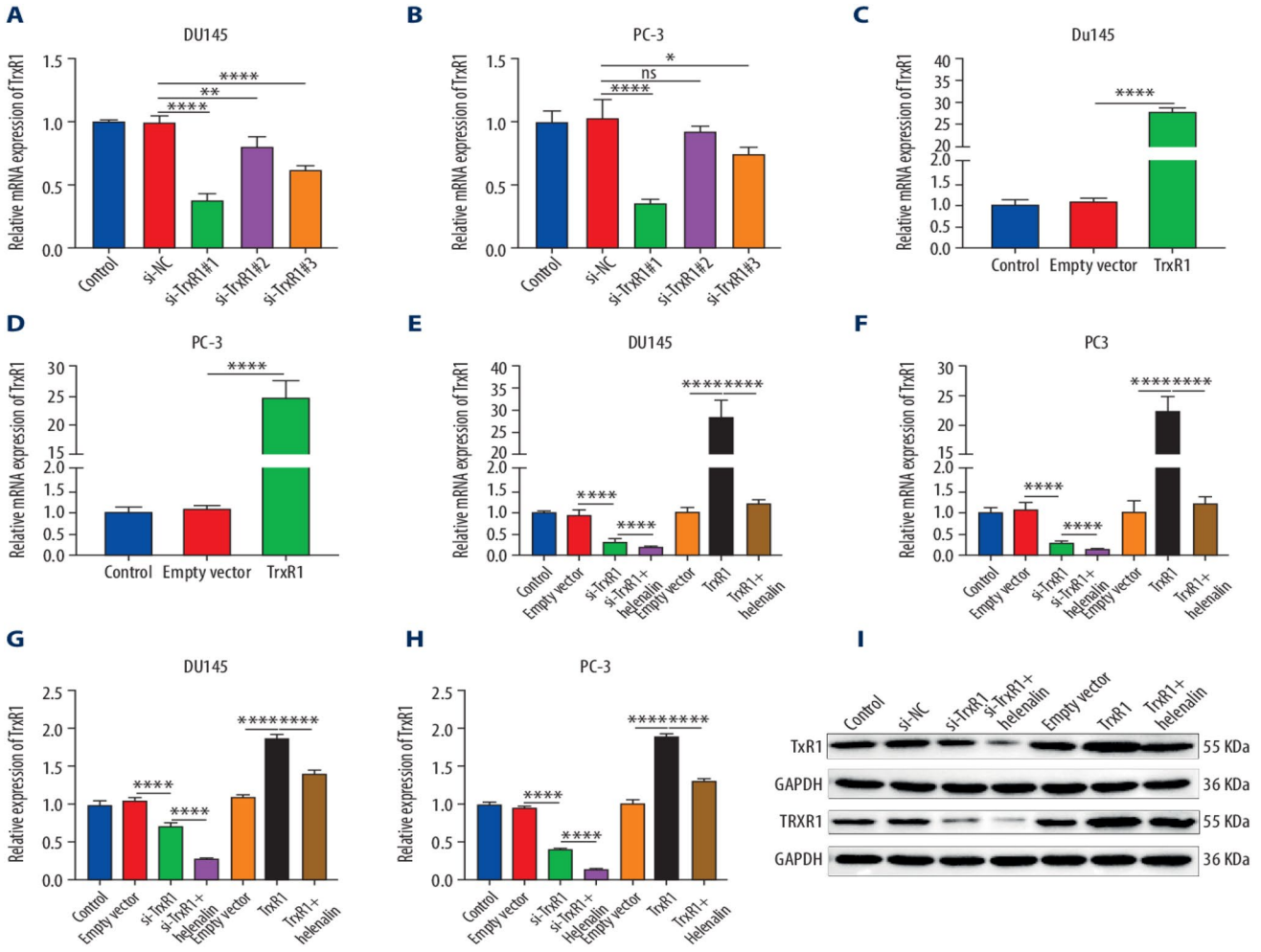


Fig. 4 Expression Analysis of helenalin on Target Proteins in DU-145 and PC-3 Prostate Cancer Cell Lines Using Western Blotting: Western blot analysis of protein expression in DU-145 and PC-3 prostate cancer cell lines. The immunoblots show the expression of target proteins (~ 55 kDa) and β-actin (~ 36 kDa) as a loading control. The corresponding densitometric quantification is presented on the right, showing the relative expression normalized to β-actin. Med Sci Monit. 2021 Jun 14;27:e930083-1–e930083-16. https://doi.org/10.12659/MSM.930083. This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

interfering RNA (siRNA) that targets the thioredoxin reductase 1 (TrxR1) gene protein expression was significantly reduced after co-treatment with helenalin, compared to transfection with the Si-TrxR1 is a small interfering RNA (siRNA) that targets the Si-TrxR1 is a small interfering RNA (siRNA) that targets the thioredoxin reductase 1 (TrxR1) gene gene plasmid. The results indicated that helenalin treatment significantly reduced TrxR1 expression in prostate cancer cells [112, 113].

Cynaropicrin

Cynaropicrin is a group of guaianolide-type sesquiterpene lactones, characterized by the chemical formula ($C_{19}H_{22}O_6$) and the skeleton of five-membered cyclohexane rings. Scientists first isolated the sesquiterpene lactone, cynaropicrin, from the artichoke flower in 1960 [114]. Approximately 5 years later, they found that same compound in two other species identified by the binomial name *Cynara cardunculus* L. and *Cynara scolymus* L. Thereby establishing its utility in chemotaxonomy. Cynaropicrin was also found in many species of the Asteraceae groups; specifically, in some species like *Centaurea drabifolia* subspecies floccosa(Boiss.) Wagenitz et Greuter [115].

Biological attributes reveal that the molecular structure of the constituent sesquiterpene lactones contains the pharmacophore, the ring of γ-butyrolactone, which is responsible for such properties [125]. There has been an increasing trend in studying the roles of flavonoids, particularly cynaropicrin, which has been extensively researched in pharmacological studies. The discovery of numerous properties such as antitrypanosomal, antitumor, anti-inflammatory, and anti-hepatitis C virus effects represents just a fraction of its potential. Considering these novel and diverse biological reactions, cynaropicrin is worth being further study for drug production. Its unique chemical structure and its pharmacological properties position cynaropicrin as a promising initial basis for drug discovery and development giving concern to many medical domains [114].

A study evaluating the potential of cynaropicrin, as an adjunct to apoptotic (cell death) strategies focused on inhibiting the STAT3 pathway. STAT3, a transcription factor is known to stay always activated irrespective of cancer type, providing a major means for anti-apoptotic function and tumor resistance to chemotherapy drugs [116].

Several studies have already highlighted the STAT3 signaling pathway as a route for suppressing survival signaling in cancer cells, thereby promoting apoptosis. This shows that a Stat3 inhibition strategy could represent a good strategy for treating cancers. In this study, the researchers utilized the THP-1 cells activated through the STAT3 signaling pathway of IL-6 cytokine, along with the human prostate cancer cell line DU-145, known for its active STAT3 expression [117, 118].

The results indicated that cynaropicrin effectively blocks the activation of STAT3, whether it is triggered by an external stimulation or by the depletion of the antioxidant glutathione (GSH). Reduced STAT3 activity led to a decline in the expression of genes related with cell growth and redundant functions. As a result, the experiment showed cell death, as well as an increased ability of the chemotherapeutic drugs cisplatin and docetaxel to kill cells. Numerous studies have highlighted that inhibiting the STAT3 signaling pathway not only slows down the propagation of PC cells but also impedes their growth. This suggests that blocking the STAT3 pathway could serve as a therapeutic approach for prostate cancer [118, 119].

Thapsigargin

Thapsigargin ($C_{34}H_{50}O_{12}$) was successfully isolated to its base structure in 1978. It had been identified as the predominant compound in the *Thapsia garganica* L., an umbelliferous species related to Apiaceae, which is widely spread in the Mediterranean area. Till today, this plant has remained a key component of folk medicine, since it is an effective remedy for acute bronchitis and pneumonia as well as for toothaches. The French Pharmacopeia has collectively described the resin of *Thapsia garganica's* root in these invaluable pharmacy treatises [120].

Thapsigargin functions as a suppressor of the SERCA pump, which is a distinct category of active calcium transporter located on the sarcoplasmic/ER membrane. Inhibiting this channel first disturbs the homeostasis of calcium inside the cell, which is crucial for regular cellular processes, eventually leading to programmed cell death [132, 133]. The ability to elicit programmed cell death at any stage of the cell cycle has also been noted for this SLs type. Huang et al. (2018) investigated the impact of thapsigargin on the development of apoptosis in PC cells. The research evaluated different doses of thapsigargin (0, 1, 10, and 100 nM) and their impact on the growth of PC-3 cells using a Cell Counting Kit-8 assay.

The results demonstrated a significant inhibitory impact of thapsigargin on the growth and division of prostate cancer cells. In addition, thapsigargin markedly enhanced apoptosis rates and the activity of caspase-3/9 in these cells. Protein expression analysis showed significant reductions in levels of phosphorylated mechanistic target of rapamycin (p-mTOR), phosphorylated RAC-α serine/threonine kinase, F-actin, and paxillin. Conversely, there was a notable increase in the levels of cofilin-1 protein following the onset of metabolic stress in PC cells [123, 124]. The findings of studies suggest a connection between thapsigargin-induced cell death in PC

cells and the regulation of signaling pathways associated with cofilin-1 and paxillin.

Parthenolide

Parthenolide ($C_{15}H_{20}O_3$), a sesquiterpene lactones of germacranolide class, is one of the most powerful ingredients for sure and are originally prepared from the leaves and flowers of *Tanacetum parthenium* feverfew plants. For centuries, this element has held a significant place in traditional Chinese medicine, valued for its diverse applications. It has been deployed for various purposes like relief of fever, the pain of conditions such as migraine and rheumatoid arthritis, and also as a cure for insect bites [125]. It was observed that parthenolide targets and inhibits cyclooxygenase (COX), an enzyme that is essential for the NF-κB signal transmission pathway and additionally it also affects STAT3, MAPK, and IKK2 signaling pathways. Multiple literatures have shown the remarkable anti-inflammatory and antitumor properties of parthenolide, as well as its analogues and derivatives.

These effects have been identified in several signaling pathways in human cancer cells, as shown by a substantial body of research [126, 127]. Parthenolide exerts its effects via a diverse range of mechanisms, targeting many specific molecules or pathways. This results in the phosphorylation of the EGF receptor, the disruption of AP-1, and the interference with the activation of STAT3, and interference in the activation of STAT3, leading to the activation of JNK. Moreover, the molecular mechanisms via which parthenolide functions primarily include the inhibition of DNA binding by crucial transcription factors, including NF-κB, as well as pro- apoptotic stimulation of p53, which consequently leads to the depletion of reduced glutathione [128, 129].

It was noted that parthenolide alone accomplishes all of these events rapidly by stimulating the production of ROS [130] which enhances the activity of histone deacetylase (HDAC) [131] and inhibits the action of DNA methyltransferase 1 (DNMT1). In addition to that it can also alter microtubule function by specifically binding to tubulin [132]. Conversely, a distinct advantage of parthenolide is its ability to exert selectivity on cancer stem cells while sparing healthy cells. It works by stimulating apoptosis through mitochondrial and caspase signaling pathways with a salient action on the cytosolic calcium. Additionally, it disrupts the cell cycle and impedes the development of new tumors [133].

The limited solubility of parthenolide in water hampers its bioavailability, leading to a modest effect size. Consequently, this poses challenges for its use as an anticancer medication. To address this issue, a sequence of parthenolide byproducts were synthesized by the production of imines using primary and secondary amines with the endocyclic component [134, 135]. It was also reported that the polarity of the compound increases significantly when the DMAPT gets formulated as fumarate salt, resulting in a 1000-fold increase in water solubility compared to that of parthenolide. At the same time, this salt acts as a prodrug and from the body fluids, it gets efficiently transformed back to parthenolide. DMAPT should be comparable to parthenolide in their mechanism of action according to early molecular research [136, 137].

Nowadays radiotherapy is remarkably an accepted modal used for treating cancer yet it may be countered by damaged surroundings of healthy tissues from radiation. In the mice studies, it is demonstrated that DMAPT increases rays dealing cell lines in prostate cancer cells in contrast to the primary pulp epithelial cells from the damaged by rays. Providing the greatest advantage, DMAPT is as safe for oral administration as for use in powerful clinical settings, without the need to change the radiation exposure schedule. The researchers suggested that DMAPT could potentially mitigate the side effects of radiotherapy for prostate cancer, which may encompass urinary incontinence, impotence, fecal urgency, and infertility [138, 139].

On the other hand, prostate cancer cells that are resilient to radiation may exhibit excessive activation of a different transcription factor called NF-κB.

This research study has the ability to be used in a clinical setting to develop DMAPT medicines that improve the efficiency of radiation in treating PC. The conclusive nature of this outcome arises from the findings of research conducted on PC-3 prostate tumor xenografts, which demonstrated a more pronounced decrease in tumor development when oral DMAPT and radiation treatment were administered concurrently, as opposed to when they were administered separately [140, 141].

Morel et al. found that castration activated NF-κB/p65 in mouse and human prostate cancer models, leading to a notable rise in AR variant-7 (AR-V7) expression and a slight increase in AR levels. Researchers found that prolonged enzalutamide treatment and AR inhibition in VCaP-CR cells significantly increased total and activated NF-κB (phosphorylated-p65) expression.

The greatest decrease in tumor growth occurred when mice were castrated alongside DMAPT treatment of end-point tumors revealed that surgical castration alone elevated phosphorylated-p65 expression [142]. DMAPT treatment reduced the significant increase in AR and AR-V7 protein expression observed after castration. It was observed that DMAPT treatment notably reduced AR-V7 expression, along with decreases in mRNA AR-FL and AR variant levels. RNA-seq of end-point tumors confirmed our IHC findings, showing that the combination of castration and DMAPT significantly reduced AR-V7-associated gene expression.

Inuviscolide

Ferula communis, a member of the Apiaceae family, produces a guaianoline-type sesquiterpene lactone known as inuviscolide, with a chemical formula of $C_{15}H_{20O3}$. This compound is the primary metabolite of *Inula viscosa*, a plant of Asteraceae family. *I.viscosa* has high value as a medicinal plant of major relevance in the areas of the Mediterranean Basin, rich in anti-inflammatory agents [143, 144].

In the research conducted by Hernández et al., 2001, inuviscolide was able to prevent inflammation in mice. The trial's purpose was to establish the correlative effects of both inuviscolide and ilicic acid, another compound derived from *I. viscosa*, on cell degranulation, neurogenic drive, leukotriene biosynthesis, and actions. Experimental methods required the application of different inflammation-inducing agents for ear and paw edema, and the utilization of PLA2 and serotonin for inflammation responses other than ear and paw. The inuviscolide ear models were treated topically and paw models were injected with subcutaneous or intraperitoneal infusion. LTB4 production on rat peritoneal neutrophils was measured by HPLC.

The study indicated that inuviscolide reduced PLA2-induced oedema by 98 (µmol/kg). Treatment did not affect serotonin-induced fluid buildup. The inuviscolide IC_{50} value of 94 µM indicated LTB4 generation inactivation. The findings showed that inuviscolide is the main anti-inflammatory component of *Inula viscosa*, outperforming ilicic acid. It inhibits mastocytes' release of inflammatory mediators and leukotriene production mediated by phospholipase [145, 146].

In an investigation researchers explored the properties of sesquiterpene lactones, specifically isolated compounds from *Inula viscosa* leaves, on melanoma cells. Notably, inuviscolide (Inv) was observed to reduce the expression of the p65 subunit of NFκB in these cells. The research examined the effect of these purified substances on the production of pro-inflammatory cytokines from human peripheral blood mononuclear cells (PBMCs) in a laboratory setting, specifically under exposure to phorbol myristate acetate (PMA) or lipopolysaccharide (LPS). During the study, PBMCs were cultured in RPMI-1640 culture medium comprising fetal bovine serum, penicillin, and streptomycin at 37 °C for 24 h. Inuviscolide was added at a final concentration of 1 µg/ml for PMA and 20 ng/ml for LPS, and during the last 4 h of incubation, the cells were stimulated [52, 147, 148].

Additionally, MG-132, a proteasomal inhibitor, was added to the samples at specific steps, with a final concentration of 3 µM compound. The research intended to explore the potential mechanism of action of these compounds among other aspects. They adopted control sample which was represented by a DMSO-treated sample to a similar extent to our samples [52, 149, 150]. The impact of Inuviscolide therapy was estimated by the detection of NFκB subunits and STAT1 in the whole blood cells with pink blood.

Cell lysates were separated using SDS-PAGE (10% SDS-PAGE). Results pointed to the reduction of IFN-grav, IL-2, and IL-1β production and the slight TNFα secretion increase due to the application of those compounds. Remarkably, despite the increased level of TNFα, the proliferation of human PBMCs remained unaffected. On combining bNSCS cells with Western blot, they noted p65/RelA of NFκB and STAT1 protein level decrease, explained by ubiquitin degradation. Though there were no changes in the levels of p50 (NFκB) or STAT3 expression, we noticed other proteins to be overexpressed. It was found that the application of such compounds are used in the treatment of inflammation, especially in cases involving excessive secretion of cytokines by cells [151, 152].

Artemisinin

Artemisinin with chemical formula ($C_{15}H_{22}O_5$) obtained from *Artemisia annua* (also called sweet wormwood or in Chinese "qinghao"), along with its derivatives, is highly effective against various strains of Plasmodium falciparum, the parasite liable for causing malaria in humans. This compound has an established track of safety applications for malaria treatment in humans [153]. It is not only functions as an antimalarial drug but also acts as an anticancer substance which was examined in lab tests and animal experiments. It provides a peroxide bridge (R–O–O–R0) which is irreplaceable for its efficacy against malaria and cancer diseases. Artemisinin functions by disintegrating the endoperoxide bridge, thereby liberating free radicals [154, 155].

This process is particularly powerful in the presence of Fe(II) ions, and it is thought to be accountable for the cytotoxic effects on the malaria parasite. While the specific molecular targets of artemisinin radicals remain unknown, research suggests that they activate the caspase cascade, which in turn triggers the suicide pathway in cancer cells. Iron is crucial for cellular growth, and in mammalian cells, it's predominantly found in the form of Fe(III), which is water-insoluble neutral conditions [156, 157].

To facilitate its transport Fe(III) with transferrin (Tf), a soluble protein, forming holo-transferrin (holo-Tf). After that, holo-Tf selectively binds to the transferrin receptor (TfR) located on the cell surface. This process is sophisticated and involves the internalization of the complex by endocytosis after receptor-mediated uptake to bring iron into the cell. As artemisinin utilizes iron intracellularly for activation, a feasible approach to further elevate its anticancer efficiency can be achieving the co-delivering iron and artemisinin to cancer cells simultaneously. This approach relies on the prodrug property of increasing artemisinin and thereby its anticancer action [158]. Artemisinin can form

peroxide inside cells when activated by iron and as a result, an endoperoxide group of reactive radicals is created. The molecular explanation for artemisinin's cancer cell specificity lies in its activation mechanism, wherein cancer cells frequently exhibit overexpression of transferrin receptors (TfR) to facilitate iron uptake, while normal cells typically display low levels of TfR expression. To capitalize on this phenomenon for commercial purposes, a researcher has developed artemisinin-conjugated transferrin (ART-Tf), a synthesized compound created by linking artemisinin units to the N-glycoside chains of transferrin (Tf) [159, 160].

This approach aims to target cancer cells specifically while minimizing impact on healthy cells. Interestingly enough, the Tf protein, which could be considered as a basis for the mentioned Tf molecule, was modified in such a way that it had 16 artemisinin units left in it. It remained functionally active as well as efficient as the artemisinin-based drugs. Subsequent experiments involving the reduction of TfR expression through TfR siRNA transfection revealed a noteworthy finding: on the other hand, we noticed that after the removal of transferrin from the conjugated agents, the cytotoxicity of ART-Tf was considerably downed, whereas dihydroartemisinin after the transferrin conjugation, lost its ability to kill the cells [161, 162]. By this, the role in the therapy of the transferrins from artemisinin conjugation which is mediated by TfR becomes apparent. However, ART-Tfs were able to tickle the pores of the TfR which caused the chain reaction and thus cell death on DU-145 cells. This concurs with the anticipated MOA, which states that ART-Tf is acted against selectively toward the cancer cells with high TfR expression due to the TfR-dependent uptake mechanism [163, 164].

In a study performed by Michaelsen et al., 2014 involving an in vivo examination, a patient diagnosed with advanced prostate carcinoma (pT3bN1M1 Gleason score 4 + 4) and a prostate-specific antigen (PSA) level exceeding 800 µg/l, exhibited remarkable outcomes following treatment for the disease. In the beginning, the bacalitumide was given with short-term administration of 50 mg/day for 14 days and then continuous intake for 5 × 50 mg/day of capsules from the plant A. annua which resulted in a notable decrease in PSA to 0.98 µg/l. Hence, further MRI, SPECT/CT, SCI, and CT scans were performed that confirmed tumor remission. After seven months, the indicators of tumor recurrence, such as PSA and ostase levels, not only remained at the same level but also started to increase.

The heightened levels of prostate-specific antigen (PSA) and ostase indicated potential tumor recurrence and skeletal metastasis. Transitioning from A. annua capsules to bicephalic injections of artesunate (2 × 150 mg twice weekly intravenously) slowed down tumor regrowth. However, PSA levels notably increased to 1245 µg/l and 434 U/l, respectively. Magnetic resonance tomography (MRT) revealed cancer resistance, with a focus on bone targeting, culminating in skeletal metastasis. This study also indicated that there was a relationship between elevated expression levels of MYC, VEGFC, TFR, and PC-3 biopsy, and similar expression patterns were observed when PC-3 cells that were artemisinin-sensitive and DU-145 cells that were artemisinin-resistant were compared [165].

Ahmad et al. investigated the caspase-dependent inhibition of the prostate cancer cell line PC-3 by anhydrodihydroartemisinin (ADHA) [166]. At the molecular level, ADHA suppressed c-Jun, p–c-Jun, p-Akt, and NF-κB expression while activating caspases 3 and 7. ADHA notably decreased cell viability, especially at concentrations of 1, 3, and 10 µM. The clonogenic assay demonstrated ADHA's cytostatic effect on PC-3 cells by inhibiting their colony-forming ability, A significant decrease in PC-3 cell colonies was observed at the highest ADHA concentration of 10 µM.

The structures and various molecular mechanism of these important SLs have been discussed in the Table 2.

Structural–activity–relationship (SAR) of proposed lactones

This review covers many research on the structure–activity relationships (SAR) of several compounds, including alantolactone, costunolide, helenalin, thapsigargin, parthenolide, inuviscolide, and artemisinin. Emphasizing the need of certain structural characteristics for anticancer action, the research concentrate on the relationship between the stereochemistry of sesquiterpene lactones and their inhibitory actions on STAT3. They also investigate the cytotoxicity of 13-amino derivatives of costunolide and its cytotoxicity against different cancer cell lines.

Focusing on their cytoprotective properties, the work also looks at the function of Michael acceptor sites in helenalin and its analogues. Elucidating SAR depending on structural changes, the paper also addresses the synthesis and assessment of parthenolide derivatives as possible anti-triple negative breast cancer drugs. The work also investigates the anti-inflammatory processes of sesquiterpenoid compounds from *Inula viscosa*, hence clarifying their SAR. The work also creates prediction models to grasp the SAR of artemisinin and its analogues, hence supporting the creation of more powerful anticancer drugs mentioned in the Table 3.

Clinical insights

Sesquiterpene lactones (SL's) have shown promising pharmacological activities in vitro and in vivo, but there is a lack of clinical studies validating their therapeutic potential in humans. Most SL's, including parthenolide, helenalin, and

Table 2 Anticancer mechanisms of sesquiterpene lactones

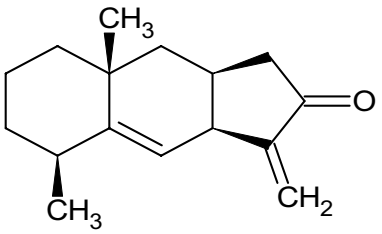
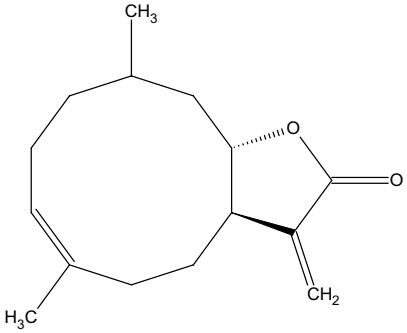
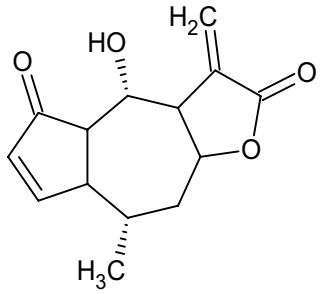
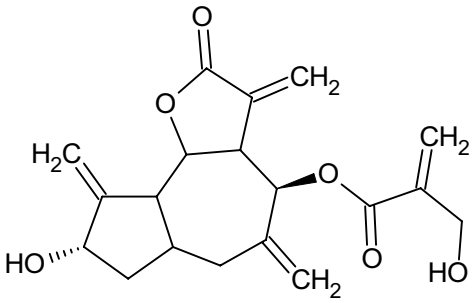
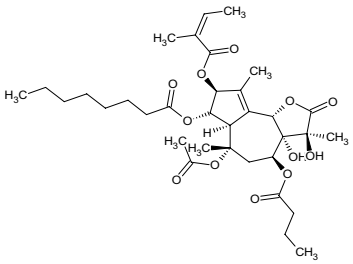
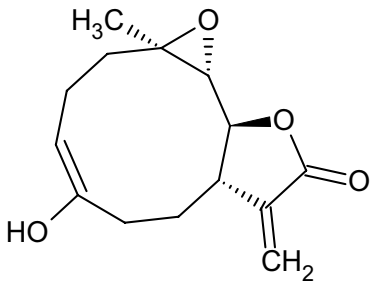
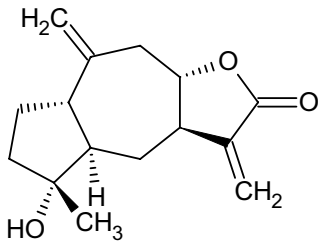
Molecules	Chemical structure	Biological source	Mechanism	References
Alantolactone		*Aucklandia lappa*	Suppression of STAT3 phosphorylation and promotion of expression of cytochrome p53	[167]
Costunolide		*Saussurea lappa Clarke*	Inhibition of the cyclin E complex and cyclin-dependent kinase 2 (CDK2) activity	[168]
Helenalin		*Arnica Montana*	Inhibit the stimulation of NF-κB, observed in T-cells, epithelial cells, and B-cells,	[169]
Cyanaropicrin		*Cynara cardunculus*	Inhibiting the STAT3 pathway	[170]
Thapsigargin		*Thapsia garganica*	Inhibition of the SERCA pump	[171]

Table 2 (continued)

Molecules	Chemical structure	Biological source	Mechanism	References
Parthenolide		*Tanacetum parthenium*	Inhibits the action of DNA methyltransferase 1 (DNMT1)	[172]
Inuviscolide		*Ferula communis*	Reduction in the expression of the p65 subunit of nuclear factor kappa B (NFκB	[146]

costunolide, have been extensively evaluated in cellular and animal models, but few have progressed into clinical trials. Parthenolide has shown selective cytotoxicity against leukemia stem cells and anti-inflammatory properties, but its clinical development is hindered by poor water solubility, bioavailability, and concerns about systemic toxicity [181].

In order to effectively translate artemisinin and its derivatives, which are SL's with antimalarial activity, owing to their safety profiles and global health priorities, the translation process has been successful. Nevertheless, investigations into their potential use in cancer and inflammatory illnesses are still in the first stages of clinical research. This demonstrates the need of doing exhaustive pharmacokinetic, toxicological, and formulation research in order to overcome obstacles in the translational process. It is recommended that future research concentrate on developing innovative delivery mechanisms in order to improve the bioavailability and therapeutic index of SL's [182].

Limitation

While SLs aren't suitable as the initial approach in treating cancer, they can serve as supplementary therapy alongside cytostatic drugs. Yet, examining how SLs interact synergistically with chemotherapy drugs is crucial. Consequently, identifying the most effective dosage and ensuring the safety of SLs in conjunction with chemotherapy pose significant therapeutic challenges and constraints. Although sesquiterpene lactones (SLs) have significant therapeutic promise, especially in anticancer and anti-inflammatory applications, their practical implementation is obstructed by major constraints, including inadequate bioavailability and possible toxicity. SLs have poor water solubility and restricted gastrointestinal absorption, significantly limiting their systemic bioavailability after oral administration. Furthermore, their fast metabolic breakdown, mainly via hepatic and intestinal routes, results in brief plasma half-lives and diminished pharmacodynamic effectiveness.

Moreover, the structural component essential to the bioactivity of several SLs—the α-methylene-γ-lactone ring—easily participates in Michael addition reactions with nucleophilic thiol groups in cellular proteins. This electrophilic characteristic underpins their cytotoxic effects on tumor cells, but it also presents a danger of off-target damage. Preclinical investigations have revealed adverse effects, including hepatotoxicity, gastrointestinal discomfort, and allergic reactions. These safety issues need meticulous dosage adjustment and more research on selective cytotoxicity.

Recent research has investigated nanoformulation-based delivery technologies, including as liposomes and solid lipid nanoparticles, as well as prodrug techniques that promote solubility and improve targeted delivery. Furthermore, structure–activity relationship (SAR) investigations have concentrated on altering the lactone ring or its substituents to preserve bioactivity while reducing toxicity.

Table 3 Structural activity relationship between various sesquiterpene lactones and their potential anticancer activity

S. no	Name of the compound	Structural features	Biological activity	Structural activity relationship highlights	References
1	Alantolactone	10-membered ring with Reactive α-methylene-γ-lactone	Anticancer	Alkylation of nucleophilic groups in proteins, such as cysteine residues in NF-κB and STAT3 pathways	[173]
2	Costunolide	C7 = C8 double bond (α,β-unsaturated carbonyl) and Hydrophobic sesquiterpene skeleton	Anticancer	Improves uptake in cancer cells and targets mitochondrial pathways, facilitating Michael addition-induced apoptosis	[174]
3	Helenalin	Cyclopentenone ring (C4 = C5 double bond) and Exocyclic methylene group at position C-13	Anticancer	Helenalin offers a unique second Michael acceptor site, enhancing reactivity and stronger inhibition of thiol-containing enzymes and Increases electrophilic reactivity and covalent bond formation, while also enhancing cytotoxic potential through protein alkylation	[175]
4	Cynaropicrin	α-Methylene-γ-lactone moiety and Epoxide ring (4,5-epoxy group)	Anticancer	Michael acceptor is essential for alkylation of thiol groups in proteins, enhancing anticancer and anti-inflammatory action, and is crucial for NF-κB and STAT3 inhibition and responsible for enhancing the reactivity and selectivity of biological nucleophiles, particularly crucial for covalent bonding to cysteine residues in enzymes	[176]
5	Thapsigargin	8-O-Acyl Group**:**, Lactone Ring**:**, and Hydrophobic Regions	Anticancer	The compound's potency is influenced by the presence of an acyl group at the 8-O position, the intact lactone ring, and hydrophobic regions, which enhance binding affinity to the SERCA enzyme or sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase	[177]
6	Parthenolide	Double bond at C2-C3and Hydrophobic framework	Anticancer	Epoxide enhances PTL's reactivity, enhancing covalent interactions with target proteins and cytotoxic effects. Its hydrophobic framework facilitates efficient intracellular access to targets	[178]
7	Inuviscolide	Hydrophobic framework	Anticancer	The substance enhances cell membrane penetration, facilitating better access to intracellular targets, thus enhancing its cytotoxic efficacy against cancer cells	[179]
8	Artemisinin	Endoperoxide Bridge (C–O–O–C)	Anticancer	It is crucial for its bioactivity, as it interacts with iron, generating reactive oxygen species, which cause cancer cell oxidative stress and apoptosis	[180]

Such methodologies are essential for the progression of SL-based treatments toward clinical implementation.

Conclusion

It has been shown that SLs have a significant amount of potential in targeting several signaling pathways that are associated with prostate cancer. These pathways include STAT3, NF-κB, TNF-α, PI3 K-AKT, MAPK, and JNK pathways. These SLs, which include substances like 6-o-angeloylplenolin, Alantolactone, and Parthenolide, are able to bind with certain domains or kinases within these pathways. As a consequence, they are able to block essential proteins or transcription factors that are crucial in the survival and proliferation of cancer cells. Furthermore, it has been discovered that SLs have the ability to trigger apoptosis in prostate cancer cells via regulating these pathways. This results in the inhibition of cancer cell development and the promotion of cell death. Furthermore, research highlights the potential of sesquiterpene lactones derived from a variety of plants, including *Carpesium divaricatum, Cichorium intybus, Artemisia kopetdaghensis, Tanacetum argenteum, Leptocarpha rivu, Ferula penninervis*, and many others. These plant sources are the primary sources for targeting distinct molecular mechanisms within prostate cancer cells, highlighting the diverse anticancer properties and therapeutic potential of these compounds. As a result, a comprehensive research program is required, which should include biotechnological studies that are centered on the bio-prospecting and synthesis of sesquiterpene lactones derived from natural sources.

Author contributions KK: Data curation. AV and MVNLC: Methodology, Original draft preparation. AS: Data curation. SK, DUK: Reviewing and editing. MS, MVNLC: Figures and Tables. SKS, AM: Proof reading.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no conflicts of interest related to this study.

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