***Review Article***

**ANTICANCER PROPERTIES AND USES OF THE COMPOUNDS FOUND IN DIFFERENT *(Saussurea)* SPECIES: A REVIEW**

**ABSTRACT:**
This review represents a comprehensive summary of the research progress of the phytochemical and pharmacological aspects of the *Saussurea* genus, focusing specifically on its potential as an anticancer/antitumor agent. Cancer is emerging globally as a crucial disease affecting human health badly. It is also causing a negative impact on world economy. Every year number of deaths due to cancer is increasing and none of the medicines or therapies could cure this disease completely in most of the cases. In our research, we conducted a comprehensive review of the available literature and electronic databases. We searched in prominent resources such as PubMed, ScienceDirect, Springer, Scopus, Google Scholar, and Wiley to gather the necessary data for our study. The genus *Saussurea* has been a subject of extensive research from both phytochemical and pharmacological perspectives over the years. This though investigation has led to the identification of numerous secondary metabolites exhibiting diverse bioactivities. *Saussurea* is a rich genus which contains many species with diverse properties. Leaf and flower extracts of plant *saussurea obvallata* showed good anticancer activities. It contained compound acid methyl ester, linolenic acid and squalene. These compounds also showed good anti-tumour properties. Important anticancer compounds such as doxorubicin, dehydro-costuslactone, cyanaropicrin are also isolated from *saussurea costus* which showed good activity against colon and liver cancer. Another compound arctigenin is obtained from *saussurea heteromalla* which showed good activity against Hela cells.

These anticancer compounds from different *saussurea* species are mentioned with their mechanism and cell lines. This study will open doors of research on these compounds which are known and more compounds which are still hidden in these species could be found out. These anticancer compounds could be further worked upon until these are officially marketed and used as anticancer drugs in different therapies and regimens.

# Keywords: *Saussurea,* antitumor, anticancer activities, cytotoxic, cell cycle arrest, phytochemical, bioactivities*.*

**INTRODUCTION:**

Saussurea is a traditional medicinal plant found in the Himalayan region. It has notable ethnopharmacological properties and has been used in scientific studies to treat various ailments such as respiratory problems, body aches, headaches, epilepsy, gastritis, bacterial, fungal, parasitic, and viral infections. Various in vivo and in vitro studies, and scientific literature strongly support the anti-carcinogenic potential of the chemical constituents present in S. costus. Previous studies showed that S. costus has minimal or no side effects and might be used as a therapeutic and preventive drug against cancer. Despite the vast variety of constituents present in S. costus dehydrocostus lactone and costunolide are the most important sesquiterpenes phytochemicals to execute the anti-neoplastic action (Kumar et al., 2024; Elnour & Abdurahman, 2024).  Plants produce a wide range of metabolites which have good therapeutic effects. Natural products are good source for the discovery of new drugs and innovation of present drugs too[1]

# Asteraceae family is an extremely important family comprising 1000 genera and 30000 species all over the world. The largest subgenus of this family saussurea [1] consists of approximately 410[1, 2] to 490[3] species, which have been utilized as traditional medicines in various countries. Its mainly distributed in Asia, North America and Europe[1] with 61 species present in India[4] and 264 species found in China. This genus has a lot of varieties having medicinal, religious and economical values also e.g. oil, food, rubber, dye, flavouring agents etc[2]. Plants of this species develop height up to 5-10cm called tall dwarf alpine species. While those with height up to 3cm are called tall thistle-like plants[2]. Numerous scientific studies have investigated and reported various compounds found in Saussurea species. These include steroids, phytosterols, lignans, alkaloids, terpenes (monoterpenes, sesquiterpenes, triterpenes), volatile oils, tannins, flavanoids, resins, glycosides, shikokiols, the cytotoxic compounds, reducing sugar, and insulin[5]. Sesquiterpene lactones are major phyto-constituents of this species[4].

**Plants of Saussurea species:**

Many saussurea plants are used as folk medicine due to their good medicinal benefits[6]. A few of them are discussed below:

*S.costus (kuth)* which is present in the Himalaya region is the most available and used species of this genus. It is used for curing several diseases like bronchial asthma, leprosy, cholera, rheumatism, and jaundice. Other than this, *Sgosypiphora* and *S obvallata* are commonly used medicinally and for religious purpose also[2]. *S obvallata* is commonly used for wounds, intestinal problems, UTIs, cerebral ischemia, mental disorders and paralysis, it also produces good anti oxidant and antibacterial properties[7]. *Saussurea lappa* is also a beneficial plant widely used for dysentery, asthma, toothache[2], spasmolysis, antihypertension and antibacterial activities[6] etc. *S. lappa* roots are rich in components responsible for its major actions[1]. *Saussurea pulchella* is also a part of Korean folk medicine as antarthritic, antihepatitis, anti-inflammatory and antihypertension [6]. *Saussurea laniceps* is a famous Tibetan medicine used for the cure of gynopathy and rheumatic arthritis. Saussurea involucrate is used as antiarthritic and for relieving lower abdominal pain. *Saussurea triangulate* is used as antihepatic, anti-inflammatory and antihypertensive[6]. *Saussurea medusa* is used for the cure of gyneopathy rheumatoid disease and for good health.

**Chemical constituents:**

Numerous secondary metabolites are extracted from genus saussurea. The main constituents of these plants are sesquiterpenes, phenolic compounds, diterpenoids, triterpenes, lignans, steroids, flavonoids[6], chlorophyll and phytosterols[1]. Some new pharmacological activities are also discovered from these compounds.121 new native compounds are discovered from saussurea genus from 1990 June till 2009[8]. A few of them are discussed below:

**Sesquiterpenoids:**



Figure 1: Examples of Sesquiterpenoids with structures.[8].

Saussurea species are abundant in sesquiterpenoids. Sesquiterpenes consist of a group of C15 compounds made by arrangement of 3 isoprene units. It is the biggest group of secondary metabolites obtained from plants[6].

Around 64 new sesquiterpenoids are extracted including 4 germacrane derivatives, 3 megastigmane, 20 eudesmane, 34 guaiane derivatives, and few others also[8]. Three new megastigmane derivatives are discovered. One was discovered from *S. medusa* by Duan *et al.* 2002 and called 3β-hydroxy-5α, 6α-epoxy-7-megastigmen-9-one. Two others are also isolated from saussurea named saussureosides A and B[8].

**Guaiane sesquiterpenoids**: Many sesquiterpenoids are composed of guaiane skeleton having 5/7/5 ring system due to a y-lactone. Three exocyclic C=C bonds are susceptible to oxidation forming epoxide rings which can be attacked by nucleophile. On positions C(3) and C(8) OH or o-glycosides groups are present[1].

**Eudesmane sesquiterpenoids:** There are 20 new eudesmane sesquiterpenoids discovered. Unlike guaiane derivatives, they are not present in the form of lactones. Between C15 and C4 positions a double bond is present, OH is often substituted on C1 and C3. Due to this group many glycosides are formed on these positions C1 and C3. Sometimes a carbonyl group is substituted at C10[8].

**Germecrane sesquiterpenoids:** Sixgermacrane-type compounds are obtained from saussurea genus, out of them 5 are obtained from *S.lappa*[1].

1. **Sterols:** 31 sterols are obtained from saussurea plants[6]. Βsitosterol is obtained and its hydroxy and glycoside derivates are also extracted.
2. **Diterpenoid**: Only 1 diterpenoid is isolated from *S.cauloptera* in 2008. This compound is 3α hydroxyl –ent-labda-8,13-dien-16,15-olide[8].
3. **Triterpenoids**: 18 new triterpenoids are obtained from saussurea genus. It includes dammarane, lanosterol and ursane types. It also includes taraxastane and oleanane[8].
4. **Steroids**: Saussrea genus is source of 7 new steroidal compounds. *S lappa* is source of 2 steroids and *S. stella* is source of 3 steroidal compounds. 1 steroid is also discovered from *S. urosiensis* and *S. gossipiphora*[8].
5. **Flavanoids:** Flavanoids are common nutrients abundant in food with good antimicrobial activity, anti-oxidants, and estrogen regulators. They can also cause prevention of cancer as they have good anticancer properties. They prohibit the growth of cancer by stopping metastasis, cell invasion, angiogenesis, They also inhibit kinases which alter transcription factors affecting cell cycle and causing cell death by apoptosis[9]. Around 18 different flavonoids are obtained from saussurea genus including apigenin, luteolin, quercetin, chrysoeriol 7-O-rutinoside, Jaceosidin. Jaceosidin has good anticancer and antiaging properties. Apigenin also prohibited the growth of cancer cells and showed anti-inflammatory properties. Quercitin protects cells against cell damage for example it protects cells affected by hydrogenperoxide[1]

**ANTICANCER ACTIVITY FOUND IN DIFFERENT SAUSSUREA SPECIES**

Many cytotoxic drugs used to combat cancer often face issues not only related to their efficacy but also due to undesirable side effects. As a result, there is a pressing need for the development of novel anticancer compounds that can effectively treat cancer without causing adverse side effects.[10] Saussurea species have a great potential for discovering many bioactive substances [11]. Many of these substances from different species of saussurea genus showed anticancer properties. Most of these compounds are mentioned below with a short description of species from which they are isolated:

**Saussurea lappa:**

*Saussurea lappa* belongs to Asteraceae family which is one of a largest angiosperm family consisting of 1620 genera and 23600 different species of plants[12]. This plant has good medicinal value globally. It is the source of many compounds of different classes extracted from different parts of this plant.

Especially roots are a source of many compounds isolated from these plants[13]. It is abundant mostly in surrounding areas of Himalaya Mountains in India. It belongs to family Asteraceae generally called costus. Its stem is vertical; roots are long up to 60cm with specific fragrance. Leaves have lobed margins with smaller upper leaves and larger lower leaves. Purple flowers appear on branches and fluffy Pappas also appear on flower heads. Its fruit is round in shape and full of hairs[14].

*Saussurea Lappa* is a rich plant with numerous active ingredients isolated and being used for their pharmacological action. It comprises mainly of terpenes, while flavonoids, anthraquinones, and alkaloids are also present[15]. Costunolide, Dihydrocostunolide, lappadilactone, mokko lactone, cynaropicrin, reynocin, santamarine, saussureamines A-C, chrysophenol and chlorogenic acid are a few components of saussurea lappa extracted from its roots oil and other parts of plant[16].

**I Dehydrocostuslactone (DHE)**:

In DU-145 human prostate cancer cell lines dehydrocostus lactone prohibited cell proliferation and promoted apoptosis.

Dehydrocostus lactone is also tested for its anticancer effect on nonsmall cell lung cancer cell lines NCI-H520, NCI-H460 and A549. It produced inhibitory effect by apoptosis in A549 and NCI-H460 cell lines[17].

A study was also conducted to examine the effect of dehydrocostus lactone on hepatocellular carcinoma. Results showed that DHE prohibited cell growth on PLC/PRF/5, and HepG2 cells by inducing apoptosis. It caused up regulation of Bax and Bak, down regulation of B cl-2 and Bcl-xl. It also produced its effect on mitochondrial factors, endonuclease G and apoptosis inducing factors. DHE also induced Endoplasmic Reticulum stress affecting RNA activated protein kinase like endoplasmic reticulum kinase phosphorylation, cytosol calcium levels, Inositol Requiring Protein 1 (IRE1) and CHOP/GADD 153upregulation. ER stress also affected Xbox transcription factor 1 mRNA splicing, and caspase 4 activation. Hence it was observed that DHE produced apoptosis by ER stress.DHE may prove to be a good anticancer agent for liver cancer[18].

**2. Costunolide:**

Sesquiterpene compound in *Saussurea lappa* is known to have cytotoxic effects. In a study costunolide effect on activity of enzyme telomerase and its substituents was observed on MCF-7(p 53 wild) and MDA-MB 231(p 53 mutant) cell lines. Costunolide prohibited cell growth and telomerase activity in cancer cells. It also caused alteration in hTERT mRNA. hTR mRNA was not affected. Costunolide also decreased bindings of transcription factors in both cells. Results showed it produced anticancer effect in breast cancer cells by decreasing telomerase activity[19].

**3. Cynaropicrin:**

Another compound cynaropicrin was examined for its inhibitory effect on nitric oxide production, cytokine release, and also effects on immune system. It showed inhibitory activity on cell lines Jurkat T cells, U-937 and Eol-1.it produced its effect on IC50 values of 2.36, 3.11 and 10.9 µM. No effect was produced on human fibroblast cell lines so it was concluded that on these cell lines effect was produced because of apoptosis. Cytotoxicity of cynaropicrin was also examined by cell cycle arrest, DNA breakage, and structural analysis on C937 cells. Cynaropicrin was less cytotoxic in fibroblast cells and more in leukocyte derived cancer cells[16].

**Saussurea involucrata:**

This is a blooming plant found in China typically at peak areas as it grows at high altitudes[20]. In Chinese folk medicine it was being used for many diseases such as cough, cold, blood circulation, enhancing bone strength, arthritis and menstrual disorders. In the modern era more effects are recognized such as it prevents oxidation, fatigue , inflammation and specifically it has tumour suppression properties for breast cancer and prostate cancer[20].

 Studies prove its anticancer effects but mechanisms are still unknown[21] anticancer compounds from S involucrate are acacetin, rutin, hispidulin, apigenin, and jaceosidin[21]. A study was conducted on human carcinoma cells which showed *saussurea involucrata* has cytotoxic and apoptotic effects. Its predicted that its involved in cell cycle arrest, prohibition of DNA synthesis and programmed cell death by causing upregulation of caspase-3,-9 and p21 and down regulation of Cdk2 and XIAP[21].

1. **Jaceosidin:**

In human mammary epithelial cells jaceosidin prohibited COX 2, E6and E7 protein activity was also depressed in HPV 16, and apoptosis was also induced in human ovary and breast cancer cells. Jaceosidin also produces apoptosis in U 87 glioma cells. It produces apoptosis by causing mitotic arrest. Caspase 3 was activated, Bax was activated and cytochrome c was released from mitochondria. It also caused activation of p 53 which is a protein which suppresses tumour cells. P53 produces apoptosis by causing permeabilization of mitochondrial outer membrane by activation of Bax and deactivation of Bcl-2[22].

1. **Rutin:**

It is a flavonoid with good anticancer properties. This compound was tested in nude mice and it showed suppressing effects on tumour. In another study rutin caused alteration of Bax/Bcl2 ratio in LAN-5 cell lines. In colorectal cancer cell lines rutin produced apoptosis, inhibition of metastasis, angiogenesis and proliferation[23].

1. **Hispidulin:**

It showed good activity in hepatocellular and gastric cancer. In human gastric adeno-carcinoma cell line it produced down regulation of COX-2 and up regulation of NSAID activated gene 1(NAG-1). NAG-1 produced apoptotic effects and caused tumour suppression. It also caused cell cycle arrest at G1 and S phase. In another study hispidulin induced apoptosis in hepG2 cells could be due to alteration in mitochondrial function, also by stopping P13k/Akt pathway[24]. In myeloid leukaemia cells hispidulin inhibited proliferation, it caused apoptosis through an intrinsic mitochondrial pathway by restricting extracellular matrix metallloprotienase inducer[23].

1. **Acacetin:**

In prostate cancer, gastric cancer, oral squamous canceracacetin produced apoptosis inhibiting cell proliferation. Acacetin stopped phosphorylation of proteins Stat-1 and stat-3. It also caused down regulation of pro-angiogenic factors: bFGF, eNOS, MMP-2, VEGF, iNOS[23].

1. **Apigenin:**

It belongs to a class of flavonoids and has good anticancer potential. It produced cell death and cell cycle cessation in many tumour cells including prostate, blood, liver, colon, stomach by altering more than 1 signalling pathways. It activates mRNA expression of caspase-3, TNF-α, caspase-8. So apoptosis is induced by stimulation of these caspase-dependent pathways. It produces intrinsic apoptosis pathway by activation of caspase 3, Bax, and cytochrome cin prostate cancer cells in humans. It also suppresses invasion by de-activation of snail slug and metallo peptidases 2 and 9[25]

**Saussurea hypoleuca:**

It is also known as *saussurea auriculata* and is also called *qust.* It is present in high altitude regions in Quetta, Pakistan[26]. Roots of this plant are already being used in many herbal medicines as liver tonic. Roots of *S. hypoleuca* is rich in phytoconstituents[27]. These compounds are pharmacologically active and responsible for many effects. This plant showed antimicrobial, anti-diabetic, antioxidant, anticancer and anti-inflammatory properties. 2 compounds are obtained from roots of *Saussurea hypoleuca* sesquiterpene and linolenic acid. These 2 compounds showed antioxidant and anticancer properties[26].

**Saussurea laniceps:**

It is the plant from which Snow lotus flower is created which is a famous Tibetan medicine being used for menstrual disorders and rheumatic arthritis. Biological active compounds of this plant are syringin, apigenin, hispidulin, coumarin, cynaropicrin, acacetin, benzyl glucopyranoside rutin. This plant shows activity against inflammation, cancer, and metastasis and relieves pain.

Anticancer compounds from this plant are: Apigenin, Acacetin, Hispidulin, Luteolin and 2 sesquiterpenes mokko lactone and cyanopicrin. Anticancer effects of this plant were studied on pancreas tumour cell lines Panc-1, Capan-2, S2-013,Capan-1. It showed cytotoxic effect on tumour cells and apoptosis also occurred. Hispidulin inhibited cell growth possibly by DNA fragmentation[28].

1. **Luteolin:**

It is a flavonoid present in many plants and exhibits good anticancer property. It promotes apoptosis and prohibits angiogenesis, cell proliferation and also metastasis. It is cytotoxic to cancer cells as it causes upregulation of pathways that promotes apoptosis e.g. enhancing production of tumor suppressor gene p53. It also causes down regulation of Nuclear factor kappa B (NF-κB), Phosphatidyl inositol 3 kinase (P13k/Akt), and X linked inhibitor of apoptosis protein (XIAP)[9].Luteolin can cross blood brain barrier so it is used in CNS related diseases. Hence its used in treatment of brain cancer[29].

**Saussurea medusa:**

*Saussurea medusa* is origin of famous herb snow lotus[30].More than 70 compounds have been extracted form *saussurea medusa* including quercetin, rutin, apigenin, sausurreoside A and B. It shows good anti oxidant, anti inflammatory, antifungal, antitumor and analgesic properties. It also showed beneficial effect on intestine, immune system.

1. **Arctin and Arctigenin:**

From active constituents of *saussurea medusa* 2 lignans are obtained, Arctiin (ARC) and arctigenin (ARC-G). These 2 compounds showed good anti tumour effects on mouse skin tumour[31]. They also showed anti tumour activity on these cell lines: HepG2, H116, Brain tumour U251N, lung cancer H125, and pancreatic cancer Panc-1 Cell lines. Arctin exhibits less toxicity as compared to arctigenin, so it could be possibly used as pro-drug. Arctin and Arctigenin could prove as good candidates for treatment of solid tumours in future[32].

**Saussurea obvallata :**

*Saussurea obvallata* (Brahma Kamal) holds importance both spiritually and medicinally [3, 33, 34]. Unfortunately due to, its popularity and high demand this herb is facing the threat of extinction [3, 33, 34]. Many research studies have been conducted to conserve and regenerate Saussurea obvallata through in vitro regeneration.[35]

*Saussurea obvallata* is a plant that is commonly found in India. It has been traditionally used in ayurvedic medicines to treat ailments such as wounds, bone aches, paralysis[33], cerebral-ischemia[33], urinary tract infections, cough, cold, cardiac[33] and mental disorders[33].[3, 33] Researchers have conducted studies on the phytochemicals, in *saussurea obvallata* and have explored its pharmacological properties, including antiseptic[33, 36], antimicrobial[3], antioxidant[3], antihypoxia[3], anticancer[3] and radio-protective activities.[3, 35] Previous research findings have reported that *Saussurea obvallata* contains a variety of bioactive components, including terpenoids, flavonoids, alkaloids, saponins and glycosides.[35]

In the previous phytochemical investigation, researches have been done by looking into the compounds present in the leaves and flower extracts of *Saussurea obvallata*. They found various natural substances, such as saponins, terpenoids, flavonoids, tannins, proteins, phenols, glycosides and alkaloids in these extracts [3, 7, 37]

1. **Squalene and** **α-Linolenic Acid Methyl Ester:**

The GC-MS analysis showed that the petroleum ether extract of *Saussurea obvallata* contains squalene and α-linolenic acid methyl ester[37]. Studies on the leaves and flower extracts of *Saussurea obvallata* showed significant anticancer activity against MCF-7 breast cancer cell lines when compared with a positive control.[3]

Another study examined the chemical in the leaves and flower extracts of *Sasussurea obvallata*, providing qualitative and quantitative analyses of these compounds[7, 38].

A systematic patent search in China found a few innovations related to *Saussurea obvallata.* One of these patents (CN106236809A) describes the extraction of compounds from the effective part of the plant and their potential use as an antitumor drug. This patent sheds light on the potential medicinal properties of *Saussurea obvallata* and its potential role in cancer treatment.[3]

**Saussurea costus:**

*Saussurea costus* is a well known species which is native to temperate cool and arctic regions of Europe, Asia, North America, Central Asia and the Himalayas[5]. It is commonly known as Kuth in Hindi.[2, 5, 39] *Saussurea costus* is traditionally being used in various Indian indigenous system for its anticancer, hepatoprotective, antiarthritic, anti-convulsant, anti-microbial and anti-viral activities[5]. These claims have been proved through diverse in-vitro and in-vivo approaches, providing a contemporary scientific basis for the ancient knowledge surrounding its use [16, 40].

This plant has a long history of traditional usage in diverse indigenous health systems for addressing various conditions, including carminative, expectorant, antiarthritic, antiseptic, aphrodisiac, anodyne and vermifuge effects, all of which have been observed without any apparent adverse consequences.[5, 16, 40]

*Saussurea costus* has been successfully cultivated and produced in various states of India, driven by its high demand both nationally and internationally. This plant has emerged as a significant drug in the global market, particularly in the form of root oil and roots, due to its essential medicinal properties.[5, 40]

The cytotoxicity and anticancer effects of the secondary metabolites extracted from *Saussurea costus* were studied against liver cancer cells (HepG2), breast cancer cells (MCF-7) and colon cancer cells (HCT116) which showed promising potential as anticancer agents for the treatment of various liver, breast and colon cancers.[5, 10]

1. **Anethole:**

 Anethole has been found to decrease prostate cancer metastasis and induce apoptosis in (DUI45), breast and oral cancer cell lines [41-45].

1. **Costunolide:**

Costunolide inhibits growth and telomerase activity of breast cancer cells (MCF-7) and MDA-MB-231 cells, promote cell apoptosis. It down regulates human leukemia cells, ovarian. bladder, colon and breast cancer cell lines [19, 41, 46-48],[16, 19, 49, 50].

1. **Cynaropicrin:**

Cynaropicrin has been found to inhibit the proliferation of leukocyte (Jurkat T cells, U-937, Eol-1) cancer cell lines. It induces apoptosis and cell cycle arrest. Causes DNA disruption and inhibits cytokine release [16, 51].

1. **Dehydrocostus lactone:**

Dehydrocostus lactone inhibits cancer cell proliferation in Prostate cancer and hepatocellular carcinoma, induce cancer cell apoptosis, alters cell cycle in breast cancer cells and leukemia can also limit metastasis of lung cancer(A549, NCIH460), inhibits tumor growth, attachment and metastases, induce cell cycle arrest and apoptosis (programmed cell death), effective against Apoptosis, inhibits cell , non small cell lung cancer [3, 16, 18, 41, 46, 52-56].

1. **γ-Curcumene:**

Induce cell cycle arrest and apoptosis in cancer cells

1. **β-sitosterol:**

Induces apoptosis in HepG2 cells

1. **β-elemene:**

Inhibit pancreatic cancer and neoplastic metastasis

1. **β-caryophyllene oxide:**

Enhance activity against colon cancer and breast cancer cells

1. **Doxorubicin:**

Doxorubicin interferes with DNA replication and inhibit cancer cells growth.

**Saussurea heteromalla:**

*Saussurea heteromalla,* a member of Compositae family, is found abundantly in the subtropical and tropical Himalayan regions, with its distribution notably extending to the Shivalik hills (India) [57, 58]. *Saussurea heteromalla* stands out as a bioactive wild medicinal plant, holding significant recognition for its contribution to ethno-pharmacology and phytochemistry[57].

In a study performed and reported previously, they employed bioassay- guided separation of the crude extract of *Saussurea heteromalla* to identify the most potent fraction with potential as an anticancer agent. Remarkable cytotoxic potency against the human cervical cancer cell lines (HeLa cells) had been demonstrated, with the findings duly documented and reported[59]. Through meticulous bioassay-guided separation, artigenin emerged as the active lead molecule, exhibiting noteworthy potential in cervical cytotoxicity[57].

1. **Arctigenin**

It has been found to exhibit a moderate inhibitory effect on the growth of HeLa cancerous cells in vitro. [57]

Structure and mechanism of anticancer compounds from *saussurea* genus are summarised in table1.

**Anticancer compounds from *saussurea* genus**

Table1: Some of the major anticancer/antitumor constituents in Saussurea species extract

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **S. No.** | **Constituent Name**  | **Structure** | **Class of compound** | **Mechanism of action/ Molecular Target** | **Plant Source** | **Reference** |
|  | Acacetin |  | Flavanoid | Inhibits cell proliferation in Prostate cancer, gastric cancer, oral squamous cancer. | *Saussurea involucrata* | [23] |
|  | Anethole |  | phenylpropanoids | Decreases prostrate cancer metastasis and induce apoptosis in (DUI45), breast and oral cancer cell lines | *Saussurea costus* | [41-45] |
|  | Apigenin |  | flavanoid | Apoptosis by activation of signalling pathways in; Blood, liver, colon, stomach, prostate and liver cancer. | *Saussurea involucrata* | [25] |
|  | Arctigenin |  | lignan | Inhibit growth of cervical cancer cells (HeLa cells) | *Saussurea heteromalla, Saussurea medusa* | [57-59] |
|  | Arctin |  | lignan | Pancreatic cancer, lung cancer, brain tumour, HepG2 cells | *Saussurea medusa* | [32] |
|  | Costunolide |  | sesquiterpenes | Inhibit growth and telomerase activity of MCF-7 and MDA-MB-231 cells, promote cell apoptosis.Down regulating human leukemia cells, ovarian. bladder, colon and breast cancer cell lines | *Saussurea costus, Saussurea lappa* | [19, 41, 46-48][16, 19, 49, 50] |
|  | Cynaropicrin |  | Sesquiterpene lactones | Inhibit the proliferation of leukocyte (Jurkat T cells, U-937, Eol-1) cancer cell lines, induces apoptosis and cell cycle arrest. DNA disruption and inhibits cytokine release | *Saussurea costus,* *Saussurea lappa* | [16, 51] |
|  | Dehydrocostus lactone |  | Sesquiterpene lactones | Inhibits cancer cell proliferation in Prostate cancer andhepatocellular carcinoma, induce cancer cell apoptosis, alters cell cycle in breast cancer cells and leukemia can also limit metastasis of lung cancer(A549, NCIH460), inhibits tumor growth, attachment and metastatse, induce cell cycle arrest and apoptosis (programmed cell death), effective against Apoptosis, inhibits cell , non small cell lung cancer,  | *Saussurea costus, Saussurea lappa, Saussurea obvallata,* | [3, 16, 18, 41, 46, 52-56] |
|  | dihydrocostunolide |  | germacrane compounds | cytotoxic | *Saussurea costus, Saussurea lappa* | [60] |
|  | Saussureamine A |  | germacrane compounds | Anti-inflammatory, gastroprotective, antiulcer  | *Saussurea lappa* | [61] |
|  | Eleganin |  | germacrane compounds | Effective on breast cancer cell lines | *Saussurea lappa* | [62] |
|  | 12methoxydihydro costunolide |  | germacrane compounds | antitumour | *Saussurea lappa* | [61, 63]  |
|  | Costunolide15OβD glucopyranoside |  | germacrane compounds | antitumour | *Saussurea lappa* | [60, 64] |
|  | Doxorubicin |  | Anthracyclines | Interfere with DNA replication and inhibit cancer cells growth | *Saussurea costus* | [41, 65] |
|  | Hispidulin |  | flavanoid | Apoptosis, tumor suppression, cell cycle arrest in Human gastric adenocarcinoma cell line, Hepatocellular, Gastric Cancer | *Saussurea involucrata* | [23] |
|  | Jaceosidin |  | flavanoid | Mitotic arrest, tumor suppression, upregulation of P53 and Bax. Act on U87 glioma cells, human ovary and breast cancer cells | *Saussurea involucrata* | [22] |
|  | Lappadilactone |  | Sesquiterpene lactone | Hepatocellular carcinoma, Ovarian cancer, Hela | *Saussurea lappa* | [61],[66] |
|  | Linoleic acid |  | Poly unsaturated fatty acids | Cytotoxic, anti tumour activity in Human melanoma cells, lung (A 549, HTB 140) carcinoma cells. | *Saussurea obvallata* | [3, 67-70] |
|  | Linolenic Acid |  | Poly unsaturated fatty acids | Human melanoma cells, lung (A 549, HTB 140) carcinoma cells.  | *Saussurea hypoleuca* | [70] |
|  | Luteolin |  | flavanoid | Brain cancer | *Saussurea laniceps* | [9] |
|  | Mokko lactone |  | Sesquiterpene lactone | leukemia | *Saussurea lappa* | [16],[61] |
|  | Palmitic acid |  | Fatty acids | Inhibit prostate cancer cell metastasis | *Saussurea obvallata* | [3, 71] |
|  | Piperine |  | Alkaloids | Inhibits cancer cells proliferation and promotes apoptosis in cancer cells. | *Saussurea obvallata* | [3, 72-77] |
|  | Rutin |  | flavanoid | Alters Bax/Bcl2, inhibits metastasis, proliferation in Colorectal cancer, Lan 15 cell lines | *Saussurea involucrata* | [23] |
|  | Sesquiterpene |  | sesquiterpene | Free radical inactivator in Hepatocellular (Hep G2 cell lines) carcinoma | *Saussurea hypoleuca* | [26] |
|  | α-terpineol  |  | terpenoid | Cell cycle inhibition and apoptosis stimulation of MCF-7 cancer cell lines | *Saussurea obvallata* | [3, 78, 79] |
|  | β-caryophyllene oxide |  | sesquiterpenes | Enhance activity against colon cancer and breast cancer cells | *Saussurea costus* | [41, 80-82] |
|  | β-elemene |  | sesquiterpenes | Inhibit pancreatic cancer and neoplastic metastasis | *Saussurea costus* | [5] |
|  | β-sitosterol |  | Fatty acid esters/sterols | Induces apoptosis in HepG2 cells | *Saussurea costus* | [41, 83-85] |
|  | γ-Curcumene |  | sesquiterpenes | Induce cell cycle arrest and apoptosis in cancer cells | *Saussurea obvallata,Saussurea costus,Saussurea lappa* | [3, 41, 86, 87] |

**DISCUSSION**

This review compiles research done on anticancer compounds from different species of *saussurea* genus. Cancer is a fatal disease and is a global threat hence searches for an anticancer compound is highly demanded. *Saussurea* is a rich genus with compounds showing good activity against different cancer cell lines. So data of this entire compound are collected by extensive and thorough study of research papers on different species of *Saussurea*.

*Saussurea lappa* contain 5 compounds showing anticancer properties including costunolide, dehydro costuslactone and cyanopicrin. They showed activity in hepatocellular carcinoma, small cell lung cancer, breast cancer, prostate cancer, leukocyte derived cancer cells. Different mechanisms are observed causing apoptosis and inhibiting cell proliferation. DHE caused ER stress, costunolide decreased telomerase activity, while cyanaropicrin caused cell cycle arrest and DNA breakage. Extensive study is done on these compounds and they should be prescribed in cancer treatment.

Five compounds are obtained from *saussurea involucrate* including; Jaceosidin, rutin, hispidulin, acacetin, apigenin which also showed good activity against glioma cells, breast cancer, hepatocellular, adeno-carcinoma, colorectal cell lines. Among all these Hispidulin is a better agent and has good anticancer potential to be further developed as anticancer drugs. Apigenin is also effective against many cancer cell lines including blood, liver, colon, prostate cancer.

Another new compound with anticancer activity lutleolin is found from *saussurea laniceps*. A sesquiterpene and linolineic acid from *saussurea hypoleuca* also showed anticancer and antioxidant properties. Sesquiterpene acted as free radical inactivator. Two more compounds are obtained from *saussurea medusa*: arctin and arctigenin which showed good antitumor activity and could be possibly used for treatment of solid tumours.

Leaf and flower extracts of plant *saussurea obvallata* showed good anticancer activities. It contained compound acid methyl ester, linolenic acid and squalene. These compounds also showed good anti tumour properties.

Important anticancer compounds such as doxorubicin, dehydro-costuslactone, cyanaropicrin are also isolated from *saussurea costus* which showed good activity against colon and liver cancer.

Another compound arctigenin is obtained from *saussurea heteromalla* which showed good activity against Hela cells.

**CONCLUSION AND FUTURE PERSPECTIVES:**

Thirty compounds are found from different species of *saussurea genus* which are summarized in a table with their structures and types of cancer for which they are effective. All these compounds show good activity with different mechanisms and could be possibly marketed as anticancer drugs. More research should be done on these compounds and they should be included in cancer therapy regimens.

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**REFERENCES:**

1. Wang, Y.F., et al., *Secondary metabolites of plants from the genus Saussurea: chemistry and biological activity.* Chemistry & biodiversity, 2010. **7**(11): p. 2623-2659.

2. Butola, J.S. and S.S. Samant, *Saussurea Species in Indian Himalayan Region: Diversity, Distribution and Indigenous Uses.* International Journal of Plant Biology, 2010. **1**(1): p. e9.

3. Semwal, P., et al., *Assesment of non-timber Brahma Kamal (Saussurea obvallata (DC.) Edgew.), an important Himalayan.* Ethnobot. Res. Appl, 2020. **19**: p. 1-15.

4. Pandey, M.M., S. Rastogi, and A.K.S. Rawat, *Saussurea costus: botanical, chemical and pharmacological review of an ayurvedic medicinal plant.* Journal of ethnopharmacology, 2007. **110**(3): p. 379-390.

5. Vijayalakshmi, M., et al., *Foresight on phytoconstituents and associated pharmacological activities of traditional medicinal plant: Saussurea costus (Falc.) Lipschitz.* Current Pharmacology Reports, 2022. **8**(4): p. 281-289.

6. Zhao, T., et al., *Chemical constituents from the genus Saussurea and their biological activities.* Heterocyclic Communications, 2017. **23**(5): p. 331-358.

7. Semwal, P., et al., *Preliminary investigation of phytochemicals of Saussurea obvallata (Brahm Kamal) and Pittosporum eriocarpum (Agni): Two endangered medicinal plant species of Uttarakhand.* International Journal of Pharmacognosy, 2014. **1**(4): p. 266-269.

8. Yang, J.-L., et al., *Phytochemicals and biological activities of Saussurea species.* Journal of Asian natural products research, 2010. **12**(2): p. 162-175.

9. Lin, Y., et al., *Luteolin, a flavonoid with potential for cancer prevention and therapy.* Current cancer drug targets, 2008. **8**(7): p. 634-646.

10. Shati, A.A., et al., *Secondary metabolites of Saussurea costus leaf extract induce apoptosis in breast, liver, and colon cancer cells by caspase-3-dependent intrinsic pathway.* BioMed Research International, 2020. **2020**.

11. Nadda, R.K., et al., *Aucklandia costus (Syn. Saussurea costus): Ethnopharmacology of an endangered medicinal plant of the himalayan region.* Journal of Ethnopharmacology, 2020. **263**: p. 113199.

12. Kaur, L., et al., *A brief review of remedial uses of Saussurea lappa.* Journal of Pharmacognosy and Phytochemistry, 2019. **8**(3): p. 4423-4430.

13. Duan, J.-a., et al., *A new sesquiterpene and other constituents from Saussurea lappa root.* Natural Product Communications, 2010. **5**(10): p. 1934578X1000501002.

14. Zahara, K., et al., *A review of therapeutic potential of Saussurea lappa-An endangered plant from Himalaya.* Asian Pacific journal of tropical medicine, 2014. **7**: p. S60-S69.

15. Wei, H., et al., *Research progress on active ingredients and pharmacologic properties of Saussurea lappa.* Studies, 2014. **43**: p. 48.

16. Madhuri, K., K. Elango, and S. Ponnusankar, *Saussurea lappa (Kuth root): review of its traditional uses, phytochemistry and pharmacology.* Oriental pharmacy and Experimental medicine, 2012. **12**: p. 1-9.

17. Hung, J.-Y., et al., *Oxidative and endoplasmic reticulum stress signaling are involved in dehydrocostuslactone-mediated apoptosis in human non-small cell lung cancer cells.* Lung Cancer, 2010. **68**(3): p. 355-365.

18. Hsu, Y.-L., L.-Y. Wu, and P.-L. Kuo, *Dehydrocostuslactone, a medicinal plant-derived sesquiterpene lactone, induces apoptosis coupled to endoplasmic reticulum stress in liver cancer cells.* Journal of Pharmacology and Experimental Therapeutics, 2009. **329**(2): p. 808-819.

19. Choi, S.-H., et al., *Inhibitory effects of costunolide on the telomerase activity in human breast carcinoma cells.* Cancer letters, 2005. **227**(2): p. 153-162.

20. Zhang, Q., et al., *Systems pharmacology–based dissection of anti-cancer mechanism of traditional chinese herb Saussurea Involucrata.* Frontiers in Pharmacology, 2021. **12**: p. 678203.

21. Byambaragchaa, M., A. Kh, and S. Hwang, *Anticancer potential of an ethanol extract of Saussurea involucrata against hepatic cancer cells in vitro.* Asian Pacific journal of cancer prevention: APJCP, 2014. **15**(18): p. 7527-7532.

22. Khan, M., et al., *Jaceosidin induces apoptosis in U87 glioblastoma cells through G2/M phase arrest.* Evidence-Based Complementary and Alternative Medicine, 2012. **2012**.

23. Gong, G., et al., *Saussureae Involucratae Herba (snow lotus): Review of chemical compositions and pharmacological properties.* Frontiers in pharmacology, 2020. **10**: p. 1549.

24. Gao, H., et al., *Hispidulin induces mitochondrial apoptosis in acute myeloid leukemia cells by targeting extracellular matrix metalloproteinase inducer.* American Journal of Translational Research, 2016. **8**(2): p. 1115.

25. Imran, M., et al., *Apigenin as an anticancer agent.* Phytotherapy Research, 2020. **34**(8): p. 1812-1828.

26. Arshad, N., et al., *Evaluation of antioxidant, antimicrobial and anticancer activities of compounds reported Saussurea hypoleuca Spreng. roots.* Pakistan Journal of Pharmaceutical Sciences, 2021. **34**.

27. Arshad, N. and S. Ishtiaq, *Proximate analysis and in vitro biological assays of Saussurea hypoleuca Spreng. root.* Pakistan Journal of Pharmaceutical Sciences, 2019. **32**.

28. Lee, K.H., B.-S. Kim, and K.-H. Rhee, *Anti-Tumor activity of saussurea laniceps against pancreas adenocarcinoma.* Natural Product Sciences, 2017. **23**(4): p. 281-285.

29. Wruck, C., et al., *Luteolin protects rat PC 12 and C6 cells against MPP+ induced toxicity via an ERK dependent Keapl-Nrf2-ARE pathway*. 2007: Springer.

30. Fan, J.-Y., et al., *Saussurea medusa, source of the medicinal herb snow lotus: a review of its botany, phytochemistry, pharmacology and toxicology.* Phytochemistry Reviews, 2015. **14**(3): p. 353-366.

31. Takasaki, M., et al., *Anti-tumor-promoting activity of lignans from the aerial part of Saussurea medusa.* Cancer Letters, 2000. **158**(1): p. 53-59.

32. Maheshwari, M., et al., *Arctin and arctigenin as a potential treatment for solid tumors.* Cancer Research, 2019. **79**(13\_Supplement): p. 366-366.

33. Kamal, B., *Brahma Kamal–the spiritually revered, scientifically ignored medicinal plant.* Current Science, 2013. **104**(6): p. 685.

34. Semwal, P., et al., *Brahma Kamal (Saussurea obvallata (DC.) Edgew.): Ethnomedicinal, phytochemical and pharmacological overview of an important Himalayan medicinal plant.* Ethnobotany Research and Applications, 2020. **19**: p. 1-15.

35. Mitra, D., et al., *Isolation and Characterization of Dominant Fungi from Rhizospheric soil of Saussurea obvallata (DC.) Edgew.(Brahma Kamal) of the Indian Himalayan Region.* J Pure Appl Microbiol, 2019. **13**(3): p. 1509-1515.

36. Phondani, P.C., et al., *Ethnobotanical uses of plants among the Bhotiya tribal communities of Niti Valley in Central Himalaya, India.* Ethnobotany Research and Applications, 2010. **8**: p. 233-244.

37. Mishra, A.P., et al., *Antibacterial potential of Saussurea obvallata petroleum ether extract: A spiritually revered medicinal plant.* Cellular and Molecular Biology, 2018. **64**(8): p. 65-70.

38. Semwal, P. and S. Painuli, *Antioxidant, antimicrobial, and GC-MS profiling of Saussurea obvallata (Brahma Kamal) from Uttarakhand Himalaya.* Clinical Phytoscience, 2019. **5**: p. 1-11.

39. Kumar, J. and M. Pundir, *Phytochemistry and pharmacology of Saussurea genus (Saussurea lappa, Saussurea costus, Saussurea obvallata, Saussurea involucrata).* Materials Today: Proceedings, 2022. **56**: p. 1173-1181.

40. Ali, S.I. and V. Venkatesalu, *Botany, traditional uses, phytochemistry and pharmacological properties of Saussurea costus – An endangered plant from Himalaya- A review.* Phytochemistry Letters, 2022. **47**: p. 140-155.

41. Mohsen, E., et al., *SPME and solvent-based GC–MS metabolite profiling of Egyptian marketed Saussurea costus (Falc.) Lipsch. concerning its anticancer activity.* Phytomedicine Plus, 2022. **2**(1): p. 100209.

42. Elkady, A.I., *Anethole inhibits the proliferation of human prostate cancer cells via induction of cell cycle arrest and apoptosis.* Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 2018. **18**(2): p. 216-236.

43. Chen, C.H. and L.A. deGraffenried, *Anethole suppressed cell survival and induced apoptosis in human breast cancer cells independent of estrogen receptor status.* Phytomedicine, 2012. **19**(8-9): p. 763-767.

44. Contant, C., et al., *Anethole induces anti-oral cancer activity by triggering apoptosis, autophagy and oxidative stress and by modulation of multiple signaling pathways.* Scientific reports, 2021. **11**(1): p. 13087.

45. Rhee, Y.-H., et al., *CXCR4 and PTEN are involved in the anti-metastatic regulation of anethole in DU145 prostate cancer cells.* Biochemical and biophysical research communications, 2014. **447**(4): p. 557-562.

46. Li, Q., et al., *Antitumor activity and mechanism of costunolide and dehydrocostus lactone: Two natural sesquiterpene lactones from the Asteraceae family.* Biomedicine & Pharmacotherapy, 2020. **125**: p. 109955.

47. El-Far, A.H., et al., *Thymoquinone and costunolide induce apoptosis of both proliferative and doxorubicin-induced-senescent colon and breast cancer cells.* Integrative Cancer Therapies, 2021. **20**: p. 15347354211035450.

48. El-Far, A.H., et al., *Nanonutraceuticals: Anti-cancer activity and improved safety of chemotherapy by costunolide and its nanoformulation against colon and breast cancer.* Biomedicines, 2021. **9**(8): p. 990.

49. Yang, Y.-I., et al., *Costunolide induces apoptosis in platinum-resistant human ovarian cancer cells by generating reactive oxygen species.* Gynecologic oncology, 2011. **123**(3): p. 588-596.

50. Rasul, A., et al., *Induction of Apoptosis by Costunolide in Bladder Cancer Cells is Mediated through ROS Generation and Mitochondrial Dysfunction.* Molecules, 2013. **18**(2): p. 1418-1433.

51. Cho, J.Y., et al., *Cytotoxic and pro-apoptotic activities of cynaropicrin, a sesquiterpene lactone, on the viability of leukocyte cancer cell lines.* European Journal of Pharmacology, 2004. **492**(2): p. 85-94.

52. Long, H.-y., et al., *Dehydrocostus lactone inhibits in vitro gastrinoma cancer cell growth through apoptosis induction, sub-G1 cell cycle arrest, DNA damage and loss of mitochondrial membrane potential.* Archives of Medical Science, 2019. **15**(3): p. 765-773.

53. Sheng, W., et al., *Dehydrocostus lactone enhances chemotherapeutic potential of doxorubicin in lung cancer by inducing cell death and limiting metastasis.* Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 2018. **24**: p. 7850.

54. Zhang, R., et al., *Dehydrocostus lactone inhibits cell proliferation and induces apoptosis by PI3K/Akt/Bad and ERS signalling pathway in human laryngeal carcinoma.* Journal of Cellular and Molecular Medicine, 2020. **24**(11): p. 6028-6042.

55. Tian, Y., et al., *Dehydrocostus lactone inhibits the proliferation and metastasis of hepatocellular carcinoma cells via modulating p53-p21-CDK2 signaling pathway.* Arabian Journal of Chemistry, 2023. **16**(8): p. 104994.

56. Su, C.-Y., et al., *Dehydrocostus lactone exerts the antitumor effect in non-small cell lung cancer H1299 cells.* TMR Cancer, 2020. **3**(3): p. 101-111.

57. Batool, A., et al., *Bioassay-guided fractionation and isolation of Arctigenin from Saussurea heteromalla for in vitro and in silico cytotoxic activity against HeLa cells.* Physiological and Molecular Plant Pathology, 2022. **117**: p. 101749.

58. Saklani, A., et al., *Saussurea heteromalla (D. Don) Hand.-Mazz.: A new source of arctiin, arctigenin and chlorojanerin.* 2011.

59. Houghton, P., et al., *The sulphorhodamine (SRB) assay and other approaches to testing plant extracts and derived compounds for activities related to reputed anticancer activity.* Methods, 2007. **42**(4): p. 377-387.

60. Robinson, A., et al., *A new sesquiterpene lactone from the roots of Saussurea lappa: Structure–anticancer activity study.* Bioorganic & medicinal chemistry letters, 2008. **18**(14): p. 4015-4017.

61. Gautam, H. and R. Asrani, *Phytochemical and pharmacological review of an ethno medicinal plant: Saussurea Lappa.* Vet Res Int, 2018. **6**(1): p. 1-9.

62. Tastan, P., et al., *Sesquiterpene lactones and flavonoids from Psephellus pyrrhoblepharus with antiproliferative activity on human gynecological cancer cell lines.* Molecules, 2019. **24**(17): p. 3165.

63. Wei, H., et al., *Research progress on active ingredients and pharmacologic properties of Saussurea lappa.* J Asian Nat Prod Res, 2008. **10**(11): p. 1045-53.

64. Matsuda, H., et al., *Absolute stereostructures and syntheses of saussureamines A, B, C, D and E, amino acid–sesquiterpene conjugates with gastroprotective effect, from the roots of Saussurea lappa.* Tetrahedron, 2000. **56**(39): p. 7763-7777.

65. Kciuk, M., et al., *Doxorubicin&mdash;An Agent with Multiple Mechanisms of Anticancer Activity.* Cells, 2023. **12**(4): p. 659.

66. Sun, C.-M., et al., *Cytotoxic Sesquiterpene Lactones from the Root of Saussurea l appa.* Journal of natural products, 2003. **66**(9): p. 1175-1180.

67. Dhar Dubey, K.K., G. Sharma, and A. Kumar, *Conjugated linolenic acids: implication in cancer.* Journal of agricultural and food chemistry, 2019. **67**(22): p. 6091-6101.

68. Xu, M.-Q., et al., *Antitumor activity of α-linolenic acid-paclitaxel conjugate nanoparticles: In vitro and in vivo.* International Journal of Nanomedicine, 2021: p. 7269-7281.

69. González-Fernández, M.J., I. Ortea, and J.L. Guil-Guerrero, *α-Linolenic and γ-linolenic acids exercise differential antitumor effects on HT-29 human colorectal cancer cells.* Toxicology Research, 2020. **9**(4): p. 474-483.

70. Jóźwiak, M., et al., *Anticancer effects of alloxanthoxyletin and fatty acids esters–In vitro study on cancer HTB-140 and A549 cells.* Biomedicine & Pharmacotherapy, 2019. **110**: p. 618-630.

71. Zhu, S., et al., *Palmitic acid inhibits prostate cancer cell proliferation and metastasis by suppressing the PI3K/Akt pathway.* Life Sciences, 2021. **286**: p. 120046.

72. Turrini, E., P. Sestili, and C. Fimognari, *Overview of the anticancer potential of the “king of spices” piper nigrum and its main constituent piperine.* Toxins, 2020. **12**(12): p. 747.

73. de Almeida, G.C., et al., *Piperine suppresses the Wnt/β-catenin pathway and has anti-cancer effects on colorectal cancer cells.* Scientific reports, 2020. **10**(1): p. 11681.

74. Smilkov, K., et al., *Piperine: old spice and new nutraceutical?* Current pharmaceutical design, 2019. **25**(15): p. 1729-1739.

75. Rehman, M.U., et al., *Piperine regulates Nrf-2/Keap-1 signalling and exhibits anticancer effect in experimental colon carcinogenesis in Wistar rats.* Biology, 2020. **9**(9): p. 302.

76. Haq, I.U., et al., *Piperine: A review of its biological effects.* Phytotherapy research, 2021. **35**(2): p. 680-700.

77. Ramos, I.N.d.F., et al., *Extraction, Characterization, and Evaluation of the Cytotoxic Activity of Piperine in Its Isolated form and in Combination with Chemotherapeutics against Gastric Cancer.* Molecules, 2023. **28**(14): p. 5587.

78. Ramandanti, S.K., N. Wijayanti, and N.D. Amalina, *α-Terpeniol Subtance As Anticancer.* Minyak Atsiri: Produksi dan Aplikasinya untuk Kesehatan, 2021: p. 204-225.

79. Candrasari, D.S., S. Mubarika, and M.S.H. Wahyuningsih, *The effect of a-terpineol on cell cycle, apoptosis and Bcl-2 family protein expression of breast cancer cell line MCF-7.* Journal of the Medical Sciences (Berkala Ilmu Kedokteran), 2015. **47**(2).

80. Di Giacomo, S., et al., *Chemosensitizing properties of β-caryophyllene and β-caryophyllene oxide in combination with doxorubicin in human cancer cells.* Anticancer Research, 2017. **37**(3): p. 1191-1196.

81. Ambrož, M., et al., *Sesquiterpenes α-humulene and β-caryophyllene oxide enhance the efficacy of 5-fluorouracil and oxaliplatin in colon cancer cells.* Acta Pharmaceutica, 2019. **69**(1): p. 121-128.

82. Wang, Z., et al., *β-sitosterol reverses multidrug resistance via BCRP suppression by inhibiting the p53–MDM2 interaction in colorectal cancer.* Journal of agricultural and food chemistry, 2020. **68**(12): p. 3850-3858.

83. Novotny, L., M. Abdel-Hamid, and L. Hunakova, *Anticancer potential of β-sitosterol.* Int. J. Clin. Pharmacol. Pharmacother, 2017. **2**(10.15344).

84. Vo, T.K., et al., *Anti-hepatocellular-cancer activity exerted by β-sitosterol and β-sitosterol-glucoside from Indigofera zollingeriana miq.* Molecules, 2020. **25**(13): p. 3021.

85. Jou, Y.J., et al., *Quantitative phosphoproteomic analysis reveals γ‐bisabolene inducing p53‐mediated apoptosis of human oral squamous cell carcinoma via HDAC2 inhibition and ERK1/2 activation.* Proteomics, 2015. **15**(19): p. 3296-3309.

86. Lunz, K. and I. Stappen, *Back to the roots—an overview of the chemical composition and bioactivity of selected root-essential oils.* Molecules, 2021. **26**(11): p. 3155.

87. Yuandani, et al., *Immunomodulatory effects and mechanisms of curcuma species and their bioactive compounds: A review.* Frontiers in pharmacology, 2021. **12**: p. 643119.

88. Kumar, R., Patel, S. K., Verma, A., Joshi, G. S., Bisen, H. K., Asrani, R. K., ... & Pandey, M. K. (2024). Saussurea costus (falc.) lipsch: A promising ally against cancer. Pharmacological Research-Natural Products, 5, 100123.

89. Elnour, A. A., & Abdurahman, N. H. (2024). Current and potential future biological uses of Saussurea costus (Falc.) Lipsch: A comprehensive review. Heliyon,11;10(18):e37790. doi: 10.1016/j.heliyon.2024.e37790