REVIEW ARTICLE

Terpenoids and the mechanism of their anticancer effects

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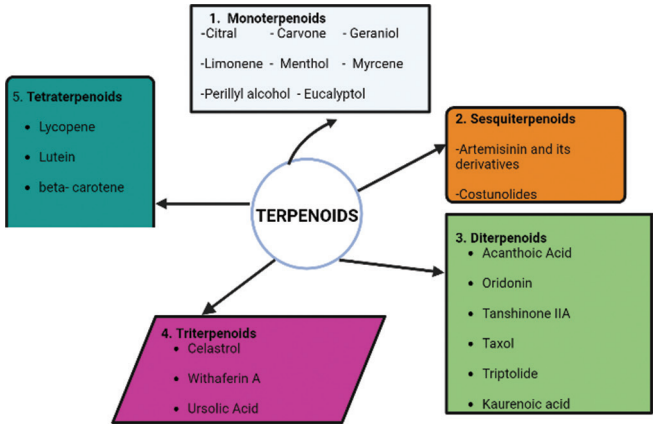
Abstract

Terpenoids otherwise called isoprenoids are secondary metabolites with diverse biological and pharmacological activities. They serve as candidate compounds for drug discovery. They are classified into mono-, sesqui-, di-, tri-, tetra-, and polyterpenoids based on their isoprenoid structural units. They exhibit anticancer properties through various mechanisms such as cell cycle arrest induction, angiogenesis suppression, decreased tumor cell differentiation, and apoptosis. Most terpenoids used in cancer therapy are derived from medicinal plants. This paper reviews important plant-derived terpenoids used in cancer treatment, their medicinal plant sources, and their mechanism of action.

Key words: Cancer, plants, terpenoids

GRAPHICAL ABSTRACT



INTRODUCTION

Cancer is a global complex disease characterized by sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality, resisting cell death, inducing angiogenesis, and activating invasion and metastasis, apart from reprogramming energy metabolism and evading immune destruction.[1] It is a worldwide health and economic concern for both developed and developing countries. It is the leading cause of global deaths. According to the World Health Organization, over 10 million people died of cancer in 2020.[2] Breast and prostate cancers have been recorded to have the highest incidence, prevalence, and mortality rates in females and males, respectively. Most cancer death rates increase as a result of late diagnosis,[3] while early detection and treatment can reduce morbidity and mortality rates.

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Surgery, chemotherapy, and radiotherapy stem cell renewal are the major effective approaches in cancer therapy.[4] However, treatment failures, drug resistance, and side effects are the major drawbacks of cancer chemotherapy. This has necessitated the search for other alternative novel drugs with better efficacy and fewer side effects. Plant diet has also been recorded to protect the human body from the risk of carcinogenesis.[5] Plants contain phytochemicals and their derivatives with varying pharmacological activities. Over the decades, plants' natural products have been documented as an important source of drug discovery. At present, plant-derived drugs are becoming major sources of cancer treatment.[6,7] This review aims at documenting information on some plant-based terpenoids and their mechanism of anticancer activity.

TERPENOIDS

Terpenoids also called isoprenoids are modified terpenes that contain different functional groups and an oxidized methyl group. Terpenoids are ubiquitously distributed in nature, the most diverse group of secondary metabolites, and present in plants and lower invertebrates. They are rich sources of candidate compounds for drug discovery. They are obtained from mevalonic acid (MVA) which consists of isoprene (C_5) structural units. Most terpenoids are isolated from medicinal plants that belong to the following plant groups: Oleaceae, Rutaceae, Labiatae, Acanthaceae, Compositae, Taxaceae, Pinaceae, Lauraceae, Araliaceae, Celastraceae, etc. Terpenoids are classified according to the number of isoprene (2-methylbuta-1, 3-diene) units into monoterpenoids (C_{10}),

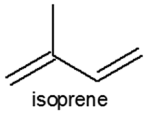
Table 1: Terpenoid classification and sources

Terpenoid subclass	Compounds	Sources	References
Monoterpenoids	Citral	Lemon grass oil (*Cymbopogon citratus*)	[12]
	Carvone	Spearmint oil (*Mentha spicata*) and Caraway oil (*Carum carvi*),	[13]
	Geraniol	Palmarosa oil, rose oil, and ninde oil (*Aeollanthus myrianthus)*	[14,15]
	Limonene	Citrus essential oils: orange (*Citrus sinensis*), lime (*Citrus aurantifolia*), grape (*Citrus paradisi*), mandarin (*Citrus reticulata*), and lemon (*Citrus limon*)	[16]
	Menthol	Peppermint oil (*Mentha piperita*)	[17]
	Myrcene	bay laurel oil (*Laurus nobilis*) and Verbena oil (*Lippia citriodora*)	[18]
	Perillyl alcohol		[19]
	Eucalyptol (1.8-cineole)	Eucalyptus leaf oil (*Eucalyptus globules*), rosemary (*Rosmarinus officinalis*)	[20]
Sesquiterpenoids	Artemisinin and its derivatives	Sweet wormwood (*Artemisia annua*)	[21]
	Costunolide	*Aucklandia lappa*	[22,23]
Diterpenoids	Acanthoic acid	*Acanthopanax koreanum Nakai, Croton oblongifolius* Roxb	[24,25]
	Oridonin	*Rabdosia rubescens*	[26]
	Tanshinone IIA	*Salvia miltiorrhiza* Bge	[27]
	Taxol (Paclitaxel)	*Taxus brevifolia*	[28]
	Triptolide	*Tripterygium wilfordii*	[29,30]
	Kaurenoic acid	*Annona senegalensis* (Annonaceae)	[31]
Triterpenoids	Celastrol	*Tripterygium wilfordii*	[29]
	Withaferin A	*Withania somnifera*	[32]
	Ursolic acid	*Rosmarinus officinalis* (rosemary), *Calluna vulgaris* and *Eugenia jambolana, Salvia officinalis, and Eriobotrya japonica*	[33]
Tetraterpenoids	Lycopene	Tomatoes (*Lycopersicon esculentum*), pink guavas, apricots, water melon, and pink grapefruits	[34,35]
	Lutein	Spinach, kale, carrot, corn, and egg yolk	[36,37]
	β-carotene	Carrot	[38]

sesquiterpenoids (C_{15}), diterpenoids (C_{20}), triterpenoids (C_{30}), tetraterpenoids (C_{40}), and polyterpenoids (C > 40) [Table 1]. They possess vast medicinal importance that includes: antitumor, antibacterial, antimalarial, anti-inflammatory, antiviral, anticancer, immunomodulatory, anti-aging, antioxidant, anti-depressants, antifungal, and antidiabetic.[8,9]

Mevalonate (MVA) and 2C-methyl-D-erythritol-4- phosphate (MEP) pathways are the two major pathways for terpenoid biosynthesis. The main metabolic intermediate for both pathways is isopentenyl diphosphate (1PP). Plants produce monoterpenoids, diterpenoids, and tetraterpenoids through the MEP in the plastids, whereas sesquiterpenoids and triterpenoids are produced through the mevalonate route in the cytoplasm.

Terpenoids of natural origin are known to possess anticancer properties. A huge number of triterpenoids have been known to subdue the growth of cancer cells without producing toxicity in normal cells.[10] The major mechanisms of anticancer activities of terpenoids include induction of cell cycle arrest, angiogenesis suppression, decreased tumor cell differentiation, apoptosis, anti-proliferative, and anti-angiogenic.[5,11]



Isoprene moiety

MONOTERPENOIDS

Citral

It is effective against P388 mouse leukemia, HeLa and ECC-1 cancer cells.[39] It also induces apoptosis driving lipogenesis in both *in vitro* and *in silico* studies. It alters the potential of the mitochondrial membrane, increases intracellular reactive oxygen species, and initiates the death of cancer cells by apoptosis.[40]

Carvone

It is a cytotoxic agent against HeLa cells.[1] It is known to increase intracellular reactive oxygen species mediated apoptotic cell death in cancer cells.[41]

Geraniol

It blocks tumor cell growth by inhibiting the G_1 phase Michigan Cancer Foundation-7 (MCF-7) breast cancer cell cycle.[14] It also inhibits the growth of HepG2 human hepatic carcinoma cells by reducing the activity of 3-hydroxymethylglutaryl coenzyme A reductase which results in a decrease in cancer growth and cholesterol biosynthesis.[1] In addition, it induces apoptosis and elevates Bak expression, a proapoptotic protein, in cultured pancreatic tumor cells[42] and induces angiogenesis.[43] Duncan *et al.* reported that geraniol reduces cell division, cell cycle progression, and cyclin-dependent kinase 2 activity in MCF-7 breast cancer cells, claim Duncan *et al.*[44]

Limonene

D-limonene antiangiogenic, proapoptotic, and anti-oxidant actions reduce the rate of tumor growth and metastasis.[45,46]

Menthol

It is a concentration-dependent cytotoxic agent against murine leukemia WEHI-3 cells.[47] Menthol decreased the proliferation and motility of prostate cancer DU145 cells, according to research by Wang *et al.*[48]

Myrcene

It is known to be cytotoxic against MCF-7 breast carcinoma, gall tumor, human colon adenocarcinoma (HT-29), and HeLa (Human Cervical carcinoma).[49] It induces oxidative stress and apoptosis in cancer cells.[50]

Perillyl Alcohol

It is a monoterpenoid derived from lavender, peppermint, and other plants that block telomerase activity in prostate cancer.[51]

SESQUITERPENOIDS

Artemisinin and Derivatives

Artemisinin and its derivatives are globally known as an antimalarial agent. The anticancer properties of artemisinin are mediated through the induction of cell cycle arrest, boosting ferroptosis and autophagy, inducing cell death, limiting cell metastasis, and suppressing cancer growth.[52-54] It is active against colorectal, cervical, hepatocellular, leukemia, breast, prostate, colon, gastric, melanoma, and lung cancer.[55,56]

Costunolide

It is a sesquiterpene lactone compound obtained from a medicinal plant *Aucklandia lappa* Decne. It manifests anticancer activity by inhibiting cancer cell proliferation, inhibiting metastasis, inhibiting angiogenesis, inducing cancer cell apoptosis and differentiation, inhibiting cell cycle progression, and reversing multidrug resistance.[57,58]

Oridonin

It is a diterpenoid that induces apoptosis in lung and breast cancer cells through the arrest of G2/M cell cycle progression,

resulting to the inhibition of cancer progression. It also facilitates the phagocytosis of apoptotic tumor cells through the regulation of macrophage functioning that involves tumor necrosis factor (TNF)-α and interleukin-1β.[27,59,60] It is effective against breast, colon, pancreatic, lung, gastric, prostate, and skin cancers.[61]

Tanshinone IIA

Its antitumor/cancer activity is attributed to its tumor growth inhibition, apoptosis induction, signaling pathway, and cell cycle regulation.[62,63] It also inhibits angiogenesis and it is active against breast cancers,[64] and leukemia,[65] lung cancer,[66,67] gastric carcinomas,[68-70] colorectal cancer,[71,72] glioma,[73] osteosarcoma,[74] cervical cancer,[75,76] ovarian cancer,[77] and prostate cancer.[78]

Triptolide

It is a diterpenoid triepoxide isolated from *Tripterygium wilfordii* Hook. All 60 cancer cell lines from the US National Cancer Institute are inhibited from proliferating by triptolide. In addition, by causing the biggest RNA polymerase II (Rpb1) subunit of cancer cells to degrade in a proteasome-dependent manner, it hinders global gene transcription.[79]

Paclitaxel

It is a well-known anti-neoplastic substance that was originally discovered in the bark of pacific yew trees (*Taxus brevifolia*). Its anticancer action is by inducting mitotic arrest through the targeting of the cytoskeleton component tubulin, resulting in mitotic activation and apoptosis.[30] It is used to treat pancreatic, ovarian, and breast cancers.

TRITERPENOIDS

Celastrol

A quinone-methide triterpene called celastrol is derived from the plant lei gong teng (*T. wilfordii Hook F*). It stops cancer growth by initiating TNF-α induced NF-kB signaling pathway.[80] In addition, it prevents the growth, migration, and invasion of chondrosarcoma cells by inhibiting the protein phosphatase 2A-Akt signaling pathway *in vivo*.[81] Celastrol activates cell cycle arrest and human cancer cell death through apoptosis.[82]

Withaferin A (WA)

WA is obtained from the medicinal plant *Withania somnifera* Dunal (Ashwagandha). It exerts its anticancer activity by activating apoptosis and G2/M cell cycle arrest.[83]

Ursolic Acid (UA)

It is an apentacyclic triterpene acid that is present in the leaves of Ocimum as well the berries, leaves, flowers, and fruits of *Eriobotrya japonica*, *Calluna vulgaris*, *Eugenia jambolana*, *Rosmarinus officinalis*, and *Salvia officinalis*.[33] Ursolic acid inhibits the development and spread of cancer by reducing proliferation and triggering apoptosis both *in vitro* and *in vivo*. Furthermore, it dose-dependently prevents the *in vitro* growth of the gastric cancer cell line BGC-803. It also prevents breast cancer multiplication by inducing G1/G2 cell arrest and regulates the expression of key proteins in signal transduction pathways.[84]

TETRATERPENOIDS

The most prevalent terpenoids are tetraterpenoids.

Lutein

According to Li *et al.*, lutein suppresses hypoxia-induced proliferation, invasion, and migration of cancer cells in the breast.[85]

Lycopene

It is the main pigment found in tomatoes. Lycopene is known to prevent cell proliferation, induce apoptosis, inhibit cell invasion, and inhibit cell cycle progression, angiogenesis, and metastasis.[86]

Beta-carotene (β-carotene)

Beta-carotene can also be referred to as provitamin A. Beta-carotenes are known to induce apoptosis, cell cycle arrest, signaling pathways, migration invasion, and metastasis.[87]

CONCLUSION

The knowledge of ethnobotanicals is one of the major approaches to new drug discovery. Plants provide the major sources for modern anticancer drug discovery. Numerous terpenoid medications have produced significant therapeutic and commercial benefits. Terpenoids have, over the years, continued to be indispensable in drug discovery. Terpenoids that are naturally produced have opened up new prospects for researchers to identify and use novel compounds against cancer and other diseases with minimal side effects.

The present review summarizes the basic natural terpenoids currently used in the treatment of cancer. The review also highlighted the plants responsible for the anticancer activity as well as their corresponding pharmacological actions.

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