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Systematic Review

Harnessing the Power of Natural Terpenoid Compounds Against Esophageal Squamous Cell Carcinoma: A Systematic Review

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Abstract: Background/Objectives: Limitations of conventional treatments for esophageal cancer, which include poor solubility, drug resistance, and undesirable side effects, make it imperative to explore new therapeutic approaches to slow the progression of this disease. This study aims to assess the potential of terpene compounds as anti-cancer agents for esophageal squamous cell carcinoma (ESCC). Methods: This work was carried out following the PRISMA 2020 guidelines to ensure rigorous methodology. Results: A systematic analysis of 34 compounds revealed various mechanisms of action, such as induction of oxidative stress and modulation of apoptotic pathways. The results also show that several compounds, including (1Z,3R,4S,5E,7Z)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene, dehydrocostus lactone, (3R,4S)-3,4,6,7-tetrachloro-3,7-dimethyl-octene-1-ene, acetyl-macrocalin B, jesridonin, longikaurin A, sphaerococcenol A, DS2, rabdocoestin B, ingenol C, ingenol-3,20-dibenzonate, JDA-202, xerophilusin B, betulinic acid, euphol, and (20S) ginsenoside Rh2, with IC_{50}s below 10 µM, show promising efficacy both in vitro and in vivo, sometimes surpassing certain conventional treatments. Conclusions: However, despite these encouraging prospects, limitations remain, notably a lack of in vivo data and clearly defined mechanisms of action for certain compounds. These challenges require further research to validate their safety and efficacy, facilitating their development as viable therapeutic options for ESCC.

Keywords: esophageal squamous cell carcinoma; terpenoid compounds; alternative treatment; systematic review

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1. Introduction

To prevent and treat disease, mankind has always turned to medicinal plants [1]. Medicinal plants contain a variety of secondary metabolites, which, alone or in combination, represent a significant therapeutic alternative for contemporary health problems [2,3]. It has played, and continues to play, a key role in the treatment and prevention of various diseases, with the prevalence of their use ranging from 50% in developed countries to 95% in developing countries [4,5]. Over 25% of all medicines on the market are derived from plants [6,7]. Among the active compounds in plants, terpenoids, also known as isoprenoids, play a key role. They are synthesized in plants from acetate and methylerythritol phosphate (MEP). The isoprenoic units thus formed can combine to give rise to a diversity of terpenoids, ranging from monoterpenes to triterpenes, via sesquiterpenes and diterpenes [8,9]. Terpenoids play several essential roles in plants. They help defend against herbivores and pathogens by acting as repellents or toxic agents (menthol) [10]. They also attract pollinators with their aromas and contribute to protection against UV rays and

oxidative stress (carotenoids) [11]. Lastly, certain terpenoids are involved in plant-to-plant communication, enabling plants to signal environmental threats (phytohormones) [12,13]. These compounds are also associated with a wide range of biological activities, including antioxidant [14], anti-inflammatory [15], antifungal [16], anxiolytic and depression [17], antibacterial [18], and anticancer properties [19]. These biological activities, especially their anticancer potential, are of growing interest due to the increasing incidence of cancer and the limitations of current therapeutic options.

Regarding anti-cancer activity, several studies have demonstrated the beneficial in vitro and in vivo effects of certain terpenoid compounds on cancer lines, particularly those of the esophagus. Esophageal cancer (EC) is a type of cancer that is particularly widespread in developing countries, particularly in Asia and the East African corridor, with around 604,100 new cases and 544,076 deaths recorded worldwide each year [20]. The exponential rise in this disease is a cause for concern, with the number of deaths set to double by 2030 if no action is taken [20]. This high incidence in low-income regions (specifically rural areas) highlights the global health disparity, further emphasizing the urgent need for accessible treatment alternatives. Various factors, such as smoking patterns [21], drinking patterns [22], eating habits [23], and socioeconomic conditions [24], are associated with this increase. Although individual studies demonstrate the efficacy of natural compounds against esophageal cancer, including alkaloids [25] and phenolic compounds [26], no systematic review has been conducted to present terpenoid compounds' effects on this type of cancer. Furthermore, the increasing resistance of cancer cells to conventional chemotherapy and radiation treatments makes exploring novel, less toxic natural compounds even more crucial. Moreover, current cancer lines have developed resistance to available drugs, often accompanied by adverse effects that hinder treatment adherence, highlighting the need to discover new alternatives [27,28]. This is particularly critical in esophageal cancer, where treatment options are limited and the prognosis is often poor, making it a priority for therapeutic development.

The aim of this work is to produce a bibliographic summary of the various terpenoid compounds with anticancer activity against ESCC, as well as to explore their mechanisms of action to guide pharmaceutical companies in their development. In addition to investigating their potential as novel therapeutic agents, this review will also consider the challenges of using terpenoid compounds in clinical practice, including their mechanisms of action and the need for further optimization to improve their efficacy and reduce toxicity. The intention is to systematically examine new terpenoid compounds that could provide an alternative treatment to control the growing incidence of this disease.

2. Methodology

2.1. Search Protocol and Eligibility Criteria

Scientific literature published prior to March 2025 was gathered from the Web of Science, PubMed/Medline, Google Scholar, and Scopus databases and systematically evaluated following the PRISMA 2020 guidelines (see Table S1) [29]. The review protocol was registered in the Open Science Framework (OSF) associated project: https://osf.io/296ba. The search terms included "anti-esophageal adenocarcinoma" OR "anti-esophageal cancer" OR "anti-esophageal squamous-cell carcinoma" AND "terpenoid compounds" AND "pharmacological activity" OR "biological activity". Research was deemed relevant if it evaluated the effects of compounds classified as terpenoids on esophageal cancer, whether as primary or secondary objectives. Exclusively original published research was considered, while studies focusing on other categories of metabolites were excluded. Review articles, conference abstracts, and editorials were also disregarded. No restrictions were imposed regarding the language of publication or the date of publication.

2.2. Data Extraction and Selection Procedure

The search results were first imported into EndNote, where duplicates were removed, and then transferred to Rayyan 1.4.4 software for better organization of the selection and review process [30]. The authors (E.J.N. and G.T.K.) conducted a thorough review process, initially assessing the titles and abstracts of relevant articles independently. They then performed a second round of independent selection by examining the full texts of the articles that had been retained from the initial review. Any disagreements that arose during this process were resolved through discussion, ensuring a consensus on the selected studies. This rigorous approach underscores the authors' commitment to maintaining the integrity and reliability of systematic review and to avoiding biases. Data related to terpenoid compounds, their structures, the plants from which they were extracted, and their biological activities were extracted from studies. Regarding biological properties, the authors independently extracted study results (such as IC_{50} values and therapeutic doses).

2.3. Synthesis Procedure

This work presents a systematic review that addresses data synthesis and analysis in a structured manner. It begins with an overview of the studies, followed by systematic categorization to gain deeper insights through a methodical selection process summarized in the flow diagram. A comprehensive summary table was created to encapsulate the characteristics of the included studies. For synthesis, a narrative approach was utilized, as noted by Kamsu and Ndebia [26]. Additionally, the studies were evaluated based on their reliability, relevance, applicability, and validity, employing the GRADE system to assess the quality of the evidence, as referenced from Hipp et al. [31]. Overall, the review highlights a meticulous method for analyzing research, focusing on the quality and applicability of the gathered evidence.

3. Results

3.1. Synthesis of Research Findings on Terpenes and ESCC

The research process yielded 26 studies on 34 compounds from different families (see Figure 1 and Table 1). Monoterpenes included (1Z,3R,4S,5E,7Z)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene, natural borneol, and (3R,4S)-3,4,6,7-tetrachloro-3,7-dimethyl-octene-1. Sesquiterpenes included isoalantolactone, dehydrocostus lactone, germacrone, and thapsigargin. As far as diterpenes are concerned, the compounds listed are acetyl-macrocalin B, jesridonin, oridonin, tanshinone IIA, longikaurin A, sphaerococcenol A, 14R-hydroxy-13,14-dihydro-sphaerococcenol, A12S-hydroxy-bromosphaerol, bromosphaerodiol, jaridonin, DS2, rabdocoestin B, ingenol A, ingenol B, ingenol C, ingenol-3,20-dibenzoate, ingenol-3-angelate, JDA-202, and xerophilusin B. Finally, the triterpenes included phaseoloide E, betulinic acid, ursolic acid, oleanolic acid, euphol, (20S) ginsenoside Rh2, lupeol acetate, and ginsenoside Rk3. The studies come from five countries: China (21 studies), Brazil (2 studies), and Japan, Greece and South Africa (1 study each), all reporting the activities of these compounds against esophageal squamous cell carcinoma (ESCC).

3.2. In Vitro Anti-Esophageal Squamous Cell Carcinoma Potential of Terpenoids

This study identified 32 compounds with proven antioxidant activities on various esophageal cancer cell lines. The terpenoids showed varying levels of activity depending on the cell line (see Table 2).

Table 1. Characteristics of included studies.

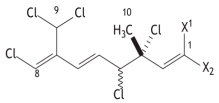
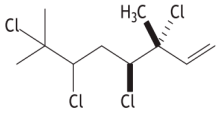
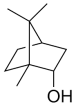
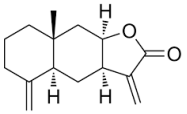
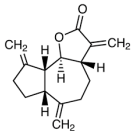
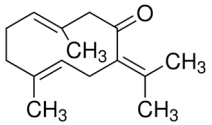
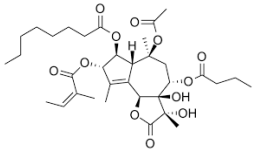
Class	Compounds	Structure	Plants of Origin	ESCC Cell Lines	Reference (Country)
Monoterpenoids	1Z,3R,4S,5E,7Z)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene	 X^1 = Br, X^2 = H, (3*R**,4*S**)	seaweeds *Plocamium suhrii*	*WHCO1*	[32] (South Africa)
	(3R,4S)-3,4,6,7-tetrachloro-3,7-dimethyl-octen-1-ene				
	Natural borneol		*Cinnamomum* spp.	*TE-1*, *TE-13*	[33] (China)
Sesquiterpenoids	Isoalantolactone		*Inula helenium* L.	*Eca-109*, *EC9706*, *TE-1*, *TE-13*	[34] (China)
	Dehydrocostus lactone		*Saussurea costus* F.	*Eca-109*, *KYSE150*	[35] (China)
	Germacrone		*Saussurea costus*	*Eca-109*, *EC9706*	[36] (China)
	Thapsigargin		*Thapsia garganica*	*Eca109*, *TE12*	[37] (China)

Table 1. *Cont.*

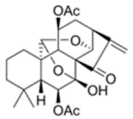
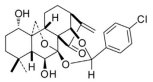
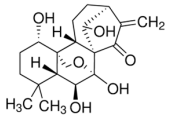
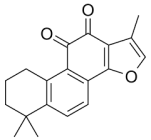
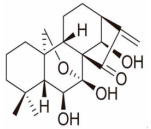
Class	Compounds	Structure	Plants of Origin	ESCC Cell Lines	Reference (Country)
Diterpenoids	Acetyl-macrocalin B		*Isodon silvatica*	*KYSE30*, *KYSE450*	[38] (China)
	Jesridonin		From Oridonin modification	*Eca-109*	[39] (China)
				Eca-109, *EC9706*, *TE-1*	[40] (China)
	Oridonin		*Rabdosia rubescens*	*KYSE70*, *KYSE410*, *KYSE450*	[41] (China)
				KYSE-30, *KYSE-150*, *EC9706*	[42] (China)
	Tanshinone IIA		*Salvia miltiorrhiza* Bunge.	*Eca-109*	[43] (China)
	Longikaurin A		*Isodon ternifolius*	*KYSE-30*, *KYSE-450*	[44] (China)

Table 1. *Cont.*

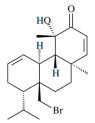
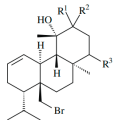
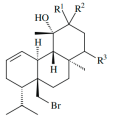
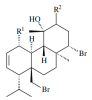
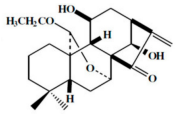
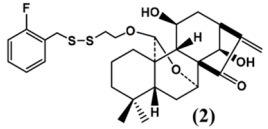
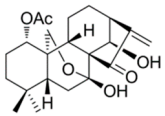
Class	Compounds	Structure	Plants of Origin	ESCC Cell Lines	Reference (Country)
Diterpenoids	Sphaerococcenol A		*Sphaerococcus coronopifolius*	*Apoptosis-resistant OE21*	[45] (Greece)
	14R-hydroxy-13,14-dihydro-sphaerococcenol A	 R^1,R^2=O, R^3=β-OH			
	12S-hydroxy-bromosphaerol	 R^1=β-OH, R^2=H, R^3=α-Br			
	Bromosphaerodiol	 R^1 =α-OH, R^2=H			
	Jaridonin		*Isodon rubescens*	*Eca-109*, *EC9706*, *EC-1*	[46] (China)
	DS2	 (2)	From Jaridonin modification	*EC9706*, *Eca-109*	[47] (China)
	Rabdocoestin B		*Isodon serra* Maxim.	*KYSE30*, *KYSE450*, *KYSE70*, *KYSE150*, *KYSE180*, *KYSE410*, *KYSE510*	[48] (China)

Table 1. *Cont.*

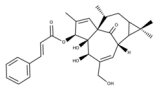
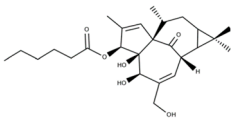
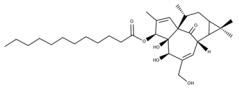
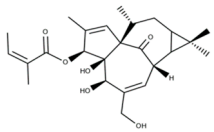
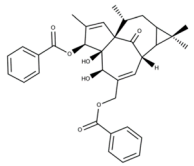
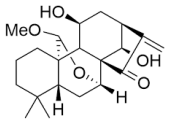
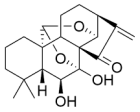
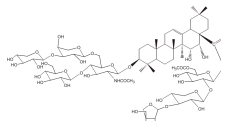
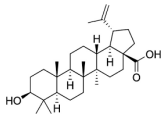
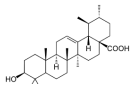
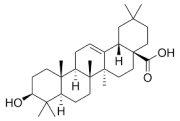
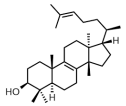
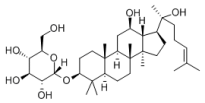
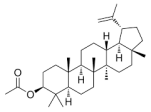
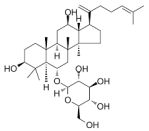
Class	Compounds	Structure	Plants of Origin	ESCC Cell Lines	Reference (Country)
Diterpenoids	Ingenol A		*Ingenol analogues*	*KYSE30*, *KYSE70*, *KYSE270*, *KYSE410*	[49] (Brazil)
	Ingenol B				
	Ingenol C				
	Ingenol-3,20-dibenzoate				
	Ingenol-3-angelate				
	JDA-202		*Isodon rubescens*	*EC9706*, *EC109*, *KYSE-450*, *HET-1A*	[50] (China)
	Xerophilusin B		*Isodon xerophilus*	*KYSE-150*, *KYSE-450*	[51] (China)

Table 1. *Cont.*

Class	Compounds	Structure	Plants of Origin	ESCC Cell Lines	Reference (Country)
Triterpenoids	Phaseoloideside E		*Entada phaseoloides* L.	*Eca-109*	[52] (China)
	Betulinic acid		*Betula pubescens*	*YES-1*, *YES-2*, *YES-3*	[53] (Japan)
	Ursolic acid		*Prunella vulgaris* L.		
	Oleanolic acid		*Olea europaea*		
	Euphol		*Euphorbia tirucalli*	*KYSE30*, *KYSE70*, *KYSE270*, *KYSE410*	[54] (Brazil)
	(20S) Ginsenoside Rh2		*Panax ginseng* Radix Rubra or Red ginseng	*Eca109*, *TE-13*	[55] (China)
	Lupeal acetate		*Cortex periplocae*	N-nitrosomethyl-benzylamine-induced rat esophageal tumorigenesis	[56] (China)
	Ginsenoside Rk3		*Panax notoginseng*	*ECA109*, *KYSE150*	[57] (China)

Legend: ESCC = esophageal squamous cell carcinoma.

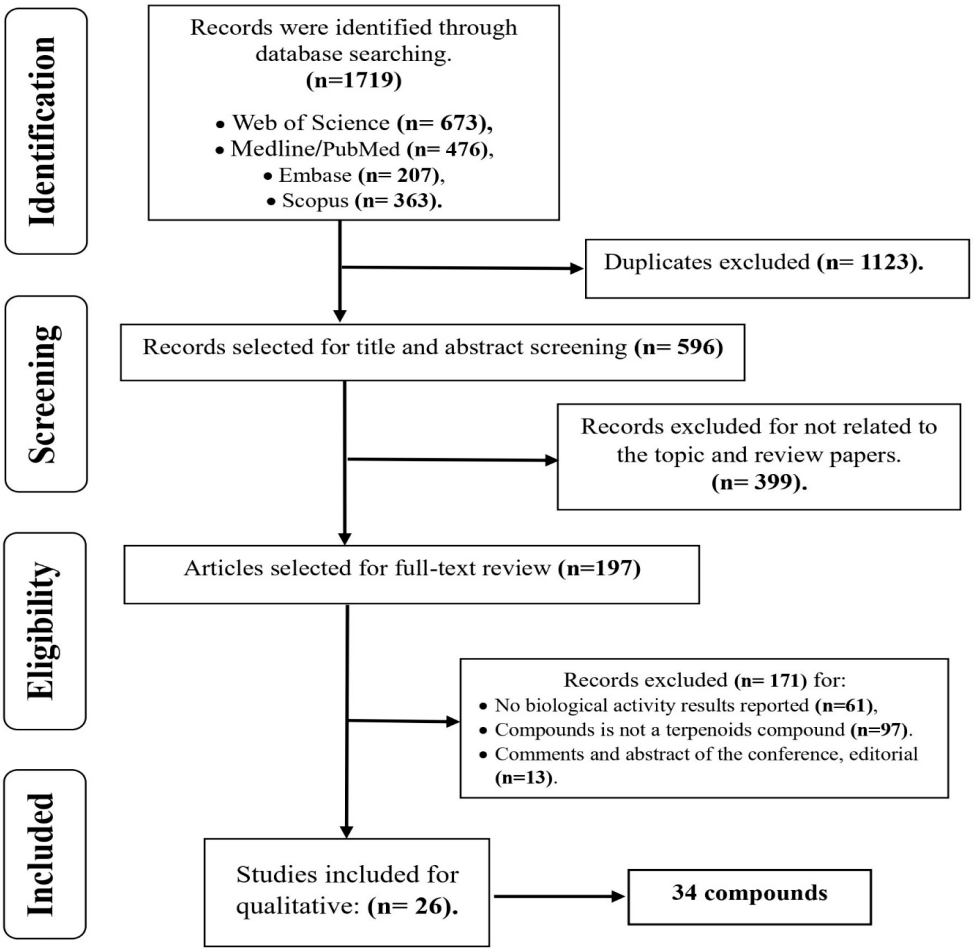


Figure 1. Flow diagram for study selection.

Table 2. Overview of the in vitro anticancer effects of terpenoid compounds.

Compounds	Types of Tests	Anticancer Activities	References
1Z,3R,4S,5E,7Z)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene	Antiproliferation assays using the MTT kit	*WHCO1* (IC_{50} = 9.3 μM)	[32]
(3R,4S)-3,4,6,7-tetrachloro-3,7-dimethyl-octen-1-ene		*WHCO1* (IC_{50} = 7.9 μM)	
Natural Borneol	Cell viability assays using CCK-8; apoptosis analysis by flow cytometry	*TE-1* and *TE-13* (no significant activity at 80 μg/mL)	[33]
Isoalantolactone	Cell viability assays using CCK-8; apoptosis analysis by flow cytometry; colony formation assay	The 40 μM concentration reduces cell viability by 28.3%), 32.1%, 45%, and 60% for the *Eca-109*, *EC9706*, *TE-1*, and *TE-13* cell lines.	[34]
Dehydrocostus lactone	Cell viability assay using the MTT kit; wound-healing assay	*Eca-109* (IC_{50} = 10.55 μM) and *KYSE150* (IC_{50} = 8.35 μM)	[35]
Germacrone	Cell viability assays using MTT assay; apoptosis analysis by flow cytometry; wound-healing assay	*Eca-109* (IC_{50} = 15.23 μg/mL) and *EC9706* (IC_{50} = 17.19 μg/mL)	[36]

Table 2. *Cont.*

Compounds	Types of Tests	Anticancer Activities	References
Thapsigargin	Cell viability assays using MTT assay; cell matrigel invasion; adhesion analysis and wound-healing assay	At a concentration of 1 μM, cell proliferation is inhibited by 60% and 73.33% for the *Eca-109* and *TE-12* cell lines.	[37]
Acetyl-macrocalin B	Cell viability assays using CCK-8; cell apoptosis analysis by flow cytometry	*KYSE30* (IC_{50} = 1.42 μM) and *KYSE450* (IC_{50} = 1.43 μM)	[38]
Jesridonin	Cytotoxicity determined by MTT assay; cell apoptosis analysis by flow cytometry	Concentration of 60 μM, inhibited approximately 76% of the viability of *Eca-109* cells and a combination index (CI) with paclitaxel (5 nM) of 0.43	[39]
	Cell proliferation assay by MTT assays; clonogenicity assay	*Eca-109* (IC_{50} = 4.1 μM), *EC9706* (IC_{50} = 4.0 μM), *KYSE450* (IC_{50} = 2.0 μM), *KYSE750* (IC_{50} = 16.2 μM), and *TE-1* (IC_{50} = 9.4 μM)	[40]
Oridonin	Cell proliferation assay by MTT assay; cell apoptosis by Annexin V-FITC Kit	76% to 98% for *KYSE70*, *KYSE410*, and *KYSE450* lines at a concentration of 20 μmol/mL	[41]
	Cell proliferation assay	*Eca-109* (IC_{50} = 38.9 μM), *EC9706* (IC_{50} = 23.9 μM), *KYSE450* (IC_{50} = 17.1 μM), *KYSE750* (IC_{50} = 14.3 μM), and *TE-1* (IC_{50} = 8.4 μM)	[40]
	Cell proliferation assay by MTT assay; cell apoptosis by Annexin V-FITC Kit	*KYSE-150* (IC_{50} = 28.69 μM), *EC9706* (IC_{50} = 34.43 μM), and *KYSE-30* (IC_{50} = 32.29 μM).	[42]
	Cell proliferation assay	The concentration of 4 μM for 48 h had no effect on the proliferation of cell lines *EC9706* and *Eca-109*.	[47]
Tanshinone IIA	Cell viability assays using MTS kit	*Eca-109* (IC_{50} = 1.925 μM)	[43]
Longikaurin A	Cell viability assays using CCK-8; colony formation assay; cell apoptosis by Annexin V-FITC Kit	*KYSE-30* (IC_{50} = 1.259 μM) and *KYSE-450* (IC_{50} = 1.370 μM)	[44]
Sphaerococcenol A	Cell viability assay using MTT colorimetric assay	*OE21* (IC_{50} = 3.0 μM)	[45]
Bromosphaerodiol		*OE21* (IC_{50} = 15 μM)	
DS2	Cell viability by MTT assay	*EC9706* (IC_{50} = 2.33 μM) and *Eca-109* (IC_{50} = 2.14 μM)	[47]
Rabdocoestin B	Cell viability assays using CCK-8; colony formation assays; cell cycle distribution and apoptosis by flow cytometry	*KYSE30* (IC_{50} = 1.56 μM) and *KYSE450* (IC_{50} = 1.94 μM)	[48]

Table 2. *Cont.*

Compounds	Types of Tests	Anticancer Activities	References
Ingenol A	Cell proliferation assay by MTS assay	*KYSE30* (IC_{50} = 15.51 μM), *KYSE70* (IC_{50} = 11.23 μM), *KYSE270* (IC_{50} = 3.38 μM), and *KYSE410* (IC_{50} = 10.78 μM)	[49]
Ingenol B		*KYSE30* (IC_{50} = 34.34 μM), *KYSE70* (IC_{50} = 26.53 μM), *KYSE270* (IC_{50} = 7.77 μM), and *KYSE410* (IC_{50} = 19.24 μM)	
Ingenol C		*KYSE30* (IC_{50} = 6.54 μM), *KYSE70* (IC_{50} = 3.58 μM), *KYSE270* (IC_{50} = 1.88 μM), and *KYSE410* (IC_{50} = 3.49 μM)	
Ingenol-3,20-dibenzoate		*KYSE30* (IC_{50} = 41.02 μM), *KYSE70* (IC_{50} = 6.01 μM), *KYSE270* (IC_{50} = 0.10 μM), and *KYSE410* (IC_{50} = 9.26 μM).	
Ingenol-3-angelate		*KYSE30* (IC_{50} = 47.20 μM), *KYSE70* (IC_{50} = 14.72 μM), *KYSE270* (IC_{50} = 4.24 μM), and *KYSE410* (IC_{50} = 24.08 μM)	
JDA-202	Cell viability by MTT assay; cell apoptosis using the Annexin V-FITC/PI Kit; analyzed by flow cytometry	*Eca-109* (IC_{50} = 8.6 μM), *EC9706* (IC_{50} = 9.4 μM), *HET-1A* (IC_{50} = 36.1 μM), and *KYSE-450* (IC_{50} = 26.2 μM)	[50]
Xerophilusin B	Cell viability assays using CCK-8; cell apoptosis by Annexin V-FITC Kit	*KYSE-140* (IC_{50} = 2.8 μM), *KYSE-150* (IC_{50} = 1.2 μM), *KYSE-450* (IC_{50} = 1.7 μM), and *KYSE-510* (IC_{50} = 2.6 μM)	[51]
Phaseoloideside E	Cell viability assay by MTT assay; cell apoptosis by acridine orange/ethidium bromide (AO/EB) staining and flow cytometry	*Eca-109* (IC_{50} = 25.3 μM)	[52]
Betulinic acid	Cell viability assay using CCK-8	*YES-2* (IC_{50} = 5.09 μM)	[53]
Ursolic acid		*YES-2*(IC_{50} = 19.1 μM)	
Oleanolic acid		*YES-2*(IC_{50} = 119 μM)	
Euphol	Cell proliferation assay by MTS assay	*KYSE30* (IC_{50} = 3.52 μM), *KYSE70* (IC_{50} = 8.77 μM), *KYSE270* (IC_{50} = 10.71 μM), and *KYSE410* (IC_{50} = 4.35 μM)	[54]
(20S) Ginsenoside Rh2	Cell viability assay by MTT assay; cell apoptosis analysis by flow cytometry and Annexin V assay	*Eca-109* (IC_{50} = 2.9 μg/mL) and *TE-13* (IC_{50} = 3.7 μg/mL)	[55]
Ginsenoside Rk3	Cell viability by MTT assay and colony formation assay	The concentration of 200 μM inhibits the proliferation of *Eca-109* and *KYSE150* lines by 83.8% and 76.8%, respectively.	[57]

Flow cytometry analysis (FACS); 3-(4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazoniumbromide (MTT); CCK-8 (Cell Counting Kit-8).

3.2.1. Monoterpenes

The monoterpenes (1Z,3R,4S,5E,7Z)-1-bromo-3,4,8- trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene and (3R,4S)-3,4,6,7-tetrachloro-3,7- dimethyl-octen-1-ene, extracted from the red macroalga *Plocamium suhrii*, had IC_{50}s of 9.3 μM and 7.9 μM, respectively, in the *WHCO1* cell line [32]. In contrast, concentrations of 80 μg/mL or less of the new borneol showed no significant effect on apoptosis and cell viability in the *TE-1* and *TE-13* cell lines. However, in combination with paclitaxel, it produced a remarkable synergistic effect, three times more potent than that of paclitaxel alone. In addition, a concentration of 1 mM pyrazole inhibited cell viability in the Eca-109 and *EC9706* lines by 82.90% and 83.00%, respectively, after 24 h [58].

3.2.2. Sesquiterpenes

Sesquiterpenes tested to date on ESCC cell lines include isoalantolactone, dehydrocostus lactone, germacrone, and thapsigargin. At a concentration of 40 μM, isoalantolactone reduces cell viability in *Eca-109* (28.3%), *EC9706* (32.1%), *TE-1* (45%), and *TE-13* (60%) cells after 24 h [34]. Dehydrocostus lactone acts on the *Eca-109* and *KYSE150* lines, with IC_{50}s of 10.55 μM and 8.35 μM, respectively, after 24 h [35]. Germacrone has IC_{50}s of 15.23 μg/mL and 17.19 μg/mL for *Eca-109* and *EC9706* after 48 h, respectively [36]. Finally, thapsigargin, at a concentration of 1 μM, inhibited cell proliferation by 60% and 73.33% in the *Eca-109* and *TE-12* cell lines, respectively, after 24 h. However, its combination with TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) (1 μM/0.1 μM) produced a synergistic effect, with an additional inhibition of cell proliferation of 26.66% [37].

3.2.3. Diterpenes

A total of 19 diterpenes have been identified in various studies for their activity against esophageal cancer (ESCC) cell lines. Among these compounds, acetyl-macrocalin B, isolated from *Isodon sylvatica*, showed notable activity against *KYSE30* and *KYSE450* cell lines, with IC_{50}s of 1.42 μM and 1.43 μM, respectively [38]. Similarly, jesridonin, at a concentration of 60 μM, inhibited approximately 76% of *Eca-109* cell viability, and when combined with paclitaxel (5 nM), generated a synergistic effect with a combination index (CI) of 0.43 on the *Eca-109* line [39]. Other studies revealed IC_{50}s of 4.1 μM for *Eca-109*, 4.0 μM for *EC9706*, 2.0 μM for *KYSE450*, 16.2 μM for *KYSE750*, and 9.4 μM for *TE-1* after 72 h [40].

Jaridonin is also known to reduce the viability of the *Eca-109*, *EC9706*, and *EC1* esophageal cancer lines [46]. Tanshinone IIA, extracted from *Salvia miltiorrhiza*, showed significant activity against Eca-109, with an IC_{50} of 1.925 μM [43]. Longikaurin A, a natural ent-kauranoid, showed activity against the *KYSE-30* and *KYSE-450* lines, with IC_{50}s of 1.259 μM and 1.370 μM, respectively [44]. Diterpenes isolated from *Sphaerococcus coronopifolius*, such as Sphaerococcenol A and Bromosphaerodiol, showed IC_{50}s of 3.0 μM and 15 μM in line *OE21* [45], while other diterpenes, such as bromosphaerol, showed moderate IC_{50}s.

Oridonin showed cell proliferation inhibition rates ranging from 76% to 98% for *KYSE70*, *KYSE410*, and *KYSE450* lines at a concentration of 20 μmol/mL after 48 h [41]. However, results from Wang et al. [40] indicated IC_{50}s of 38.9 μM for *Eca-109*, 23.9 μM for *EC9706*, 17.1 μM for *KYSE450*, 14.3 μM for *KYSE750*, and 8.4 μM for *TE-1* after 72 h. Jiang et al. [42] also reported IC_{50}s for *KYSE-150*, *EC9706*, and *KYSE-30* of 28.69 μM, 34.43 μM, and 32.29 μM, respectively. DS2 showed 70% and 80% growth inhibition on *EC9706* and *Eca-109* at a concentration of 4 μM for 48 h, with IC_{50}s of 2.33 μM and 2.14 μM, respectively [47]. However, at the same concentration (4 μM for 48 h), oridonin had no significant effect on the proliferation of these cell lines.

Rabdocoestin B showed remarkable activities, with IC_{50}s of 1.56 µM for *KYSE30* and 1.94 µM for *KYSE450* [48]. Diterpenes extracted from *Euphorbia tirucalli*, such as Ingenol A, had IC_{50} values of 15.51 µM for *KYSE30*, 11.23 µM for *KYSE70*, 3.38 µM for *KYSE270*, and 10.78 µM for *KYSE410* [49]. Ingenol B had IC_{50} values of 34.34 µM for *KYSE30*, 26.53 µM for *KYSE70*, 7.77 µM for *KYSE270*, and 19.24 µM for *KYSE410* [49]. Ingenol C had IC_{50} values of 6.54 µM for *KYSE30*, 3.58 µM for *KYSE70*, 1.88 µM for *KYSE270*, and 3.49 µM for *KYSE410* [49]. Ingenol 3,20-dibenzoate had IC_{50} values of 41.02 µM for *KYSE30*, 6.01 µM for *KYSE70*, 0.10 µM for *KYSE270*, and 9.26 µM for *KYSE410*. Ingenol-3-angelate had IC_{50} values of 47.20 µM for *KYSE30*, 14.72 µM for *KYSE70*, 4.24 µM for *KYSE270*, and 24.08 µM for *KYSE410* [49]. JDA-202 demonstrated a notable ability to inhibit the growth of several esophageal cancer (ESCC) cell lines. It exhibited IC_{50}s of 8.6 µM for *Eca-109* cells, 9.4 µM for *EC9706*, 36.1 µM for *HET-1A*, and 26.2 µM for *KYSE-450* [50]. Xerophilusin B also stood out for its efficacy against various cell lines. It showed IC_{50}s of 2.8 µM for *KYSE-140*, 1.2 µM for *KYSE-150*, 1.7 µM for *KYSE-450*, and 2.6 µM for *KYSE-510* [51]. These results highlight the therapeutic potential of diterpenes for the treatment of esophageal cancers.

3.2.4. Triterpenes

Triterpenes are chemical compounds, some variants of which have shown interesting properties in terms of antiproliferative activity. Among them, phaseoloideside E, extracted from *Entada phaseoloides*, has an IC_{50} of 25.3 µM, comparable to that of cisplatin (25.5 µM) on the *Eca-109* cell line [52]. Euphol, a triterpene extracted from *Euphorbia tirucalli*, showed significant antiproliferative activity against several ESCC cell lines, with IC_{50}s of 3.52 µM for *KYSE30*, 8.77 µM for *KYSE70*, 10.71 µM for *KYSE270*, and 4.35 µM for *KYSE410* [54]. Ginsenoside Rh2, from red ginseng, demonstrated cytotoxic activity against *Eca-109* and *TE-13* cells, with IC_{50}s of 2.9 and 3.7 µg/mL, respectively [55]. In contrast, ginsenoside Rk3, extracted from Panax notoginseng, showed inhibition of the proliferation of the *Eca-109* and *KYSE150* cell lines of 83.8% and 76.8%, respectively, at a concentration of 200 µM [56].

On the other hand, triterpenes such as betulinic acid, ursolic acid, and oleanolic acid showed inhibition of *YES-2* cell proliferation, with IC_{50}s of 5.09 µM, 19.1 µM, and 119 µM, respectively [53]. Betulinic acid was more active than 5-FU (IC_{50} = 72.15 µM) and comparable to irinotecan (IC_{50} = 1.59 µM) and cisplatin (IC_{50} = 3.17 µM) in the *YES-2* cell line [53].

3.3. In Vivo Anti-Esophageal Squamous Cell Carcinoma Potential of Terpenoids

The potential of terpenes against ESCC has been evaluated in vivo in several studies, showing promising effects. Table 3 summarizes their anti-cancer activities, offering an overview of their efficacy.

Table 3. Overview of the in vivo anticancer effects of terpenoid compounds.

Compounds	Animal Model	Cell Lines Used for Induction	Administration Route of Compounds	Anticancer Activities	Ref.
Isoalantolactone	Female *BALB/c* nude mice	*Eca-109*	Intragastrical administration	The 80 mg/kg dose reduces the volume of the artificially induced tumor by more than 50% in 27 days.	[34]
Dehydrocostus lactone	Female *BALB/c* nude mice	*Eca-109*	Intraperitoneal injection	The 40 mg/kg dose of lactone decreases the tumor mass by approximately 61%.	[35]

Table 3. *Cont.*

Compounds	Animal Model	Cell Lines Used for Induction	Administration Route of Compounds	Anticancer Activities	Ref.
Thapsigargin	Mice	*Eca-109*	Intraperitoneal injection	The combination of thapsigargin and hrTRAIL (1 mg/kg/60 mg/kg) reduces the volume of the artificially induced tumor by about 87% in 28 days.	[37]
Acetyl-macrocalin B	Mice	*KYSE30*	Intraperitoneal injection	A dose of 12 mg/kg alone inhibits tumor mass by approximately 38% over 29 days. Acetyl-macrocalin B combined with AZD7762 (12 mg/kg/25 mg/kg) inhibits tumor mass by around 77% over 29 days.	[38]
Jesridonin	Nude mice	*Eca-109*	/	The combination of paclitaxel and jesridonin (5 mg/kg/10 mg/kg) reduces the volume of the artificially induced tumor by 77.21% in 21 days.	[39]
	Female *BALB/c* nude mice	*Eca-109*	Vena caudalis injection	A 10 mg/kg dose reduces tumor mass by 45%, while 5-FU reduces it by 44% at a concentration of 12 mg/kg.	[40]
Oridonin	Female SCID mice	*ESCC*	Oral by gavage	A 40 mg/kg dose reduces the size of the ESCC tumor induced in a PDX model by approximately 35% over 52 days.	[41]
	Female *BALB/c* nude mice	*KYSE-150*	Intraperitoneal injection	A 10 mg/kg dose reduces tumor mass by about 75% in 14 days.	[42]
Longikaurin A	Female *BALB/c* nude mice	*KYSE-30*	Intraperitoneal injection	A 12 mg/kg dose of longikaurin A inhibits tumor proliferation by about 79% in 20 days.	[44]
Rabdocoestin B	Female Athymic nude mice	*KYSE30*	Intraperitoneal injection	A 12 mg/kg dose reduces the volume of artificially induced tumors by approximately 60%.	[48]
JDA-202	Male *BALB/c* nude mice	*EC109*	Intravenous injection	After 21 days of treatment, artificially induced tumor volumes are reduced by 61.7%.	[50]

Table 3. *Cont.*

Compounds	Animal Model	Cell Lines Used for Induction	Administration Route of Compounds	Anticancer Activities	Ref.
Xerophilusin B	Female *BALB/c* nude mice	*KYSE-150 and KYSE-450*	Intraperitoneal injection	A 15 mg/kg dose reduces tumor masses by about 87.5% and 85%, respectively, over 20 days.	[51]
Lupeal acetate	*F344* rats (Fisher 344 rats)	/	Intramuscularly injection	The incidence of esophageal tumors decreases from 93.3% to 33.3% after 25 weeks.	[56]
Ginsenoside Rk3	Female *BALB/c* nude mice	*KYSE150*	Intraperitoneal injection	A 40 mg/kg dose reduces the volume of artificially induced tumors by 66.2%.	[57]

Ref.: reference.

Regarding sesquiterpenes, the 80 mg/kg dose of isoalantolactone reduced the volume of tumors artificially induced by the *Eca-109* cell line by more than 50% after 27 days of treatment in *BALB/c* nude mice [34]. Dehydrocostus lactone reduced the tumor mass artificially induced by *Eca-109* in female *BALB/c* nude mice by approximately 61% at a dose of 40 mg/kg [34]. The combination of thapsigargin and hrTRAIL (1 mg/kg/60 mg/kg) reduced *Eca-109*-induced tumor volume by approximately 87% compared to control over 28 days [37].

Regarding diterpenes, in an artificially induced in vivo model using the *KYSE30* cell line in mice, acetyl-macrocalin B inhibited tumor mass by approximately 38% at a dose of 12 mg/kg alone and by about 77% when combined with AZD7762 (12 mg/kg/25 mg/kg) over a period of 29 days [38]. The same experiment conducted using the PDX model in mice revealed a tumor mass inhibition of approximately 35% for acetyl-macrocalin B alone and 73% for the combination of acetyl-macrocalin B and AZD7762 (12 mg/kg/25 mg/kg) [38]. In a similar vein, the combination of paclitaxel and jesridonin (5 mg/kg/10 mg/kg) reduced the volume of artificially induced tumors in nude mice with the *Eca-109* cell line by 77.21% over 21 days [39]. In female *BALB/c* nude mice, jesridonin at a dose of 10 mg/kg inhibited tumor proliferation of the *Eca-109* cell line more effectively than 5-FU at 12 mg/kg. Although not statistically significant, jesridonin reduced tumor growth by 45%, while 5-FU reduced it by 44% [40]. At a dose of 12 mg/kg, longikaurin A inhibited tumor proliferation by approximately 79% in female *BALB/c* nude mice artificially induced with the *KYSE-30* cell line over 20 days [44]. Oridonin, at a dose of 40 mg/kg, reduced the size of ESCC tumors induced in female SCID mice by about 35% over 52 days [41]. In contrast, oridonin at a dose of 10 mg/kg significantly reduced the tumor mass induced by the *KYSE-150* cell line by approximately 75% in female BALB/c nude mice over 14 days [42].

The tumor masses induced by the *KYSE-150* and *KYSE-450* cell lines were inhibited by approximately 87.5% and 85%, respectively, at a dose of 15 mg/kg of xerophilusin B in female *BALB/c* nude mice over 20 days [51]. A dose of 12 mg/kg of rabdocoestin B reduced the tumor volume induced by the *KYSE30* cell line by about 60% in female athymic nude mice [48]. In male *BALB/c* nude mice, the volume of tumors induced by the *Eca-109* cell line decreased by 61.7% after 21 days of treatment with JDA-202 [50].

Triterpenes have also distinguished themselves by their remarkable efficacy against esophageal tumors in vivo. Ginsenoside Rk3 demonstrated a 66.2% reduction in the volume of artificially induced tumors in female BALB/c nude mice using the *KYSE150* cell line at a dose of 40 mg/kg [57]. Furthermore, lupeal acetate, extracted from the plant *Cortex periplo-*

cae, significantly decreased the incidence of esophageal tumors observed after 25 weeks. The incidence dropped from 93.3% in controls treated with N-nitrosomethylbenzylamine (0.5 mg/kg) to 33.3% in *F344* rats receiving a combination of N-nitrosomethylbenzylamine and lupeal acetate (0.5 mg/kg/20 mg/kg) [56]. It is important to note that no in vivo studies have yet reported on the anti-cancer properties of compounds such as phaseoloideside, euphol, ginsenoside Rh2, betulinic acid, oleanolic acid, or ursolic acid in relation to esophageal cancer.

3.4. Mechanism of Action of Terpenoid Compounds on ESCC Cell Lines

Although the mechanisms of action of several compounds have not yet been fully elucidated, terpenes exhibit various modes of action against esophageal cancer cell lines (Figure 2). Compounds such as dehydrocostus lactone [35], acetyl-macrocalin B [38], phaseoloideside E [52], isoalantolactone [34], DS2 [47], longikaurin A [44], JDA-202 [50], thapsigargin [37], and jaridonin [46] act by inducing oxidative stress (ROS) in esophageal squamous cell carcinoma (ESCC) cells.

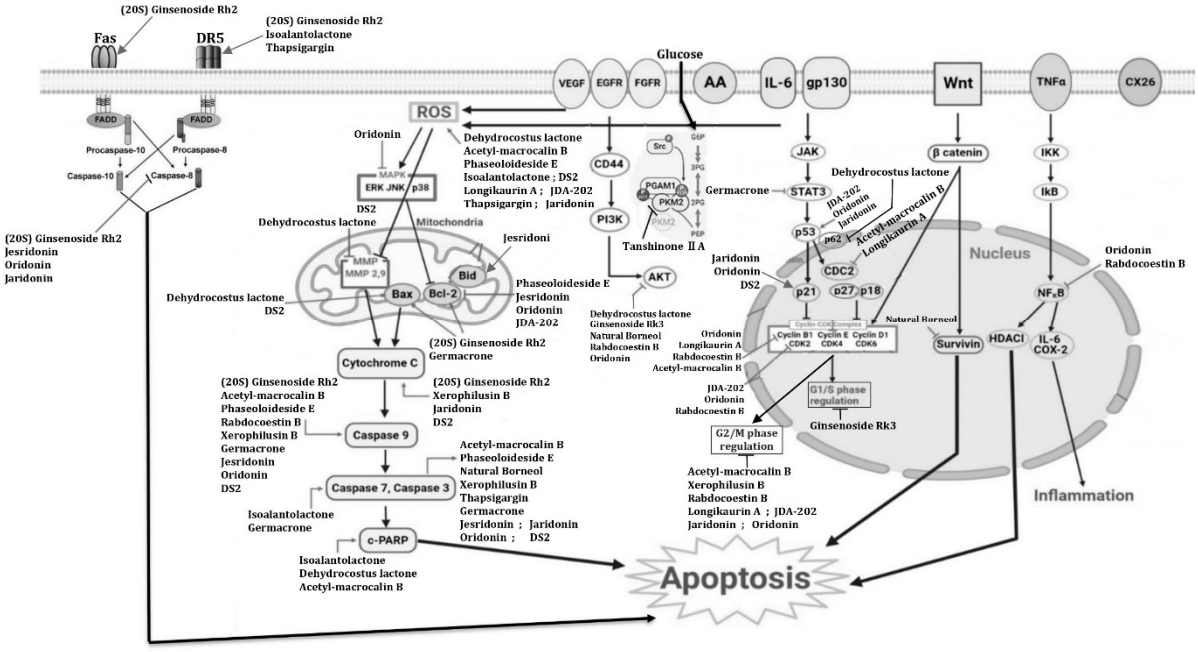


Figure 2. Schematic overview of how terpenoid compounds act against esophageal cancer [59].

Ginsenoside Rh2 (20S), acetyl-macrocalin B, phaseoloideside E, rabdocoestin B, xerophilusin B, germacrone, jesridonin, oridonin, and DS2 increase caspase-9 levels [38,39,48,51]. Similarly, acetyl-macrocalin B, phaseoloideside E, natural borneol, xerophilusin B, thapsigargin, germacrone, jesridonin, jaridonin, oridonin, and DS2 elevate caspase-3 levels. Isoalantolactone, dehydrocostus lactone, and acetyl-macrocalin B enhance phosphorylated PARP (P-PARP) levels. Isoalantolactone and germacrone increase caspase-7 levels [34,36]. The compounds ginsenoside Rh2 (20S), xerophilusin B, jaridonin, and DS2 raise cytochrome C levels [46,47,51]. Phaseoloideside E, jesridonin, oridonin, and JDA-202 inhibit Bcl-2 production [41,46,50,52].

The compounds dehydrocostus lactone [35], ginsenoside Rk3 [57], natural borneol [33], rabdocoestin B [48], and oridonin [41] inhibit the expression of the AKT protein. JDA-202 [50], oridonin [41], and jaridonin [46] stimulate the expression of the p53 protein. Acetyl-macrocalin B [38], xerophilusin B [51], rabdocoestin B [48], longikaurin A [44], JDA-202 [50], jaridonin, and oridonin [41] induce a G2/M phase cell cycle arrest, while ginsenoside Rk3 [57] causes a G1/S phase arrest. Oridonin and rabdocoestin B inhibit the

expression of NFKB [41,48]. Tanshinone II A inhibits PKM2, which is involved in glucose degradation necessary for the nutrition of ESCC cells [43].

The compounds (20S) ginsenoside Rh2 [55], isoalantolactone [34], and thapsigargin [47] stimulate death receptor 5 (DR5), thereby engaging the extrinsic apoptotic pathway. Additionally, the Fas receptor is also activated by (20S) ginsenoside Rh2, representing another extrinsic apoptotic pathway [55].

4. Discussion

This study's findings highlight terpenoid compounds' significant potential in treating esophageal squamous cell carcinoma (ESCC). The discovery of 34 compounds from various families, including monoterpenes, sesquiterpenes, diterpenes, and triterpenes, emphasizes the abundant natural biodiversity and its critical role in developing new anticancer therapies. Most of the research included comes from China, reflecting concentrated expertise probably linked to the significant interest and priority given by the country to alternative medicine and herbal medicine. According to the WHO [60] and Wachtel-Galor and Benzie [61], traditional medicine accounts for around 40% of all healthcare delivered in China, and over 90% of general hospitals have traditional medicine units. This explains the high concentration of studies coming out of this country and encourages other countries to take a significant interest in alternative medicine.

Regarding pharmacological properties, except for oleanolic acid, which exhibits moderately significant cytotoxic activity (IC_{50} = 119 μM), all other compounds demonstrate notable cytotoxic effects, with IC_{50} ranging from 0.10 μM to 47.20 μM against various ESCC cell lines, based on the cut-off established by Kuete and Efferth [62]. Notably, compounds such as (1Z,3R,4S,5E,7Z)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene, (3R,4S)-3,4,6,7-tetrachloro-3,7-dimethyl-octen-1-ene, dehydrocostus lactone, acetylmacrocalin B, jesridonin, longikaurin A, sphaerococcenol A, DS2, rabdocoestin B, ingenol C, ingenol-3,20-dibenzoate, JDA-202, xerophilusin B, betulinic acid, euphol, and (20S) ginsenoside Rh2 exhibit highly significant cytotoxicity (IC_{50} < 10 μM) against ESCC cells, closely aligning with the activity of doxorubicin (0.9 μM) as per the cutoff by Kamsu and Ndebia [26]. These compounds show efficacy at very low concentrations, often indicative of potent anticancer activity, suggesting a substantial capacity to inhibit ESCC cell growth at relatively low doses. This presents promising prospects for their future development as potential therapeutic agents against cancer, warranting thorough investigation, as they could transform EC treatment.

Given that the therapeutic variations observed in animals have substantial predictive value regarding therapeutic efficacy in humans, in vivo studies focusing on specific compounds have shown that they can reduce tumor sizes in mice more effectively than traditional cancer treatments like 5-FU [40]. This suggests that the in vitro effects are also present in live subjects. One possible explanation is that these compounds undergo metabolic processes in vivo, enhancing activity. Herman and Santos [63] state that secondary metabolites can exhibit increased effectiveness when processed by a living organism, resulting in more significant outcomes. A substance may be transformed into a toxic, inactive, less active, or active form as it moves through an organism [64,65].

The mechanisms of action of terpenes and the compounds mentioned reveal notable similarities and differences compared to reference chemotherapeutics such as doxorubicin, cisplatin, and paclitaxel. Like these treatments, terpenes induce oxidative stress in cancer cells, contributing to apoptosis [66–68]. This induction of reactive oxygen species (ROS) is a commonality with chemotherapies, which often target the survival mechanisms of tumor cells. However, terpenes appear to act more selectively by modulating specific pathways, such as increasing levels of caspases (e.g., caspase-3 and caspase-9) and proteins like P53.

These mechanisms offer potential for inducing apoptosis that could be more effective and less toxic than traditional chemotherapies, which often act non-specifically, affecting both cancerous and healthy cells [69]. Moreover, the inhibition of proteins such as Bcl-2 by certain terpenes (e.g., phaseoloideside E, jesridonin, oridonin, and JDA-202) suggests an innovative approach to overcoming treatment resistance, a significant challenge faced with conventional drugs. Ginsenoside Rh2 (20S) modulates apoptosis by interacting with both DR5 and Fas receptor signaling pathways, representing a complementary strategy that is underutilized by classic anticancer agents [70,71]. This compound may be considered a potential alternative for treating esophageal squamous cell carcinoma (ESCC). Finally, the induction of cell cycle arrest at specific phases (G1/S and G2/M) by these compounds (e.g., acetyl-macrocalin B, xerophilusin B, rabdocoestin B, longikaurin A, JDA-202, jaridonin, and oridonin) could provide interesting alternatives to conventional treatments like cisplatin, which often lead to undesirable side effects by affecting cell cycle phases less selectively [72]. Overall, while the mechanisms of action of terpenes share similarities with those of reference chemotherapeutics, their ability to act more specifically and modulate apoptotic pathways may offer significant therapeutic advantages in the fight against esophageal cancer.

Although terpenes show strong anticancer potential in vitro against ESCC, it has been found that the route of administration plays a considerable role in the efficacy of these compounds in vivo. This is due to their low solubility in water, their metabolic instability, and their low bioavailability, which limit their efficacy in vivo [73,74]. These constraints mean that alternative routes of administration have to be used, such as intraperitoneal or intravenous routes, which partially circumvent these barriers, as observed with oridonin, which showed 75% tumor inhibition by the intraperitoneal route [42] compared with only 35% by the oral route at a higher dose [41]. Similarly, compounds such as xerophilusin B or longikaurin A administered by intraperitoneal route achieved tumor reductions of over 79% [44,51]. In contrast, routes such as intragastric or oral required higher doses for lesser effects, probably due to limited intestinal absorption and first-pass metabolism [34,41]. These results highlight the urgent need to develop innovative delivery systems (nanoparticles, liposomes, etc.) to improve terpenes' solubility, stability, and pharmacokinetics [74,75] and thus fully exploit their therapeutic potential in ESCC.

5. Limitations and Perspectives

The compounds being examined exhibit considerable promise as treatments for esophageal cancer, showcasing multiple mechanisms of action and positive results in suppressing tumor growth in both in vitro and in vivo studies. However, several limitations persist. A primary challenge is the lack of toxicological data for these compounds, emphasizing the need for comprehensive safety evaluations. Additionally, gaps in understanding their bioavailability and pharmacokinetics hinder our assessment of their actual efficacy in clinical settings. Furthermore, while some compounds show remarkable anticancer activity, their mechanisms of action remain poorly defined, complicating their evaluation. The absence of in vivo studies for many of these compounds raises concerns about the influence of metabolic processes on their effectiveness. Another important concern is the absence of positive controls and the lack of standard anticancer agents in some in vitro and in vivo studies, which makes it difficult to assess the comparative efficacy of the tested compounds. Ultimately, clinical trials in humans are essential to validate the beneficial effects observed in vitro and to determine whether these effects can be replicated in clinical practice. In summary, these gaps in toxicology, bioavailability, mechanisms of action, in vivo studies, and positive controls pose significant barriers to the rapid and effective clinical application of these compounds. Addressing these challenges is essential for progressing their development as viable therapeutic options.

6. Conclusions

The results of this study highlight the significant potential of terpenoid compounds as anticancer treatments for ESCC. Among the 34 compounds identified, those with IC_{50} values of 10 μM or lower, such as (1Z,3R,4S,5E,7Z)-1-bromo-3,4,8-trichloro-7-(dichloromethyl)-3-methylocta-1,5,7-triene, dehydrocostus lactone, (3R,4S)-3,4,6,7-tetrachloro-3,7-dimethyl-octen-1-ene, acetyl-macrocalin B, jesridonin, longikaurin A, sphaerococcenol A, DS2, rabdocoestin B, ingenol C, ingenol-3,20-dibenzoate, JDA-202, xerophilusin B, betulinic acid, euphol, and (20S) ginsenoside Rh2, demonstrate highly promising cytotoxic activity against ESCC cells. These compounds exhibit diverse mechanisms of action that may provide effective alternatives to conventional therapies. However, several limitations remain, and their further evaluation in upcoming research will represent a significant advancement. In conclusion, while terpenoid compounds show promising potential for the treatment of esophageal squamous cell carcinoma (ESCC), it is crucial to address these challenges to promote their development as viable therapeutic options.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/futurepharmacol5020021/s1, Table S1: PRISMA Checklist.

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