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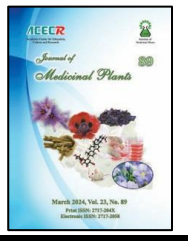

Review Article

A review of the anticancer effects of sesquiterpene nerolidol on different malignant conditions

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ABSTRACT

Background: Nerolidol (NER) is a sesquiterpene alcohol with various biological and pharmacological activities, especially antitumor effects against different cancer models. The anticancer properties of NER are reportedly mediated by increased reactive oxygen species (ROS) production, apoptosis, and DNA damage. Nevertheless, this compound has low solubility, poor bioavailability, and fast hepatic metabolism, which could be overcome by designing proper nanoformulation scenarios. **:Objectives**This review focuses on the anticancer effect of NER against multiple cancers to highlight the promising features of NER as an applicable anticancer agent. **Methods:** A collection of papers based on the 'cancer' and 'NER' MeSH terms was chosen from NCBI/PubMed, Scopus, and Google Scholar to synthesize the current review. **Results:** NER was found to act as an adjuvant with contemporary chemotherapy that enhanced the efficacy of chemotherapy drugs on various cancer cells, including osteosarcoma, gastrointestinal, gynecological, breast, skin, blood, liver, and head and neck cancers. **Conclusion:** NER is an effective antitumor compound against different types of cancers, and its inclusion in the current chemotherapy regimen could improve cancer therapy. Because of low solubility, NER nanoformulation can improve its bioavailability and relatedcancer treatment.

1. Introduction

Although many efforts have been made to fight cancer, management of malignant conditions needs more effective therapeutic modalities. Amongst, natural products are a rich source of bioactive compounds that have been

Abbreviations: cAMP, cyclic adenosine monophosphate; CDK, cyclin-dependent kinase; DMBA, 7,12-dimethylbenz(a)anthracene; DOX, doxorubicin; 5-FU, 5-fluorouracil; 5-HT3Rs, 5-hydroxytryptamine 3 receptor; ICAM, intercellular adhesion molecule; IC_{50}, half-maximal inhibitory concentration; IGF1R, insulin-like growth factor 1 receptor; IL, interleukin; MTT ,2,5-diphenyl-2H-tetrazolium bromide; NER, nerolidol; ROS ,reactive oxygen species; TNF, tumor necrosis factor

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widely considered as anticancer candidates. Sesquiterpenes, with a structure of three isoprene units, have been shown to exert anticancer effects [1]. Previously, we have shown that these kinds of compounds could also reverse drug resistance and improve the efficacy of chemotherapeutic agents in cancerous cells [2-5]. In the current study, we review the potential of sesquiterpene nerolidol (NER) as an anticancer agent.

NER (3,7,11-trimethyl-1,6,10-dodecatrien-3-ol) is an alcohol found in the essential oil of various plants, such as aerial parts of *Warionia saharae* (23.0 %), *Scutellaria abida* (9.0 %), and *Capparis tomentosa Lam* (5.1 %); leaf of *Baccharis dracunculifolia* (33.5 %), *Melaleuca quinquenervia* (24.19 %), *Lantana radula* (19.0 %), *Peperomia serpens* (38.0 %), *Piper chaba Hunter* (5.1 %), *Piper claussenianum* (81.4 %), *Swinglea glutinosa* (28.4 %), *Zanthoxylum hyemale* (51.0 %), and *Zornia brasiliensis* (48.0 %); stem of *Oplopanax horridus* (54.5 %); flower of *Achillea millefolium* (11.6% – 31.9 %), and *Cassia fistula* (38.0 %); root of *Oplopanax horridus* (54.6 %); seed of *Momordica charantia* (61.6 %); fruit of *Swinglea glutinosa* (19.1 %); resin of *Canarium schweinfurthii* (14.0 %); wood of *Fokienia hodginsii* (34.8 %) and *Myrocarpus fastigiatus* (80.0 %) [6]. This compound is a colorless liquid at the room temperature (25 °C) and has odor reminiscent of rose and apple with a density of 0.872 g/cm^3 and a boiling point of 122 °C [7]. NER has four isomers, two enantiomers and two geometric isomers, which differ in the geometry dependent to the existence of central double bond and configuration of the hydroxyl-bearing carbon [8] (Fig. 1) [6]. NER has various pharmacological and biological activities, including antiulcer [9], antioxidant [10], antibacterial, antifungal [11], anticancerantitumor [12], antinociceptive, anti-inflammatory [13], anticholinesterase, antiparasitic, and insect repellent activities [14], alongside skin penetration enhancer activity [15]. NER is frequently incorporated in cosmetics products, such as shampoos, perfumes, cleansers, and detergents. Besides, NER is widely applied as a safe flavor enhancer in many food products because of its approval by U.S. Food and Drug Administration [16]. In the chemical synthesis of NER, linalool produces a mixture of (E)- and (Z)-geranylacetone by the Carroll reaction, then addition of acetylene to them led to the production of (E)- and (Z)-dehydro NER, which were hydrogenated respectively to the *trans*- and *cis*-NER by the aid of a Lindlar catalyst [17].

The present article reviews the anticancer properties of NER as well as its underlying mechanisms in different malignant conditions.

Anticancer effects of NER

According to the obtained results, NER could suppress the cancer cells growth in both *in vitro* and *in vivo* experimental systems (Table 1). Therefore, in the future, this compound could be a promising choice as an anticancer drug, either alone or in combinational forms.

Gastrointestinal cancer

Gastrointestinal cancer is the uncontrolled growth of abnormal (cancer) cells of digestive tract and other abdominal organs. These malignant conditions of the gastrointestinal tract could be observed in the esophagus, biliary system, stomach, pancreas, colon, small bowel, rectum, and anus. A combination of both genetic and environmental factors contributes to the majority of human cancers, particularly gastrointestinal tract [18].

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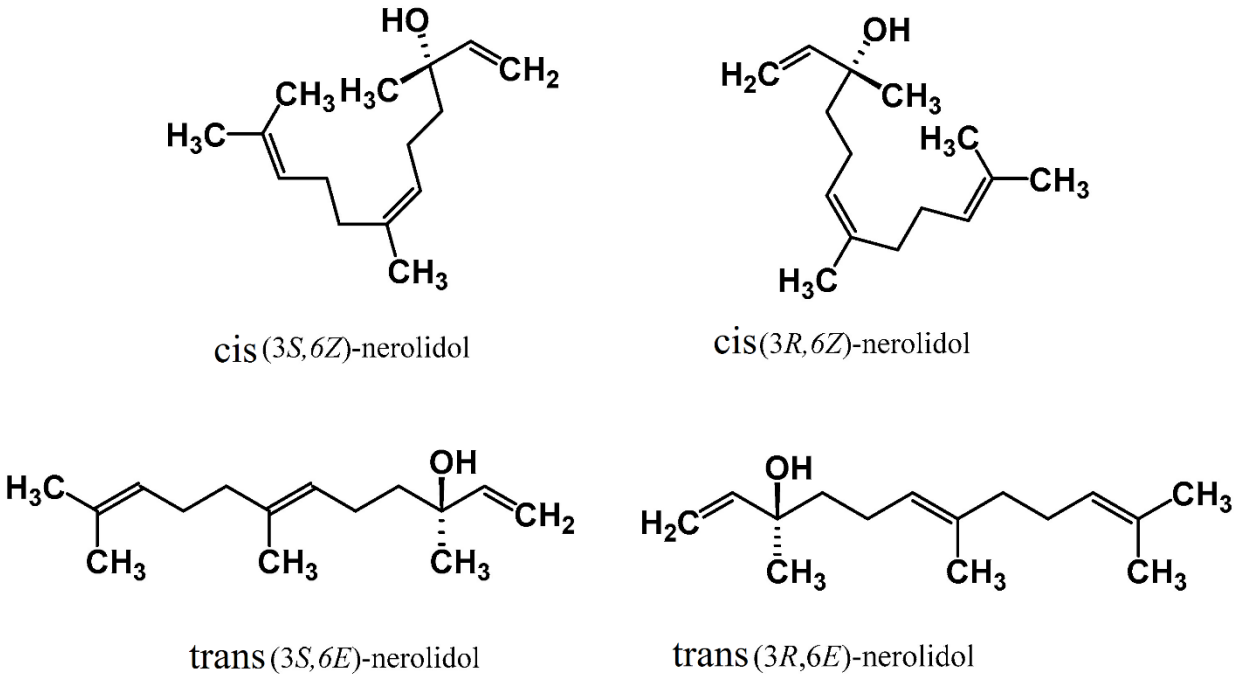

Fig. 1. Chemical structure of *cis*- and *trans*-NER [6]

Table 1. Summary of studies reporting anticancer effects of NER

Type of cancer	*cis*- or *trans*-NER	Experimental model	Dose	Effects and mechanisms	*In vitro* or *in vivo* system	Reference
Colon cancer	Trans-NER	HCT-116 cell line	5-100 µM	-Half-maximal inhibitory concentration (IC_{50}): 25 µM. -Boosted reactive oxygen species (ROS) level. -Increased apoptotic incidences	*In vitro*	[19]
	Trans - NER	Caco-2 and SW-620 cell lines	50-150 µM	-Ineffective in enhancement of antiproliferative effects of 5-fluorouracil (FU) and oxaliplatin in cancer cell lines	*In vitro*	[21]
	Trans - NER	Caco-2 cell line	0-50 µg/mL	-Selective increase of doxorubicin (DOX) accumulation in cancer cells -Ineffective in DOX concentration in hepatocytes	*In vitro*	[22]
	Trans - NER	HT29 cell line	30 µg/mL	-Significantly suppressed adhesion of tumor necrosis factor (TNF)-α induced cells due to the downregulation of intercellular adhesion molecule (ICAM)-1. -Decreased activation (phosphorylation) of NF-κB and increased activity of caspases, resulted in apoptosis induction in cancer cells.	*In-vitro*	[20]

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Table 1. Summary of studies reporting anticancer effects of NER (Continued)

Type of cancer	*cis*- or *trans*-NER	Experimental model	Dose	Effects and mechanisms	*In-vitro* or *in vivo* system	Reference
Liver cancer	*cis*- and *trans*-NER	HepG2/C3A cells	100 to 250 µM	-*cis*-NER possesses higher cytotoxic potential than trans and *m*-NER (mix of both NER) -*cis*-NER did not demonstrate genotoxic activity -*cis*-NER downregulated genes related to apoptosis (*BAK1, BAX, CAPN1, CASP8, CASP9, PARP1*, and *TP53*), cell cycle (*cyclin D1, cyclin E1, CDK1*, and *CDK2*), xenobiotic metabolism (*CYP2D6* and *CYP3A4*), and paraptosis (*IGF1R*).	*In vitro*	[23]
Breast cancer	*trans*-NER	-Epithelial breast adenocarcinoma, MCF7 and MDA-MB-231 cells -Ehrlich solid tumor bearing mice	5-500 µM	-Increased the efficacy (antiproliferative and migration potentials) of DOX in breast cancer cells, MDA-MB-231 cells, *in vitro*, but did not improve its effects *in vivo*.	*In vitro* and *in vivo*	[25]
Head and neck cancer	*cis*-NER	Hep-2 cells	-	-Inhibited cell viability -Increased reactive oxygen species, apoptosis, and DNA damage -NER could probably bind to the PI3K/Akt and proliferating cell nuclear antigen	*In vitro*	[30]
	-	Oral squamous cell carcinoma	1.83-13.28 µg/mL	-Reversed tumor growth in DMBA-induced oral carcinoma evidenced by modulation of the detoxification, antioxidants, lipid peroxidation, and renal activity markers	*In vivo* and *in vitro* model	[31]
	-	DMBA-induced hamster buccal pouch cancer	50 and 100 mg/kg body weight	-Restored the immunohistoexpression of inflammatory proteins and glycoconjugates status -Potentially prevented the altered immunohistoexpression of TNF-α, NF-κB, and cyclooxygenase-2 and abnormalities of cell surface glycoconjugates level	*In vivo* and *in silico*	[32]

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Table 1. Summary of studies reporting anticancer effects of NER (Continued)

Type of cancer	*cis*- or *trans*-NER	Experimental model	Dose	Effects and mechanisms	*In vitro* or *in vivo* system	Reference
Osteosarcoma	Cis- and trans-NER	MG-63 cells	15 and 20 µM/ml	-Significantly reduced the progression of osteosarcoma cells in a dose-dependent manner -Induced oxidative stress and morphological changes of apoptosis.	*In vitro*	[27]
Skin cancer	Trans-NER	B16-F10 cells	1.83–13.28µg/mL	-NER could not reduce cell proliferation by IC_{50} of > 25 µg/mL compared to IC_{50} = 0.87 µg/mL of 5-FU	*In vitro* and *in vivo*	[35]
Gynecological cancer	Trans-NER	Ovarian cancer cells (A2780 and SKOV3)	20, 40, 100, and 200 µM	-Inhibited proliferation of A2780 (IC_{50} = 119 µM), but SKOV3 was much less sensitive to NER -Strong synergism of DOX with NER in the A2780 cells) combination index = 0.19(No traces of-ABCB1 efflux transporter in A2780 and SKOV3cells increase DOX Could not-accumulation in A2780 and SKOV3 cells -Increased production of reactive ROS	*In vitro*	[38]
	cis- and *trans*-NER	leiomyoma cells (ELT3 cells)	0-200 µM	-Reduced the proliferation of ELT3 cells (IC_{50} = 172.9 µM for *cis*- and 216.8 µM for *trans*-NER) -Increased percentage of cells in the G1 phase -Reduced Akt and phosphorylated Akt^{Ser473} levels -Increased intracellular ROS generation -Induced DNA damage in ELT3 cells -Downregulated the G1-S checkpoint proteins, *cyclin D1* and CDK4/6	*In vitro*	[39]

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Table 1. Summary of studies reporting anticancer effects of NER (Continued)

Type of cancer	*cis*- or *trans*-NER	Experimental model	Dose	Effects and mechanisms	*In vitro* or *in vivo* system	Reference
Bladder cancer	*cis*-NER	T24 and TCCSUP cell lines	25-100 mg/L	-Induced cell death -Inhibited cell proliferation -Increased levels of DNA damage, endoplasmic reticulum stress, beta-adrenergic receptor signaling, cytoplasmic calcium levels, and glucose-regulated protein 78 expression -Induced the displacement of Ca^{2+} from the endoplasmic reticulum through RYR Ca^{2+} channels	*In vitro*	[40]
Blood cancer	*trans*-NER	CCRF-CEM and CEM/ADR cell lines	40 and 200 µM	-Inhibited human T lymphoblasts CCRF-CEM proliferation (IC_{50}=120 µm) -Low sensitivity of CEM/ADR cells to NER (IC_{50}=232 µm) Ineffective in- increase of DOX efficacy in the CEM/ADR cells -Synergism of DOX with NER in CCRF-CEM cells via ROS formation -Inhibited the efflux of rhodamine 123	*In vitro*	[38]
	trans-NER	HL-60 cells	0.19–25 µg/mL	-Weak cytotoxicity (IC_{50} > 20 µg/mL) on HL-60 *v.s.* 5-FU (IC_{50} = 0.18 µg/ mL)	*In vitro* and *in vivo*	[35]
Liver cancer	*cis*- and *trans*-NER	HepG2/C3A cells	0-250µM	-Only *cis*-NER displayed cytotoxic activity -*cis*-NER arrested cell cycle in G1 phase -*cis*-NER modulated the cyclins and cyclin-dependent kinases -*cis*-NER increased activity of cytochrome P450 enzymes	*In vitro*	[23]
	Trans- NER	Hep G2 cells	0.19–25 µg/mL	-Weak cytotoxicity on cancer cells (IC_{50} > 25 µg/mL)	*In vitro* and *in vivo*	[35]

Colon cancer as the most prevalent cancer starts when colon normal cells begin to grow and change uncontrollably. This cancer has the highest cancer-associated mortality globally and it is attributed to the environmental and genetic factors. Different researchers have been investigated the effects of NER on colon cancer management. Amongst, Zhao X et al.,

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investigated the impacts of NER on ROS accumulation and apoptosis of colorectal cancer cells, HCT-116 cells, using diacetyldichlorofluorescein/4′,6-diamidino-2-phenylindole (DCFHDA/DAPI) dual staining, and MTT assay. Their result showed that the different doses of NER (5-100 µM) can inhibit the HCT-116 cell survival with the IC_{50} of 25 µM, increase ROS level accumulation, and suppress the cell cycle, in addition to higher apoptotic factors in the NER-treated HCT-116 cells [19].

In Hanušová et al., study, the influence of *Myrica rubra* essential oil and its α-humulene and *trans*-NER compounds was studied on the cell adhesion, the levels of adhesion molecules (ICAM-1, β-catenin, and E-cadherin), and apoptotic factors (NF-κB, caspases) in human colon adenocarcinoma HT29 cells. Their results showed that *Myrica rubra* essential oil was able to reduce adhesion of HT29 cells to collagen. Moreover, the essential oil, α-humulene, and *trans*-NER noticeably inhibited the adhesion of TNF-α-stimulated cells due to the reduced expression of ICAM-1. Also, *trans*-NER decreased activation (phosphorylation) of NF-κB and enhanced the activity of caspases, resulted in apoptosis induction in cancer cells [20].

In another study, Ambroz et al., found out that the NER was ineffective in improvement of antiproliferative effects of 5-FU and oxaliplatin on colon cancer cells, Caco-2 and SW-620 cells [21]. In a similar study design, Ambroz et al., evaluated the effects of (±)-*trans*-NER on the pharmacological efficacy of doxorubicin (DOX) in Caco-2 cells and rat hepatocytes. Their results demonstrated that NER synergistically augmented the DOX efficacy and suppressed the Caco-2 cell growth, despite its ineffectiveness on the viability of hepatocytes [22].

Hepatocellular carcinoma, a malignancy of hepatocytes, ranks as the fifth most common reason of cancer in the world. This cancer could be found in > 90 % of the liver primary tumor. Regarding anticancer effects of NER on gastrointestinal cancers, Biazi et al., evaluated the potential of *trans*-NER and/or *cis*-NER in inducing endoplasmic reticulum stress as well as cell death in human hepatocellular carcinoma cell line (HepG2/C3A). Results showed that only *cis*-NER (100 to 250 µM) could induce higher cytotoxic effects, while it did not show genotoxic activity due to the fact that *cis*-NER decreased the expression of genes associated with apoptosis (*CAPN1*, *CASP8*, *CASP9*, *BAX*, *BAK1*, *PARP1*, and *TP53*), paraptosis (*IGF1R*), cell cycle (*CDK1*, *CDK2*, *cyclin D1*, and *cyclin E1*), and xenobiotic metabolism (*CYP3A4* and *CYP2D6*). Therefore, *cis*-NER regulates important molecular targets of cellular viability and growth, which makes it as a considerable potential anticancer therapeutic [23].

Breast cancer

Breast cancer is among the prominent cause of cancer deaths in women which could be distinguished by uncontrolled proliferation of breast cells. Early diagnosis of malignant breast cells is one of the best ways to arrest this cancer [24]. To elevate the effects of NER on breast cancer treatment, Hanusova et al., used *trans*-NER on DOX efficacy against epithelial breast cancer cells, MCF7 and MDA-MB-231, with the especial focus on cell proliferation, migration, apoptosis, and DOX accumulation. Findings showed that the combination of NER + DOX enhanced anti-proliferative effect of drug in MDA-MB-231 cells, in spite of MCF7 cells [25].

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Osteosarcoma

Bone tumors, such as osteosarcoma, can grow anywhere in the bones, but they usually develop at the ends of the long bones. Osteosarcoma is developed by a malignant osteoid derived from primary mesenchymal cells [26]. In an article by Yu et al., the effect of NER was investigated on the suppression of MG-63 osteosarcoma cancer cells. The results showed that NER at a dose of 15 µM could stop the growth of 50 % of the cancer cells. NER significantly reduced the progression of osteosarcoma cells, evidenced by the induction of oxidative stress and morphological changes associated with apoptosis mediated by PI3K/AKT pathway [27].

Head and neck cancers

Laryngeal cancer accounts for approximately 25 to 30 % of head and neck cancers and is classified based on the affected areas [28]. Most laryngeal cancers are squamous cell carcinomas associated with risk factors, such as tobacco use, alcohol consumption, obesity, infection with human papillomavirus and asbestos exposure, alongside epigenetics [29]. Balakrishnan and colleagues investigated the effect of NER on larynx cancer cells, Hep-2 cells. They revealed that NER could enhanced the effectiveness of cisplatin on oral squamous cancer cell indicated by suppressed cell survival as well as increased ROS production, apoptosis, and DNA damage. The NER mechanism of action could be probably mediated through its binding to the PI3K/Akt and proliferating cell nuclear antigen [30]. In another research, Balakrishnan et al., provided evidence that NER had chemopreventive effects on hamster buccal pouch carcinogenesis, a model of oral squamous cell carcinoma induced by 7,12-dimethylbenz(a)anthracene (DMBA). In detail, NER could reverse tumor growth in DMBA-induced oral carcinoma evidenced by modulation of detoxification, antioxidants, lipid peroxidation, and renal activity markers [31]. Also, Balakrishnan et al., showed that oral consumption of NER with the doses of 50 and 100 mg/kg of body weight in DMBA-stimulated buccal pouch hamsters could potentially inhibited the altered expression of inflammatory proteins (NF-κB, TNF-α, and cyclooxygenase-2) and abnormality levels of glycoconjugates status [32].

Skin cancer

Skin cancers are defined as the most common malignancies especially in the white population. The increasing occurrence of skin malignancies has announced the need for various treatment options. In addition to surgical procedures, new researches and innovations are still needed to reduce morbidity and mortality of this cancer [33]. The main risk factor for skin cancers is the enhanced exposure to ultraviolet radiation [34]. Costa et al., found that *trans*-NER derived from *Zornia brasiliensis* did not show any promising cytotoxicity against skin cancer cells, B16-F10, with the IC_{50} of > 25 µg/mL compared to IC_{50} of 5-FU, 0.87 µg/mL. While, *Zornia brasiliensis* leaf essential oil could inhibit the proliferation of B16-F10 cells, both *in vitro* with IC_{50} of 4.93 µg/mL and in the mice model with the tumor growth inhibition rate of 1.68–38.61 % for 50 and 100 mg/kg of concentrations, respectively [35].

Gynecological cancers

Gynecologic cancers are the malignancy of woman's reproductive organs, including cervical, uterine, ovarian, vulvar, vaginal, and rarely fallopian tube [36, 37]. Ambrož et al. 2017 tested the effects of sesquiterpenes, such as *trans*-NER derived from *Myrica rubra* on the cell proliferation of ovarian cancer cells, DOX-sensitive A2780 and DOX-resistant SKOV3

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cells. The effects of sesquiterpenes (20-200 µM) on the cells were tested after 72-h using Alamar Blue assay or neutral red uptake. ABCB1 protein level was evaluated by western blot analysis. Their results showed that *trans*-NER, one of main sesquiterpenes derived from *Myrica rubra* essential oil, inhibited the proliferation of A2780 cells by IC_{50} of 119 µM, but SKOV3 cells was much less sensitive to NER. Also, a strong synergism with a combination index of 0.19 was observed between DOX and NER in the A2780 cells. Besides, no traces of ABCB1 efflux transporter in A2780 and SKOV3 cells .were foundSince the upregulation of the efflux transporter P-glycoprotein, ABCB1, is the mechanism of DOX resistance in cancer cells, increased accumulation of DOX is not the main mechanism of NER synergistic action with DOX. However, the probable mechanism could be defined by increased production of ROS [38]. Uterine fibroids, found in 70–80 % of women, are benign form of tumors in the uterus smooth muscle. In the Dong et al., study, anticancer activity of NER was studied in ELT3 cells (leiomyoma cell line) in an *in vitro* model. The study of antiproliferative activity of *cis*- and *trans*-NER (0-100 µM) in ELT3 cells was studied by Trypan blue exclusion and MTT assays. Also, the cell cycle-related proteins expression, protein concentration, and intracellular ROS detection were examined using western blotting, dual-range bicinchoninic acid assay, and 5(6)-carboxy-2′,7′-dichlorofluorescein diacetate (DCFDA) fluorescent probe, respectively. The results showed that NER inhibited leiomyoma cells proliferation (IC_{50} values of 172.9 µM and 216.8 µM for *cis*- and *trans*-NER, respectively) after 48 h by cell cycle arresting in the G1 phase evidenced by propidium iodide staining. These two compounds dose-dependently decreased the amount of viable cells and G1 checkpoint proteins, CDK4, CDK6, and cyclin D1. Following 48 h of rat leiomyoma cells treatment with NER, this compound considerably downregulated Akt and phosphorylated Akt^{Ser473}, induced intracellular ROS, impaired mitochondrial membrane potential, stimulated p-$\gamma H2AX^{Ser139}$ expression, and reduced the levels of the protein kinase ataxia telangiectasia mutated (ATM) and its phosphorylation [39].

Bladder cancer

Bladder cancer is a common type of cancer that begins in the cells of the bladder. The antitumor activity of *cis*-NER (25-100 mg/L) in human bladder tumor cell lines (T24 and TCCSUP cells) was investigated by Glumac et al., in both *in vitro* and *in vivo* models. Cell viability was evaluated by trypan blue and Annexin-V/ propidium iodide staining. Intracellular ROS levels were detected by the ROS-Glo^{TM} H_2O_2 assay and continuous calcium dynamics after NER exposure. Changes in the intracellular ATP levels were measured using a luciferin/luciferase system. Also, changes in the intracellular cyclic adenosine monophosphate (cAMP) levels were determined by the cAMP-Glo^{TM} assay. Cell lysates were analyzed by western blotting using phosphorylated histone H2Ax as a marker of DNA damage. The results showed that NER inhibited cell proliferation and reduced the cell count in a concentration-dependent manner after 24 h. The NER (100 mg/L) caused cell death in bladder carcinoma cell lines, in almost 70 % of TCCSUP cells and 90 % of T24 cells, 4 h post-treatment. In addition to inhibition of cell growth, NER could change the cells morphology. Also, *cis*-NER enhanced DNA damage and endoplasmic reticulum stress. In detail, endoplasmic reticulum stress could be induced by common cAMP, MAPK axis, and

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Ca^{2+}. The two mechanisms of cell death, early and late cell death, differed by the involvement of caspases. In the early cell death pathway, cell swelling and cell membrane blebbing are happened, which can be suppressed by the inhibited caspase activation. In the late cell death pathway, a caspase-independent pathway, vacuolization of cytoplasm and changes in cellular morphology could be detected. Therefore, *cis*-NER could help to fight against resistant forms of bladder cancer malignancies [40].

Blood cancer

Blood cancers, affecting blood cells and bone marrow, are caused by mutations in the DNA within blood cells, changing the way blood cells behave and work. Lymphoma, leukemia, and myeloma are the most types of blood cancers [41]. In one study by Martin Ambrož et al., the effects of sesquiterpenes, such as NER derived from *Myrica rubra* essential oil, was assessed on lymphoblast cancer cells proliferation with different sensitivity to DOX, human T lymphoblasts CCRF-CEM (DOX-sensitive) and CEM/ADR (DOX-resistant). NER could suppress the CCRF-CEM proliferation by IC_{50} = 120 µM, but CEM/ADR exhibited low sensitivity to the NER (IC_{50} = 232 µm). In test of NER on DOX efficacy, NER did not increase DOX efficacy in the CEM/ADR cells, but a synergism between DOX and NER was observed in the CCRF-CEM cells. NER was able to inhibit the efflux of Rhodamine 123 (a substrate for ABCB1 transporter) [38]. In another study by Costa et al., *in vitro* cytotoxicity potential of *Zornia brasiliensis* essential oil and pure NER (0.19–25 µg/mL) was evaluated towards human promyelocytic leukemia, HL-60 cells, using the Alamar Blue assay. Their results showed that *trans*-NER, a major constitute (48 %) of *Zornia brasiliensis* essential oil, presented weak cytotoxicity (IC_{50} > 20 µg/mL) on HL-60 cells, butthe IC_{50} < 10 µg/mL strongly inhibted these cells compared to 5-FU (positive control; IC_{50} = 0.18 µg/ mL). Besides, the essential oil was not cytotoxic on human peripheral blood mononuclear cells [35].

Liver cancer

Liver cancer is the fifth and seventh most common cancer in males and females, respectively. Also, this cancer is ranked as a third leading cause of cancer-related death worldwide. Liver cancer is an aggressive tumor frequently observed in the chronic liver disease and cirrhosis [42]. In Biazi et al. 2017 study, the effect of *cis*- and *trans*-NER was studied on HepG2/C3A cells, human hepatocellular carcinoma cell line. The results showed only *cis*-NER could inhibit cell survival from 89 % to 3 %. Although *cis*-NER did not induce genotoxic activity, it can alter the mitochondrial membrane potential, inhibit cell growth by arresting cell cycle in G1 phase, and stimulate cell death. RT-qPCR results provided evidence that *cis*-NER decreased the expression of genes related to cell cycle (*CCNE1*, *CCND1*, *CDK1* and *CDK2*), apoptosis (*BAK1*, *BAX*, *CASP8*, *CASP9*, *CAPN1*, *PARP1*, and *TP53*), paraptosis (IGF1R), and xenobiotic metabolism (*CYP2D6* and *CYP3A4*). While, the genes related to cell survival (*BBC3* and *MYC*), xenobiotic metabolism (*CYP1A2* and *CYP2C19*), and reticulum stress protein response (*EIF2AK3* and *ERN1*) were upregulated. The *cis*-NER could evoke antiproliferative function on the cells by modulation of the cyclins and cyclin-dependent kinases, necessary for G1/S phase transition. Besides, increased activity of cytochrome P450 enzymes upregulated *EIF2AK3*, *ERN1*, *CYP2C19* and *CYP1A2*, suggestive of endoplasmic reticulum stress induction [23]. In

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the other study by Costa et al., *in vitro* cytotoxic potential of essential oil and pure NER (0.19–25 μg/mL) was evaluated against tumor cell line, HepG2/C3A cells. The IC_{50} values of essential oil and *trans*-NER on HepG2/C3A cell lines were 1.05 and > 25 μg/mL, respectively. So, the essential oil presented promising results associated with its constitutes, despite the weak cytotoxicity of the pure compounds [35].

The potential of NER as an adjuvant in cancer therapy

Since chemotherapeutic drugs cause adverse effects, such as nephrotoxicity, hepatotoxicity, and cardiomyopathy, scientist are interested in establishment of adjuvant therapy to attenuate the systemic toxic effects induced by chemotherapeutics [44]. In this concept, combination of chemo-agents with natural compounds could be considered as a potential antitumor strategy to reduce the above-mentioned adverse effects [45].

Lee et al., evaluated the antiemetic efficacy of NER on a rat-pica model. To do so, NER (100 or 500 mg/kg) was intraperitoneally given to the animals before treating with cisplatin (6 mg/kg). Then, food and water intake, body weight, and kaolin consumption were measured. The results showed that 100 mg/kg of *m*-NER considerably suppressed increased kaolin intake induced by cisplatin at days 2 in comparison with the cisplatin-saline group. The similar result could be seen for 500 mg/kg of *m*-NER at days 1 and 2. In contrast, *m*-NER had no effect on cisplatin-induced weight loss and cisplatin-induced reduction in food and water intake. Due to the fact of predominant expression of 5-hydroxytryptamine 3 receptor (5-HT_3Rs) in vagal afferents, the effects of three forms of NER were investigated on 5-HT_3R–mediated currents in visceral afferent nodose neurons, which were totally blocked by the ondansetron, 5-HT_3R-selective antagonist. The inhibitory potency of NERs against 5-HT or serotonin currents was respectively as follows; *cis*-NER, *m*-NER, and *trans*-NER. Also, *cis*-NER inhibited responses of 5-HT nodose in a noncompetitive fashion. Thus, NER may induce antiemetic efficacy mediated by inhibition of 5-HT signaling and interruption of emetogenic signaling; however, NER could not inhibit cisplatin-induced weight loss and anorexia [46]. In another effort, Iqubal et al., evaluated cardioprotective potential of NER against cyclophosphamide. Therefore, Swiss Albino mice were treated with 200 and 400 mg/kg NER along with 200 mg/kg drug. The results of molecular docking showed the ability of NER in targeting of NF–κB p65. Despite the effectiveness of NER 200 mg/kg against glutathione, NER 400 and fenofibrate were effective against all oxidative/nitrative stress markers in the cardiac tissue, such as thiobarbituric acid reactive substances, superoxide dismutase, reduced glutathione, catalase, and nitrite levels. Regarding cardiac injury markers, NER 200 significantly reduced the lactate dehydrogenase level. While, NER 400 could effectively decrease lactate dehydrogenase, cardiac troponin-T, B-type natriuretic peptide, and creatine kinase-MB. Only treatment with NER 400 could significantly reduce the inflammatory markers in cardiac tissue, such as TNF-α, interleukin-(IL)-6, IL-10, and IL-1β. Also, NER 400 effectively decreased expression of inducible nitric oxide synthase, p-NF–κB, cleaved caspase 3, fibrotic markers, connective tissue growth factor, and transforming growth factor-(TGF)-β1, in the cardiac tissue. Besides, NER 400 could attenuate the vacuolization, myofibrillar degeneration, pyknosis, and fibrotic lesions induced by cyclophosphamide administration. Treatment

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with NER 400 and the iron supplement ferrous fumarate 80 mg reduced damages in mitochondria and increased healthy mitochondria. As a result, NER could act as a potent cardioprotective agent and reduced cyclophosphamide-induced cardiotoxicity [44]. Iqubal et al., studied the myeloid-protective ability of NER in cyclophosphamide-stimulated myelotoxic mice. Their results showed that 200 and 400 mg/kg of NER adminstarted orally could decresae α-esterase activity, bone marrow cellularity, colony-forming unit erythroid (CFU-E), colony-forming unit granulocyte-macrophage (CFU-GM), and burst-forming unit-erythroid (BFU-E) levels. In the hematological findings, these doses of NER could reduce granulocyte-colony stimulating factor (G-CSF) levels and peripheral blood count. Whereas, biochemical analysis showed the enhnacement of the levels of malondialdehyde, IL-6, IL-1β, and TNF-α, and reduction of catalase, superoxide dismutase, and IL-10 levels. As a result, NER treatment could significantly not only relive the myelotoxic and hematotoxic aberrations, but also retain the bone marrow structural integrity [47].

Conclusion and future perspective

NER could exert antitumor effects against different cancer models, which propose it as a potential anticancer candidate for further researches. Nevertheless, its anticancer activity could be limited due to its less bioavailability, and solubility, alongside its fast hepatic metabolism. To solve these issues, Parvez et al., developed a nanocarrier platform, solid lipid nanoparticles, to encapsulate this bioactive compound and evaluate its anticancer properties in Caco-2 cells. The findings showed that NER loaded lipid nanoparticles have the particles size of 159 nm with the entrapment efficiency of 71.3 %. Also, this kind of formulation enhanced the solubility and biological activity of NER in addition to its better uptake with cells. Besides, NER-lipid nanoparticles, in the range of 40-320 µg/ml, were noticeably decreased cell viability compared to the free NER [48]. Therefore, the future studies about NER could be more concentrated on its nanoformulation to reach the best anticancer effects of this compound.

Author contributions

A.M., P.Z.M., Z.S., F.S., and M.T. drafted the first version of the manuscript. S.M. revised and improved the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts of interests.

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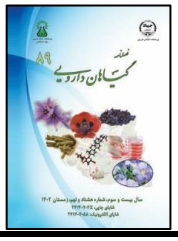

مقاله تحقیقاتی

مروری بر اثرات ضد سرطانی سزکوئی‌ترپن نرولیدول بر روی شرایط بدخیم مختلف

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اطلاعات مقاله

گل‌واژگان:

نرولیدول

ضد سرطان

سزکوئی‌ترپن

فعالیت‌های بیولوژیکی

علوم دارویی

چکیده

مقدمه: نرولیدول یک سزکوی‌ترپن الکلی با طیف وسیعی از فعالیت‌های بیولوژیکی و دارویی، بویژه اثر ضد توموری در مدل‌های مختلف سرطان است. بر اساس گزارش‌ها، خواص ضد سرطانی نرولیدول با افزایش تولید ROS، آپوپتوز و آسیب‌های DNA همراه است. با این وجود، این ترکیب حلالیت کم، فراهمی زیستی پایین و متابولیسم سریع کبدی دارد که با طراحی نانوفرمولاسیون مناسب می‌توان از آن عبور کرد. **هدف:** مقاله حاضر بر روی اثرات نرولیدول در برابر سرطان‌های مختلف متمرکز شده است تا ویژگی‌های امیدوارکننده نرولیدول را به عنوان یک عامل ضد سرطانی کاربردی در چشم‌انداز آینده بهتر مشخص کند. **روش بررسی:** مجموعه‌ای از مقالات بر اساس کلمات کلیدی سرطان و نرولیدول از NCBI/PubMed، Scopus و Google scholar جهت تهیه مطالعه مروری حاضر انتخاب شدند. **نتایج:** نرولیدول به‌عنوان یک ترکیب کمکی در شیمی‌درمانی می‌تواند اثربخشی داروهای شیمی درمانی را بر روی سلول‌های سرطانی مختلف از جمله سرطان استئوسارکوم، دستگاه گوارش، زنان، پستان، پوست، خون، کبد و سرطان سر و گردن افزایش دهد. **نتیجه‌گیری:** نرولیدول یک ترکیب ضد تومور موثر در برابر انواع مختلف سرطان است و گنجاندن آن در رژیم شیمی‌درمانی فعلی می‌تواند درمان سرطان را بهبود بخشد. از طرفی، به دلیل حلالیت کم این ترکیب، نانوفرمولاسیون آن می‌تواند فراهمی زیستی و اثر ضدسرطانی آن را بهبود بخشد.

مخففها: cAMP، آدنوزین مونوفسفات حلقوی؛ CDK، کیناز وابسته به سیکلین؛ DMBA، ۷،۱۲-دی متیل بنز(a)آنتراسن؛ DOX، دوکسوروبیسین؛ 5-FU، ۵- فلوئوروراسیل؛ 5-HT3Rs، گیرنده ۵-هیدروکسی تریپتامین ۳؛ ICAM، مولکول چسبندگی بین سلولی؛ IC50، نیمه حداکثر غلظت مهاری؛ IGF1R، گیرنده فاکتور رشد ۱ شبه انسولین؛ IL، اینترلوکین؛ MTT، ۵،۲-دی فنیل-۲-H- تترازولیوم بروماید؛ NER، نرولیدول؛ ROS، گونه‌های اکسیژن واکنش‌پذیر؛ TNF، فاکتور نکروز تومور

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