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# TERPENES: NATURAL COMPOUNDS WITH POTENTIAL USES IN LUNG CANCER CHEMOTHERAPY

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### Abstract:

Several natural products are currently available as chemotherapeutic agents against frequently occurring cancer. This review reports terpenes from plants that have showed chemotherapeutic activity against lung cancer. In this review, 40 references were found in the period from 1998 to 2018. Terpenes were compiled according to their chemical structures and pharmacological data obtained from different experimental models. From consulted references, 31 terpenes had chemotherapeutic activity in cells of lung cancer, and among them, the triterpenes were the most studied. The MTT assay was the most utilized method in order to evaluate pharmacological activity. According to the specialized literature, terpenes are a great promise as chemotherapeutic agents in the treatment of lung cancer. Some of them are remarkably active, and further research on its anticancer activity seems to be promising.

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**Keywords:** Terpenes; Lung cancer; Natural chemotherapeutics.

### 1. Introduction

The rapid emergence of hundred of new drugs offers great hope for patients with cancer. On the other hand, it represents a huge challenge for basic research, pre-clinical and clinical to analyze and possibly implement these new drugs in clinical

routine. The possibility of a new drug being effective in cancer therapy can only be verified by clinical studies. However, due to ethical, medical, and economic reasons most research needs to be done in experimental systems. Besides that, the small number of patients able to undergo to

clinical testing is another important limitation for testing new anticancer medicines. For many years, researchers in the cancer pharmacology field have developed

safe and reliable methods *in vivo* and *in vitro* for assessing the effectiveness of many drug candidates (Capellozi, 2009).

Classical chemotherapy offers a number of chemicals that help in the treatment and healing of injuries caused by lung carcinoma (LC). Paclitaxel and platinum derivatives (cisplatin or carboplatin) are widely used, with a effective response in 25% of cases. In addition to the chemotherapy, the surgery (lobectomy, pneumonectomy and segmentectomy) and radiotherapy can complete the therapeutic scheme. Despite these treatment options, a great percentage of patients do not respond to the treatment and the need to implement new alternatives to combat injuries caused by LC increases each day. (Bezerra, et al., 2008).

Plants have been used since ancient times as medicines by population, providing good sources of pharmacologically active compounds to improving the therapeutic arsenal (Silva et al., 2006; Costa et al., 2009). Vegetable species are considered promising source of molecules for treatment of various cancer types and it is significant that over 50% of currently used anti-cancer agents were developed from natural sources (Cragg et al., 2005). Even if the isolated natural product could not be strictly used as a medicine, it is often a model for synthesis or structural modifications in order to develop new chemotherapeutic agents (Brandão et al., 2010).

Drugs originated from natural sources that are part of the anticancer arsenal include the terpenes derivatives taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine and vinblastine), anthracyclines (doxorubicin, daunorubicin, etc.),

## 2. Results and Discussion

Terpenes or terpenoids compose a diverse class of natural compound or secondary metabolites from plant origin. They can be found in the leaves, flowers, seeds, wood and roots of higher plants as

podophyllotoxin and its derivative (etoposide, teniposide), camptothecin, and others (Bhanot et al., 2011).

The use of natural products is the most successful strategy aiming discovering new anticancer compounds. Different mechanisms of action were identified for plant-derived

anticancer drugs, such as interaction with DNA, enzyme inhibition and interaction with other proteins. All mechanisms aim the blockage of cancerous cell cycle, and the compounds have as an essential requirement the maximum distinction between the cancerous and the normal cells (Alberts, et al., 2003).

In recent years a large number of natural products from plants such traditional Chinese herb is shown highlighted as potential inhibitors of cell proliferation, induce apoptosis, angiogenesis suppressors, and delay metastasis and enhance the action of other substances chemotherapy, exhibiting *in vitro* and *in vivo* anticancer activity. Among these natural products we can mention the terpenes, one of the larger groups of naturally occurring secondary metabolites. They are present in many plants, marine organisms, and in common foods such as apples and olives, and have showed many pharmacological activities combined with a low toxicity profile. All these characteristics led to raise researchers interest in testing terpenes pharmacological actions, and many important activities have already been proved, e.g., anti-inflammatory, analgesic, antipyretic, cardiogenic, and anticancer activities (Bishayee et al., 2011; Silva et al., 2009b).

By knowing the anticancer potential of terpenes and the activities already established in literature, the present work aim to compile the anticancer terpenes actives against lung carcinoma (LC), based on studies *in vitro* and *in vivo*.

well as in algae, moss, lichens, and some are found in mammals (Pan & Ho, 2008).

Several terpenes isolated from many plant species have shown anticancer activities on various tumor cell lines, among them the lung cancer cell lines (A549) (ACS, 2009). Monoterpenes, diterpenes, sesquiterpenes and triterpenes were assayed

regarding their antineoplastic activity in LC, being effective in several trials, with emphasis on the in vitro MTT assay [3 (4,5-dimethyl-thiazol 2-yl) -2,5-diphenyl-tetrazolium] (Jayaprakasha et al., 2008). Table 1 summarizes the terpenes considered active against lung cancer as well as the experimental method tested.

Among the reported monoterpenes, the chemopreventive potential of perillyl alcohol (POH) is remarkable. POH can be found as an essential oil component of peppermint, spearmint, sage, and cherries, reducing the incidence and multiplicity of tumors (Cho et al., 2012). The same chemopreventive effect is reported to another monoterpene, the euglobal - G1, which is able to reduce lung tumor growing in a dose-dependent way

(Table 1). Both of them are potential chemopreventive agents on LC carcinogenesis (Belanger, 1998; Takasaki et al., 2000).

Several sesquiterpenes were evaluated for their cytotoxic activities in A549 cell line. Elegansidiol, carboxylic acid furan-sesquiterpene and  $\alpha$ -cadinol were shown to be active in various tests, as reported in literature (Yadav et al., 2010; Rajaram et al., 2013; Yang et al., 2011).

Yuanhuadine was the most potent antiproliferative compound among various diterpenoids isolated from flowers *Daphnane genkwa* on cell lung cancer. Potent antiproliferative activity is associated to stopping cell cycle and cell signaling modulation. According to authors, the cell cycle blockage occurred in G0/G1 and G2/M phases in A549 non-small lung cancer cell. The event is correlated to the expression of checkpoint proteins, including up-regulation of p21 and sub-regulation of cyclin-dependent kinases 2 (CDK2) and 4 (CDK4), combined with removal of Akt / mTOR (intracellular signaling pathway of apoptosis) and EGFR signaling pathways (receptor for epidermal growth factor) (Hong et al., 2011). Other diterpenes assessed by various methods showed cytotoxic activity on A549 cells (Table 1), and yuanhuadine was proved to be the most promising anticancer agent for LC (Hong et al., 2010; Duh et al., 2000; Liu et al., 2001).

A growing number of triterpenoids have been reported to exhibit activity against cancer cells with no toxicity to normal cells in vitro and in vivo, by preclinical testing in LC animal models (Zhang et al., 2012; Gomes, 2008; Almeida et al., 2007; Rajaram et al., 2013; Wang et al., 2011). Among the evaluated compounds the frondoside a (Table 1), a glycoside triterpenoid isolated from *Cucumaria frondosa*, raises as a new promising therapeutic agent for lung cancer treatment, by reducing A549 cells viability through the caspase-3/7 dependent pathway, as well as by reducing microvessel density and by

reversing angiogenesis. Furthermore, the compound inhibited cell migration (time and concentration dependent), invasion and metastasis in vitro and in vivo (Attoub et al., 2013).

Ursolic and maslinic acids are pentacyclic triterpenes isolated from *Rubia* genera that have shown great anticancer activity, indicating that these compounds can be useful in the treatment of LC (Huang et al., 2011; Xu et al., 2013).

Bioactive triterpenes such as ganoderic acid G, ganoderenic acid A, ganoderic acid C2 and lucideric acid A, have been described from the *Ganoderma lucidum*. Recently, their antitumor activity has attracted attention of many researchers, mainly because of its stimulatory effect on cytokine IL-6 and TNF- $\alpha$ . The compounds act by improving immunity to fight against tumor, inducing apoptosis to A549 cells, and decreasing expression of anti-apoptotic bcl-2 protein. These data indicate that these anticancer triterpenes from *Ganoderma lucidum* have great potential for clinical use in lung cancer therapy (Feng et al., 2013).

Asian acid (AA), a natural triterpene isolated from the *Centella asiatica* plant has antitumor activity. studies have evaluated the effect of AA reversal on multidrug resistance (MDR) and possible molecular mechanisms of action of AA on cisplatin overexpression resistant (DDP), A549 / DDP lung cancer cells, which have shown that AA may be useful as an MDR reversal agent for combination therapy in clinical trials for acting in various ways on inhibiting P-gp expression, probably related to the down-regulation of YB1, and this effect was mediated by the NF- $\kappa$ B

pathways and MAPK-ERK (Cheng Q et al., 2018).

There is a growing interest in the search for the cancer preventive or therapeutic potential of natural compounds, which are inexpensive and have few side effects. Linalool is a

monoterpenoid alcohol that is present in abundance in red wine and coriander and exhibits anticancer effects in some types of human cancer such as lung cancer (Iwasaki et al., 2016).

### 3. Materials and Methods

This paper surveys the literature related to terpenes that have showed in vivo and in vitro anticancer activity on cells and lung tumors. Then, we describe the classes of terpenes reported, their natural sources and their chemical structures. Besides that, we discuss the main mechanisms of action by which terpenes act as inhibitors of tumor cells and the most promising chemicals for future application in chemotherapy.

The literature review covered the period from 1998 to 2018. Relevant databases were used for researching, e.g., PubMed, Medline, Sibi (USP), Portal Journals Capes, BIREME, ISI, Scirus, IBICT, Web of Science and Dissertation Abstracts. In the survey, were used the following keywords: terpenes, monoterpenes, diterpenes, triterpenes, lung cancer and lung carcinomas. The articles were selected according to their information relevance and their relationship with the interested subject.

### 4. Conclusions

The present work brings up a useful approach for deepening the study of these natural terpenes as future LC treatments. Twenty-four terpenes were found to possess anticancer activity against lung cancer and among them the triterpenes were group that have shown more interesting results. Regarding the experimental methods, the MTT in vitro assay was the most used to evaluate the anticancer potential of terpenes.

According to the specialized literature, terpenes are a great promise as chemotherapeutic agents in the treatment of lung cancer. Some of them are remarkably active, and further research on its anticancer activity seems to be promising.

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