TERPENES: NATURAL COMPOUNDS WITH POTENTIAL USES IN LUNG CANCER CHEMOTHERAPY

Rafaela Araújo da Silva[1], Luciana Dos Santos Felinto[1], Maria Denise Leite Ferreira[1,2] *

[1]Faculdade Nova Esperança-Facene/Famene

[2]Universidade Federal da Paraíba– *PgPNSB*

* denisecaiana@yahoo.com.br

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.

Keywords: Terpenes; Lung cancer; Natural chemotherapeutics.

Resumo: Vários produtos naturais estão atualmente disponíveis como agentes quimioterápicos contra câncer de ocorrência frequente. Esta revisão relata terpenos de origem vegetal que mostraram atividade quimioterapêutica contra câncer de pulmão.

Nesta revisão 40 referências foram consultadas, no período de 1998 à 2018. Os terpenos foram compilados de acordo com suas estruturas químicas e com os dados farmacológicos obtidos a partir de diferentes modelos experimentais. De acordo com as referências consultadas, 31 terpenos apresentaram atividade quimioterapêutica em células de câncer de pulmão, e, dentre eles, os triterpenos foram os mais estudados. O ensaio MTT foi o mais empregado para avaliação da atividade farmacológica. Segundo a literatura especializada, os terpenos são uma grande promessa como agentes quimioterápicos no tratamento do câncer de pulmão. Alguns deles são incrivelmente ativos, e pesquisas adicionais sobre sua atividade anticancerígena parecem ser promissoras.

Palavras-chave: Terpenos; Câncer de pulmão; Quimioterápicos naturais.

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.), 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, cardiotonic, 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*.

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.

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 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 effectives 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 actives 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 α-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 pentaciclic triterpenes isoated 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 luncidum*. Recently, their antitumor activity has attracted attention of many researchers, mainly because of its stimulatory effect on cytokine IL-6 and TNF-α. 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 luncidum* 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-κB 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).

FINAL CONSIDERATIONS

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 posses 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 potencial 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.

Acknowledgment

The authors thank CAPES and Faculdade Nova Esperança-Facene for financial support.

References

ACS – American Cancer Society. Breast Cancer Facts and Figures 2009-2010. Atlanta: American Cancer Society; 2009.

Alberts WN. Lung Cancer Guidelines. Chest Journal, 2003.

Almeida MMB, Arriaga AMC, Santos AKL, Lemos TLG, Braz-Filho R., Vieira IJC. Ocorrência e Atividade Biológica de Quassinóides da Última Década. Quim Nova. 2007; 30(4): 935-951.

Anita Thyagarajan; Andrej Jedinak; Nguyen Hai; Colin Terry; Lee Ann Baldridge; ,Jiahua Jiang e Daniel Sliva. Triterpenos do *Ganoderma Lucidum* induzem autofagia no câncer de cólon através da inibição da quinase ativada por mitógeno p38 (p38 MAPK). 2018.

Attob S, Arafat K, Gélaude A, Al Sultan MA, Bracke M, Collin P, Takahashi T, Adrian TE, Wever O. Frondoside a suppressive effects on lung cancer survival, tumor growth, angiogenesis, invasion and metastasis. PLoS ONE. 2013; 8(1): e53087.

Belanger J. Perillyl Alcohol: Applications in Oncology. Altern Med Rev. 1998; 3 (6): 448-57.

Bezerra DP, Castro FO, Alves AP, Pessoa C, Moraes MO, Silveira ER, Lima MA, Elmiro FJ, Alencar NM, Mesquita RO, Lima MW, Costa-Lotufo LV. In Vitro and in Vivo Antitumor Effect of 5-FU Combined With Piplartine and Piperine. J Appl Toxicol. 2008; 28(2): 156-63.

Bhanot A, Sharma R, Noolvi M.N. Natural sources as potential anti-cancer agents: A review. Phytomedicine. 2011; 3(1)09-26.

Bishayee A, Ahmed S, Brankov N, Perloff M. Triterpenoids as potential agents for the chemoprevention and therapy of breast cancer. Front Biosci (Landmark Ed). 2011; 1(16): 980-96.

Brandão HN, David JP, Couto RD, Nascimento JAP, David JM. Química e Farmacologia de Quimioterápicos Antineoplásicos Derivados de Plantas. Quím Nova. 2010; 33(6): 1359-1369.

Capelozzi VL. Role of immunohistochemistry in the diagnosis of lung cancer. J Bras Pneumol. 2009; 35(4): 375-382.

Cheng Q; Liao H; Hu H; Li H; Wu L . Ácido Asiático (AA) Sensibiliza Adenocarcinoma Pulmonar Humano Multirresistente A549 / Células DDP para Cisplatina (DDP) via Downregulation de P-Glicoproteína (MDR1) e Seus Alvos. 2018; 47 (1): 279-292.

Cho HY, Wang W, Jhaveri N, Torres S, Tseng J, Leong MN, Lee DJ, Goldkorn A, Xu T, Petasis NA, Louie SG, Schönthal AH, Hofman FM, Chen TC. Perillyl Alcohol for the Treatment of Temozolomide-Resistant Gliomas. Mol Cancer Ther. 2012; 11(11): 2462-72.

Costa DAC, Matias WN, Lima IO, Xavier AL, Costa ABM, Diniz MFFMD, Agra MF, Batista LM, Souza MFV, Silva DA. First secondary metabolites from Herissantia crispa L (Brizicky) and the toxicity activity against Artemia salina Leach. Quím Nova. 2009; 32(1): 48-50.

Cragg GM, Kingston DGI, Newman DJ. Anticancer Agents From Natural Products. Boca Raton. CRC Press. 2005.

Crowell PL. Prevenção e terapia do câncer por monoterpenos dietéticos. Mar de 1999; 129 (3): 775S-778S.

Crowell PL; Gould MN. Quimioprevenção e terapia do câncer pelo d-limoneno. 1994; 5 (1): 1-22

Duh CY, Wang SK, Chen IS. Cytotoxic prenyleudesmane diterpenes from the fruits of Dysoxylum kuskusense. Nat Prod J. 2000; 63(1): 1546-1547.

Feng L, Yuan L, Du M, Chen Y, Zhang M, Gu JF, He JJ, Wang Y, Cao W. Anti-Lung Cancer Activity through Enhancement of Immunomodulation and Induction of Cell Apoptosis of Total Triterpenes Extracted from *Ganoderma luncidum* (Leyss. ex Fr.) Karst. Molecules. 2013; 18(8): 9966-9981.

Gomes, J.P.M. Pesquisa de Atividade Antitumoral e Mutagênica in Vitro de Produtos Naturais [Dissertação]. Araraquara: Universidade Estadual Paulista. 2008.

Gomide, MS. et al. O efeito dos óleos essenciais de cinco espécies diferentes de *Lippia* na viabilidade de linhas celulares tumorais. Rev. bras. farmacogn. [conectados]. 2013, vol.23, n.6, pp.895-902.

Hong J, Chung H, Lee H, Park HJ, Lee SK. Growth Inhibition of Human Lung Cancer Cells via Down-regulation of Epidermal Growth Factor Receptor Signaling by Yuanhuadine, a Daphnane Diterpene from Daphne genkwa. Nat Prod J. 2011; 74(10): 2102-2108.

Hong J-Y, Nam J-W, Seo E-K, Lee SK. Daphnane Diterpene Esters with Anti-proliferative Activities against Human Lung Cancer Cells from Daphne genkwa. Chem Pharm Bull. 2010; 58(2): 234-237.

Huang C-Y, Lin C-Y, Tsai C-W, Yin M-C. Inhibition of cell proliferation, invasion and migration by ursolic acid in human lung cancer cell lines. In Vitro Toxicol. 2011; 25(7): 1274-1280.

Jayaprakasha GK, Girennavar B, Patil BS. Radical Scavenging Activities of Rio Ted Grapefruits and Sour Orange Fruit Extracts in Different in Vitro Model Systems. Bioresour Technol. 2008; 99(10): 4484-94.

Jin X; Yang Q; Cai N. Preparação de micelas mistas de composto de ginsenosídeo- K com melhor retenção e eficácia antitumoral. 2018 Jul 3; 13: 3827-3838.

Kenichi Iwasaki; Yun-Wen Zheng; Soichiro Murata; Hiromu Ito; Ken Nakayama; Tomohiro Kurokawa; Naoki Sano; Takeshi Nowatari; Myra O Villareal; Yumiko N Nagano; Hiroko Isoda; Hirofumi Matsui e Nobuhiro Ohkohchi. Efeito anticancerígeno do linalol via geração de radicais hidroxila específica para câncer no câncer de cólon humano. 2016; 22 (44): 9765-9774.

Liu Y, Bae BH, Alam N, Hong J, Sim CJ, Lee C, Im KS, Jung JH. New Cytotoxic Sesterterpenes from the Sponge Sarcotragus Species. Nat Prod J. 2001; 64(10): 1301-1304.

MH Cháirez-Ramírez , [1] Sr. Moreno-Jiménez , [1] RF González-Laredo , [1] JA Gallegos-Infante , [1] eNuria Elizabeth Rocha-Guzmán. Triterpenos do tipo Lupano e suas atividades anticancerígenas contra tumores malignos mais comuns. 2016.

Mihoub M, Pichette Um; Sila B; Gauthier C; Legault J. A saponina bidesmidica contendo pores L-ramnopiranidas induz a apoptose e a inibio do crescimento de culas de cancro do pulm in vitro e in vivo. 2018 14 de Mar; 13 (3): e0193386.

Ou-Yang DW, Wu L, Li YL, Yang PM, Kong DY, Yang XW, Zhang WD. Miscellaneous terpenoid constituents of Abies nephrolepis and their moderate cytotoxic activities. Phytochemistry. 2011; 72(17): 2197-204.

Pan MH, Ho CT. Chemopreventive effects of natural dietary compounds on cancer development. Chem Soc Rev. 2008; 37(11): 2558-74.

Rajaram S, Ramulu U, Ramesh D, Srikanth D, Bhattacharva P, Prabhakar P, Kalivendi SV, Babu KS, Venkateswarlu Y, Navath S. Anti-cancer evaluation of carboxamides of furano-sesquiterpene carboxylic acids from the soft coral Sinularia kavarattiensis. Bioorg Med Chem Lett. 2013; 23(23): 6234-8.

Rawat P; Kumar A; Singh TD; Pal M. Composição Química e Atividade Citotóxica do Extrato Metanólico e suas Frações de Folhas de Asper Streblus em Linhagens de Câncer Humano. 2018 Apr-Jun; 14 (54): 141-144.

Sabry OM; Goeger DE; Valeriote FA; Gerwick WH. Monoterpenos halogenados citotóxicos de Plocamium cartilagineum. 2017 fev; 31 (3): 261-267.

Silva DA, Falcão-Silva VS, Gomes AYS, Costa DA, Lemos VS, Agra MF, Braz-Filho R, Siqueira-Junior JP, Souza MFV. Triterpenes and phenolic compounds isolated from the aerial parts of *Herissantia tiubae* and evaluation of 5,4'-dihydroxy-3,6,7,8,3'-pentamethoxyflavone as a modulator of bacterial drug resistance. Pharm Biol. 2009; 47(4): 279-84.

Silva DA, Silva, TMS, Lins ACS, Costa DA, Cavalcante JMS, Matias WN, Souza MFV, Braz Filho R. Constituintes Químicos e Atividade Antioxidante de *Sida galheirensis* Ulbr. (Malvaceae). Quim Nova. 2006; 29(6): 1250-1254.V

Sobral, VM; Xavier, LA; Lima, CT; D Sousa, PD. Antitumor Activity of Monoterpenes Found in Essential Oils. 2014, Article ID 953451, 35 pages.

Takasaki M, Konoshima T, Etoh H, Pal Singh I, Tokuda H, Nishino H. Cancer chemopreventive activity of euglobal-G1 from leaves of Eucalyptus grandis. Cancer Lett. 2000; 155(1):61-65.

Ukiya M; Hayakawa T; K. Okazaki; H. Hikawa ; Akazawa H; Li W; Koike K; Fukatsu M. Síntese de N - Glicosídeos Triterpenóides Tipo Lanostano e sua Citotoxicidade contra Linhas Celulares de Câncer Humano. 2018 Jul; 15 (7): e1800113.

Wang,O.; Liu,S.;Zou,J.;Lu,L.;Chen,L.; Qiu,S.; Li,H.; Lu,X. Anticancer Activity of 2a, 3a, 19b, 23b-Tetrahydroxyurs-12-en-28-oic Acid (THA), a Novel Triterpenoid Isolated from Sinojackia sarcocarpa; PLoS ONE. 2011; 6(1): e21130.

Weng Y; Yu X; Li J; Dong Q; Li F; Cheng F; Zhang Y; Yao C; Zou Z; Zhou W; Tan G; Xu K. Diterpenóides de abietano de Lycopodium complanatum. 2018 Jul; 128: 135-141.

Xu,K.;Wang,P.;Yuan,B.;Cheng,Y.;Li,Q.;Lei,H. Structural and bioactive studies of terpenes and cyclopeptides from the Genus Rubia. Chem Cent J. 2013; 7(1): 81.

Yadav JS, Kamani S, Pamu S, Pabbaraja S, Thokhir BS, Shasi VK. Total synthesis of elegansidiol, farnesiferol B and farnesiferol D. Bioorg. Med Chem Lett. 2010; 20(1): 3814–3817.

Zhanq Y, Ma Z, Hu C, Wang L, Li L, Song S. Cytotoxic triterpene saponins from the leaves of Aralia elata. Fitoterapia. 2012; 83(4): 806-811.

Table 1. Terpenes considered actives against lung cancer, their structures, the experimental method tested and the demonstrated effect.

1-3-O-D-glucopiranosyl (1-3)-D-glucoranosyl (1-3)-D-glucopiranosyl oleanolic acid	Triterpene	MTT (*in vitro*)	Cytotoxicity against A549; IC_{50}: 7.93 uM	Zhanq et al (2012)
Elegansidiol	Sesquiterpene	SRB (*in vitro*)	Cytotoxicity against A549; IC_{50}: 6.9 uM	Yadav et al (2010)
Carboxilic acid furano-sesquiterpene	Sesquiterpene	MTT (*in vitro*)	Cytotoxicity against A549 IC_{50}: 24.6 ± 3.1 uM	Rajaram et al (2013)
5-α Cadinol	Sesquiterpene	MTT (*in vitro*)	Cytotoxicity against A549, 8.6 ug/ml	Yang et al (2011)
Trans-Phytol	Diterpene	MTT (*in vitro*)	Cytotoxicity against A549, IC_{50}: 11.5 ug/ml	Almeida et al (2007)
(24R)-cycloartane-3b,24,25-triol	Triterpene	MTT (*in vitro*)	Cytotoxicity against A549, IC_{50}:17.3 µg/ml	Wang et al (2011)
Euglobal G1 (Acylphloroglucinol)	Monoterpene	*In vivo*, using 4 nitroquinoline-N-oxide (4-NQO) as starter and glicerol as promotor	Reduction of tumor formation	Takasaki et al (2000)

Yuanhuadine (4)	Diterpene	SRB (*in vitro*)	Anti – proliferative effect against A549, IC_{50}: 0.012 μM	Hong et al (2010)
Bruceanol D	Triterpene	Cell culture (*in vitro*)	Cytotoxicity against A-549, IC_{50}: 0.55 μg mL^{-1}	Almeidaet al (2007)
Perillyl alcohol	Monoterpene	Randomized groups of rats (*in vivo*)	Reduction of tumor formation	James et al (1998)
Ursolic acid	Triterpene	Normal lung cells (HNBE) and A549, H3255 and Calu – 6, on RPMI media	Increment of DNA fragmentation; Activation of Na^+ /K^+ ATPase; Decrease production VEGF and TGF -β; suppression: CAM-1, fibronectin and MMPs	Huang et al (2011)
Maslinic acid	Triterpene	MTT (*in vitro*)	Cytotoxicity against A549, IC_{50}:10.75~18. 87 μg/ml; Induces apoptose	Xu et al (2013)

			caspase-dependent apoptosis	
Ganoderic acid C2	Triterpene	MTT(*in vitro*) Lewis carcinoma C57BL /6 (*in vitro*)	Cytotoxicity against A549 IC_{50}: 24.63 ug/ml; Increase expression of IL- 6 and TNFα; Decrease expression of protein Bcl-2 and pro-caspase 9; cellular cycle interruption on G2/M phase	Feng et al (2013)
Ganoderic acid G	Triterpene	MTT (*in vitro*), Lewis carcinoma C57BL / 6 (*in vitro*)	Cytotoxicity against A549 IC_{50}: 24.63 ug / ml; Decrease expression of protein Bcl-2 and pro-caspase 9; cellular cycle interruption on G2/M phase	Feng et al (2013)

Ganoderenic acid A	Triterpene	MTT (*in vitro*) Lewis carcinoma C57BL / 6 (*in vitro*)	Cytotoxicity against A549 IC_{50}: 24.63 ug/ml; Increase expression of IL- 6 and TNFα; Decrease expression of protein Bcl-2 and pro-caspase 9; cellular cycle interruption on G2/M phase	Feng et al (2013)
Lucideric acid A	Triterpene	MTT (*in vitro*), Lewis carcinoma *C57BL / 6 (in vivo)*	Cytotoxicity against A549 IC_{50}: 24.63 ug/ml; Increase expression of IL- 6 and TNFα; Decrease expression of protein Bcl-2 and pro-caspase 9; cellular cycle interruption on G2/M phase	Feng et al (2013)
Dysokusone D	Diterpene	American type culture collection (*in vitro*)	Cytotoxicity against A549, ED_{50}: 2.39 g/ml	Duh et al (2000)

Dysokusone E	Diterpene	American type culture collection (*in vitro*)	Cytotoxicity against A549, ED_{50}: 3.76 g/ml	Duh et al (2000)
Sarcotin N	Furano terpenoid	Cell culture (*in vitro*)	Cytotoxicity against A549, ED_{50}: 19.4 g/ml	Rajaram et al (2013)
2a, 3a, 19b, 23b-tetrahydroxyurs-12-en-28-oic acid	Triterpene	MTT (*in vitro*)	Cytotoxicity against A549, IC_{20}:12.0 µg/ml, IC50-25.0 µg/ml, IC_{80}:72.0 µg/ml	Wang et al (2011)
Yuanhuadine (1)	Diterpene	SRB (*in vitro*); Xenograft (*in vivo*)	Cytotoxicity against A549, IC_{50}: 12 x 10^{-3} µM; cellular cycle interruption on G0/G1 e G2/M phases; Regulation of protein p21 and supra-regulation of CDK2 and CDK4; Expression suppression of Akt /mTOR, p70S6K, 4EBP1, EGFR	Hong et al (2011)

Frondoside A	Terpenoid glycoside	Motility, invasion, vascular tube formation, CAM, tumour growth and metastasis; Xenograft (*in vivo*)	Cytotoxicity against A549; Reduction of microvessel density; Decrease capillary structure, Increase cisplatin action	Attoub et al (2013)
Dasycarpuside A	Terpenoid glycoside	SRB (*in vitro*)	Inhibition of cells A549, IC_{50}: 0.002 μM.	Liu et al (2001)
Pristimerin	*Nor*-triterpene	MTT (*in vitro*)	Cytotoxicity against LP07, IC_{50}: 0.005 μmol	Gomes, JPM (2008)
Ginsenoside K	Triterpene	MTT *(in vitro)*	Regulation of the cell cycle, inhibition of tumor growth and induction	Xin Jin et al (2018)

			of apoptosis of A549 cells.	
1 [(-) - (5E, 7Z) - 348-tricloro-7-diclorometil-3-metil-157-octatrieno]	Monoterpene	*(in vitro)*	Cytotoxic in lung cancer cells (NCI-H460).	Douglas E. Goeger (2016)
Saponina Betuminida	Triterpene	Resazurina *(in vitro)*	Cytotoxic in lung cancer cells A549.	Mihoub et al (2018)
Xanthoperol e Sugiol	Diterpene	*(in vitro)*	Cytotoxic (MSTO-211H, NCI-H2052 e NCI-H226)	Weng Y et al (2018)
Terpineol	Monoterpene	In vitro	Inhibition of the NF-xB pathway	Saadia Bashir Hassan (2010)
Cymene	Monoterpene	*In vitro*	Cytotoxic against contra A549	S. Bourgou et al (2010)
Linalool	Monoterpene	*In vitro*	Cytotoxicid against A549	J. M. Cherng et al (2007)

Lanostano	Triterpene	MTT *(in vitro)*	Cytotoxicid against HL-60, A549, MKN45, e células WI-38 (IC $_{50}$ 0,0078-2,8 M)	Ukiya M et al (2018)
Ácido asiático (AA)	Triterpene	*MTT and RT-PCR (In vitro)*	Reversal in lung cancer cells resistant to the overexpression of cisplatin A549/DDP cells	Cheng Q et al (2018)
Lippia	Monoterpene	*In vitro*	Cytotoxic in the cell line A549	. Gomide et al (2013)
D – Limoneno	Monoterpene	*In vivo*	Inhibition of metastasis	Crowell PL et al (1999)
Lupano	Triterpene	*In vivo*	It induces apoptosis in the A549 cell line.	Cháirez-Ramírez et al (2016)
Myrcene	Monoterpene	*In vivo*	A549 lineage cytotoxicity.	Sobral et al (2014)