Anticancer activity of lichen substances: a systematic review

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Sumário

Os líquenes são fonte de uma grande variedade de metabolitos secundários, frequentemente exclusivos desta associação, com actividades biológicas importantes como a antibiótica, anti-inflamatória, antioxidante e anticancerígena, entre outras. A evidência científica demonstra que os efeitos anticancerígenos dos líquenes se produzem através da inibição da iniciação, crescimento e invasão de vários tipos de células cancerígenas *in vitro* e *in vivo*. Foi efectuada uma revisão sistemática da actividade anticancerígena e dos mecanismos de acção de extractos e respectivas substâncias isoladas de líquenes. Os termos "lichen", "tumo(u)r" e "cancer" foram utilizados para pesquisar artigos científicos no PubMed e Web of Science publicados até dezembro de 2018. De um total de 368 artigos pesquisados, 142 cumpriram os critérios de inclusão e exclusão estabelecidos. O ácido úsnico foi a substância liquénica isolada mais vezes e citada em 40 artigos. A espécie de líquene mais utilizada, citada em 9 artigos, foi *Evernia prunastri* (L.) Nyl. Os extractos e substâncias liquénicas têm a capacidade de interferir com todas as propriedades biológicas das células cancerígenas que conduzem ao desenvolvimento de tumores, da seguinte forma: indução da inibição do ciclo celular, inibição das vias de sinalização do crescimento celular, activação da imunidade antitumoral, bloqueio da imortalidade replicativa por inibição da actividade da telomerase, inibição da inflamação, inibição da invasão e metástase, bloqueio da angiogénese, supressão da instabilidade do genoma, induzindo morte celular por apoptose, autofagia e necrose, e modulação do metabolismo energético. Muitas substâncias liquénicas revelaram-se eficazes contra muitos tipos de linhas celulares cancerígenas, quer isoladas quer em combinação com outros agentes anticancerígenos, e constituem por isso bons candidatos ao desenvolvimento de fármacos anticancerígenos.

Palavras-chave

Tumor, Farmacognosia, Fitoterapia, Angiogénese, Apoptose, Autofagia, Migração celular, Invasão celular, Viabilidade celular, Proliferação celular, Citotoxicidade, Senescência celular, Stress oxidativo.

Abstract

Lichens are a source of a great variety of unique secondary metabolites with important biological activities, including antibiotic, anti-inflammatory, antioxidant and anticancer, among others. A large body of research has demonstrated anticancer effects of lichens by inhibition of initiation, growth and invasion of several cancer cell types *in vitro* and *in vivo*. We performed a systematic review of the anticancer activity and mechanisms of action of lichen extracts and substances isolated from lichens. The search terms “lichen”, “tumo(u)r” and “cancer” were used to retrieve articles in PubMed and Web of Science published until December 2018. From a total of 368 articles surveyed, 142 met the established inclusion and exclusion criteria. The most commonly isolated lichen substance was usnic acid, cited in 40 research articles. The species more frequently used was *Evernia prunastri* (L.) Nyl., cited in 9 research articles. Lichen extracts and isolated lichen substances are able to interfere with all currently recognized biological capabilities necessary for tumour growth and progression. They do so by inducing cell cycle arrest, inhibiting growth factor signalling, activating anti-tumour immunity, disabling replicative immortality by inhibiting telomerase activity, inhibiting tumour-promoting inflammation, inhibiting invasion and metastasis, blocking angiogenesis, supressing genome instability, inducing apoptotic, autophagic and necrotic cell death, and modulating energy metabolism. Many lichen substances have proved effective against many types of cancer cell lines, either isolated or in combination with other anticancer agents, and are therefore suitable candidates for anticancer drug development.

Keywords

Tumour, Pharmacognosy, Phytotherapy, Angiogenesis, Apoptosis, Autophagy, Cell migration, Cell invasion, Cell viability, Cell proliferation, Citotoxicity, Cellular senescence, Oxidative stress.

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1. Introduction

The World Health Organization defines cancer as a generic term for a large group of diseases characterized by the uncontrolled proliferation of abnormal cells that are capable of invading adjoining parts of the body and/or spread to other organs. According to the global cancer statistics presented by the Global Cancer Observatory (GCO) (https://gco.iarc.fr/), cancer is the second leading cause of death globally, and is estimated to have accounted for 9,6 million deaths in 2018. Lung and breast cancers were the most common cancers worldwide, each contributing to approximately 12% of the total number of new cases diagnosed in 2018. Colorectal cancer was the third most common cancer, with 1,8 million new cases in 2018. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common among women. Regardless of developments in the tools of disease diagnosis, treatment, and prevention measures, the number of cases is constantly increasing and estimated to reach an incidence of 29,5 million by 2040.

Anticancer drugs currently approved by the Food and Drug Administration can be classified in four major groups: a) cytotoxic drugs; b) targeted-based agents; c) hormones and hormone antagonists; and d) immunomodulators (Liu *et al.*, 2017). More than 70% of these drugs can be traced to natural products or synthetic to semi-synthetic substances derived from natural products (Katz and Baltz, 2016). Despite current progress in anticancer drug development, shifting from conventional nonspecific cytotoxic agents to specific target-based therapies and immune-related modulators (Liu *et al.*, 2017), the discovery of new anticancer drugs from nature continues to be important for modern cancer research, as many potential sources of natural products remain largely unexplored (Stanojković, 2019).

1.1. Relevant aspects of lichen biology for cancer research

Lichens are symbiotic associations formed between at least one fungus, acting as host, and a mutualistic photosynthetic partner that is usually an alga and/or a cyanobacteria (Lumbsch and Rikkinen, 2017). The lichen fossil record is particularly poor but the probable origin of this association is currently set around 400–600 million years ago (Honegger *et al.*, 2013; Yuan *et al.*, 2005). The association has been such an evolutionary success that lichens can be found in most terrestrial ecosystems of the world and in a wide

variety of natural habitats, from sea level to high mountain peaks and from the hot deserts to the cold Arctic and Antarctic (Galloway, 1996). All over the world, they have been used in folk medicine, as a source of food, and also in the preparation of raw materials for dyes and perfumes (Crawford, 2019; Yamamoto *et al.*, 2015). Almost 20 000 different lichen species have been described to date (Lücking *et al.*, 2017), but since many regions of the world have been poorly collected, an even higher estimate may well be more realistic.

1.1.1. Biochemistry and secondary metabolites

Lichens produce a wide array of characteristic and unique primary (intracellular) and secondary (extracellular) metabolites (Elix, 1996). Primary metabolites include proteins, amino acids, polyols, carotenoids, polysaccharides and vitamins. Lichen secondary metabolites, often called lichen acids, are small but chemically complex substances grouped according to their chemical structure into the following classes: a) N-containing compounds; b) P-containing compounds; c) S-containing compounds; d) aliphatic and cycloaliphatic compounds; e) aromatic compounds; f) quinones; g) chromanes and chromones; h) xanthones; i) dibenzofurans; j) diphenylethers; k) biphenyls; l) diphenylmethanes; m) nostoclines; n) depsides; o) depsidones; p) depsones; q) naphthopyranes; r) terpenoids; s) pulvinic acid derivatives; and t) cleavage products of depsides and depsidones (Elix, 1996; Huneck and Yoshimura, 1996).

Research shows that both primary and secondary metabolites exert a wide variety of biological activities that include antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, anticancer, analgesic, antipyretic, enzyme inhibitory, anti-insecticidal and plant growth inhibitory (Calcott *et al.*, 2018; Crawford, 2019; Molnár Katalin and Farkas Edit, 2014; Yamamoto *et al.*, 2015; Zambare and Christopher, 2012). About 700 lichen substances were known by the time Huneck and Yoshimura (1996) published their compendium of lichen metabolites, and much more have been described since, with unique biological properties (e.g. Duong *et al.*, 2017; Huneck, 2001; Le Pogam and Boustie, 2016; Nguyen *et al.*, 2019). There are recent literature reviews addressing the anticancer activity of natural compounds isolated from lichens (Boustie and Lohézic-Le Dévéhat, 2008; Kim *et al.*, 2015; Shrestha and Clair, 2013; Stanojković, 2019) but a detailed overview of all research available on their anticancer properties was still lacking. We have therefore performed, for the first time, a systematic review of all high-quality

research evidence of the anticancer activity of lichens and possible anticancer mechanisms of lichen extracts and isolated lichen substances.

2. Methods

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA Statement in Moher *et al.*, 2009 and PRISMA Elaboration and Explanation in Liberati *et al.*, 2009).

2.1. Search strategy

Two internet sources were used to search for research articles that met the purpose of this review - PubMed (U. S. National Library of Medicine) and Web of Science (Clarivate Analytics) - using different combinations of the following search terms: "lichen", "tumo(u)r" and "cancer". In order to avoid confusion with the array of skin diseases named under the term "lichen" (ex: "lichen planus") these were excluded as follows: "-aureus", "-amyloidosis", "-myxedematosus", "-nitidus", "-planopilaris", "-planus", "-purpuricus", "-sclerosus", "-simplex", "-spinulosus", "-striatus".
The databases were searched for research articles published in the period up to and including December, 2018. Eligibility criteria were set to include any published research article that evaluated the anticancer activity of natural compounds obtained from lichens.

2.2. Study selection

All electronic search titles, selected abstracts, and full-text articles were independently reviewed by two reviewers (Joana Marques and Marina Swerts). The following exclusion criteria were defined: research articles focusing exclusively on endolichenic fungi, lichenicolous fungi, antimutagenic effects, normal cell lines or drug delivery systems; research articles not specifying the lichen species or lichen substance; review articles; meta-analyses; abstracts; conference proceedings; editorials/letters; and case reports (Figure 1).

2.3. Data extraction

Data were extracted by one reviewer (Joana Marques) using a predefined standardized form, and checked for completeness and accuracy by a second reviewer (Marina Swerts). Extracted information included data on the lichen substance (if specified), its origin

(natural, synthetic or commercial), chemical class (according to Huneck and Yoshimura, 1996), source (lichen species, if specified, and respective geographical origin), type of cancer addressed, applied assays and respective result, and suggested mechanism of action. Data on the experimental design was also extracted (use of controls and replicates).

3. Results and discussion

The primary search identified 368 research articles for preliminary review from electronic and manual searches, with 221 from PubMed, 101 from Web of Science and 46 from manual selection. After the removal of duplicates (64) and screening for relevant titles and abstracts, a total of 154 research articles was submitted for a full-text review. A total of 142 research articles met the inclusion and exclusion criteria established. A flowchart illustrating the selection process and number of research articles at each stage was performed as suggested in Liberati *et al.*, 2009 (Figure 1).

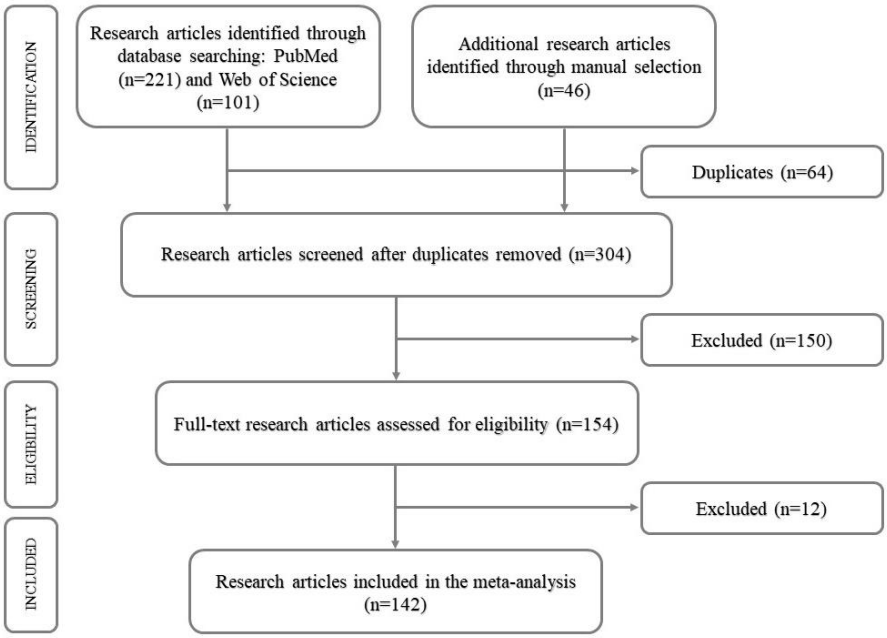

Figure 1. Flowchart of included research articles.

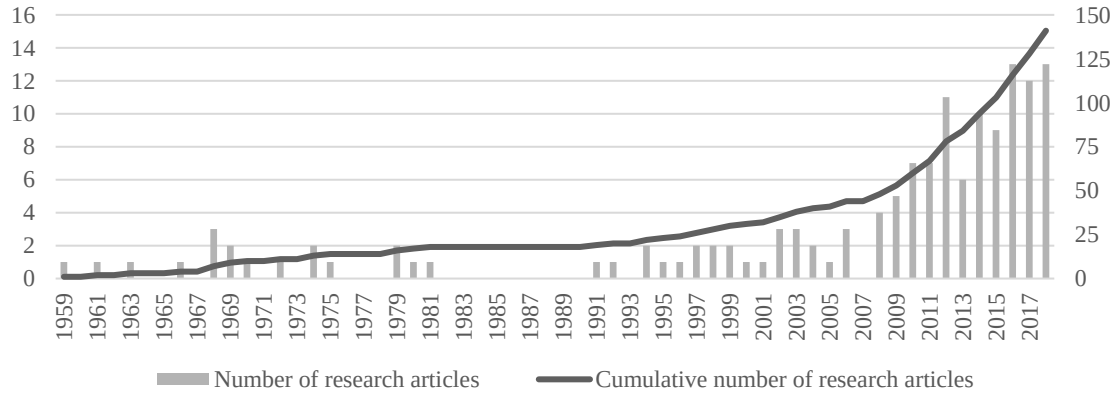

Figure 2. Number and cumulative number of research articles respecting the inclusion criteria published since 1959.

The 142 research articles here reviewed (Figure 2) mention 296 lichen species collected in 31 countries (Figure 3). Only 70% of the mentioned lichen names are accompanied by the name of their author(s). A species name is only complete if including author citation, i.e. the name(s) of the author(s) responsible for the establishment or introduction of a species name (Turland *et al.*, 2018). Author citation is essential to track down the original species description and guarantee proper linking to species identity - quite frequently there are cases where at least two different author names are given after the same scientific species name; if after a taxonomic revision these are found to be different species, with different chemistry and medicinal/pharmaceutical usage, author citation is the only means to distinguish between the two. The most cited lichen species include: *Evernia prunastri* (L.) Ach. (n= 9), *Cetraria islandica* (L.) Ach. (n= 9), *Hypogymnia physodes* (L.) Nyl. (n= 8), *Cladonia furcata* (Huds.) Schrad. (n= 7), *Stereocaulon alpinum* Laur. (n= 7), *Gyrophora esculenta* Miyoshi (n= 7), *Parmelia caperata* (L.) Ach. (n= 6), *Thamnolia vermicularis* (dubious author citation) (n= 5), *Lasallia pustulata* (L.) Mérat (n = 5), *Parmelia sulcata* Taylor (n= 5) and *Xanthoria parietina* (L.) Th. Fr. (n= 5) (Figure 4).

Among the reviewed research articles, 50 use lichen extracts and 114 use isolated lichen substances. A total of 137 isolated substances have been tested, belonging to 18 classes of primary and secondary metabolites (adapted from Huneck and Yoshimura, 1996): 1) depsidones (represented by physodic acid, lobaric acid, salazinic acid and 23 other substances); 2) depsides (represented by atranorin, diffractaic acid, lecanoric acid and 20 other substances); 3) aliphatic and cycloaliphatic compounds (represented by protolichesterinic acid and 17 other substances); 4) aromatic compounds (represented by 18 substances); 5) quinones; 6) dibenzofurans (represented by usnic, usnetic and usnolic acids), 7) polysaccharides (mainly glucans like lichenin and isolichenin); 8) N-containing compounds; 9) diphenylethers; 10) xanthones; 11) cleavage products of depsides and depsidones; 12) terpenoids; 13) peptides; 14) glutamic acid derivatives; 15) alkaloids; 16) pulvinic acid derivatives; 17) flavanols; and 18) tannins. Top ten cited substances are usnic acid (n= 40) - including its enantiomers (+)-usnic acid (n= 14) and (-)-usnic acid (n= 8), and salt forms (n= 1) - atranorin (n= 13), glucans (n= 10), protolichesterinic acid (n= 8), diffractaic acid (n= 7), physodic acid (n= 7), lobaric acid (n= 7), vulpinic acid (n= 6), salazinic acid (n= 5) and lecanoric acid (n= 4).

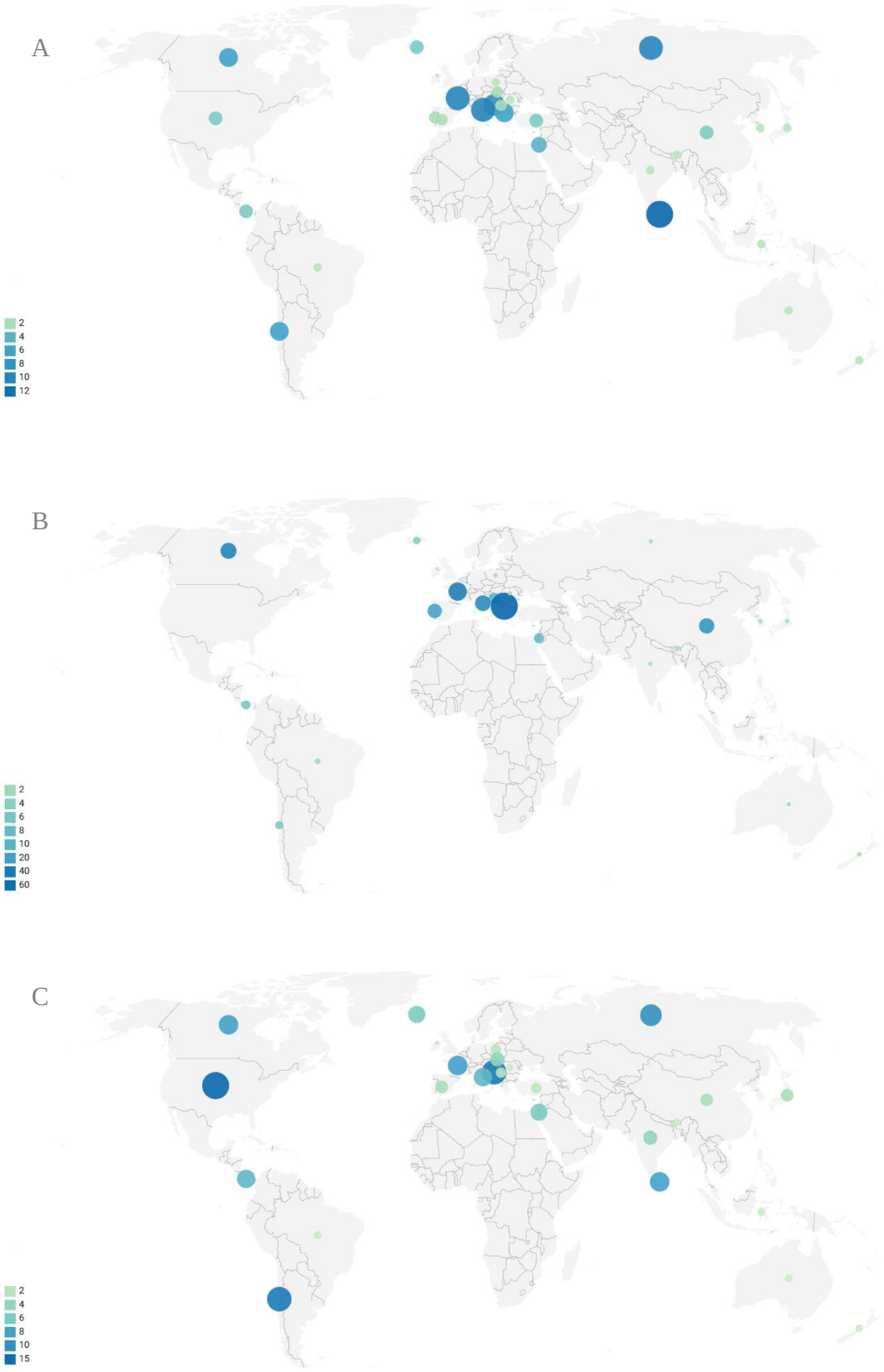

Figure 3. Geographical origin of the included research articles (A), mentioned lichen species (B), and lichen substances (C).


A
B
C
D
E
F
G
H

Figure 4. Most cited lichen species in the included research articles. (A) *Evernia prunastri*, (B) *Cetraria islandica*, (C) *Hypogymnia physodes*, (D) *Cladonia furcata*, (E) *Stereocaulon alpinum*, *Gyrophora esculenta* (no image available), (F) *Parmelia caperata*, (G) *Thamnolia vermicularis*, (H) *Lasallia pustulata*, (I) *Parmelia sulcata*, (J) *Xanthoria paritina*.

Lichen substances have been tested against breast cancer (31% of the included research articles), colorectal cancer (22%), leukaemia (18%), lung cancer (16%), melanoma (13%), sarcoma (13%), cervical cancer (9%), brain cancer (8%), liver cancer (8%), prostate cancer (7%), pancreas cancer (4%), ovary cancer (4%), kidney cancer (4%), stomach cancer (4%), larynx cancer (2%), myeloma (2%), endometrial cancer (1%), oral cavity and pharynx cancer (1%), lymphoma (1%), bone and joint cancer (1%), head and neck cancer (1%), uterus cancer (1%), bladder cancer (1%), vulvar cancer (1%) and mastocytoma (1%) cell lines (Table 1).

Table 1. Number of research articles testing anticancer effects of isolated lichen substances or lichen extracts per type of cancer based on organ location.

Substance	bladder	bone and joint	brain	breast	cervical	colon and rectum	endometrial	head and neck	Kidney	larynx	leukemia	liver	lung	lymphoma	mastocytoma	melanoma	myeloma	oral cavity and pharynx	ovary	pancreas	prostate	sarcoma	stomach	uterus	vulvar	Number of research articles
usnic acid		1	2	5	4	5					3	2	4			4			1		1	1	1			17
(+)-usnic acid			2	4		2	1				2	1	3						1	1		1	1		1	14
atranorin		1	1	2	1	4					2		1			5			2		1					13
glucan																						9				10
(-)-usnic acid			2	3					1		3	1	5							1	1					8
protolichesterinic acid				4	2	2			1		3		2						1	1	2		1			8
diffractaic acid			1	1	1	1										1					1					7
lobaric acid			1	3	2	3					2		1			1			1	1	1		1			7
physodic acid	1		1	1	1	3					1					2				1						7
vulpinic acid				1	1	1			1			2										2			1	6
salazinic acid			1	1		3										1						1			1	5

Substance	bladder	bone and joint	brain	breast	cervical	colon and rectum	endometrial	head and neck	Kidney	larynx	leukemia	liver	lung	lymphoma	mastocytoma	melanoma	myeloma	oral cavity and pharynx	ovary	pancreas	prostate	sarcoma	stomach	uterus	vulvar	Number of research articles
evernic acid						1										1						1			1	4
glucan derivative																						3				4
gyrophoric acid				1	1	2					1					1			2			1			1	4
lecanoric acid				1	1	1			1	1	1					1										4
lichenin											1											3				4
polysaccharide					1						1											3				4
norstictic acid				1		1										2										3
parietin				2	1	2					1								2							3
polyporic acid derivative											3															3
protocetraric acid						1										2										3
baeomycesic acid				1		1					1		1							1	1	2		1		2
barbatic acid										1			1					1					1			2
divaricatic acid																1					1					2
ethyl orsellinate				1					1	1						1					1					2
everninic acid				1		1															1					2
fumarprotocetraric acid			1	1		1					1		1			1					1					2
lichesterinic acid						1							1								1		1			2
lichexanthone			1	1		1										1										2
lobarstin			1		1	1																				2
methyl orsellinate				2		1			1	1						1				1						2
olivetoric acid			1																							2
pannarin																1					1					2
polyporic acid				1							2											1				2
psoromic acid			1													1										2
ramalin				1		1																				2
rangiformic acid											1															2
sphaerophorin																1					1					2
squamatic acid						1															1					2
stictic acid				1		1					1															2
usnic acid derivative			1	1							2		2													2
variolaric acid	1			1	1	2					1															2
vicanicin				1	1	1															1					2
(+)-D-montagnetol				1								1	1													1
(+)-protolichesterinic acid																	1			1						1
(+)-usnic acid analogue				1																						1
16-O-acetyl-leucotylic acid											1															1
3-hydroxy physodic acid					1																					1
6-methyl praesorediosate A				1	1								1													1
6-methyl vinapraesorediosate A				1	1								1													1
9'-(O-methyl)protocetratic acid			1	1							1		1								1					1
ambewelamide A											1															1
barbatolic acid				1																						1
caperatic acid						1																				1
catechin				1									1													1
D-(+)-erythrin				1	1								1													1
epiphorellic acid-1																					1					1
hydrofurylmontagnetol				1	1								1													1
isolichenin																						1				1
isopropyl orsellinate				1					1	1						1										1
leucotylic acid											1															1
lobarin																1										1
methyl-β-orcinol carboxylate																1										1
n-butyl orsellinate				1					1	1						1										1
norlichexanthone			1	1		1																				1
norlichexanthone derivative			1	1		1																				1
norlobaridone	1					1					1									1						1
n-pentyl orsellinate				1					1	1						1										1
n-propyl orsellinate				1					1	1						1										1
orcinol					1						1															1
orsellinic acid methyl ester					1						1															1
orsellinylmontagnetol A				1									1													1
orsellinylmontagnetol C												1	1													1
parmoether A												1	1													1
parmoether B				1								1	1													1
parmosidone A				1								1	1													1
parmosidone C				1								1	1													1
parmosidone D													1													1
perlatolic acid																1										1
physciosporin													1													1
physodalic acid					1																					1
praesorediosic acid				1	1								1													1
purpurin				1									1													1
pygmeine																1										1

Substance	bladder	bone and joint	brain	breast	cervical	colon and rectum	endometrial	head and neck	Kidney	larynx	leukemia	liver	lung	lymphoma	mastocytoma	melanoma	myeloma	oral cavity and pharynx	ovary	pancreas	prostate	sarcoma	stomach	uterus	vulvar	Number of research articles
pygmeine derivative																1										1
reserpin				1									1													1
roccellic acid				1		1																				1
salazinic acid derivative			1	1		1																				1
scabrosin acetate butyrate				1											1											1
scabrosin diacetate															1											1
scabrosin dibutyrate				1																						1
scabrosin ester														1												1
sec-butyl orsellinate				1					1	1						1										1
stereocalpin A						1						1				1										1
stictamide A			1																							1
tannic acid				1									1													1
tenuiorin				1		1														1						1
tert-butyl orsellinate				1					1	1						1										1
thamnoliadepside A																					1					1
thamnoliadepside B																					1					1
thamnolic acid A																					1					1
tumidulin						1																				1
usnolic acid											1															1
UTP-1				1	1	1						1				1							1			1
UTP-2				1	1	1						1				1							1			1
vermicularin																					1					1
vinapraesorediosic acid A				1	1								1													1
vinapraesorediosic acid B				1	1								1													1
vinapraesorediosic acid C				1	1								1													1
β-orcinol																					1					1
β-resorcylic acid																					1					1
ω-aminoalkoxylxanthone derivative				1		1			1							1			1							1
ω-bromoalkoxylxanthone derivative				1		1			1							1			1							1
extract (substance not specified)			4	17	3	14	1	1	1	2	8	3	10	1		9	2	2	1		5	4	3	1		51

About 77% of the included studies are based on *in vitro* assays (Table 2) addressing cell viability/proliferation or cytotoxicity (92%), apoptosis (44%), gene and protein expression (16%), cell migration and invasion (12%), autophagy (4%), angiogenesis (4%) and cellular senescence (3%). A good number of studies (12%) address oxidative stress induced by lichen substances since oxidative stress is known to activate inflammatory pathways leading to transformation of normal cells into tumour cells, and influence tumour cell survival, proliferation, resistance to anticancer therapies, invasion and angiogenesis. Antioxidant activity of lichen substances is also addressed in 13% of the included studies (data not shown) as it is well documented that antioxidants help reducing the risk of cancer development by means of chemically induced apoptosis (White *et al.*, 2014). *In vivo* assays are used in 23% of the included research articles, achieved by injection of tumour-bearing mice with lichen substances and measurement of variation in tumour volume or weight, after a certain period of time.

Methylthiazolyldiphenyl-tetrazolium bromide (MTT) assay, Propidium Iodine (PI) assay and Trypan Blue Dye assay are among the most common assays used for the determination of cell viability. Apoptosis is more commonly addressed by the detection

of the expression of apoptosis-related genes and proteins through western blotting, followed by the caspase activity assay and Annexin-V staining assays. Cell migration and cell invasion processes were mainly assessed by Boyden chamber/transwell migration assays and scratch/wound-healing assays, respectively.

Lichen substances, either isolated or in extracts, have been found to act on the three classical forms of cell death (Chen *et al.*, 2018): apoptosis, autophagy and necrosis - often with low cytotoxicity to normal cells (78% of the tested cases). The general mechanisms of anticancer activity of isolated lichen substances and lichen extracts are summarized in Tables 3-4. The following sections will detail current knowledge about the anticancer activity of the most promising and frequently reported lichen substances.

Table 2. In vitro assays and techniques used in the included research articles for detection of anticancer activity of lichen substances or lichen extracts, following Ediriweera *et al.* (2019), with adaptations.

Angiogenesis	**Apoptosis**	**Autophagy**	**Cell migration/invasion**	**Cell viability/proliferation**	**Cellular senescence**	**Gene/protein expression**	**Oxidative stress**
CAM assay	**Light microscopy**	**Fluorescence microscopy**	**BME (Basement Membrane Chamber) invasion assay**	**Based on cellular enzymes and proteins**	TRAP assay	**Immunoassays**	**Enzymes**
Tube formation assay	**Confocal microscopy**	Muse autophagy LC3-antibody assay	**Boyden chamber/transwell migration assay**	Acid phosphatase assay		immunocytochemistry assay	CAT activity
	Acridine orange staining	Lysotracker assay	**Invasion assay**	Arachidonic acid release		p53/p21 induction	Thioredoxin reductase inhibition assay
	Fluorescence microscopy	**Detection of the expression of autophagy related genes and proteins**	**Scratch/wound-healing assay**	ATP assay		Plk1 enzyme assay	**Markers**
	Acridine orange/EB staining assay	Immunocytochemistry assay	**Spheroid-based migration assay**	ATPase activity assay		ser15 phosphorylation	8-OH-dG assay
	Annexin-V/FITC staining assay	Reporter assay	**Detection of the expression of migration/invasion related genes and proteins**	CCK-8 assay		AIF translocation	GSH levels
	DAPI staining assay	Western blotting	Western blotting	Cytochrome P450 activity assay		**qPCR**	LPO levels
	FITC assay		**Real-time cell monitoring of cell proliferation and imaging**	DNA ligase adenylation assay		**Reporter assay**	RNS production assay
	FRAP assay			DNA ligase ligation		**UPLC-MS/MS**	ROS production assay
	Hoechst dye staining assay			GTPases precipitation		**Western blotting**	TOS assay
	PI assay			LDH leakage assay			DCF assay
	Electron microscopy			MTS assay			
	Coulter counter			MTT assay			
	Flow cytometry			Resazurin assay			
	Acridine orange staining			SRB assay			
	Annexin-V staining assay			Taurine release			
	Annexin-V/7-AAD staining assay			WST assay			
	Annexin-V/FITC staining assay			**Based on DNA synthesis**			
	Annexin-V/FITC/PI staining assay			BrdU assay			
	Annexin-V/PI double staining assay			Mitotic index assay			
	PI assay			PCNA assay			
	Cell death detection ELISA			PI assay			

Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
	acridine orange staining			PicoGreen dsDNA quantitation assay			
	DNA fragmentation and damage			Thymidine incorporation assay			
	COMET assay			**Colony formation assay**			
	TUNEL assay			**Dye exclusion assays**			
	Electroforesis			Crystal violet assay			
	Mitochondial membrane potential			NRU assay			
	rhodamine 123 dye assay (plate reader)			Trypan blue assay			
	mitochondrial membrane potential assay			**Coulter counter**			
	DiOC6 assay (flow cytometry)			**Flow cytometry**			
	JC-1 assay (fluorescence microscopy)			**Fluorescence microscopy**			
	Detection of caspases			Cytoskeletal immunofluorescence			
	caspase activity assay			Cytoskeleton staining			
	M30 assay			**Real-time cell monitoring of cell proliferation and imaging**			

Table 3. Summary of the general mechanisms associated with anticancer activity of lichen extracts mentioned in the included research articles.

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Alectoria nigricans					Ingolfsdottir *et al.* (2000) Nguyen *et al.* (2014)			
Alectoria ochroleuca				Yang *et al.* (2016)	Einarsdottir *et al.* (2010) Ingolfsdottir *et al.* (2000)			
Alectoria sarmentosa				Yang *et al.* (2016)	Nguyen *et al.* (2014) Shrestha *et al.* (2015)			
Alectoria sulcata		Yamamoto *et al.* (1995)						
Anaptychia runcinata					Ingolfsdottir *et al.* (2000)			
Arthrorhaphis alpina					Perry *et al.* (1999)			
Asahinea chrysantha		Yamamoto *et al.* (1995)						
Bacidia stipata		Cardile *et al.* (2017) Russo *et al.* (2012)			Cardile *et al.* (2017) Russo *et al.* (2012)			Cardile *et al.* (2017)
Baeomyces placophyllus		Yamamoto *et al.* (1995)						
Bryoria capillaris	Varol (2018)			Varol (2018) Yang *et al.* (2016)	Nguyen *et al.* (2014) Varol (2018)			
Bryoria fuscescens					Shrestha *et al.* (2015)			
Bulbothrix setschwanensis		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016)			
Bunodophoron insigne					Perry *et al.* (1999)			
Bunodophoron ramuliferum					Perry *et al.* (1999)			
Caloplaca scopularis		Yamamoto *et al.* (1995)						
Cetraria aculeata					Ingolfsdottir *et al.* (2000) Zeytinoglu *et al.* (2008)			
Cetraria ericetorum					Nguyen *et al.* (2014)			
Cetraria islandica		Bessadóttir *et al.* (2015) Thorsteinsdottir *et al.* (2016) Yamamoto *et al.* (1995)			Bessadóttir *et al.* (2014) Haraldsdóttir *et al.* (2004) Ingolfsdottir *et al.* (2000) Nguyen *et al.* (2014) Ogmundsdottir *et al.* (1998) Sangkook *et al.* (1996) Thorsteinsdottir *et al.* (2016)		Bessadóttir *et al.* (2014) Bessadóttir *et al.* (2015) Thorsteinsdottir *et al.* (2016)	
Cetraria ornata		Yamamoto *et al.* (1995)						
Cetrariella delisei					Ingolfsdottir *et al.* (2000)			
Cetrelia japonica		Yamamoto *et al.* (1995)						

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Chondropsis semiviridis					Perry *et al.* (1999)			
Cladia aggregata		Yamamoto *et al.* (1995)			Martins *et al.* (2016) Perry *et al.* (1999)			
Cladia retipora					Perry *et al.* (1999)			
Cladia sullivanii					Perry *et al.* (1999)			
Cladina confusa					Brandão *et al.* (2013) Perry *et al.* (1999)			
Cladina dendroides					Nascimento *et al.* (1994)			
Cladina mitis					Perry *et al.* (1999)			
Cladonia amaurocraea		Yamamoto *et al.* (1995)						
Cladonia arbuscula		Bessadottir *et al.* (2012) Einarsdottir *et al.* (2010) Galanty *et al.* (2017)	Bessadottir *et al.* (2012)	Galanty *et al.* (2017)	Bessadottir *et al.* (2012) Einarsdottir *et al.* (2010) Galanty *et al.* (2017)			
Cladonia coniocraea					Delebassée *et al.* (2017)			
Cladonia convoluta		Bézivin *et al.* (2004) Coskun *et al.* (2015)			Açıkgöz *et al.* (2014) Bézivin *et al.* (2003) Bézivin *et al.* (2004) Coskun *et al.* (2015)			
Cladonia crispatula					Nascimento *et al.* (1994)			
Cladonia cristatella		Yamamoto *et al.* (1995)						
Cladonia ecmocyna					Ingolfsdottir *et al.* (2000)			
Cladonia fimbriata					Perry *et al.* (1999)			
Cladonia foliacea	Koparal *et al.* (2015)	Mitrovic *et al.* (2011)			Koparal *et al.* (2006) Koparal *et al.* (2015) Mitrovic *et al.* (2011)			
Cladonia furcata		Lin *et al.* (2001) Lin *et al.* (2003) Yamamoto *et al.* (1995)			Ingolfsdottir *et al.* (2000) Kosanić *et al.* (2014) Lin *et al.* (2001) Lin *et al.* (2003) Ranković *et al.* (2011) Shrestha *et al.* (2015)	Lin *et al.* (2003)		
Cladonia glauca					Delebassée *et al.* (2017)			
Cladonia gracilis					Ingolfsdottir *et al.* (2000)			
Cladonia gracilis tenerrima					Perry *et al.* (1999)			
Cladonia gracilis var. dilatata		Yamamoto *et al.* (1995)						
Cladonia lepidophora					Brisdelli *et al.* (2013)			Brisdelli *et al.* (2013)

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Cladonia macrophylla					Nguyen *et al.* (2014)			
Cladonia mitis					Nguyen *et al.* (2014)			
Cladonia nigripes		Yamamoto *et al.* (1995)						
Cladonia parasitica					Delebassée *et al.* (2017)			
Cladonia pleurota		Yamamoto *et al.* (1995)						
Cladonia pocillum		Ersoz *et al.* (2017)			Ersoz *et al.* (2017)			Ersoz *et al.* (2017)
Cladonia pyxidata					Kosanić *et al.* (2014)			
Cladonia rangiferina		Yamamoto *et al.* (1995)			Ingolfsdottir *et al.* (2000) Kosanić *et al.* (2014)			
Cladonia rangiformis		Coskun *et al.* (2015)			Açıkgöz *et al.* (2014) Bézivin *et al.* (2003) Coskun *et al.* (2015) Delebassée *et al.* (2017)			
Cladonia squamosa					Delebassée *et al.* (2017)			
Cladonia stricta					Ingolfsdottir *et al.* (2000)			
Cladonia substellata					Nascimento *et al.* (1994)			
Cladonia uncialis		Paluszczak *et al.* (2018)			Paluszczak *et al.* (2018)		Paluszczak *et al.* (2018)	
Cladonia vulcani		Yamamoto *et al.* (1995)						
Coccocarpia palmicola					Perry *et al.* (1999)			
Coeleocaulon aculeatum					Perry *et al.* (1999)			
Coenogonium implexum					Perry *et al.* (1999)			
Collema flaccidum					Řezanka *et al.* (2006)			
Cornicularia aculeata		Brisdelli *et al.* (2013) Brisdelli *et al.* (2016)			Brisdelli *et al.* (2013) Brisdelli *et al.* (2016)			Brisdelli *et al.* (2013)
Cornicularia epiphorella		Russo *et al.* (2006)			Russo *et al.* (2006)			Russo *et al.* (2006)
Dirinaria aspera					Brandão *et al.* (2013)			
Evernia divaricata				Yang *et al.* (2016)	Nguyen *et al.* (2014)			
Evernia prunastri		Mitrovic *et al.* (2011) Yamamoto *et al.* (1995)			Bézivin *et al.* (2003) Burlando *et al.* (2009) Delebassée *et al.* (2017) Kosanić *et al.* (2013) Mitrovic *et al.* (2011) Shrestha *et al.* (2015) Triggiani *et al.* (2009)			

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Everniastrum catawbiense					Shrestha *et al.* (2015)			
Everniastrum vexans				Zhou *et al.* (2017)	Zhou *et al.* (2017)		Zhou *et al.* (2017)	
Everniopsis trulla							Yang *et al.* (2018)	
Flavocetraria cucullata		Nguyen *et al.* (2014)		Nguyen *et al.* (2014)	Nguyen *et al.* (2014)		Nguyen *et al.* (2014)	
Flavocetraria nivalis				Yang *et al.* (2016)	Ingolfsdottir *et al.* (2000) Nguyen *et al.* (2014)			
Flavoparmelia caperata		Fernandez-Moriano *et al.* (2016) Mitrovic *et al.* (2011)		Yang *et al.* (2015)	Fernandez-Moriano *et al.* (2016) Mitrovic *et al.* (2011)			
Flavoparmelia euplecta		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016)			
Flavoparmelia haysomii		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016)			
Fuscoderma applanatum					Perry *et al.* (1999)			
Gymnoderma coccocarpum		Yamamoto *et al.* (1995)						
Hypocenomyce scalaris		Paluszczak *et al.* (2018)			Paluszczak *et al.* (2018)		Paluszczak *et al.* (2018)	
Hypogymnia lugubris		Cardile *et al.* (2017)			Cardile *et al.* (2017) Perry *et al.* (1999)			Cardile *et al.* (2017)
Hypogymnia physodes		Ari *et al.* (2014) Mitrovic *et al.* (2011) Paluszczak *et al.* (2018) Studzinska-Sroka *et al.* (2016) Yamamoto *et al.* (1995)		Paluszczak *et al.* (2018) Yang *et al.* (2016)	Ari *et al.* (2014) Mitrovic *et al.* (2011) Nguyen *et al.* (2014) Paluszczak *et al.* (2018) Stojanovic *et al.* (2014) Studzinska-Sroka *et al.* (2016)		Paluszczak *et al.* (2018)	
Hypotrachyna cirrhata		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016)			
Hypotrachyna sinuosa				Yang *et al.* (2015)				
Lasallia pustulata					Burlando *et al.* (2009) Delebassée *et al.* (2017)			
Lecanora atra					Ranković *et al.* (2011)			
Lecanora epibryon* subsp. *broccha					Perry *et al.* (1999)			
Lecanora muralis					Ranković *et al.* (2011)			
Leifidium tenerum					Perry *et al.* (1999)			
Leprocaulon microscopicum					Delebassée *et al.* (2017)			
Leproloma membranaceum					Delebassée *et al.* (2017)			
Leptogium cyanescens					Perry *et al.* (1999)			
Letharia vulpina	Koparal *et al.* (2015)	Yamamoto *et al.* (1995)			Burlando *et al.* (2009) Koparal *et al.* (2015) Shrestha *et al.* (2015)			

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Lethariella canariensis		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016)			
Lethariella zahlbruckneri		Lee *et al.* (2012) Ren *et al.* (2009)			Lee *et al.* (2012) Ren *et al.* (2009)		Lee *et al.* (2012) Ren *et al.* (2009)	
Lichina pygmaea					Roullier *et al.* (2010)			
Lobaria pulmonaria					Delebassée *et al.* (2017) Pejin *et al.* (2017) Shrestha *et al.* (2015)			
Melanelia hepatizon					Ingolfsdottir *et al.* (2000)			
Micarea austroternaria					Perry *et al.* (1999)			
Myelochroa aurulenta					Tokiwano *et al.* (2009)			
Myelochroa irrugans		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016)			
***Neocatapyrenium* sp.**							Yang *et al.* (2018)	
Nephroma australe					Perry *et al.* (1999)			
Nephroma expallidum					Ingolfsdottir *et al.* (2000)			
Nephroma laevigatum					Delebassée *et al.* (2017)			
Nephroma parile					Delebassée *et al.* (2017)			
Nephroma plumbeum* var. *isidiatum					Perry *et al.* (1999)			
***Nephroma* sp.**				Yang *et al.* (2015)				
Neuropogon acromelanus					Perry *et al.* (1999)			
***Niebla* sp.**				Yang *et al.* (2018)	Yang *et al.* (2018)		Yang *et al.* (2018)	
Ochrolechia deceptionis		Cardile *et al.* (2017)			Brisdelli *et al.* (2013) Cardile *et al.* (2017)			Brisdelli *et al.* (2013) Cardile *et al.* (2017)
Pannaria hookeri					Perry *et al.* (1999)			
Parmelia caperata					Bézivin *et al.* (2003) Kosanić *et al.* (2012) Manojlovic *et al.* (2012)			
Parmelia omphalodes		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016) Ingolfsdottir *et al.* (2000)			
Parmelia perlata					Bézivin *et al.* (2003)			
Parmelia saxatilis					Delebassée *et al.* (2017) Ingolfsdottir *et al.* (2000) Kosanić *et al.* (2012) Manojlovic *et al.* (2012)			
Parmelia signifera					Perry *et al.* (1999)			

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Parmelia subrudecta					Ivanova *et al.* (2010)			
Parmelia sulcata		Ari *et al.* (2014) Ari *et al.* (2015) Mitrovic *et al.* (2011) Paluszczak *et al.* (2018)			Ari *et al.* (2014) Ari *et al.* (2015) Kosanić *et al.* (2012) Mitrovic *et al.* (2011) Paluszczak *et al.* (2018)		Paluszczak *et al.* (2018)	
Parmelia tenuirima					Perry *et al.* (1999)			
Parmotrema dilatatum					Brandão *et al.* (2013)			
Parmotrema lichexanthonicum					Brandão *et al.* (2013) Micheletti *et al.* (2009)			
Parmotrema praesorediosum					Huynh *et al.* (2016)			
Parmotrema reticulatum		Ghate *et al.* (2013)			Ghate *et al.* (2013) Shrestha *et al.* (2015)			
***Parmotrema* sp.**							Williams *et al.* (2011)	
Parmotrema tinctorum					Bogo *et al.* (2010)			
Parmotrema tsavoense					Duong *et al.* (2015)			
Peltigera aphtosa					Shrestha *et al.* (2015)			
Peltigera canina					Ingolfsdottir *et al.* (2000) Munzi *et al.* (2014)			
Peltigera degenii					Perry *et al.* (1999)			
Peltigera dolichorhiza					Perry *et al.* (1999)			
Peltigera elisabethae					Munzi *et al.* (2014)			
Peltigera horizontalis					Delebassée *et al.* (2017)			
Peltigera leucophlebia					Ingolfsdottir *et al.* (2000) Ingolfsdottir *et al.* (2002)			
Peltigera membranacea					Perry *et al.* (1999)			
Peltigera praetextata					Munzi *et al.* (2014)			
Peltigera venosa					Nguyen *et al.* (2014)			
Pertusaria oculata					Ingolfsdottir *et al.* (2000)			
***Physcia* sp.**				Yang *et al.* (2015)				
Placopsis contortuplicata		Cardile *et al.* (2017)			Cardile *et al.* (2017)			Cardile *et al.* (2017)
Placopsis trachyderma					Perry *et al.* (1999)			

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Platismatia glauca		Paluszczak *et al.* (2018)		Paluszczak *et al.* (2018)	Bézivin *et al.* (2003) Delebassée *et al.* (2017) Nguyen *et al.* (2014) Paluszczak *et al.* (2018)		Paluszczak *et al.* (2018)	
Pleurosticta acetabulum		Delebassée *et al.* (2017)			Delebassée *et al.* (2017)			
Protousnea magellanica		Russo *et al.* (2012)			Brisdelli *et al.* (2013) Russo *et al.* (2012)			Brisdelli *et al.* (2013)
Protousnea malacea		Russo *et al.* (2012)			Russo *et al.* (2012)			
***Protousnea* sp.**				Yang *et al.* (2015)				
Pseudevernia furfuracea		Yamamoto *et al.* (1995)			Emsen *et al.* (2016) Kosanic *et al.* (2013) Nguyen *et al.* (2014)			Emsen *et al.* (2016)
Pseudevernia furfuracea* var. *ceratea	Koparal *et al.* (2010)				Koparal *et al.* (2010)			
Pseudocyphellaria ardesiaca					Perry *et al.* (1999)			
Pseudocyphellaria argyracea				Yang *et al.* (2015)				
Pseudocyphellaria billardierei					Perry *et al.* (1999)			
Pseudocyphellaria carpoloma					Perry *et al.* (1999)			
Pseudocyphellaria cinnamomea					Perry *et al.* (1999)			
Pseudocyphellaria colensoi					Perry *et al.* (1999)			
Pseudocyphellaria coriacea				Yang *et al.* (2015)	Perry *et al.* (1999) Yang *et al.* (2015)		Yang *et al.* (2015)	
Pseudocyphellaria coronata					Perry *et al.* (1999)			
Pseudocyphellaria degelii					Perry *et al.* (1999)			
Pseudocyphellaria dissimilis					Perry *et al.* (1999)			
Pseudocyphellaria faveolata					Perry *et al.* (1999)			
Pseudocyphellaria fimbriatoides					Perry *et al.* (1999)			
Pseudocyphellaria glabra				Yang *et al.* (2015)	Perry *et al.* (1999)			
Pseudocyphellaria granulata					Perry *et al.* (1999)			
Pseudocyphellaria homoeophylla					Perry *et al.* (1999)			
Pseudocyphellaria maculata					Perry *et al.* (1999)			
Pseudocyphellaria multifida					Perry *et al.* (1999)			
Pseudocyphellaria murrayi					Perry *et al.* (1999)			

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Pseudocyphellaria pickeringii					Perry *et al.* (1999)			
Pseudocyphellaria rubella					Perry *et al.* (1999)			
Pseudocyphellaria rufovirescens					Perry *et al.* (1999)			
Pseudocyphellaria verrucosa				Yang *et al.* (2015)				
Psoroma buchananii					Perry *et al.* (1999)			
Psoroma dimorphum		Russo *et al.* (2012)			Russo *et al.* (2012)			Russo *et al.* (2012)
Psoroma hirsutulum					Perry *et al.* (1999)			
Psoroma leprolomum					Perry *et al.* (1999)			
Psoroma microphyllizans					Perry *et al.* (1999)			
Psoroma pallidum					Brisdelli *et al.* (2013) Perry *et al.* (1999)			
***Psoroma* spp.**		Russo *et al.* (2006) Russo *et al.* (2008)			Russo *et al.* (2006) Russo *et al.* (2008)			Russo *et al.* (2006) Russo *et al.* (2008)
Ramalina celastri		Leão *et al.* (1997)						
Ramalina cuspidata					Bézivin *et al.* (2003)			
Ramalina farinacea					Koparal *et al.* (2006)			
Ramalina menziesii					Shrestha *et al.* (2015)			
***Ramalina* sp.**				Zhou *et al.* (2017)	Brandão *et al.* (2013)		Yang *et al.* (2018)	
Ramalina terebrata		Lee *et al.* (2016) Suh *et al.* (2017)	Lee *et al.* (2016)	Suh *et al.* (2017)	Lee *et al.* (2016) Suh *et al.* (2017)		Suh *et al.* (2017)	
Rhizoplaca chrysoleuca				Zhou *et al.* (2017)	Shrestha *et al.* (2015)			
Rhizoplaca melanophthalma		Russo *et al.* (2012)		Yang *et al.* (2015)	Emsen *et al.* (2016) Russo *et al.* (2012)			Emsen *et al.* (2016) Russo *et al.* (2012)
Rhizoplaca peltata					Shrestha *et al.* (2015)			
Roccella montagnei					Duong *et al.* (2017) Mishra *et al.* (2017)			
***Roccella* sp.**							Yang *et al.* (2018)	
Siphula dissoluta					Perry *et al.* (1999)			
Solorina crocea		Yamamoto *et al.* (1995)			Ingolfsdottir *et al.* (2000)			
Sphaerophorus fragilis					Ingolfsdottir *et al.* (2000)			

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Sphaerophorus globosus		Russo *et al.* (2006) Russo *et al.* (2008)			Ingolfsdottir *et al.* (2000) Russo *et al.* (2006) Russo *et al.* (2008)			Russo *et al.* (2006) Russo *et al.* (2008)
Sphaerophorus stereocauloides					Perry *et al.* (1999)			
Stereocaulon alpinum		Hong *et al.* (2018)			Brisdelli *et al.* (2013) Haraldsdóttir *et al.* (2004) Hong *et al.* (2018) Ingolfsdottir *et al.* (2000) Nguyen *et al.* (2014) Ogmundsdottir *et al.* (1998)			Brisdelli *et al.* (2013)
Stereocaulon arcticum					Ingolfsdottir *et al.* (2000)			
Stereocaulon fronduliferum					Perry *et al.* (1999)			
Stereocaulon halei					Ismed *et al.* (2012)			
Stereocaulon intermedium		Yamamoto *et al.* (1995)						
Stereocaulon ramulosum					Perry *et al.* (1999)			
Stereocaulon spathuliferum					Ingolfsdottir *et al.* (2000)			
Sticta filix					Perry *et al.* (1999)			
Sticta latifrons					Perry *et al.* (1999)			
Sticta martinii					Perry *et al.* (1999)			
***Sticta* sp.**				Liang *et al.* (2011)	Liang *et al.* (2011)			
Teloschistes fasciculatus					Perry *et al.* (1999)			
Thamnolia subliformis		Yamamoto *et al.* (1995)						
Thamnolia vermicularis				Zhou *et al.* (2017)	Guo *et al.* (2011) Manojlović *et al.* (2010) Nguyen *et al.* (2014) Perry *et al.* (1999)			
Thamnolia vermicularis* var. *subuliformis					Haraldsdóttir *et al.* (2004)			
Toninia candida					Ranković *et al.* (2012)			
Trapeliopsis congregans					Perry *et al.* (1999)			
Tuckermannopsis ciliaris		Shrestha *et al.* (2015)			Shrestha *et al.* (2015)		Shrestha *et al.* (2015)	
Umbilicaria arctica					Ingolfsdottir *et al.* (2000)			
Umbilicaria crustulosa					Kosanić *et al.* (2012)			
Umbilicaria cylindrica					Kosanić *et al.* (2012) Perry *et al.* (1999)			

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
Umbilicaria esculenta		Sun *et al.* (2018)			Sun *et al.* (2018) Xu *et al.* (2014)	Xu *et al.* (2014)		Sun *et al.* (2018)
Umbilicaria hirsuta		Bačkorová *et al.* (2011) Bačkorová *et al.* (2012)			Bačkorová *et al.* (2011)			Bačkorová *et al.* (2012)
Umbilicaria kisovana		Yamamoto *et al.* (1995)						
Umbilicaria mammulata					Shrestha *et al.* (2015)			
Umbilicaria polyphylla					Kosanić *et al.* (2012)			
Umbilicaria proboscidea					Ingolfsdottir *et al.* (2000)			
Umbilicaria tornata					Shang *et al.* (2018)			
Usnea aurantiacoatra		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016)			
Usnea barbata		Zugic *et al.* (2016)			Ranković *et al.* (2012) Zugic *et al.* (2016)			
Usnea capillacea					Perry *et al.* (1999)			
Usnea* cf. *inermis					Perry *et al.* (1999)			
Usnea ciliifera					Perry *et al.* (1999)			
Usnea contexta		Fernandez-Moriano *et al.* (2016)			Fernandez-Moriano *et al.* (2016)			
Usnea diffracta					Dincsoy & Duman (2017)			
Usnea fasciata					Periera (1994)			
Usnea filipendula		Ari *et al.* (2014)			Ari *et al.* (2014)			
Usnea florida				Yang *et al.* (2016)	Nguyen *et al.* (2014)			
Usnea longissima		Yamamoto *et al.* (1995)						
Usnea rubicunda					Bézivin *et al.* (2003)			
***Usnea* sp.**					Brandão *et al.* (2013)			
Usnea strigosa				Ebrahim *et al.* (2016)	Ebrahim *et al.* (2016) Shrestha *et al.* (2015)		Ebrahim *et al.* (2016)	
Usnea subcavata					Brandão *et al.* (2013)			
Vulpicida canadensis					Shrestha *et al.* (2015)			
Xanthoparmelia chlorochroa		Shrestha *et al.* (2015)			Shrestha *et al.* (2015)		Shrestha *et al.* (2015)	
Xanthoparmelia scabrosa		Moerman *et al.* (2003)			Ernst-Russell *et al.* (1999) Moerman *et al.* (2003)			
Xanthoparmelia somloensis				Zhou *et al.* (2017)	Burlando *et al.* (2009)			

Lichen	Angiogenesis	Apoptosis	Autophagy	Cell migration/invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
***Xanthoparmelia* sp.**				Yang *et al.* (2015)				
Xanthoria elegans					Ingolfsdottir *et al.* (2000)			
Xanthoria fallax		Yamamoto *et al.* (1995)						
Xanthoria parietina		Bačkorová *et al.* (2011) Bačkorová *et al.* (2012) Basile *et al.* (2015)			Bačkorová *et al.* (2011) Basile *et al.* (2015) Ingolfsdottir *et al.* (2000) Triggiani *et al.* (2009)			

Table 4. Summary of the general mechanisms associated with anticancer activity of lichen substances mentioned in the included research articles.

Substance	Angiogenesis	Apoptosis	Autophagy	Cell migration and invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
(-)-usnic acid	Koparal *et al.* (2015)	Bézivin *et al.* (2004) Takai *et al.* (1979) Yamamoto *et al.* (1995)			Bazin *et al.* (2008) Bézivin *et al.* (2004) Einarsdottir *et al.* (2010) Koparal *et al.* (2006) Koparal *et al.* (2015)			
(+)-protolichesterinic acid		Bessadóttir *et al.* (2015)			Bessadóttir *et al.* (2015)		Bessadóttir *et al.* (2015)	
(+)-usnic acid		Bazin *et al.* (2008) Bačkorová *et al.* (2012) Bessadottir *et al.* (2012) Einarsdottir *et al.* (2010) Geng *et al.* (2018) Sahu *et al.* (2012) Yamamoto *et al.* (1995)	Bessadottir *et al.* (2012) Ebrahim *et al.* (2017) Wu *et al.* (2018)	Ebrahim *et al.* (2017) Wu *et al.* (2018) Yang *et al.* (2016)	Bazin *et al.* (2008) Bessadottir *et al.* (2012) Burlando *et al.* (2009) Ebrahim *et al.* (2017) Einarsdottir *et al.* (2010) Emsen *et al.* (2018) Geng *et al.* (2018) Koparal *et al.* (2006) Sahu *et al.* (2012) Wu *et al.* (2018) Yang *et al.* (2016)		Sahu *et al.* (2012) Wu *et al.* (2018) Yang *et al.* (2016)	Bačkorová *et al.* (2012) Emsen *et al.* (2018) Sahu *et al.* (2012)
(+)-usnic acid analogue			Ebrahim *et al.* (2017)	Ebrahim *et al.* (2017)	Ebrahim *et al.* (2017)			
16-O-acetyl-leucotylic acid					Tokiwano *et al.* (2009)			
3-hydroxy physodic acid					Stojanovic *et al.* (2014)			
atranorin		Bačkorová *et al.* (2011) Bačkorová *et al.* (2012) Cardile *et al.* (2017) Galanty *et al.* (2017) Russo *et al.* (2012) Solar *et al.* (2016)		Galanty *et al.* (2017) Zhou *et al.* (2017)	Bačkorová *et al.* (2011) Brandão *et al.* (2013) Cardile *et al.* (2017) Galanty *et al.* (2017) Kosanić *et al.* (2014) Paluszczak *et al.* (2018) Russo *et al.* (2012) Solar *et al.* (2016) Zhou *et al.* (2017)		Paluszczak *et al.* (2018) Zhou *et al.* (2017)	Bačkorová *et al.* (2012) Cardile *et al.* (2017)

Substance	Angiogenesis	Apoptosis	Autophagy	Cell migration and invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
baeomycesic acid					Haraldsdóttir *et al.* (2004)			
barbatic acid					Martins *et al.* (2016)			
barbatolic acid	Varol (2018)			Varol (2018)	Varol (2018)			
caperatic acid		Paluszczak *et al.* (2018)		Paluszczak *et al.* (2018)	Paluszczak *et al.* (2018)		Paluszczak *et al.* (2018)	
catechin					Ghate *et al.* (2013)			
colleflaccinoside A					Řezanka *et al.* (2006)			
colleflaccinoside B					Řezanka *et al.* (2006)			
diffractaic acid		Russo *et al.* (2012)			Brandão *et al.* (2013) Brisdelli *et al.* (2013) Emsen *et al.* (2018) Russo *et al.* (2012)			Emsen *et al.* (2018) Ozgencli *et al.* (2018)
divaricatic acid		Russo *et al.* (2012)			Brandão *et al.* (2013) Russo *et al.* (2012)			
epiphorellic acid-1		Russo *et al.* (2006)			Russo *et al.* (2006)			Russo *et al.* (2006)
ethyl orsellinate					Bogo *et al.* (2010)			
evernic acid		Yamamoto *et al.* (1995)			Kosanic *et al.* (2013)			Ozgencli *et al.* (2018)
everninic acid					Mishra *et al.* (2017)			
fumarprotocetraric acid					Kosanić *et al.* (2014)			
glucan		Leão *et al.* (1997)						
glucan derivative		Leão *et al.* (1997)			Leão *et al.* (1997)			
gyrophoric acid		Bačkorová *et al.* (2011) Bačkorová *et al.* (2012) Cardile *et al.* (2017)			Bačkorová *et al.* (2011) Cardile *et al.* (2017)			Bačkorová *et al.* (2012) Cardile *et al.* (2017)
isopropyl orsellinate					Bogo *et al.* (2010)			
lecanoric acid					Bogo *et al.* (2010) Ivanova *et al.* (2010) Paluszczak *et al.* (2018)		Paluszczak *et al.* (2018)	Ozgencli *et al.* (2018)
leucotylic acid					Tokiwano *et al.* (2009)			
lichenin		Lin *et al.* (2003)			Lin *et al.* (2003)	Lin *et al.* (2003)		
lichesterinic acid		Yamamoto *et al.* (1995)						
lobaric acid		Hong *et al.* (2018)			Brisdelli *et al.* (2013) Emsen *et al.* (2018) Haraldsdóttir *et al.* (2004) Hong *et al.* (2018) Ogmundsdottir *et al.* (1998)			Emsen *et al.* (2018) Ozgencli *et al.* (2018)
lobarstin		Hong *et al.* (2018) Kim *et al.* (2013)			Hong *et al.* (2018) Kim *et al.* (2013)		Kim *et al.* (2013)	
methyl orsellinate					Bogo *et al.* (2010) Ingolfsdottir *et al.* (2002)			
n-butyl orsellinate					Bogo *et al.* (2010)			
norlichexanthone					Micheletti *et al.* (2009)			
norlichexanthone derivative					Micheletti *et al.* (2009)			

Substance	Angiogenesis	Apoptosis	Autophagy	Cell migration and invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
norlobaridone					Talapatra *et al.* (2016)			
norstictic acid				Ebrahim *et al.* (2016)	Brandão *et al.* (2013) Ebrahim *et al.* (2016) Ranković *et al.* (2012)		Ebrahim *et al.* (2016)	
n-pentyl orsellinate					Bogo *et al.* (2010)			
n-propyl orsellinate					Bogo *et al.* (2010)			
olivetoric acid	Koparal *et al.* (2010)				Emsen *et al.* (2016) Koparal *et al.* (2010)			Emsen *et al.* (2016)
orcinol					Ivanova *et al.* (2010)			
orsellinic acid methyl ester					Ivanova *et al.* (2010)			
orsellinylmontagnetol A					Duong *et al.* (2017)			
pannarin		Russo *et al.* (2006) Russo *et al.* (2008)			Russo *et al.* (2006) Russo *et al.* (2008)			Russo *et al.* (2006) Russo *et al.* (2008)
parietin		Bačkorová *et al.* (2012)			Bačkorová *et al.* (2011)			
parmoether A					Duong *et al.* (2015)			
parmoether B					Duong *et al.* (2015)			
parmosidone C					Duong *et al.* (2015)			
perlatolic acid					Brandão *et al.* (2013)			
physciosporin				Yang *et al.* (2015)	Yang *et al.* (2015)		Yang *et al.* (2015)	
physodalic acid					Stojanovic *et al.* (2014)			
physodic acid		Cardile *et al.* (2017) Paluszczak *et al.* (2018)			Cardile *et al.* (2017) Emsen *et al.* (2016) Kosanic *et al.* (2013) Paluszczak *et al.* (2018) Stojanovic *et al.* (2014) Studzinska-Sroka *et al.* (2016) Talapatra *et al.* (2016)		Paluszczak *et al.* (2018)	Cardile *et al.* (2017) Emsen *et al.* (2016)
protocetraric acid					Brandão *et al.* (2013) Manojlovic *et al.* (2012)			
protolichesterinic acid		Brisdelli *et al.* (2013) Russo *et al.* (2012) Thorsteinsdottir *et al.* (2016)			Bessadóttir *et al.* (2014) Brisdelli *et al.* (2013) Brisdelli *et al.* (2016) Haraldsdóttir *et al.* (2004) Ogmundsdottir *et al.* (1998) Russo *et al.* (2012) Sangkook *et al.* (1996) Thorsteinsdottir *et al.* (2016)		Bessadóttir *et al.* (2014)	Russo *et al.* (2012)
psoromic acid					Brandão *et al.* (2013) Emsen *et al.* (2016)			Emsen *et al.* (2016)
purpurin					Ghate *et al.* (2013)			
pygmeine					Roullier *et al.* (2010)			
pygmeine derivative					Roullier *et al.* (2010)			
ramalin		Lee *et al.* (2016) Suh *et al.* (2017)	Lee *et al.* (2016)	Suh *et al.* (2017)	Lee *et al.* (2016) Suh *et al.* (2017)		Suh *et al.* (2017)	

Substance	Angiogenesis	Apoptosis	Autophagy	Cell migration and invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
reserpin					Ghate *et al.* (2013)			
roccellic acid					Mishra *et al.* (2017)			
salazinic acid					Manojlovic *et al.* (2012) Paluszczak *et al.* (2018)			
salazinic acid derivative					Micheletti *et al.* (2009)			
scabrosin acetate butyrate					Ernst-Russell *et al.* (1999)			
scabrosin diacetate					Ernst-Russell *et al.* (1999)			
scabrosin dibutyrate					Ernst-Russell *et al.* (1999)			
scabrosin ester		Moerman *et al.* (2003)			Moerman *et al.* (2003)			
sec-butyl orsellinate					Bogo *et al.* (2010)			
sphaerophorin		Russo *et al.* (2006) Russo *et al.* (2008)			Russo *et al.* (2006) Russo *et al.* (2008)			Russo *et al.* (2006) Russo *et al.* (2008)
squamatic acid					Paluszczak *et al.* (2018)			
stictamide A				Liang *et al.* (2011)				
stictic acid					Pejin *et al.* (2017)			
tannic acid					Ghate *et al.* (2013)			
tert-butyl orsellinate					Bogo *et al.* (2010)			
thamnoliadepside A					Guo *et al.* (2011)			
thamnoliadepside B					Guo *et al.* (2011)			
tumidulin				Yang *et al.* (2018)	Yang *et al.* (2018)		Yang *et al.* (2018)	
usnic acid	Song *et al.* (2012)	Bačkorová *et al.* (2011) Galanty *et al.* (2017) Nguyen *et al.* (2014) Singh *et al.* (2013) Song *et al.* (2012) Yurdacan *et al.* (2018) Zugic *et al.* (2016) Zuo *et al.* (2015)	Yurdacan *et al.* (2018)	Galanty *et al.* (2017) Nguyen *et al.* (2014) Song *et al.* (2012)	Bačkorová *et al.* (2011) Brandão *et al.* (2013) Brisdelli *et al.* (2013) Dincsoy & Duman (2017) Galanty *et al.* (2017) Ivanova *et al.* (2010) Mayer *et al.* (2005) Nguyen *et al.* (2014) Perry *et al.* (1999) Ranković *et al.* (2012) Singh *et al.* (2013) Song *et al.* (2012) Yurdacan *et al.* (2018) Zugic *et al.* (2016) Zuo *et al.* (2015)		Dincsoy & Duman (2017) Mayer *et al.* (2005) Nguyen *et al.* (2014) Song *et al.* (2012)	Zugic *et al.* (2016) Zuo *et al.* (2015)
usnic acid derivative		Bazin *et al.* (2008) Takai *et al.* (1979)			Bazin *et al.* (2008)			
UTP-1					Shang *et al.* (2018)			
UTP-2					Shang *et al.* (2018)			
variolaric acid					Talapatra *et al.* (2016)			
vicanicin		Russo *et al.* (2012)			Brisdelli *et al.* (2013) Russo *et al.* (2012)			Russo *et al.* (2012)

Substance	Angiogenesis	Apoptosis	Autophagy	Cell migration and invasion	Cell viability/proliferation	Cellular senescence	Gene/protein expression	Oxidative stress
vinapraesorediosic acid A					Huynh *et al*. (2016)			
vulpinic acid	Koparal *et al*. (2015)	Kılıç *et al.* (2018)			Burlando *et al*. (2009) Kılıç *et al.* (2018) Koparal *et al*. (2015)		Kılıç *et al.* (2018)	Ozgencli *et al.* (2018)
β-alectoronic acid							Williams *et al*. (2011)	
β-collatolic acid							Williams *et al*. (2011)	
ω-aminoalkoxylxanthone derivative					Micheletti *et al.* (2011)			

3.1. Usnic acid

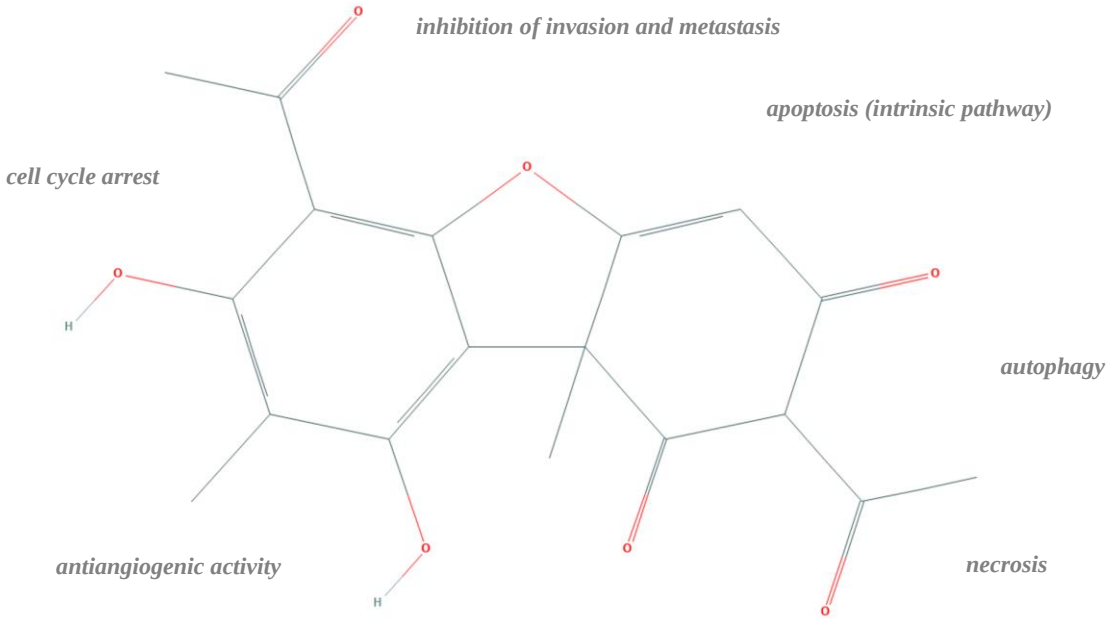

Figure 5. Structure of usnic acid and respective mechanisms of anticancer activity. Image source: PubChem.

Usnic acid (Figure 5) is a dibenzofuran that has been extensively studied for its wide range of bioactivities, including antibiotic, antiviral, anticancer, antioxidant, anti-inflammatory, and analgesic properties (Luzina and Salakhutdinov, 2018). It is one of the few lichen substances that are commercially available and used as such in 50% of the research articles focusing on its anticancer properties. Natural sources of usnic acid identified in cancer literature include *Alectoria ochroleuca* (Hoffm.) Massal, *Cladonia arbuscula* (Wallr.) Rabenh., *Cladonia convoluta* (Lam.) Anders, *Cladonia foliacea* (Huds.) Wild., *Cladonia lepidophora* Ahti & Kashiw., *Cladonia leptoclada* des. Abb., *Flavocetraria cucullata* (Bellardi) Karnefelt & A. Thell, *Parmelia subrudecta* Nyl., *Ramalina farinacea* (author not cited), *Usnea barbata* (L.) Mott., *Usnea diffracta* (author not cited), *Usnea longissima* Ach., *Usnea subcavata* Motika and *Xanthoparmelia somloensis* (Gyelnik) Hale (Bessadottir *et al.*, 2012; Bézivin *et al.*, 2004; Brandão *et al.*, 2013; Brisdelli *et al.*, 2013; Burlando *et al.*, 2009; Dincsoy and Duman, 2017; Einarsdottir *et al.*, 2010; Emsen *et al.*, 2018; Galanty *et al.*, 2017; Ivanova *et al.*, 2010; Koparal *et al.*, 2006; Koparal, 2015; Kupchan and Kopperman, 1975; Nguyen *et al.*, 2014; Perry *et al.*, 1999; Ranković *et al.*, 2012; Yamamoto *et al.*, 1995). Usnic acid and its synthetic

derivatives have been tested successfully against a wide variety of cancer cell lines, including bone and joint cancer, brain cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, kidney cancer, leukaemia, liver cancer, lung cancer, melanoma, ovary cancer, pancreas cancer, prostate cancer, sarcoma, stomach cancer and vulvar cancer (Table 2). Usnic acid exhibited the strongest cytotoxicity towards breast cancer (lowest IC_{50} = 4 µg/ml), pancreas cancer (lowest IC_{50} = 5 µg/ml), leukaemia (lowest IC_{50} = 6 µg/ml) and prostate cancer (lowest IC_{50} = 8,2 µg/ml) cell lines. Cytotoxicity against breast cancer cell lines was highly improved by usnic acid benzylidene analogues. These analogues inhibited the mechanistic (formerly "mammalian") target of rapamycin (mTOR) and induced autophagy without affecting nontumorigenic mammary epithelial cells. Additionally, they showed potent *in vivo* anticancer activity in breast tumour-bearing mice (Ebrahim *et al.*, 2017). Anticancer activity of usnic acid and its analogues or synthetic derivatives is associated with cell cycle arrest at G0/G1, G2/M and S phases (Bačkorová *et al.*, 2011; Geng *et al.*, 2018; Nguyen *et al.*, 2014; Su *et al.*, 2017; Yurdacan *et al.*, 2018); inhibition of invasion and metastasis (Ebrahim *et al.*, 2017; Galanty *et al.*, 2017; Nguyen *et al.*, 2014; Wu *et al.*, 2018; Yang *et al.*, 2016); inhibition of angiogenesis through vascular endothelial growth factor (VEGF) suppression (Song *et al.*, 2012); inhibition of the intrinsic pathway of apoptotic cell death shown by the depolarization of mitochondrial membrane, activation of caspase-3, increased expression of pro-apoptotic Bax, decreased expression of anti-apoptotic Bcl-xl and increased expression of tumour suppressor p53 (Bačkorová *et al.*, 2011, 2012; Bézivin *et al.*, 2004; Dincsoy and Duman, 2017; Einarsdottir *et al.*, 2010; Galanty *et al.*, 2017; Geng *et al.*, 2018; Mayer *et al.*, 2005; Nguyen *et al.*, 2014; Singh *et al.*, 2013; Suh *et al.*, 2017; Zuo *et al.*, 2015); autophagy (Bessadottir *et al.*, 2012; Ebrahim *et al.*, 2017; Geng *et al.*, 2018; Wu *et al.*, 2018; Yurdacan *et al.*, 2018) and necrosis (Bessadottir *et al.*, 2012; Einarsdottir *et al.*, 2010).

Despite the promising anticancer activity of usnic acid, clinical testing has been hampered by its poor water solubility and high hepatotoxicity. Strategies to improve the anticancer activity of usnic acid *in vivo* included solubilization, nanoencapsulation, conjugation, preparation of nanocrystal suspensions and, more recently, salinization (Yang *et al.*, 2018). The later strategy generated potassium usnate, a water-soluble usnic acid salt which significantly enhanced the bioavailability of usnic acid and increased its *in vitro* and *in vivo* anticancer activity against colorectal cancer.

3.2. Atranorin

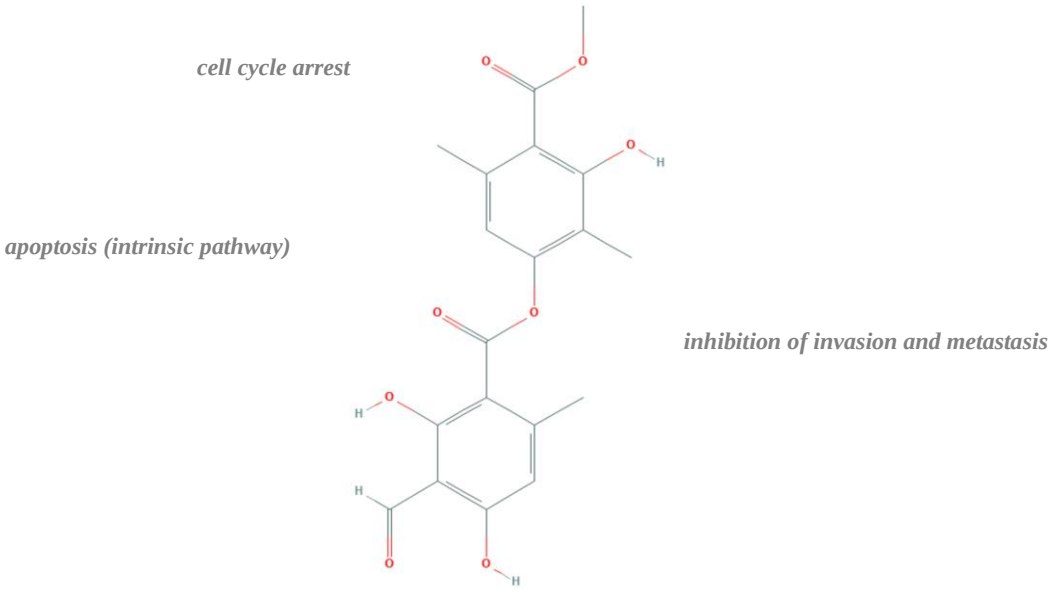

Figure 6. Structure of atranorin and respective mechanisms of anticancer activity. Image source: PubChem.

Atranorin (Figure 6) is an important member of the depside class, isolated from *Bacidia stipata* (author not cited), *Cladonia furcata* (Huds.) Schrad., *Everniastrum vexans* (author not cited), *Parmotrema dilatatum* (Vain.) Hale, *Platismatia glauca* (author not cited) and *Stereocaulon halei* Lamb (Brandão *et al.*, 2013; Cardile *et al.*, 2017; Ismed *et al.*, 2012; Kosanić *et al.*, 2014; Paluszczak *et al.*, 2018; Russo *et al.*, 2012; Zhou *et al.*, 2017). It has been tested against bone and joint cancer, brain cancer, breast cancer, cervical cancer, colorectal cancer, lung cancer, ovary cancer, prostate cancer, melanoma and leukaemia cell lines (Table 2). Atranorin exerted strong cytotoxic activity against all tested types of cancer (IC_{50} between 12,5 and 26,5 µg/ml), except for leukaemia cell lines (IC_{50} = 93,5 µg/ml). Cytotoxicity of atranorin has been associated with cell cycle arrest at G0/G1 and S phases in melanoma and colorectal cancer cell lines (Bačkorová *et al.*, 2011; Kosanić *et al.*, 2014), as well as with activation of the intrinsic pathway of apoptotic cell death, shown by the activation of caspase-3, depolarization of mitochondrial membrane, increased pro-apoptotic Bax expression, decreased anti-apoptotic Bcl-xl and Hsp70 expression, and increased Hsp90 expression in all tested cell lines (Bačkorová *et al.*, 2012, 2011; Cardile *et al.*, 2017; Galanty *et al.*, 2017; Solar *et al.*, 2016). Anti-migratory and anti-invasive activity of atranorin against lung cancer cells is due to the inhibition of actin

cytoskeleton organization and suppression of β-catenin-mediated and KAI1 C-terminal interacting tetraspanin (KITENIN)-mediated signalling activity (Galanty *et al.*, 2017; Zhou *et al.*, 2017).

3.3. Glucans

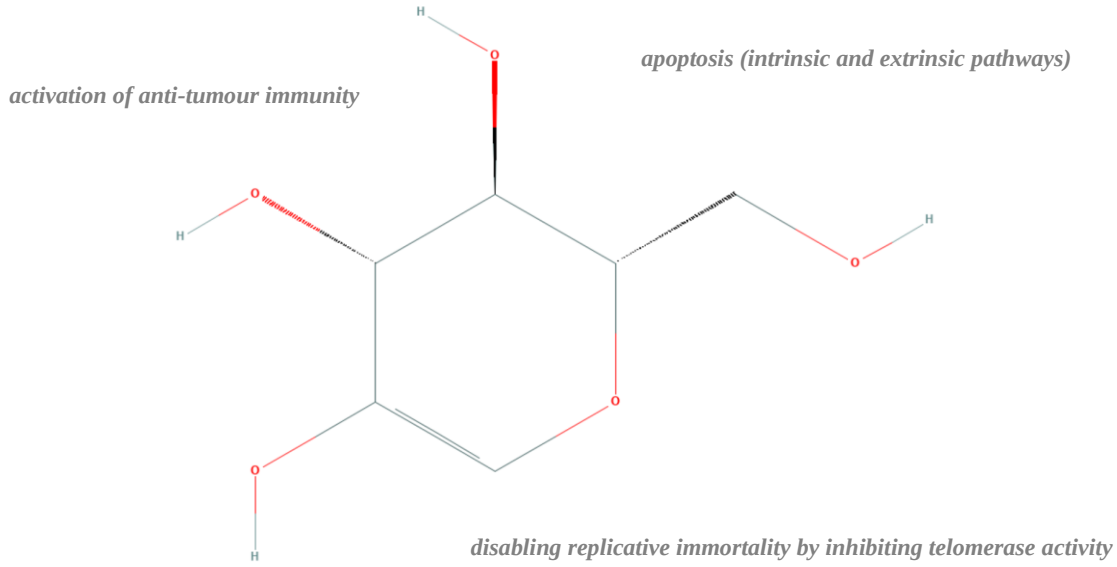

Figure 7. Structure of a glucan (lichenin) and respective mechanisms of anticancer activity. Image source: PubChem.

Lichenin (Figure 7) and isolichenin are complex glucans, i.e. a type of polysaccharide, used by lichens as carbohydrate reserves. Glucans have been isolated from *Acroscyphus sphaerophoroides* Lev., *Alectoria sarmentosa* (Ach.) Ach., *Alectoria sulcata* (Lev.) Nyl., *Cetraria islandica* (L.) Ach. var. *orientalis* Asahina, *Cladonia furcata* (Huds.) Schrad., *Evernia prunastri* (L.) Ach., *Gyrophora esculenta* Miyoshi, *Lasallia papulosa* (Ach.) Llano, *Lasallia pensylvanica* (Hoffm.) Llano, *Ramalina celastri* (Sprengel) Krog & Swinscow, *Umbilicaria angulata* Tuck., *Umbilicaria caroliniana* Tuck., *Umbilicaria polyphylla* (L.) Baumg. and *Usnea rubescens* Stirt., among others. Polysaccharide content has been linked to many beneficial effects of lichens (Olafsdottir and Ingólfsdottir, 2001) and glucans are among the earliest lichen substances studied for their anticancer properties (Table 4). They have proved to be effective against Ehrlich ascites carcinoma and Sarcoma 181, by activating anti-tumour immunity and inhibiting tumour growth *in vivo* (Assef *et al.*, 2002; Fukuoka *et al.*, 1968; Leão *et al.*, 1997; Nishikawa, 1969;

Nishikawa *et al.*, 1979, 1974, 1970, 1969; Nishikawa and Ohno, 1981; Shibata *et al.*, 1968a; Shibata *et al.*, 1968b; Takeda *et al.*, 1972). Lichenin tested against leukaemia cell lines, caused decreased telomerase activity as well as characteristic ultrastructural changes, DNA fragmentation and increased Bax, Fas and FasL expression levels attributable to the involvement of both intrinsic and extrinsic pathways of apoptotic cell death (Lin *et al.*, 2003).

3.4. Protolichesterinic acid

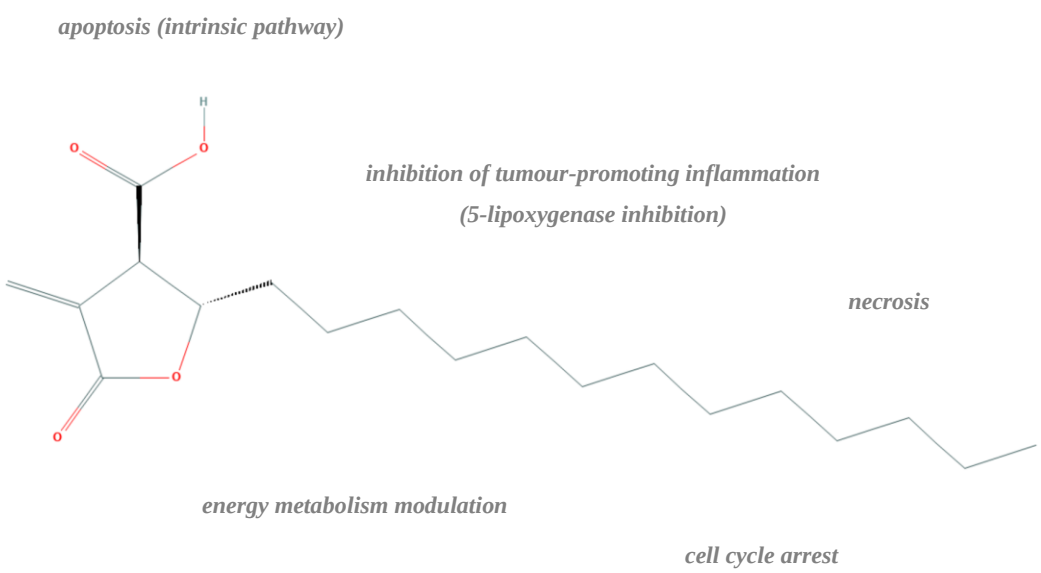

Figure 8. Structure of protolichesterinic acid and respective mechanisms of anticancer activity. Image source: PubChem.

Protolichesterinic acid (Figure 8) is a member of the class of aliphatic and cycloaliphatic compounds. It has been isolated from *Cetraria islandica* (L.) Ach., *Cornicularia aculeata* (Schreb.) Ach. and *Rhizoplaca melanophthalma* (author not cited), and tested against breast cancer, cervical cancer, colorectal cancer, kidney cancer, lung cancer, ovary cancer, pancreas cancer, stomach cancer, leukaemia and myeloma cell lines (Bessadóttir *et al.*, 2015, 2014; Brisdelli *et al.*, 2013; Haraldsdóttir *et al.*, 2004; Ogmundsdottir *et al.*, 1998; Russo *et al.*, 2012; Sangkook *et al.*, 1996; Thorsteinsdottir *et al.*, 2016). Protolichesterinic acid showed strong inhibitory effects on breast cancer cell viability (IC_{50} = 10,8 µM) associated with the inhibition of fatty acid synthase (FASN), a lipogenic multienzyme that catalyses fatty acid synthesis (Bessadóttir *et al.*, 2014) and

lipoxygenases (LOXs), enzymes that oxidize polyunsaturated fatty acids and have been implicated in many aspects of carcinogenesis (Haraldsdóttir *et al.*, 2004; Ogmundsdottir *et al.*, 1998). Protolichesterinic acid is also highly cytotoxic to colorectal cancer, lung cancer, pancreas cancer, prostate cancer and myeloma cell lines (EC_{50} = 18,1 µg/ml, IC_{50} = 18 µg/ml, IC_{50} = 3,5 µg/ml, $IC_{50} \approx$ 10 µg/ml and IC_{50} = 1,8 µg/ml, respectively) without involvement of LOX inhibition (Bessadottir *et al.*, 2015; Thorsteinsdottir *et al.*, 2016). Moderate cytotoxic activity has been observed against cervical cancer cell lines (IC_{50} = 46,7 µg/ml). Apoptosis in these cell lines induced by protolichesterinic acid appears to be mediated, at least in part, by the inhibition of anti-apoptotic Hsp70 expression, modulation of Bax/Bcl-2 ratio and caspase-3, 8 and 9 activation.

3.5. Diffractaic acid

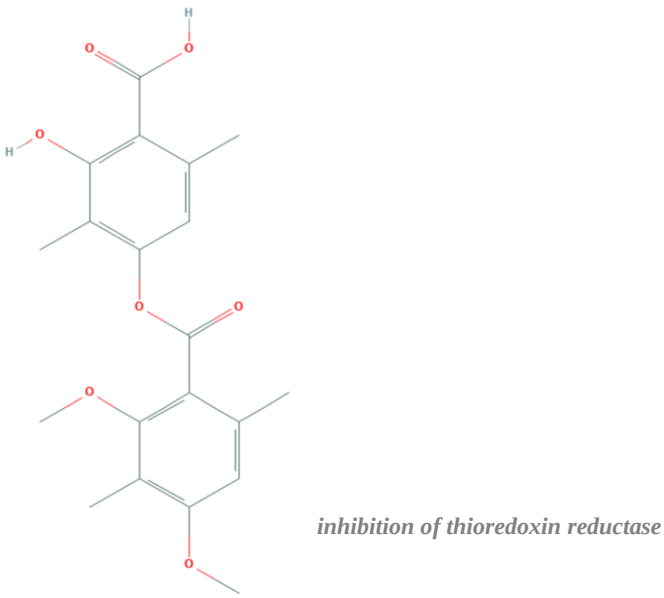

Figure 9. Structure of diffractaic acid and respective mechanisms of anticancer activity. Image source: PubChem.

Diffractaic acid (Figure 9) is a depside isolated from *Usnea longissima* Ach., *Usnea subcavata* Motika and *Protousnea magellanica* (Mont.) Krog. It has been tested against brain cancer, breast cancer, cervical cancer, colorectal cancer, prostate cancer and melanoma (Brandão *et al.*, 2013; Brisdelli *et al.*, 2013; Emsen *et al.*, 2018; Karagoz *et al.*, 2014; Ozgencli *et al.*, 2018; Russo *et al.*, 2012; Yamamoto *et al.*, 2015). Diffractaic

acid is able to inhibit the growth of androgen-sensitive and androgen-insensitive prostate cancer cells at 25 and 50 µM, respectively, by some unknown mechanism different from apoptosis (Russo *et al.*, 2012). Diffractaic acid was also highly cytotoxic to melanoma cells (IC_{50} = 24,7 µg/mL) and moderately toxic to brain, breast, cervical and colorectal cancer cell lines (IC_{50} = 35,67 µg/mL, IC_{50} = 93,4 µg/mL, IC_{50} = 64,6 µg/mL and IC_{50} = 42,2 µg/mL, respectively). Diffractaic acid exhibited inhibitory effects on thioredoxin reductase (Ozgencli *et al.*, 2018), an enzyme that has been shown to play a major role in tumour's drug resistance. Thioredoxin reductase inhibitors are involved in several anticancer mechanisms ranging from induction of oxidative stress to cell cycle arrest and apoptosis, and may constitute successful anticancer drugs used in single, combinatory or adjuvant cancer therapies (Urig and Becker, 2006).

3.6. Physodic acid

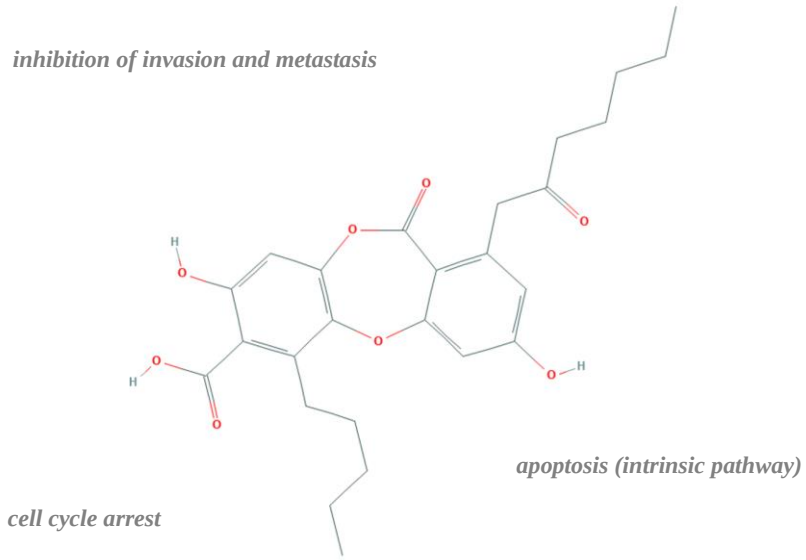

Figure 10. Structure of physodic acid and respective mechanisms of anticancer activity. Image source: PubChem.

Physodic acid (Figure 10) is a depsidone isolated from *Hypogymnia lugubris* (Pers.) Krog, *Hypogymnia physodes* (L.) Nyl. and *Pseudevernia furfuracea* (L.) Zopf. (Cardile *et al.*, 2017; Emsen *et al.*, 2016; Kosanić *et al.*, 2013; Paluszczak *et al.*, 2018; Stojanovic *et al.*, 2014; Studzinska-Sroka *et al.*, 2016). It has been tested against bladder cancer, brain cancer, breast cancer, cervical cancer, colorectal cancer, pancreas cancer, leukaemia

and melanoma (Table 2). Cytotoxicity of physodic acid appears to be strong against colorectal cancer cells (IC_{50} = 17,89 µg/ml), associated with increased number of cells in sub-G1 phase (Talapatra *et al.*, 2016) and decreased expression of anti-apoptotic protein survivin (known as baculoviral inhibitor of apoptosis repeat-containing 5 or BIRC5). Physodic acid also led to a reduction in the expression of matrix metalloproteinase-7 (MMP-7) and several genes of the β-catenin-dependent wnt signaling pathway, implicated in cancer cell proliferation, invasion and migration. Cytotoxic activity of physodic acid was also strong against melanoma cell lines (IC_{50} = 19,52 µg/ml) associated with increased pro-apoptotic Bax expression and decreased anti-apoptotic Bcl-2 and Hsp70 expression (Cardile *et al.*, 2017; Kosanić *et al.*, 2013). Cytotoxicity against bladder cancer, breast cancer, cervical cancer, pancreas cancer and leukaemia cell lines (IC_{50} = 31,8 µM, $IC_{50} \geq$ 46,0 µM, IC_{50} = 65,96 µg/ml, IC_{50} = 32,6 µM and IC_{50} = 37,3 µM, respectively) may be considered moderate. Low citotoxicity (IC_{50} = 410,72 µg/ml) was observed against brain cancer cell lines (Emsen *et al.*, 2016).

3.7. Lobaric acid

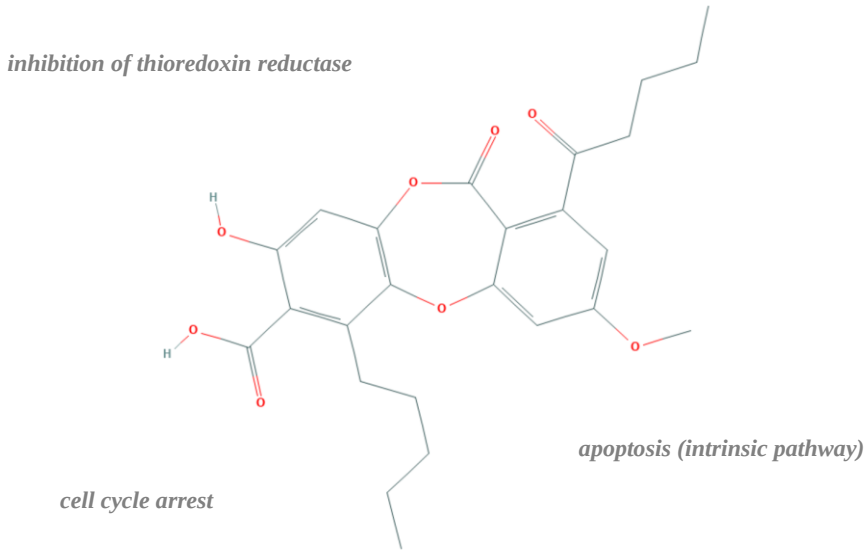

Figure 11. Structure of lobaric acid and respective mechanisms of anticancer activity. Image source: PubChem.

Lobaric acid (Figure 11) is a depsidone isolated from *Stereocaulon alpinum* Laurer ex Funck and *Stereocaulon halei* Lamb. (Brisdelli *et al.*, 2013; Haraldsdóttir *et al.*, 2004;

Hong *et al.*, 2018; Ismed *et al.*, 2012; Ogmundsdottir *et al.*, 1998). It has been tested against brain cancer, breast cancer, cervical cancer, colorectal cancer, lung cancer, ovary cancer, pancreas cancer, prostate cancer, stomach cancer, melanoma and leukaemia (Table 2), exhibiting at least moderate cytotoxic effects (IC_{50} value of ≤ 100 µg/ml) against all tested cancer cell lines. Strong cytotoxic activity (IC_{50} value of ≤ 30 µg/ml) has been observed in brain cancer, breast cancer, lung cancer, pancreas cancer, prostate cancer and leukaemia cell lines, with better results against brain cancer cell lines (IC_{50} = 5,77 µg/ml). Anticancer activity of lobaric acid has been associated with cell cycle arrest at G2/M phase and activation of the intrinsic pathway of apoptotic cell death, shown by increased levels of PARP cleavage and decreased expression of anti-apoptotic gene Bcl-2 (Hong *et al.*, 2018). Lobaric acid also exhibited a strong inhibitory effect on thioredoxin reductase (Ozgencli *et al.*, 2018) and is therefore a potential anticancer agent inducing oxidative stress as well as cell cycle arrest and apoptosis (Urig and Becker, 2006).

3.8. Vulpinic acid

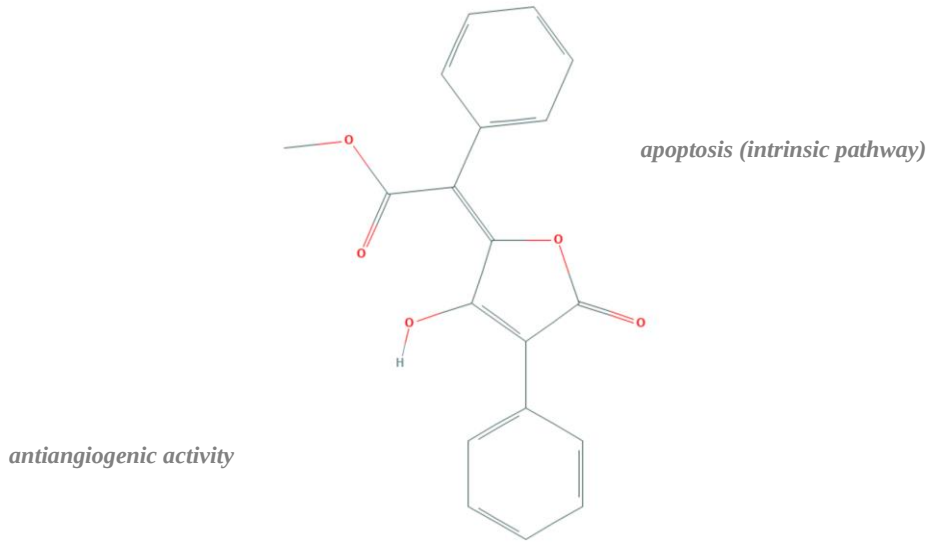

Figure 12. Structure of vulpinic acid and respective mechanisms of anticancer activity. Image source: PubChem.

Vulpinic acid (Figure 12) is a pulvinic acid derivative isolated from *Letharia vulpina* (L.) Hue (Burlando *et al.*, 2009; Koparal, 2015). It has been tested against breast cancer, cervical cancer, colorectal cancer, kidney cancer, liver cancer, vulvar cancer and sarcoma

(Table 2). Moderate cytotoxicity of vulpinic acid against cervical cancer, colorectal cancer, liver cancer and sarcoma is associated with the activation of the intrinsic pathway of apoptotic cell death, showed by the increased expression of pro-apoptotic Bax and tumour suppressor p53, and decreased expression of anti-apoptotic Bcl-2 genes (Kılıç *et al.*, 2018). Like usnic acid, vulpinic acid exhibited strong antiangiogenic activity, with the advantage of being less cytotoxic to normal cells than usnic acid (Koparal, 2015).

3.9. Salazinic acid

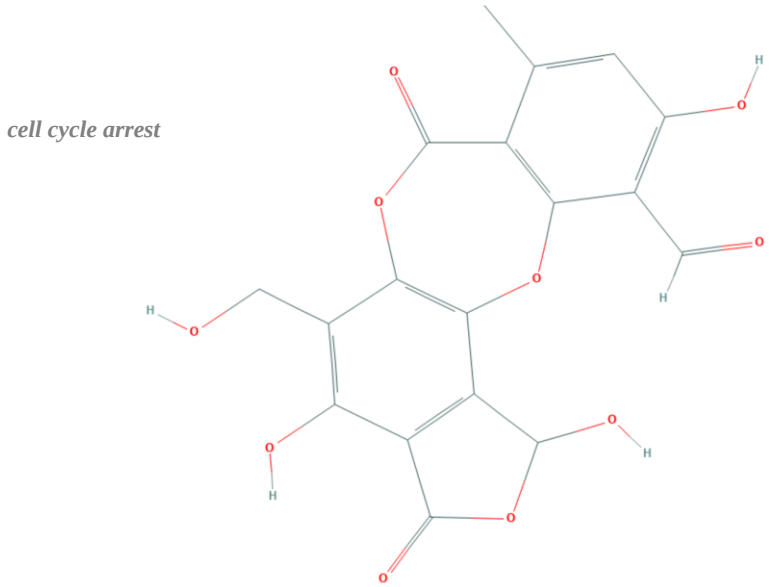

Figure 13. Structure of salazinic acid and respective mechanisms of anticancer activity. Image source: PubChem.

Salazinic acid (Figure 13) is a depsidone isolated from *Parmelia saxatilis* (L.) Ach., *Parmelia sulcata* (author not cited), *Parmotrema lichexanthonicum* Eliasaro & Adler and *Xanthoparmelia somloensis* (Gyelnik) Hale. (Burlando *et al.*, 2009; Hirayama *et al.*, 1980; Manojlovic *et al.*, 2012; Micheletti *et al.*, 2009; Paluszczak *et al.*, 2018). It has been tested against colorectal cancer, brain cancer, breast cancer, melanoma, sarcoma and vulvar cancer cell lines (Table 2). Cytotoxic activity against colorectal cancer and melanoma cell lines (IC_{50} = 35,67 µg/ml and IC_{50} = 39,02 µg/ml, respectively), associated with a G1 phase cell cycle arrest (Manojlovic *et al.*, 2012), was highly improved by structural modifications which lowered IC_{50} values down to 1,73 µg/ml (Micheletti *et al.* 2009). Low cytotoxicity has been observed against sarcoma and vulvar cancer cell lines

(Burlando *et al.* 2009). Salazinic acid has also been tested *in vivo* (mice) against ascitic and solid-type Ehrlich carcinoma, with week effects on both types of tumours (Hirayama *et al.*, 1980).

3.10. Lecanoric acid

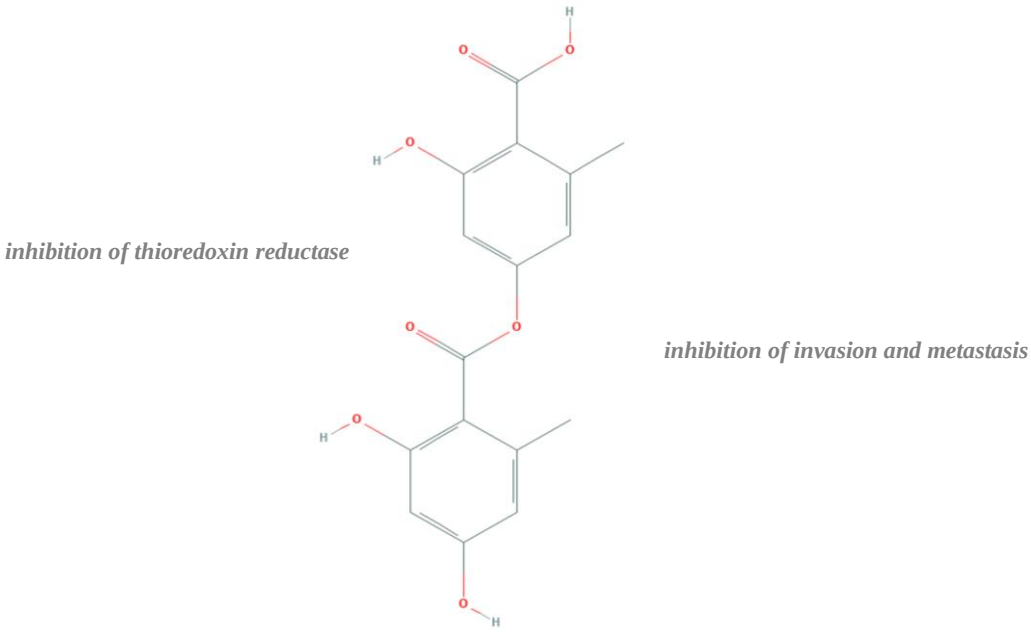

Figure 14. Structure of lecanoric acid and respective mechanisms of anticancer activity. Image source: PubChem.

Lecanoric acid (Figure 14) is a depside isolated from several lichens, including *Hypocenomyce scalaris* (author not cited), *Parmotrema tinctorum* (Nyl.) Hale and *Parmelia subrudecta* Nyl. (Bogo *et al.*, 2010; Ivanova *et al.*, 2010; Ozgencli *et al.*, 2018; Paluszczak *et al.*, 2018). It has been tested against colorectal cancer, breast cancer, kidney cancer, larynx cancer, cervical cancer, melanoma and leukaemia cell lines (Table 2). It exerted only moderate cytotoxic effects against colorectal cancer cell lines at the concentration of 100 μM, associated with a slightly reduction in the expression of axin2, the classical target gene in the wnt/β-catenin signalling pathway (Paluszczak *et al.*, 2018). Cytotoxic activity against other cancer cell lines was also moderate, with IC_{50} values equal to or higher than 50 μg/ml (Bogo *et al.*, 2010; Ivanova *et al.*, 2010). However, lecanoric acid exhibited a strong inhibitory effect on thioredoxin reductase (Ozgencli *et al.*, 2018) and is therefore a potential anticancer agent like lobaric and diffractaic acids (Urig and Becker, 2006).

3.11. Lichen extracts and other substances

The molecular mechanisms associated with anticancer activity of lichen extracts is summarized in Table 5. Among the 296 species reported in the reviewed literature, 116 are cytotoxic, 46 have anti-apoptotic effects and 14 inhibit cell migration and invasion. The most common solvents used in the extraction protocols include acetone, ethanol, methanol and water, but influence of extraction method has not been properly addressed. Comparison between species in terms of their anticancer properties is difficult, because extraction methods varied greatly. Another source of confusion, relevant for both lichen extracts and isolated substances, is the discrepancy in the interpretations of IC_{50}/EC_{50}/GI_{50} values found in the reviewed literature. A reference standard is lacking, allowing for rigorous determination of anticancer efficacy of lichen species and respective substances. Besides the ones mentioned in the previous sections, other less cited lichen substances were also isolated from lichens and tested against a wide range of cancer cell lines in the reviewed research articles (Table 2). Table 6 summarizes the current knowledge about the molecular mechanisms of anticancer activity of all lichen substances mentioned in literature. Angiogenesis inhibitors include barbatolic and olivetoric acids in addition to usnic and vulpinic acids. Lichen substances with anti-apoptotic properties also include caperatic acid, divaricatic acid, evernic acid, gyrophoric acid, lichesterinic acid, lobarstin, pannarin, parietin, ramalin, sphaerophorin and vicanicin, among others. Autophagy is also induced by ramalin. Barbatolic acid, caperatic acid, norstictic acid, physciosporin, ramalin, stictamide A and tumidulin are cell migration and invasion inhibitors, besides usnic acid and atranorin. Most substances mentioned in the reviewed articles proved to be effective inhibitors of cell viability including evernic acid, fumarprotocetraric acid, gyrophoric acid, norstictic acid, parietin, protocetraric acid, psoromic acid, squamatic acid and stictic acid, just to cite a few of the most commonly found lichen substances.

The analysed research articles report lichen substances able to interfere with each of the ten biological capabilities necessary for tumour growth and progression, i.e. the hallmarks of cancer defined by Hanahan and Weinberg (2011) namely: 1) sustaining proliferative signalling; 2) evading growth suppressors; 3) avoiding immune destruction; 4) enabling replicative immortality; 5) tumour-promoting inflammation; 6) activating invasion and metastasis; 7) inducing angiogenesis; 8) genome instability and mutation; 9) resisting cell death; and 10) deregulating cellular energetics. They do so by inducing cell cycle arrest, inhibiting growth factor signalling, activating anti-tumour immunity, disabling

replicative immortality by inhibiting telomerase activity, inhibiting tumour-promoting inflammation, inhibiting invasion and metastasis, blocking angiogenesis, supressing genome instability, inducing apoptotic, autophagic and necrotic cell death, and modulating energy metabolism; as illustrated by the examples presented in Figure 15.

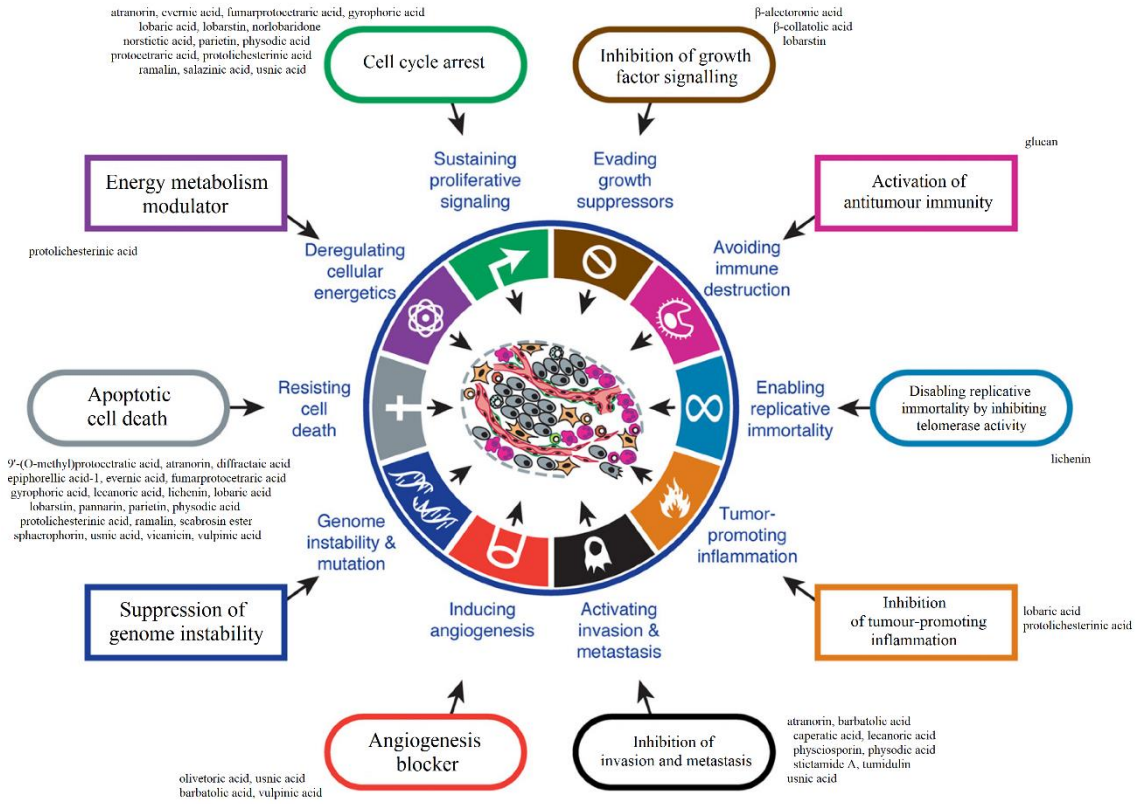

Figure 15. Schematic illustration of reported anticancer mechanisms of lichen substances. Modified from (Hanahan and Weinberg, 2011; Kim *et al.*, 2015).

Table 5. Summary of the molecular mechanisms associated with anticancer activity of lichen extracts mentioned in the included research articles.

Substance	Mechanism	Reference
	Cell cycle arrest	
Cladonia furcata	G0/G1 phase cell cycle arrest	Kosanić *et al.* (2014) Lin *et al.* (2001)
Cladonia pyxidata	G0/G1 phase cell cycle arrest	Kosanić *et al.* (2014)
Cladonia rangiferina	G0/G1 phase cell cycle arrest	Kosanić *et al.* (2014)
Evernia prunastri	G0/G1 phase cell cycle arrest	Kosanic *et al.* (2013)
Flavocetraria cucullata	G0/G1 phase cell cycle arrest	Nguyen *et al.* (2014)
Lethariella zahlbruckneri	G0/G1 phase cell cycle arrest	Lee *et al.* (2012) Ren *et al.* (2009)
Parmotrema reticulatum	G0/G1, G2/M and S phase cell cycle arrest (inhibited expression of cell cycle related proteins cyclin B1, Cdc25C, tumour suppressor genes p53 and p21)	Ghate *et al.* (2013)
Pseudevernia furfuracea	G0/G1 phase cell cycle arrest	Kosanic *et al.* (2013)

Substance	Mechanism	Reference
Toninia candida	G0/G1 and G2/M phase cell cycle arrest	Ranković *et al.* (2012)
Tuckermannopsis ciliaris	G0/G1 phase cell cycle arrest (increased expression of tumour suppressor gene p53)	Shrestha *et al.* (2015)
Usnea barbata	G0/G1 and G2/M phase cell cycle arrest	Ranković *et al.* (2012)
Xanthoparmelia chlorochroa	G0/G1 phase cell cycle arrest (increased expression of tumour suppressor gene p53)	Shrestha *et al.* (2015)
Xanthoria parietina	G0/G1 phase cell cycle arrest (modulation of expression of cell cycle regulating genes such as p16, p27, cyclin D1 and cyclin A)	Basile *et al.* (2015)
	Inhibition of growth factor signalling and DNA repair	
***Parmotrema* sp.**	Inhibition of Polo-like kinase Plk1	Williams *et al.* (2011)
	Disabling replicative immortality by inhibiting telomerase activity	
Umbilicaria esculenta	Telomerase inhibitors	Xu *et al.* (2014)
	Inhibition of invasion and metastasis	
Alectoria ochroleuca	Modulation of β-catenin-mediated and KITENIN-mediated signalling activity, regulation of Rho GTPases	Yang *et al.* (2016)
Alectoria sarmentosa	Modulation of β-catenin-mediated and KITENIN-mediated signalling activity, regulation of Rho GTPases	Yang *et al.* (2016)
Bryoria capillaris	Modulation of β-catenin-mediated and KITENIN-mediated signalling activity, regulation of Rho GTPases	Yang *et al.* (2016)
Evernia divaricata	Modulation of β-catenin-mediated and KITENIN-mediated signalling activity, regulation of Rho GTPases	Yang *et al.* (2016)
Everniastrum vexans		Zhou *et al.* (2017)
Flavocetraria cucullata	Inhibition of Epithelial-Mesenchymal Transition (EMT)	Nguyen *et al.* (2014)
Flavocetraria nivalis	Modulation of β-catenin-mediated and KITENIN-mediated signalling activity, regulation of Rho GTPases	Yang *et al.* (2016)
Flavoparmelia caperata	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
Hypogymnia physodes	Modulation of β-catenin-mediated and KITENIN-mediated signalling activity, regulation of Rho GTPases	Yang *et al.* (2016)
Hypotrachyna sinuosa	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
***Nephroma* sp.**	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
***Niebla* sp.**	Inhibition of stemness potential	Yang *et al.* (2018)
***Physcia* sp.**	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
***Protousnea* sp.**	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
Pseudocyphellaria argyracea	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
Pseudocyphellaria coriacea	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
Pseudocyphellaria glabra	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
Pseudocyphellaria verrucosa	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
Rhizoplaca melanophthalma	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
Usnea florida	Modulation of β-catenin-mediated and KITENIN-mediated signalling activity, regulation of Rho GTPases	Yang *et al.* (2016)
***Xanthoparmelia* sp.**	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
	Supression of genome instability	
Tuckermannopsis ciliaris	Increased expression of repair gene TK1	Shrestha *et al.* (2015)
	Apoptotic cell death	
Cladonia coniocraea		Delebassée *et al.* (2017)
Cladonia convoluta	Intrinsic pathway	Coskun *et al.* (2015)
Cladonia foliacea		Mitrovic *et al.* (2011)
Cladonia glauca		Delebassée *et al.* (2017)
Cladonia parasitica		Delebassée *et al.* (2017)
Cladonia pocillum		Ersoz *et al.* (2017)
Cladonia rangiformis	Intrinsic pathway	Coskun *et al.* (2015) Delebassée *et al.* (2017)
Cladonia squamosa		Delebassée *et al.* (2017)
Evernia prunastri		Delebassée *et al.* (2017) Mitrovic *et al.* (2011)
Flavocetraria cucullata	Intrinsic pathway	Nguyen *et al.* (2014)
Flavoparmelia caperata		Mitrovic *et al.* (2011)

Substance	Mechanism	Reference
Hypogymnia physodes	Intrinsic pathway (caspase-3-dependent)	Ari *et al.* (2014)
Lasallia pustulata		Delebassée *et al.* (2017)
Leprocaulon microscopicum		Delebassée *et al.* (2017)
Leproloma membranaceum		Delebassée *et al.* (2017)
Lethariella zahlbruckneri	Intrinsic pathway (caspase-3-dependent, increased pro-apoptotic Bax expression, decreased anti-apoptotic Bcl-xl expression, increased Bid cleavage and AIF expression)	Lee *et al.* (2012) Ren *et al.* (2009)
Lobaria pulmonaria		Delebassée *et al.* (2017)
Nephroma laevigatum		Delebassée *et al.* (2017)
Nephroma parile		Delebassée *et al.* (2017)
Parmelia saxatilis		Delebassée *et al.* (2017)
Parmelia sulcata	Intrinsic pathway (caspase-3-independent)	Ari *et al.* (2014) Ari *et al.* (2015)
Parmotrema reticulatum	Intrinsic pathway (caspase-3-dependent, increased Bax expression and decreased Bcl-2 expression)	Ghate *et al.* (2013)
Peltigera horizontalis		Delebassée *et al.* (2017)
Platismatia glauca		Delebassée *et al.* (2017)
Pleurosticta acetabulum		Delebassée *et al.* (2017)
Tuckermannopsis ciliaris	Increased expression of tumour suppressor gene p53	Shrestha *et al.* (2015)
Umbilicaria esculenta	Intrinsic pathway (mitochondrial membrane depolarization, caspase-3-dependent)	Sun *et al.* (2018)
Usnea filipendula	Intrinsic pathway (caspase-3-independent)	Ari *et al.* (2014)
Xanthoparmelia chlorochroa	Increased expression of tumour suppressor gene p53	Shrestha *et al.* (2015)
Xanthoria parietina	Intrinsic pathway (decrease in expression of anti-apoptotic protein Bcl-2); Extrinsic pathway (increased expression of TNF-related apoptosis-inducing ligand TRAIL)	Basile *et al.* (2015)
	Necrosis	
Hypogymnia physodes		Ari *et al.* (2014) Mitrovic *et al.* (2011)

Table 6. Summary of the molecular mechanisms associated with anticancer activity of lichen substances mentioned in the included research articles.

Substance	Mechanism	Reference
	Cell cycle arrest	
atranorin	G0/G1 and S phase cell cycle arrest	Bačkorová *et al.* (2011) Kosanić *et al.* (2014)
evernic acid	G0/G1 phase cell cycle arrest	Kosanić *et al.* (2013)
fumarprotocetraric acid	G0/G1 phase cell cycle arrest	Kosanić *et al.* (2014)
gyrophoric acid	S phase cell arrest	Bačkorová *et al.* (2011)
lobaric acid	G2/M phase cell cycle arrest	Hong *et al.* (2018)
lobarstin	G2/M phase cell cycle arrest	Hong *et al.* (2018)
norlobaridone	M-Phase Phosphoprotein 1 (MPP1) inhibition	Talapatra *et al.* (2016)
norstictic acid	G0/G1 phase cell cycle arrest	Ranković *et al.* (2012)
parietin	S phase cell arrest	Bačkorová *et al.* (2011)
physodic acid	G0/G1 phase cell cycle arrest; M-Phase Phosphoprotein 1 (MPP1) inhibition	Kosanić *et al.* (2013) Talapatra *et al.* (2016)
protocetraric acid	G0/G1 phase cell cycle arrest	Manojlovic *et al.* (2012)
protolichesterinic acid	G0/G1 phase cell cycle arrest	Bessadóttir *et al.* (2015)
ramalin	G2/M phase cell cycle arrest via modulation of hallmark genes TP53, CDKN1A, CDK1	Suh *et al.* (2017)
salazinic acid	G0/G1 phase cell cycle arrest	Manojlovic *et al.* (2012)
usnic acid	G0/G1, G2/M and S phase cell cycle arrest via modulation of CDK-cyclin-CDK1; modulation of p53/p21/cyclin pathway	Bačkorová *et al.* (2011) Bazin *et al.* (2008) Einarsdottir *et al.* (2010) Geng *et al.* (2018) Nguyen *et al.* (2014) O'Neill *et al.* (2010) Ranković *et al.* (2012) Singh *et al.* (2013) Suh *et al.* (2017) Yurdacan *et al.* (2018)
	Inhibition of growth factor signalling and DNA repair	
β-alectoronic acid	Inhibition of Polo-like kinase Plk1	Williams *et al.* (2011)
β-collatolic acid	Inhibition of Polo-like kinase Plk1	Williams *et al.* (2011)
lobarstin	Inhibition of DNA repair	Kim *et al.* (2013)
	Activation of antitumor immunity	
glucan	Increased phagocytic activity	Nishikawa & Ohno (1981) Stuelp-Campelo *et al.* (2002)

Substance	Mechanism	Reference
	Disabling replicative immortality by inhibiting telomerase activity	
lichenin	Telomerase inhibitors	Lin *et al.* (2003)
	Inhibition of tumour-promoting inflammation	
lobaric acid	5-lipoxygenase inhibitory activity	Ogmundsdottir *et al.* (1998)
protolichesterinic acid	5-lipoxygenase inhibitory activity	Ogmundsdottir *et al.* (1998)
	Inhibition of invasion and metastasis	
atranorin	Inhibition of actin cytoskeleton organization; modulation of β-catenin-mediated and KITENIN-mediated signalling activity; regulation of Rho GTPases; downregulation of cell motility-related genes	Galanty *et al.* (2017) Zhou *et al.* (2017)
barbatolic acid		Varol (2018)
caperatic acid	Inhibition of the expression of β-catenin-dependent gene transcription (Wnt signaling pathway)	Paluszczak *et al.* (2018)
lecanoric acid	Inhibition of the expression of β-catenin-dependent gene transcription (Wnt signaling pathway)	Paluszczak *et al.* (2018)
physciosporin	Inhibition of Epithelial-Mesenchymal Transition EMT; regulation of KITENIN and KAI1 expressions; reduction of Rho GTPase activity	Yang *et al.* (2015)
physodic acid	Inhibition of the expression of -catenin-dependent gene transcription (Wnt signaling pathway); Matrix Metalloproteinase-7 (MMP-7) inhibition	Paluszczak *et al.* (2018)
stictamide A	Matrix Metalloproteinase-12 (MMP-12) inhibition	Liang *et al.* (2011)
tumidulin	Inhibition of stemness potential	Yang *et al.* (2018)
usnic acid	Inhibition of actin cytoskeleton organization; inhibition of Epithelial-Mesenchymal Transition (EMT); inhibition of Stem Cell Factor (SCF); inhibition of the mammalian target of rapamycin (mTOR); modulation of β-catenin-mediated and KITENIN-mediated signalling activity; regulation of Rho GTPases	Ebrahim *et al.* (2017) Galanty *et al.* (2017) Nguyen *et al.* (2014) Wu *et al.* (2018) Yang *et al.* (2016)
	Angiogenesis blocker	
olivetoric acid	Inhibition of actin cytoskeleton organization	Koparal *et al.* (2010)
usnic acid	VEGF signaling inhibition	Koparal *et al.* (2015) Song *et al.* (2012)
barbatolic acid		Varol (2018)
vulpinic acid		Koparal *et al.* (2015)
	Apoptotic cell death	
9'-(O-methyl)protocetratic acid		Bézivin *et al.* (2004)
atranorin	Intrinsic pathway (mitochondrial membrane depolarization, caspase-3-dependent, increased pro-apoptotic Bax expression, decreased anti-apoptotic Bcl-xl expression, increased Hsp90 expression, decreased Hsp70 expression); increased ROS production	Bačkorová *et al.* (2011) Bačkorová *et al.* (2012) Cardile *et al.* (2017) Galanty *et al.* (2017) Solar *et al.* (2016)
diffractaic acid	Thioredoxin reductase inhibition	Ozgencli *et al.* (2018)
epiphorellic acid-1	Intrinsic pathway (caspase-3-dependent); DNA fragmentation	Russo *et al.* (2006)
evernic acid	Thioredoxin reductase inhibition	Ozgencli *et al.* (2018)
fumarprotocetraric acid		Bézivin *et al.* (2004)
gyrophoric acid	Intrinsic pathway (increased pro-apoptotic Bax expression, decreased anti-apoptotic Bcl-xl, decreased Hsp70 expression); increased ROS production	Bačkorová *et al.* (2011) Cardile *et al.* (2017)
lecanoric acid	Thioredoxin reductase inhibition	Ozgencli *et al.* (2018)
lichenin	Intrinsic pathway (increased Bax expression); Extrinsic pathway (increased Fas and FasL expression)	Lin *et al.* (2003)
lobaric acid	Intrinsic pathway (increased PARP cleavage, decreased Bcl-2 expression); nuclear fragmentation, cytoplasmic vacuolization and blebbing; thioredoxin reductase inhibition	Hong *et al.* (2018) Ogmundsdottir *et al.* (1998) Ozgencli *et al.* (2018)
lobarstin	Intrinsic pathway (increased PARP cleavage, decreased Bcl-2 expression)	Hong *et al.* (2018)
pannarin	Intrinsic pathway (caspase-3-dependent); DNA fragmentation	Russo *et al.* (2008) Russo *et al.* (2006)
parietin		Bačkorová *et al.* (2011)
physodic acid	Intrinsic pathway (increased pro-apoptotic Bax expression, decreased anti-apoptotic Bcl-xl, decreased Hsp70 expression); increased ROS production	Cardile *et al.* (2017)
protolichesterinic acid	Intrinsic pathway (caspase-3-dependent, increased pro-apoptotic Bax expression, decreased anti-apoptotic Bcl-xl, decreased Hsp70 expression); Extrinsic pathway (increased expression of TNF-related apoptosis-inducing ligand TRAIL); nuclear fragmentation, cytoplasmic vacuolization and blebbing	Bessadóttir *et al.* (2015) Brisdelli *et al.* (2013) Ogmundsdottir *et al.* (1998) Russo *et al.* (2012)
ramalin	Intrinsic pathway (caspase-3-dependent, caspase-3-independent, increased Bax expression, decreased Bcl-2 expression, independent of p53 expression, release of cytochrome c and AIF)	Lee *et al.* (2016)
scabrosin ester	Intrinsic pathway (mitochondrial membrane hyperpolarization, caspase-dependent)	Moerman *et al.* (2003)
sphaerophorin	Intrinsic pathway (caspase-3-dependent); DNA fragmentation	Russo *et al.* (2006) Russo *et al.* (2008)
usnic acid	Intrinsic pathway (mitochondrial membrane depolarization, caspase-3-dependent, increased pro-apoptotic Bax expression, decreased anti-apoptotic Bcl-xl expression, increased p53 expression); increased ROS production	Bačkorová *et al.* (2011) Bačkorová *et al.* (2012) Bézivin *et al.* (2004) Dincsoy & Duman (2017) Einarsdottir *et al.* (2010) Galanty *et al.* (2017) Geng *et al.* (2018) Mayer *et al.* (2005) Nguyen *et al.* (2014) Singh *et al.* (2013) Suh *et al.* (2017) Zuo *et al.* (2015)

Substance	Mechanism	Reference
vicanicin	Intrinsic pathway (increased pro-apoptotic Bax expression, decreased anti-apoptotic Bcl-xl, decreased Hsp70 expression); Extrinsic pathway (Increased expression of TNF-related apoptosis-inducing ligand TRAIL)	Russo *et al.* (2012)
vulpinic acid	Intrinsic pathway (increased Bax expression, decreased Bcl-2 expression, increased p53 expression); thioredoxin reductase inhibition	Kılıç *et al.* (2018) Ozgencli *et al.* (2018)
	Autophagy	
ramalin		Lee *et al.* (2016)
usnic acid	Inhibition of the mammalian target of rapamycin (mTOR)	Bessadottir *et al.* (2012) Ebrahim *et al.* (2017) Geng *et al.* (2018) Wu *et al.* (2018) Yurdacan *et al.* (2018)
	Necrosis	
epiphorellic acid-1		Russo *et al.* (2006)
pannarin		Russo *et al.* (2006)
protolichesterinic acid		Russo *et al.* (2012)
scabrosin ester		Moerman *et al.* (2003)
sphaerophorin		Russo *et al.* (2006)
usnic acid		Bessadottir *et al.* (2012) Einarsdottir *et al.* (2010)
vicanicin		Russo *et al.* (2012)
	Energy metabolism modulation	
protolichesterinic acid	Inhibition of FASN activity	Bessadóttir *et al.* (2014)

4. Conclusions

Lichens are an interesting source of compounds for anticancer drug development, although further studies are still needed to clarify the molecular mechanisms and signalling pathways involved in the activity of many substances. Despite the large number of lichen species available worldwide, the number of species studied and lichen-derived substances tested is very small. Considering the rising interest in natural sources of anticancer agents and tendency for an increasing body of research focused on lichen bioactivities, new substances will certainly be described from poorly studied species and unexplored geographical regions. Developments in analytical techniques have resulted in new chemical components still being described from species that are commonly used and chemically well known. There are still no lichen-derived anticancer drugs in clinical use or involved in clinic trials, though. Among lichen substances, usnic acid, atranorin and protolichesterinic acid have proved effective against certain types of cancer either isolated or in combination with other anticancer drugs, and are therefore potential candidates for novel cancer therapy.

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