Medicinal Mushrooms for Cancer: Science and Practice

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ABSTRACT

Based on traditional and folk medicines, mushrooms have been developed into anti-cancer therapeutics. A brief overview is given about the most important medical mushroom species and their specific anti-cancer functions and mechanisms. *Taiwanofungus camphoratus* (*Antrodia cinnamomea*) is selected as example of a medical fungus in order to illustrate the general process from ethnomedicine to developing new products for the market based on scientific, analytic, and experimental evidence. The bioactive compounds have indirect effects in cancer treatment by benefiting the immune system as well as having direct cytotoxic effects on cancer cells. The complex mixture of bioactive compounds in natural fruit bodies is a challenge for artificial production *in vitro*. Particular problems in developing *T. camphoratus* into therapeutics for the global market are its rarity in nature and its close dependence on an endemic tree in Taiwan. These challenges initiate new solutions which could be transferred to other medical fungi in the future.

Keywords: Medicinal mushrooms, anti-cancer therapeutics, ethnomedicine, botanical new drug, *Antrodia cinnamomea*, immune system, cytotoxic.

INTRODUCTION

The usage of mushrooms as therapeutics has had a long history of more than 2000 years, including *Laricifomes officinalis* in Europe and *Ganoderma lingzhi* in China. Fruitbodies of *Piptoporus betulinus* (Figure 1G) were found among the items of "Ötzi the Iceman," a 5,000-year-old European mummy, and these were presumably used as a remedy for parasitic worms [1]. The traditional usage of mushrooms in European folk medicine, e.g. of "Jew's Ear," *Auricularia auricula-judae* (Figure 1B) gradually disappeared in the 18th and 19th centuries [2]. *Trametes versicolor* (Figure 1I) in the West was only used for ornamental purposes, but as medicine in the East. Compared to the uninterrupted development in East Asia for many centuries, however, cultivation as well as medical research and usage of mushrooms experience a relatively recent revival and development in western countries. In traditional Chinese medicine and folk medicines, mushrooms have not been used specifically against cancer, but against different other diseases or rather for general disease prevention, for example, one of the most commonly used medical fungi in Chinese medicine, *Wolfiporia cocos* ("fu ling"). The antitumor properties of medical fungi were discovered mainly while screening them with modern scientific methods. In contrast to other diseases traditionally treated with medical mushrooms, little experience, therefore, exists with the treatment of cancer. This may be one of the reasons why few mushroom-based anticancer therapeutics are currently available.

Figure 1. Examples of medical mushrooms with antitumor properties. A. *Agaricus blazei*, dried fruitbodies from the market. B. *Auricularia auricula-judae* on its natural wood substrate. C. *Cordyceps militaris*, ascostromata from artificial cultivation medium. D. *Ganoderma* species from wild collection sold on the market. E. *Sanghuangporus sanghuang* from the market. F. *Ophiocordyceps sinensis*, mummified caterpillars with ascostromata. G. *Piptoporus betulinus* on the natural wood substrate. H. *Taiwanofungus camphoratus* artificially grown on wood log. I. *Trametes versicolor* on the natural habitat. J. Dessert made of *Tremella fuciformis* from artificial cultivation and *Lycium chinense* (gouqi) berries.

Scientific research devoted to anticancer properties of mushrooms, however, started worldwide ca. in the 1960s [2]. For this reason, we first list the most important mushrooms with antitumor

properties (Table 1) and briefly review some general features which are particular for medical mushrooms, and then focus on a recent development of a mushroom from Taiwan as example in order to illustrate the process from ethnomedicine to new, science-based anticancer therapeutics.

Taxonomy of medical fungi

Mushrooms with traditional and folk medicinal usage belong to two major systematic groups of fungi namely the phyla (divisions) Basidiomycota and Ascomycota, which form macroscopically visible fruitbodies. The fruitbody types of medically used basidiomycetous mushrooms are mainly gilled mushrooms, jelly mushrooms, polypores, and tooth fungi, which are confined to different orders of the subphylum/subdivision Agaricomycotina (Hymenomycetes). The main orders are Agaricales, Auriculariales, Boletales, Hymenochaetales, Polyporales, Russulales, and Tremellales (Table 1). In the fruitbodies of medical ascomycetous mushrooms, perithecia (microscoscopic, flask-shaped structures with a small apical opening) are embedded in a macroscopically visible stroma, the ascostroma. Systematically, these fungi mainly belong to the orders Hypocreales and, to a lesser extent, Xylariales (class Sordariomycetes, subphylum/subdivision Pezizomycotina).

In spite of the long tradition of using medical fungi, particularly in East Asia, scientific research is still in its pioneer stage so that even basic taxonomical classification of medical mushrooms used for many centuries is an object of recent discovery and debate of new species. For some of the most famous species, taxonomy has become confusing by the existence of several synonyms. Several "scientific" names used in the market are doubtful, out-of-date, or simply wrong. In Table 1, these names are considered synonyms or "commercial names." The current scientific name in Table 1 is given for the species presumably most commonly used for application and research; in some cases, however, not this species, but another closely related one may have been used.

Exact classification is mandatory for effective application of medical fungi, because different species may show different biochemical profiles. For example, there is some debate whether *Agaricus blazei* (Figure 1A) is the same species as *A. subrufescens* and *A. brasiliensis* or whether different species are comprised by the commercial name *A. blazei* [3]. The reishi mushroom (Figure 1D) cultivated widely in East Asia was believed to be identical with the European *Ganoderma lucidum*, but recently revealed to include an East Asian species, which was described as *Ganoderma lingzhi* [4]. Both species differ considerably in the amount of triterpenic acids indicating that previous reports about "*G. lucidum*" as medical mushroom with high triterpenoid contents refer to *G. lingzhi* [5]. Further research is urgently needed, because in addition to the prevalent *G. lingzhi*, true *G. lucidum* also occurs in China and is occasionally cultivated as medical mushroom [6]. Another polypore used in ethnomedicine in Taiwan (Figure 1H) was first described as *Ganoderma camphoratum* in 1990, which was challenged by other authors who described it as *Antrodia cinnamomea*. This synonym is still widely used as commercial name, although the correct scientific name is *Taiwanofungus camphoratus* [7]. A further polypore with antitumor usage in East Asia was only recently described as new species, *Sanghuangporus sanghuang* [8-10]. (Figure 1E). It differs from the closely related species, with which it was lumped together in the previous literature as *Inonotus linteus* or *Phellinus linteus*, by its specific host tree, mulberry, whereas the closely related other species without medical usage occur on other host plants [9]. For these reasons, we may keep in mind that some discrepant reports about bioactive compounds or clinical studies of medical fungi may be based on taxonomic confusion of closely related, but distinct species.

Table 1. List of 35 alphabetically arranged scientific species names of fungi with anti-cancer potential activity, including synonyms and commercial names in brackets, classification, experimental anticancer evidence, detailed mechanisms, and references.

Scientific name (synonyms and commercial names)	Class	Experimental anti-cancer evidence	Anti-cancer mechanism
Albatrellus confluens	Ru (B)	Anti-tumor activity [11]	The secondary metabolite from fresh fruiting bodies "grifolin" can inhibit the growth of some cancer cell lines in vitro by up-regulating death-associated protein kinase 1 DAPK1 via p53 to induce cell cycle G1 phase arrest in nasopharyngeal carcinoma cells.
		Human nasopharyngeal carcinoma (CNE1) cell line [12]	The inhibition of cyclin D1, cyclin E, CDK4 expression, subsequent reduction in pRB phosphorylation, and a significant up-regulation of CKI (p19INK4D) were observed after grifolin treatment in the human nasopharyngeal carcinoma (CNE1) cell line.
Albatrellus confluens	Ru (B)	Human nasopharyngeal carcinoma (CNE1) cell line [12]	Both the ERK1/2 and the ERK5 pathways are involved in the inhibition and cause cell-cycle arrest in G1 phase. The grifolin can further induce dephosphorylation and upregulates death-associated protein kinase 1 (DAPK1) in nasopharyngeal carcinoma cells NPCs and HONE1, promote the protein–protein interaction of DAPK1 and ERK1/2 to prevent ERK1/2 nucleolus translocation.
Agaricus blazei	Ag (B)	Human prostate cancer [13]	Induction of lactate dehydrogenase leakage and activity of caspase 3 and DNA fragmentation in androgen-independent PC3 cells.
		Human promyelocytic leukemia (NB-4) cells-bearing nude mice [13]	The extract showed potent tumor-selective growth inhibitory activity against human leukemia NB-4 and K-562 cells.
Agaricus bisporus	Ag (B)	Prevent breast-cancer cell proliferation [14]	The extract can suppress aromatase activity and prevent breast-cancer cell proliferation.
		DU145 and PC3 prostate cancer cell [15]	The extract, conjugated linoleic acid can decrease the DU145 and PC3 prostate tumor size and tumor cell proliferation in nude mice.
Auricularia auricula-judae (Auricularia auricula)	Au (B)	Acinar cell carcinoma of the pancreas [16]	The heteropolysaccharide can up-regulate the apoptosis-related proteins Bax and down-regulate Bcl- 2 to suppress cell proliferation *in vitro* and induce S-180 tumor cell apoptosis in mice.
Clitocybe nebularis	Ag (B)	Human leukemic T cells [17]	The immunomodulatory protein CNL belonging to the ricin B-like lectin superfamily has anti-proliferative effect which appears to be elicited by binding to carbohydrate receptors on human leukemic T cells, and also can affect hematopoietic malignancies.
Clitocybe nebularis	Ag (B)	Hep G2 and MCF-7 tumor cells [18]	The laccase enzyme exhibits the anti-proliferative activity against Hep G2 and MCF-7 tumor cells.
		Inhibitor of the growth of lung, breast, colon, and gastric cancer cell lines [19]	The ethanolic extract can inhibit the growth of lung (NCI-H460), breast, colon, and gastric cancer cell lines. It can induce an S-phase cell cycle arrest, increase the percentage of apoptotic cells, and enhance the levels of p53.
Coprinus comatus	Ag (B)	Malignant estrogen-independent breast cancer [20]	The extract can affect IkBa phosphorylation, and the ethyl acetate extract can inhibit the activity of IKK complex.
Coprinus comatus	Ag (B)	Prostate cancer LNCaP cells [21]	The extract can inhibit dihydrotestosterone-induced LNCaP cell viability - causes a G1 phase arrest.
Cordyceps militaris	Hyp (A)	Prostate (PC-3), colon 205 and hepatoma (HepG2) cells [22]	Inhibiting the nitric oxide, tumor necrosis factor-a, and interleukin-12 production from LPS/IFN-c-stimulated macrophages with anti-proliferation against human cancer cells.
		Immune activator or anti-cancer [23]	Enhancing of P1 promoter region to induce level of IL-18 transcription in mouse brain and liver, and activate the IFN-c production in mouse leukemic monocyte macrophage cell line (RAW 264.7).
Flammulina velutipes	Ag (B)	Anti-tumor effect [24]	A fungal immunomodulatory protein (FIP-fve) has shown anti-tumor effect on oral administration in murine hepatoma model as an activator of human T lymphocytes.
		Anti-tumor substance [25]	The aqueous extract is an anti-tumor substance. A stable hemagglutinin isolated from the fruiting bodies can inhibit proliferation of leukemia L1210 cells.

Scientific name (synonyms and commercial names)	Class	Experimental anti-cancer evidence	Anti-cancer mechanism
		Anti-breast-cancer agents [26]	The extracts can inhibit growth of (estrogen receptor) ER+ (MCF-7) and ER- (MDA-MB-231) breast cancer cells by inducing a rapid apoptosis on both types of cancer cells. The ER- breast cancer cells are inhibited by about 99% by the extracts.
Fomes fomentarius	Po (B)	Human gastric cancer cell lines SGC-7901 and MKN-45 [27]	The ethanol extract and polysaccharide play crucial roles in gastric cancer intervention.
		SGC-7901 cells [28]	The exopolysaccharide has a direct anti-proliferative effect in vitro on SGC-7901 cells. Furthermore, this exopolysaccharide sensitized doxorubicin (Dox) and induced growth inhibition of SGC-7901 cells at concentration of 0.25 mg/mL after 24 h treatment.
Ganoderma lingzhi / G. lucidum species complex (*Ganoderma lucidum, G. sichuanense, G. tsugae*)	Po (B)	Human gastric carcinoma (AGS) cells [29]	The treatment induced the expression of death receptor 5 and tumor necrosis factor-related apoptosis-inducing ligand and then triggers the activation of caspase-8 and the cleavage of Bid.
		Inhibition of tumor invasion and metastasis [30]	Ganoderic acid T can induce cell aggregation, inhibit cell adhesion, and suppress cell migration in human colon tumor cell lines of HCT-116 p53-/- and p53+/+.
		In vitro against mouse lymphocytic leukemia (L1210) cells [31]	LZ-D-4, a native glycopeptide, showed antitumor test *in vitro* against mouse lymphocytic leukemia (L1210) cells.
		Anti-tumor effects, colorectal adenocarcinoma [32]	The extracts caused tumor shrinkage in nude mice, and colorectal adenocarcinoma cells are inhibited by induction of G2/M cell cycle arrest after treating the extracts.
Ganoderma lingzhi / G. lucidum species complex (*Ganoderma lucidum, G. sichuanense, G. tsugae*)	Po (B)	Anti-human papillomavirus 16 (HPV 16) E6 oncoprotein activity [33]	HPV 16 E6 production was suppressed by treating the crude dichloromethane extracts in epidermoid cervical carcinoma (CaSki) cells.
		Human lung adenocarcinoma (A549) cells [34]	Treated lung cancer cells undergo premature cellular senescence and are arrested at G1 phase.
Grifola frondosa	Po (B)	Human gastric carcinoma (SGC-7901) cells [35]	Polysaccharide can inhibit SGC-7901 cells growth and induce cell apoptosis.
		Inhibited the proliferation of human gastric adenocarcinoma (SGC-7901 cells), whereas slightly influenced the growth of human normal liver (L-02) cell line [36]	The SGC-7901 cell cycle was arrested in the G2/M phase by a polysaccharide-peptide GFPPS1b.
Hericium erinaceus		Anti-tumor activity [37]	Enhancing doxorubicin (Dox)-mediated apoptotic signaling by reducing c-FLIP expression via JNK activation, and also enhancing intracellular Dox accumulation via the inhibition of NF-κB activity.
Hericium erinaceus		Balb/c mice transplanted with CT-26 colon cancer cells [38]	The vascular endothelial growth factor (VEGF), cyclooxygenase 2 (COX-2), and 5-lipoxygenase (5-LOX) were reduced in mRNA and protein Expression by tumor genes and further triggered the inhibition of neo-angiogenesis inside the tumors.
Imleria badia (Boletus badius, Xerocomus badius)	Bo (B)	Anti-tumor activity [39]	L-theanine has synergistic effect on the anti-tumor activities of doxorubicin, anthracyclines, cisplatin, and irinotecan.
Inocybe rimosa (Inocybe umbrinella)	Ag (B)	Tumor HepG2 and MCF7 cells [40]	The extract can inhibit proliferation of tumor HepG2 and MCF7 cells.
Inonotus obliquus	Hym (B)	Human colon cancer (DLD-1) cells [41]	The extract can induce apoptosis in human colon cancer (DLD-1) cells by prevention of reactive oxygen species (ROS)-induced tissue damage.
Inonotus obliquus	Hym (B)	Murine melanoma (B16-F10) cells [42]	The extract can inhibit the growth of B16-F10 cells by arresting cell cycle at G0/G1 phase and causing apoptosis, and further inducing cell differentiation. These effects are related to the down-regulation of pRb, p53, and p27 expression levels. The extract caused a G0/G1 cell cycle arrest with reduction of cyclin E/D1 and Cdk 2/4 expression levels. Intraperitoneal administration of the extract can inhibit the growth of tumor mass in B16-F10 cells implanted Balb/c mice, causing a 3-fold inhibition at dose of 20 mg/kg/day for 10 days.
Inonotus obliquus	Hym (B)	Anti-tumor activity [43]	The ethanol extract can cause anti-tumor activity.

Scientific name (synonyms and commercial names)	Class	Experimental anti-cancer evidence	Anti-cancer mechanism
Lactarius flavidulus	Ru (B)	Anti-cancer properties [44]	The polysaccharides administered intraperitoneally into white mice at a dosage of 300 mg/kg inhibited the growth of Sarcoma 180 by 100%. A dimeric 29.8-kDa lectin can suppress proliferation of HepG2 and L1210 cells with an IC50 of 8.90 μM and 6.81 μM.
Lentinula edodes	Ag (B)	Suppress leukemia cell proliferation [45]	The ethanol extract can decrease cell proliferation of CH72 cells.
Lentinus tuber-regium (Pleurotus tuber-regium)	Po (B)	HL-60 cells ,in vitro anti-proliferative activities [46]	The extract can cause G2/M arrest in HL-60 cells by depressing the Cdk1 expression, and cause S arrest in the HL-60 cells by a reduction of Cdk2 and an increase in cyclin E expression.
Lycoperdon utriforme (Calvatia utriformis, Handkea utriformis)	Ag (B)	Breast cancer cells [47]	An ubiquitin-like peptide represents a high anti-proliferative activity to breast cancer cells.
		Breast cancer cells [48]	A novel ribosome-inactivating protein calcaelin with translation-inhibiting and anti-mitogenic activities can reduce the viability of breast cancer cells.
Lycoperdon utriforme (Calvatia utriformis, Handkea utriformis)	Ag (B)	Gastric cancer pathogen *Helicobacter pylori* [49]	Strong antibiotic activity of calvatic acid and some of its analogs against gastric cancer pathogen *Helicobacter pylori*.
Ophiocordyceps sinensis (Cordyceps sinensis)	Hyp (A)	Anti-tumor activity [50]	Over 30 bioactivities, such as immunomodulatory, antitumor, anti-inflammatory, and antioxidant activities, have been reported for wild DongChongXiaCao and for the mycelia and culture supernatants of *O. sinensis*.
Phellinus igniarius	Hym (B)	Human hepatocarcinoma (SK-Hep-1) and rat heart vascular endothelial (RHE) cells [51]	The extract can inhibit the proliferation of human hepatocarcinoma (SK-Hep-1) and rat heart vascular endothelial (RHE) cells.
Piptoporus betulinus	Po (B)	Human lung carcinoma (A549), colon adenocarcinoma (HT-29) and rat glioma (C6) cell cultures [52]	The extract stimulated anti-cancer effects that were recognized to decreased tumor cell proliferation, motility, and the induction of morphological changes without toxicity in tested normal cells.
Pleurotus ostreatus	Ag (B)	HT-29 colon cancer cells [53]	An aqueous polysaccharide (POPS-1) can induce anti-proliferative and pro-apoptotic effects on HT-29 colon cancer cells.
Pleurotus citrinopileatus	Ag (B)	Anti-tumor activity in mice [54]	The lectin showed anti-tumor activity in mice bearing sarcoma 180, and caused approximately 80% inhibition of tumor growth.
Polyozellus multiplex (Thelephora multiplex)	Th (B)	Stomach cancer [55]	It can increase expression of p53 proteins to inhibit the cell proliferation in stomach cancer.
		Human myeloid leukaemic cell lines [56]	Polyozellin can induce phase 2 detoxifying enzymes with cancer-preventive potential in mouse hepatoma cells, and also induce differentiation in human myeloid leukemia cell lines.
Russula cyanoxantha	Ru (B)	HepG2 cells [57]	HepG2 cells treated with extract showed the markers of apoptosis: (a) G2/M cell cycle arrest, (b) chromatin condensation, (c) nuclear fragmentation, (d) phosphatidylserine exposure. Furthermore, PARP-cleavage; activation of caspase-3, -8, and -9; up-regulation of Bax and downregulation of Bcl-2 were observed in HepG2 cells.
Russula rosea (Russula lepida)	Ru (B)	Hep G2 cells and MCF-7 cells [58]	A lectin has anti-proliferative activity to Hep G2 cells and MCF-7 cells with an IC50 of 1.6 uM and 0.9 uM, respectively. Daily intraperitoneal injections of the lectin (5.0 mg/kg) for 20 days took about 67.6% reductions in the weight of S-180 tumor.
Sanghuangporus sanghuang (Phellinus linteus)	Hym (B)	Anti-tumor, immunomodulating and anti-metastasis [59]	The extract has anti-mutagenic activities and plays a role in the prevention of cancer by inducing NAD(P)H quinone oxidoreductase and glutathione S-transferase activities.
		Breast- and bladder-cancer [60]	The phenolic extract can induce apoptosis of breast- and bladder-cancer cells.
		SW480 human colon cancer cells [61]	A protein-bound polysaccharide can induce G2/M phase arrest and apoptosis in SW480 human colon cancer cells.
		Hepatoma [62]	The extract causes a reduction in tumor size and an increase in T cell numbers; IL-12, IFN-c, and TNF-a secretion; NK cell activity and phagocytic ability in Human hepatoma (Hep3B) cell-transplanted mice.

Scientific name (synonyms and commercial names)	Class	Experimental anti-cancer evidence	Anti-cancer mechanism
		Human hepatocellular liver carcinoma (HepG2), Human colon adenocarcinoma (HT-29), human lung cancer (NCIH 460) and human breast adenocarcinoma (MCF-7) cells [63]	Proteoglycan has an anti-proliferative effect.
Schizophyllum commune	Ag (B)	Immunomodulatory and anti-neoplastic agent [64]	Schizophyllan, consisting of a linear chain of b-D-(1-3)-gluco-pyranosyl groups and b-D-(1-6)-glucopyranosyl groups, can be an immunomodulatory and anti-neoplastic agent.
Suillus placidus	Bo (B)	Anti-tumor activity [65]	Human liver cancer cells (HepG2 cells, Hep3B cells, and SK-Hep-1) were killed by suillin which induces apoptosis in HepG2 cells as characterized by DNA fragmentation, phosphatidyl-serine externalization, activation of caspase-3, -8, and -9, depolarization of mitochondrial membrane potential, as well as release of cytochrome c into the cytosol. Suillin also caused increases in the protein levels of Fas death receptor, adaptor FADD protein, pro-apoptotic protein Bad and a decline of Bid.
Taiwanofungus camphoratus (Antrodia camphorata, Antrodia cinnamomea)	Po (B)	Human estrogen-non-responsive breast cancer (MDA-MB-231) cells [66]	Non-cytotoxic concentrations (20–80 μg/mL) of extract can inhibit the invasion/migration of highly metastatic MDA-MB-231 cells through suppression of the MAPK signaling pathway.
		Pancreatic cancer (PANC-1 and AsPC-1) cells [67]	Antroquinonol can induce G1 arrest of the cell cycle and a following apoptosis in human pancreatic cancers through an inhibitory effect on PI3-kinase/Akt/mTOR pathways that in turn down-regulates cell cycle regulators.
Taiwanofungus camphoratus (Antrodia camphorata, Antrodia cinnamomea)	Po (B)	Pancreatic cancer (PANC-1 and AsPC-1) cells [67]	Antroquinonol also can induce the connection between apoptosis, autophagic cell death, and accelerated senescence in cancer cells.
		Hepatoma (C3A and PLC/PRF/5) cells and xenografted cells in tumor-implanted nude mice	Intervention of MDR gene expressions and COX-2- dependent inhibition of p-AKT.
		Transitional cell carcinomas cell lines, superficial cancer cell line RT4, and metastatic cell lines TSGH-8301 and T24	On treatment with the extract at 100 lg/mL, the p53-independent overexpression of p21 with simultaneous down alteration of pRb was observed in RT4. The treatment with the extract at 50 lg/mL also causes simultaneous downregulations of Cdc2 and Cyclin B1, with suppression of the migrating capability of the two cell lines TSGH-8301 and T24, and finally cell death.
		A549 cell	The alcohol extract can induce apoptosis in A549 cell by decreasing the expression level of four tumor-related genes, e.g. calpain 1/2 small subunit, galectin-1, Rho GDP inhibitor A. Apoptosis is caused by the mitochondrial pathway and endothelium reticulum stress. The extract also could decrease the production level of eukaryotic translation initiation factor 5A, which is a potential cancer intervention target.
Taiwanofungus camphoratus (Antrodia camphorata, Antrodia cinnamomea)	Po (B)	MDA-MB-231 cancer cells	Apoptosis in the MDA-MB-231 cells was followed by release of cytochrome c, activation of caspase-3, -8, and -9, and specific proteolytic cleavage of poly (ADP-ribose) polymerase (PARP). The extract can also inhibit COX-2 protein expression and prostaglandin E2 (PGE2) production in MDA-MB-231 cells, and induce apoptosis in MDA-MB-231 cells *in vitro* and *in vivo* in nude mice.
		MDA-MB-231 cells [68]	The cell cycle blockade in extract-treated MDA-MB-231 cells was related to reductions in cyclin D1, cyclin E, CDK4, cyclin A, and proliferating cell nuclear antigen (PCNA), and increased CDK inhibitor p27/KIP and p21.
		Hepatocellular carcinoma cell lines (HepG2, HepG2.2.15, Mahlavu, PLC/PRF/5, SK-Hep1 and Hep3B) [69]	Antroquinonol can stop the cell-cycle progression and cause apoptosis. The loss of mitochondrial membrane potential and depletion of mitochondrial content showed the mitochondrial stress caused by antroquinonol, which exhibits anti-cancer activity against the hepatocarcinoma cells through AMPK activation and inhibition of mTOR translational pathway, leading to G1 arrest of the cell-cycle and subsequent cell apoptosis.
Taiwanofungus camphoratus (Antrodia camphorata, Antrodia cinnamomea)	Po (B)	A549 cell [70]	Antroquinonol-induced apoptosis related to disrupted mitochondrial membrane potential and activation of caspase 3 and PARP cleavage in A549 cells. Antroquinonol treatment also can down-regulate the expression of apoptosis regulatory proteins Bcl2, which was correlated with decreased PI3K and mTOR protein levels without altering pro-apoptotic and anti-apoptotic proteins. Antroquinonol changed the expression level of miRNAs in A549 cells.

Scientific name (synonyms and commercial names)	Class	Experimental anti-cancer evidence	Anti-cancer mechanism
		Oral cancer (OECM1 and OC-2) cell lines [71]	The mechanism of growth inhibition was apoptosis induction, resultant of caspase-3 activation and DNA fragmentation.
		Liver cancer (PLC/PRF/5) cell line [72]	The effect was related to a decrease in either the level or activity of VEGF, matrix metalloproteinases (MMP-2, MMP-9 and MT1-MMP), and an increase in the expression of tissue inhibitor of metalloproteinase (TIMP-1 and TIMP-2). The extract can further inhibit activated and inducible NF-kB in both its DNA-binding activity and transcriptional activity, also can inhibit the TNF-a-activated NF-kB dependent reporter gene expression of MMP-9 and VEGF. The extract also exhibited an inhibitory effect on angiogenesis.
Trametes trogii (Funalia trogii)	Po (B)	Anti-tumor toxicity [73]	A 4 h exposure of HT29, LNCaP, PC3, MCF-7, and MDA-MB-231 tumor cells to extract (0.5–5.0 mg/mL) cause the cytotoxicity. IC50 values were found to range from 0.4 to 0.72 mg/mL; exposing fibroblast cells to the extract resulted in no cell death, while proliferating endothelial cells were killed. When tumors grown in immune compromised mice injected intratumourally with extract (5 mg/mL twice a week for two weeks), a 9-day tumor-growth delay was observed.
Trametes versicolor (Coriolus versicolor)	Po (B)	Prostate cancer LNCaP cells [74]	The extracts can reduce the growth of hormone responsive prostate cancer LNCaP cells.
		Gastric cancer (7907), lung cancer (SPC), leukemia (MCL), and lymphoma (SLY) [75]	Inhibition was caused by a crude extract.
		Human hepatoma cancer (QGY) cell lines [76]	Apoptosis and decrease in the expression of the cell cycle-related genes (p53, Bcl-2, and Fas) indicate the therapeutic potential of the fungal polysaccharides.
Tremella fuciformis	Tr (B)	Anti-tumor activity [77]	Polysaccharides can induce monocytes to produce interleukins (IL-1 and IL-6) and tumor necrosis factor by monocytes in vitro and have radical-scavenging activity.
Wolfiporia cocos (Poria cocos, Wolfiporia extensa)	Po (B)	Inhibition of tumor growth of S-180 in vivo [78]	Polysaccharides from cultivated mycelia depending on medium can induce growth inhibition. Sulfated derivatives cause apoptosis in S-180 and HepG2 tumor cells by up-regulation of Bax and down-regulation of Bcl-2. Triterpenoids show cytotoxicity against cancer cell lines.

Class = Classification, A = Ascomycota, B = Basidiomycota, Ag = Agaricales, Au = Auriculariales, Bo = Boletales, Hym = Hymenochaetales, Hyp = Hypocreales, Po = Polyporales, Ru = Russulales, Th = Thelephorales, Tr = Tremellales.

Which part of the fungus is used?

Macrofungi develop in different stages during their life-cycle, which have different biological functions for the fungus and, therefore, often also differ in their chemical composition (Table 2).

Table 2. Different growth stages with their function in the life-cycle of medical mushrooms

Growth stage	Mycelium	Sclerotium/ pseudosclerotium	Fruitbody
Function in the life-cycle	Growth by exploitation of the substrate	Storage and dormancy	Dispersal of spores
Examples	Theoretically all medical fungi in artificial culture	*Inonotus obliquus* (on stems of birch trees) *Ophiocordyceps sinensis* (mummified insect body) *Wolfiporia cocos* (surrounding roots of pine trees)	Agaricus blazei (agaric) Auricularia auricula-judae (jelly fungus) Ganoderma lingzhi (polypore) Hericium erinaceus (tooth fungus) *Ophiocordyceps sinensis* (ascostroma with perithecia)

Mycelia usually develop from dispersed spores, exploiting the substrate by degradation and uptake of nutrients. When sufficient nutrients and water is taken up, fruitbodies are formed, which produce new spores for dispersal. Sclerotia and pseudosclerotia (in contrast to sclerotia, pseudosclerotia at least initially include parts of the substrate [79]) are compact mycelial masses which store nutrients and water under conditions unfavorable for growth (dormancy) or as a prerequisite for fruitbody formation.

Most of the traditionally used mushrooms form fruitbodies and/or sclerotia/peudosclerotia that occur at sufficient quantities and/or are relatively long-lived. Compared to short-lived fruitbodies e.g. of ink caps or soft-fleshy boletes, polypore fruitbodies and sclerotia usually persist for several weeks to years and are easy to preserve. It might be speculated that long-lived fruitbodies and sclerotia have particularly been equipped with some protection against feeding by animals or microbial degradation and for this reason, are particularly rich in bioactive compounds. In traditional usage, only fruitbodies or sclerotia/pseudosclerotia or a combination of both are collected and, if possible, are preferred also in modern usage. For many macrofungi, methods for commercial production of fruitbodies or sclerotia have, therefore, been developed [80]. For some species, such methods are not yet available, e.g. *Ophiocordyceps sinensis* which is parasitic on specific moth larvae which are killed and mummified by the fungus (for this reason and in order to have an analog classification as for Basidiomycota, we may call this mummified substrate of an ascomycete also "pseudosclerotium"). Such fungi continue to be collected at large quantities in the wild, which raises concerns of species protection. Cultivation of mycelia may be the only method to overcome this problem. Mycelium cultivation and screening also allows exploration of mushrooms which are not considered in traditional medicines, because fruitbodies are too small, too rare, too short-lived or otherwise too difficult to harvest and preserve in sufficient quantities. Generally, for all fungi at least for producing spawn (inoculum) for fruitbody production, cultivation of mycelia under clean laboratory conditions is the first step for modern large scale production. Some compounds are released by the mycelium into the surrounding cultivation medium so that the medium with or without the mycelium can also be developed into products for the market [80]. When sclerotia or fruitbodies are used, they are used in total, i.e. there is usual no further differentiation between the stipe and the cap of the fruitbody, although they may differ in the concentration of compounds. Exceptions are the pseudoclerotia of *W. cocos*, which can be differentiated into the skin, the inner and most inner parts, whereas the inner part is most commonly used [80].

Infraspecific variability of bioactive compounds in medical fungi

In addition to species specificity, chemical compounds also vary within a single species, depending on the specific strain and environmental factors such as substrate as well as on processing e.g. by drying. Examples are two fungi used in traditional East Asian medicines, *Cordyceps militaris* (Figure 1C) and *Ophiocordyceps sinensis* (Figure 1F), which parasitize pupae or larvae of caterpillars, respectively, and these are therefore called caterpillar fungi. In the traditional application, the parasitized insect ("pseudosclerotium") is used together with the fungal fruitbody growing out from the corpse of the insect. The compound most representative for bioactivity was identified as cordycepin, which also has antitumor activity, but whose production depends largely on the substrate. In *C. militaris*, cordycepin production and fruitbody development can be induced more easily under optimized artificial culture conditions [81] than in *O. sinensis*. In the latter species, the content of cordycepin and related bioactive compounds does not only differ between

fresh and dried (processed) samples from the wild, but also between wild samples and cultivated mycelia, whereas drying (processing) of mycelia has no increasing effect on the content of compounds [82]. Since it is easier and cheaper to produce large quantities of mycelia, it is tempting to use mycelia as raw material for therapeutics. As it is obvious from the example of the pseudosclerotia of *Wolfiporia cocos* ("fu ling" in Chinese medicine) which in contrast to the mycelium storages the bioactive compounds at high concentration in specific storage cells [79], mycelia do not have necessarily the same medical value as sclerotia or fruitbodies of the same species. The same principle applies to other medical fungi, such as *Taiwanofungus camphoratus* (see below). *Tremella fuciformis* (Figure 1J) is a mushroom which is parasitic on a wood-decomposing fungus and has also been shown to have antitumor properties based on its polysaccharides [83]. Different strains differ by their contents of polysaccharides and proteins [84].

Previous Findings

Recently, there were more than 35 species of fungi investigated for cancer therapy (Table 1). The scope of these studies is very extensive, including a variety of important cancers, such as liver cancer [85-88], stomach cancer [89], breast cancer [90-92], and so on. As mentioned in the introduction, these fungal species with anti-cancer potential activity belong to a wide range of systematic groups. The methods and technologies used to study the antitumor activity of these fungi are also quite diverse: including testing the extracts of mycelia, fruitbodies, or culture media on different cancer cells to inhibit the cell growth [93-95], cell proliferation [96-98], cancer cell metastasis [99-101], gene expression [87,102]), or protein expression [103,104], or by which pathways cancer cell apoptosis is induced [105-107]. Furthermore, there are many studies using animal experiments to observe the various physiological phenomena in cancer model mice after oral [108] or intraperitoneal administration [107,109,110] of these extracts. These extracts have different targets, such as promoters of certain genes [86], or related enzymes of biochemical reactions [111,112], or the activity of mitochondria [113-115], and even some studies involve microRNAs [115], which in turn affect cell operation. In addition to the inhibition of cancer cells or cytotoxicity studies, some extracts have the effect of activating the immunomodulatory [108,116,117] and immune cells [86].

Some of these extracts come from aqueous extraction [118,119], some are alcohol extraction [92,113,120], or other organic solvent extraction technology [99,121]. Some experiments use crude extracts [121,122] more or less of which are distinguished into different fractions [113], some are structurally complex polysaccharides [95,120,123], peptides [123-125], and proteins [108], and for several components their chemical structures have been clarified and scientific chemical names given [93,100,126].

All of the above studies are summarized in Table 1, and alphabetically arranged according to the current scientific names of the fungi, including their synonyms and commercial names, classification, the experimental anticancer evidence, detailed mechanisms proposed for the anticancer activities, and references.

Taiwanofungus camphoratus is the most studied species from all of the fungi with anti-cancer potential activity. More than 900 related scientific research reports were published in international journals. The following subchapter deals with *Taiwanofungus camphoratus* as example of a medical fungus in order to illustrate the general process from ethnomedicine to developing new products for the market based on scientific analytic and experimental evidence.

TAIWANOFUNGUS CAMPHORATUS (*ANTRODIA CINNAMOMEA*) - A CASE IN SCIENCE AND APPLICATION

History and traditional application

Antrodia cinnamomea, also known as *Antrodia camphorata* or *Taiwanofungus camphoratus*, is a precious and unique edible fungus that grows naturally only on the aromatic tree *Cinnamomum kanehirae* (Lauraceae; Figure 2), which is native to Taiwan [127,128]. Wild *A. cinnamomea* grows between June and October at altitudes between 600 and 1800 m. The mushroom prefers to grow on the inner wall inside cavities of old tree trunks. Some fruit bodies grow on moist surfaces of dead trees or on the stumps of cut trees. The growth rate of wild *A. cinnamomea* mushroom is extremely slow. A ten years old fruit body has a dimension of only 25x15x12 mm. The scarcity of the natural host and the slow growth rate of the mushroom earned this treasured mushroom the name, the "ruby in Taiwanese forests."

A. cinnamomea has been medically used by aboriginal tribes for centuries to treat disease of food and drug intoxication, diarrhea, abdominal pain, hypertension, skin itching, and cancer [129]. The earliest record of a medical recipe against intoxication using *A. cinnamomea* was given by the traditional Chinese medicine doctor Tsai in 1983 with the formula of the recipe reported in 1987 [130]. Scientific study of *A. cinnamomea* started in 1990 and the first reports of its biological functions have been documented in National Digital Library of Theses and Dissertations in Taiwan [131]. Over the past decade, far more than 300 papers and 150 Taiwan patent applications for *A. cinnamomea* have been documented [132,133]. Numerous studies have been conducted on its physiology, biological, and pharmacological properties. Genomic and transcriptomic analyses of the medicinal fungus *A. cinnamomea* have been reported [134]. A 32.15-Mb genome draft containing 9,254 genes was cloned and genome ontology enrichment and pathway analyses were studied to uncover the sexual development and the biosynthesis of sesquiterpenoids, triterpenoids, ergostanes, antroquinonol, and antrocamphin.

Medicinal uses of A. cinnamomea

The host specificity, scarcity in nature, and slow growth rate makes the large scale production of *A. cinnamomea* very difficult. In the last decade many scientists searched for optimal culture conditions for mass production. Four major culture techniques have been developed: submerged liquid fermentation, solid support culture, timber culture, and dish culture. Each culture method has its advantages and disadvantages, for example: the submerged fermentation technique can produce tons of *A. cinnamomea* mycelia within 2-4 weeks but the product contains less biologically active compounds. Both the timber, and the dish cultivations (Figure 2) produce *A. cinnamomea* fruiting bodies with most of the biologically active compounds but the growth of the former takes 0.5-2 years and the latter takes 4-6 months. Since biological activity differs between *A. cinnamomea* originating from different cultivation methods and collections in the wild, it is necessary to define clearly the profiles of secondary metabolites and their biological functions to prevent confusion in *A. cinnamomea* products.

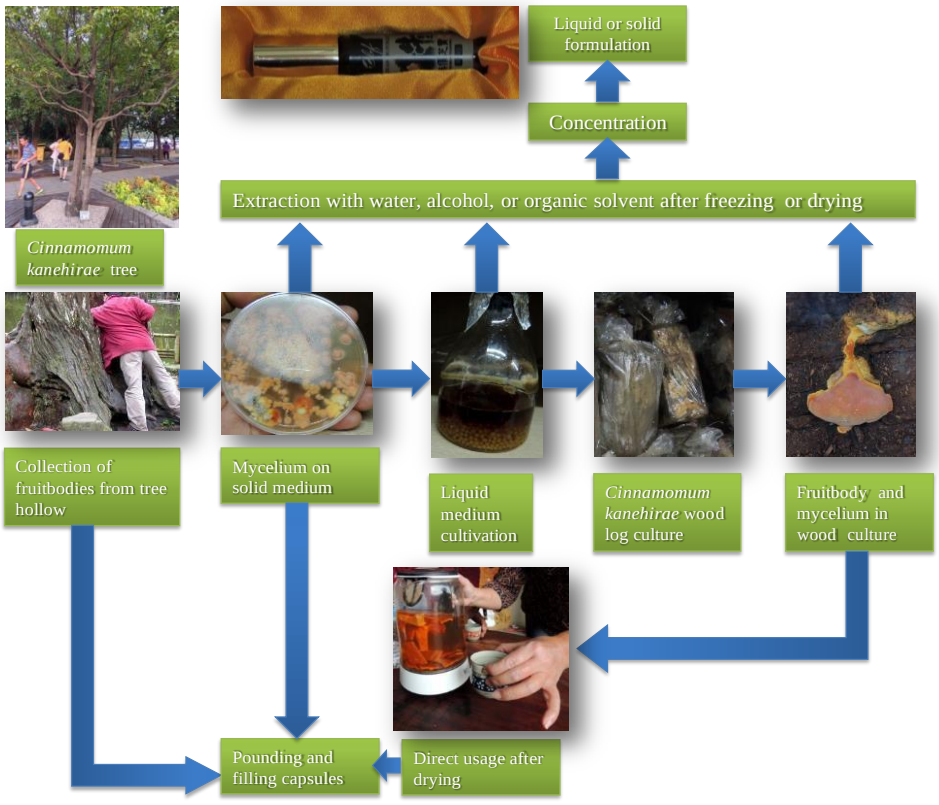

Figure 2. Processing of *Taiwanofungus camphoratus* from nature, liquid culture, solid culture and cultivation on wood of *Cinnamomum kanehirae*.

Bioactive compounds and anti-cancer mechanism

The most studied biological activities of *A. cinnamomea* are its 1) anti-inflammatory activity; 2) cytotoxic activity; 3) hepato-protective activity; 4) antioxidant activity; 5) immune modulatory effect and 6) miscellaneous activities, such as anti-allergic effect. The anti-cancer activity of *A.*

cinnamomea is a combination of the cytotoxic activity and the immune modulatory effects, and is reported in this text.

Recently, *in vivo* and *in vitro* studies of the biological functions using extracts of *A. cinnamomea* or isolated pure compounds against cancer or tumor cells revealed two mechanisms: the direct cytotoxic activity to inhibit cancerous growths and the stimulation of immune cells to enhance activity of both the innate and adaptive systems to eliminate pathogens or cancerous cells.

In general, the cytotoxic compounds can directly trigger apoptosis leading to programmed cell death. The cytotoxic activity of a compound against the testing cells is expressed with its half maximum inhibitory concentration (IC_{50}) which is the concentration for the compound that inhibits 50% population growth of the tested cells. When the experiment is conducted with both the cancer and the normal cells, the selectivity index (SI) is used to show the specificity of the drug against the cancer and compared to the normal cells. The SI was determined by the proportion of the IC_{50} value of cancer cells relative to that of normal cells.

The immune systems can be classified into the innate immune system (i.e. the non-specific immune system or in-born immunity system), and adaptive immune system (i.e. the acquired immune system or specific immune system). The innate immune system is comprised of the cells and mechanisms that defend the host from infection by other organisms. The cells of the innate system recognize and respond to pathogens in a general way. The adaptive immune system is composed of highly specialized cells and processes to eliminate pathogens or prevent their growth. Natural killer (NK) cells hold an important role in immunity and chemo-preventive activity in human beings. They are crucial in innate immunity capturing viruses and killing cancer cells and they also participate in adaptive immunity.

The innate immune system provides immediate defense against infection by: 1) recruiting immune cells to sites of infection, through the production of chemical factors called cytokines; 2) activation of the complement cascade to identify bacteria, activate cells, and promote clearance of antibody complexes or dead cells; 3) identification and removal of foreign substances present in organs, tissues, blood and lymph, by specialized white blood cells; 4) activation of the adaptive immune system through a process known as antigen presentation; 5) acting as a physical and chemical barrier to infectious agents.

The adaptive immunity creates an immunological memory after an initial response to a specific pathogen, and leads to an enhanced response to subsequent encounters with that pathogen. This process of acquired immunity is the basis of vaccination. Like the innate system, the adaptive system includes both humoral immunity components and cell-mediated immunity components.

Some of these compounds are responsible for the stimulation of the immune system in a way that is shared by many medical mushrooms [135], whereas other compounds appear to be more specific to *A. cinnamomea* and show specific cytotoxic activity against cancer cells. Many biologically active compounds have been isolated from *A. cinnamomea* and some of the structures have been determined [136,137]. The most widely studied components among the isolated numerous compounds of *A. cinnamomea* are: 1) antroquinonol and its derivatives; 2) succinic and maleic acid derivatives; 3) triterpenoids; 4) benzenoids; 5) polysaccharides; 5) volatile essential oils.

Both polysaccharides and volatile essential oils have low cytotoxic activity against normal and cancerous cells. They can activate all the cells of the innate immune system, such as NK cells, and cells of the adaptive immune system, such as B cells. [138,139].

The essential oil -dodecalactone

Natural volatile oils are extensively used in cosmetics and in folk medicine to prevent various specific pathologies. The influence of natural volatile oils on the cellular components of the immune system was reported recently [140]. A volatile compound from the culture medium of *A. cinnamomea* has been isolated [140] and its structure has been identified as -dodecalactone (-DDL compound **1**) (Figure 3). -DDL was found to potentiate NK cell activity through the Th_1 pathway. Cytomic screening was applied using CD56+ NK cells isolated from human peripheral-blood mononuclear cells (hPB-NK) and enriched by a negative magnetic bead-cell separation method. A flow cytometry was used to measure the immune-modulating activity so that it was found that -DDL can activate human NK cells to express the early activation marker CD69.

-DDL stimulates hPB-NK cells to kill HepG2-EGFP cells. The effect cells (hPB-NK cells) were co-cultured with target cells (HepG2-EGFP cells) with a ratio of 10:1 in the absence or in the presence of-DDL. Q-PCR analysis showed that γ-DDL did not only induce NK cells to express CD69 but also stimulated NK cells to secrete cytotoxic molecules (FasL and granzyme B) as well as Th_1 cytokines (TNF-α and INF-γ) to kill the HepG2-EGFP cells. Further study using synthetic (R,S)-4-hydroxydodecanoic acid (compound **2**) to activate NK cells expressing CD69 mRNA found that -DDL has been converted to 4-hydroxydodecanoic acid (compound **2**) and to stimulate the NK cells to express CD69. Optically pure (R)-(+)-4-hydroxydodecanoic acid (compound **3**) was resolved chemically and proofed to be the active compound to activate NK cells.

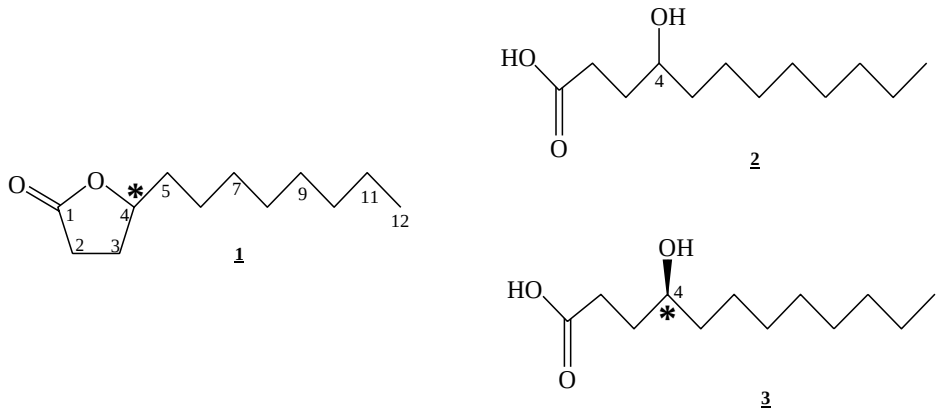

Figure 3. Chemical structures of: -dodecalactone **1**, (R,S)-4-hydroxydodecanoic acid **2**, and (R)-4-hydroxydodecanoic acid **3**.

Polysaccharides

Polysaccharides/oligosaccharides of plant or fungal origins are characterized by a wide spectrum of pharmacological effects, including immune modulation [141]. For example, polysaccharides from the herb *Astragalus membranaceus Radix* and the mushroom *Ganoderma lucidum* have been studied extensively in Asian medicine [142]. It was reported that these polysaccharides used as dietary supplements or vaccine adjuvants have immunomodulatory properties. Furthermore, polysaccharides/oligosaccharides with-glucan structural features extracted from oat, wheat, yeasts, and mushrooms have been shown to possess immunity- enhancing behaviors [143]. On the other hand, several receptors on immune cell surfaces have been identified as being able to

recognize these carbohydrate components and process their downstream signaling [144]. The concentration of mushroom polysaccharides depends on the stage of development, culture, and storage conditions [145]. Polysaccharides isolated from *A. cinnamomea* mycelia and fruiting bodies have different sugar compositions. The composition was determined using acid hydrolysis and GC-MS quantization [128]. A two-month cultured mycelium of *A. cinnamomea* contains mannose (4.7%), galactose (25.8%), GlcNac (35.5%), and arabinose (34%), and a two year-old *A. cinnamomea* fruiting body was found to have mannose (1.9%), glucose (6.6%), xylose (31.6%), and arabinose (59.9%). The high concentrations of arabinose and xylose in the *A. cinnamomea* fruiting bodies may be a good indication to differentiate the fruiting bodies from mycelia [146]. The heterogeneity of the *A. cinnamomea* polysaccharides makes structure determination very difficult. Polysaccharide fractions isolated from *A. cinnamomea* mycelia showed anti-hepatitis B virus effects [147]. A fraction of molecular weight 1.17×10^4 Daltons of *A. cinnamomea* polysaccharides showed immune function of cytokine expression and immune modulatory activity by induction of high levels of interferon-γ and tumor necrosis factor-α mRNA in BALB/c mice spleen cells [148].

Antroquinonol derivatives

Antroquinonols (Figure 4) belong to the ubiquinone family. The compound is only found in the cultured mycelia of *A. cinnamomea* and never reported from fruiting bodies. Anticancerous study showed antroquinonol (compound **4**) has cytotoxic activity in the □M scale against MCF-7 and MDA-MB-231 of human breast carcinoma, and Hep3B and HepG2 of human liver carcinoma, and DU-145 and LNCaP of human prostate carcinoma cell lines. The most potent cytotoxic activity of **4** was found against Hep3B with an IC_{50} 0.13±0.02 μM [149]. Another analogue, 4-acetylantroquinonol (compound **6**) isolated from the ethanolic extract of culture mycelia, was found to be highly potent against HepG2 with IC_{50}=0.2 □M compared to the parent derivative antroquinonol B (compound **5**) (IC_{50}=4.3 μM). The cytotoxic activity of **6** was due to the increase of cells in the G1 phase of the cells cycle and decreased proportion of S-phase cells and cell cycle arrest by sub-G1 accumulation [150].

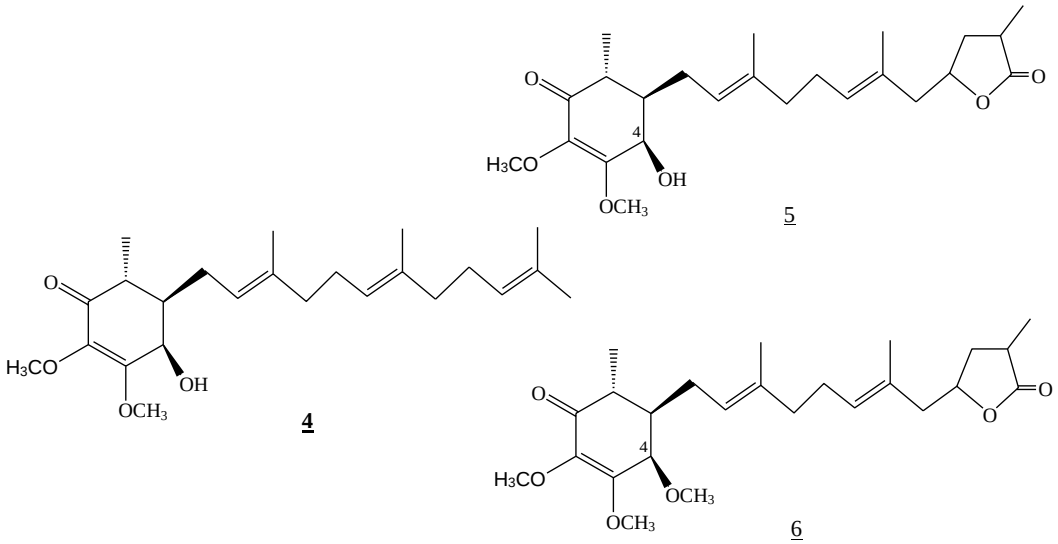

Figure 4. The structure of antroquinonol 4, antroquinonol B 5 and 4-acetyl antroquinonol B 6.

Succinic and maleic acid derivatives

Succinic acid is a di-carboxylic acid with four carbon atoms and naturally occurring in plant and animal tissues. Succinic derivatives are widely used as flavoring agents for food and beverages, perfumes, lacquers, and in pharmaceuticals [151]. They were also used as natural antibiotics and general curatives in the nineteenth century. Maleic acid is the unsaturated derivative of succinic acid which is also used in several industrial processes. Succinic and maleic acids are intermediates of the tricarboxylic acid cycle (TCA) and are produced industrially through fermentation (utilizing *E. coli*) by the C2-C6 platform bio-based production or through petrochemical synthetic routes.

The structure of succinic and maleic acid derivatives such as antrodin A (compound **7**), antrodin B (camphorataimide B) (compound **8**), antrodin C (camphorataimide C) (compound **9**), antrodin D (compound **10**), antrocinnamomin A (compound **11**), are shown in Figure 5. Due to the small quantity in the natural source, **7** and **8** were synthesized to study their cytotoxic activities *in vitro* and *in vivo* [152]. **8** exhibited a potent cytotoxic activity against four tested cancer cell lines including: human MDA-MB-231 breast cancer cells, MCF7 breast cancer cells, human HL-60 leukemia cancer cells, and human A549 lung cancer cells with IC_{50} 10.8-15.4 μM. The cytotoxic activity was due to induction of DNA fragmentation, and the sub-lethal dose of **8** caused arrest of the cell cycle at the G2/M phase through decreasing cyclin-A and cyclin-B1 protein levels.

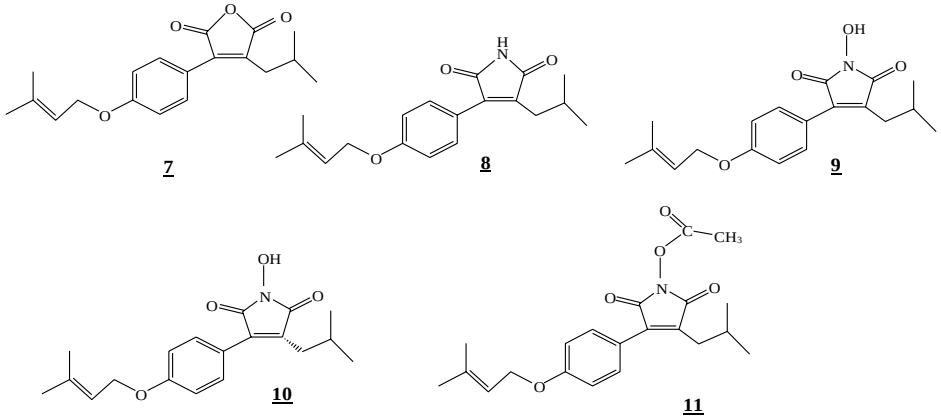

Figure 5. Succinic and maleic acid derivatives: Antrodin A **7**, camphorataimide B (antrodin B) **8**, camphorataimide C (antrodin C) **9**, Antrodin D **10** and antrocinnmomin A **11**.

Triterpenoids

Triterpenoids are a class of chemical compounds composed of three terpene units with the molecular formula $C_{30}H_{48}$; they may also be considered as consisting of six isoprene units. Triterpenoids are synthesized from the precursor unit isoprene in plants to form a triterpene hydrocarbon, followed by cyclization to generate a squalene, the precursor of all steroids [153]. More than two hundred triterpenenes have been identified and their structures have been determined.

Since triterpenoids possess low cytotoxic activity against normal cells, they are used for medicinal purposes in Asia for anti-inflammatory, analgesic, antipyretic, hepatoprotective, and cardiotonic agents as dietary supplements in the last few decades. Recent studies suggested their potential application as a cytotoxic agent against cancerous cells. Among the numerous compounds, over forty triterpenoids have been isolated either from wild fruiting bodies in the tree hollows of *C. kanehirae*, or from the mycelium from submerged fermentation cultured mycelia of

A. cinnamomea. The triterpenoids isolated from *A. cinnamomea* can be classified into two types of triterpenoids: ergostanes and lanostanes.

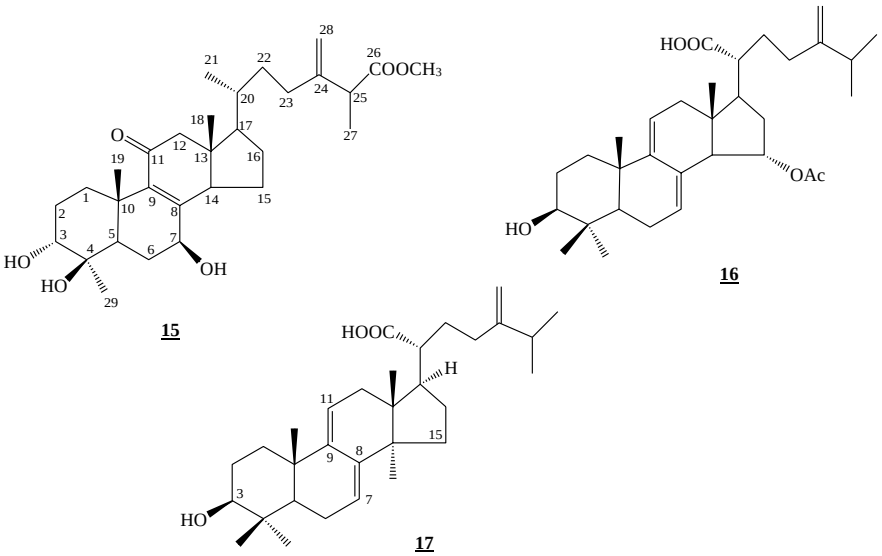

Figure 6. Structure of lanostane type triterpenoids: methyl antcinate K 15, eburicoic acid 16, and dehydroeburicoic acid 17.

Ergostane type triterpenoids

Ergostane triterpenoids, synthesized from squalene by the ergosterol biosynthetic pathway via lanostane triterpenoids, are major components of the fungal plasma membrane for maintaining the membrane fluidity and permeability [154]. *A. cinnamomea* ergostane triterpenoids possess a 29-carbons skeleton (Figure 6).

Methyl antcinate A (compound **12**) (Figure 6), isolated from the chloroform extract of *A. cinnamomea* fruiting bodies, exhibited a cytotoxic activity against two oral squamous cell carcinoma cell lines with IC_{50} 37.4 μM of OC-2 and with IC_{50} 24.5 μM of OEC-M [155]. Fluorescence analysis using annexin v-FITC/PI stain showed that **12** induced apoptosis of oral squamous carcinoma cells as indicated by the increased fluorescence intensity of annexin v-FITC/PI positive cells. It also increased caspase-3 activation, PARP cleavage, expression of Bax/Bcl-2 ratio and DNA fragmentation as indicated by TUNEL assay. **12** also showed potent cytotoxic activity with IC_{50} between 78.0 and 30.2 μM against HepG2, Hep3B, and Huh7 cells. In the three cancerous cell lines, **12** caused DNA fragmentation and accumulation of sub-G1 population to trigger cell death. As a systematic study of the cytotoxic activity of 11 triterpenoids against 14 different cancer cell lines and two normal cell lines has shown, **12** exhibited the most potent activity against all tested cancer cell lines and showed a high selectivity index (CC_{50}/IC_{50}). In another study on the cytotoxic activity of **12** and antcin B (compound **13**) on HepG2 cells, the cytotoxic effect against HepG2 cells revealed IC_{50} 25.8 and 38.4 μM, respectively [156].

Lanostane type triterpenoids

Lanostane triterpenoids are important intermediates in the biosynthesis of other steroids in plants and fungi. The lanostane usually possess an eburicane skeleton (compound **14**) (Figure 4) with double bonds between C-7, C-8, C-9, and C-11 and have a 24-exo-methylen-21-oic acid side-chain. The abundance of lanostanes in *A. cinnamomea* fruiting bodies makes it a rich source of the

important secondary metabolites compared to other mushrooms [157]. Various triterpenoids isolated from *A. cinnamomea* fruiting bodies exhibited potent cytotoxic effects against two glioblastoma cell lines (U87MG and GBM8401). Among these triterpenoids, methyl antcinate K (compound **15**), eburicoic acid (compound **16**), and dehydroeburicoic acid (compound **17**) (Figure 5) exhibited the most potent activity [158]. **17** led to a marked increase in the released LDH, a marker for cell injury, with IC_{50}25.7 μM, after 24 h. Staining the **17**-treated cells with annexin v-FITC/PI stain resulted in a double positive staining. This suggested that **17** treatment led to the induction of late apoptotic or narcotic stage in U87MG cells.

Benzenoid derivatives

Benzenoids, defined to have an electronic structure analogous to that of benzene and containing at least one benzene ring, are volatile secondary metabolites which are derived from L-phenylalanine for the purpose of defending against predators [159]. Figure 7 shows the chemical structure of three benzenoids: 4,7-dimethoxy-5-methyl -1,3-benzodioxole (compound **18**); 5-methyl-benzol[1,3]-dioxole-4,7-diol (compound **19**); and 2,3-dimethoxy-5-methyl-1,4-bezoquinone (compound **20**) isolated from *A. cinnamomea* fruiting bodies. The cytotoxic activity of **18** exhibited a significant G0/G1 arrest on human COLO 205 colon cancer cells. Since the level of p53 protein remained unchanged in the **18**-treated human colonic epithelial cells, the results showed that the p53-activated signaling pathway is involved in SY-1-induced G0/G1 arrest. DNA fragmentation which is detected in apoptotic cells, was also observed in COLO 205 upon treatment with SY-1 but not in other cells with mutant p53. Another study, using 75 μM of the *A. cinnamomea* fruiting body extract **18** fraction, the cytotoxic activity was equivalent to the effect of 150 μM of pure **18**. The results suggested the cytotoxic effect of the total extract may have the synergistic effect of other constituents in the extract [160].

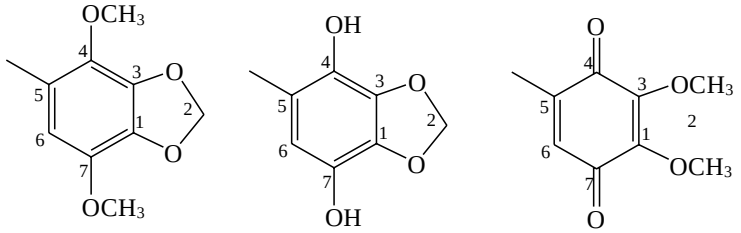

Figure 7. Chemical Structure of benzenoids: 4,7-dimethoxy-5-methyl-1,3- benzodioxole 18; 5-methyl-benzol[1,3]-dioxole-4,7-diol 19 and 2,3-dimethoxy-5-methyl-1,4-bezoquinone 20.

APPLICATION AND GLOBAL MARKETING

Although the detailed procedure of manufacturing *Taiwanofungus camphoratus* for the market is the secret of the companies, some basic information is presented (Figure 7). Fruitbodies collected in hollows of wild old trees of *Cinnamomum kanehirae* are considered the best for accompanying anticancer treatment, but because of the exorbitant prices and concerns of nature conservation, the second choice of using fruitbodies from artificial cultivation on wood logs from plantations of *C. kanehirae* is a good alternative. Mycelia grown on wood logs or artificial solid substrates are considered the third choice. Mycelia grown in liquid culture are cheaper, particularly, when they

are not separated from the cultivation medium. Mycelia are less recommended for usage against cancer, but can be involved in the treatment of less severe diseases and as a health food.
Fruitbodies or mycelia are frozen or dried and can be extracted with hot water or organic solvents (alcohol) for direct uptake. In order to ensure standardized amounts, dried fruitbodies or mycelia are also powdered and made into pressed tablets or filled into capsules, or their liquid extract is filled into small vials. Extracts provide the advantage that their compounds can be enriched by concentration and used conveniently as liquid or after spraying the highly concentrated extracts onto globuli also in solid form.

The total number of edible and medicinal fungi is over 2,300 species. Cultivated mushrooms have become popular with over 200 genera of useful macro-fungi in the world. According to the mushroom market reports on 2017-trends, analysis, and statistics: the mushroom market will reach US $50,034.12 million by 2019. Although there are no published figures related to the total world market value of medicinal mushrooms, the market value for *Ganoderma* medicinal mushroom in 1995 was estimated to be about US $1,628.4 million [161]. The market values of the mushroom products were estimated to be US $350 million in China, US $600 million in Korea, US $300 million in Japan, US $215 million in Taiwan, US $91.2 million in Malaysia, US $60 million in Hong Kong, US $2.2 million in Singapore and US $10 million in other countries.

Medicinal mushrooms have emerged as integral ingredients of dietary supplements in the last several decades. It is estimated that between 80 and 85% of all medicinal mushrooms products are derived from the fruiting bodies, which have been either artificially cultured or collected from nature. The total market value of *A. cinnamomea* products in Taiwan is estimated to be over 100 million US dollars per year (www. businesstoday.com.tw/article-content-80392-93594).

SUMMARY

Medically used macrofungi systematically belong to the orders Agaricales, Auriculariales, Boletales, Hymenochaetales, Polyporales, Russulales, and Tremellales of Agaricomycotina (Basidiomycota) and Hypocreales and Xylariales of Pezizomycotina (Ascomycota). More than 30 species demonstrate anticancer activity.

Research on the taxonomy of the species is incomplete but progressing. Different strains of the same species and different parts of the same fungus can differ by their biologically active compounds.

Antitumor activity of fungal compounds is exhibited as cancer cell apoptosis, inhibition of cell growth, cell proliferation, and of cancer cell metastasis, as well as alternated gene or protein expression, indicating a high diversity of anticancer mechanisms.

Taiwanofungus camphoratus (synonym *Antrodia cinnamomea*) is an endemic polypore with red fruitbodies only formed on a tree of the laurel family also endemic to Taiwan. The fungus has been used in ethnomedicine.

Fruitbodies of *T. camphoratus* have the best effect; mycelium from liquid culture has the weakest effect.

Among the main groups of anticancer compounds of *T. camphoratus* -dodecalactone (-DDL) and polysaccharides are mainly responsible for immunomodulatory effects, whereas cytotoxic effects are exerted by derivatives of antroquinonol as well as succinic and maleic acid,

triterpenoids, and benzenoids. Triterpenoids are particularly highly specific for *T. camphoratus* and rich with respect to concentration and structural diversity.

Taiwanofungus camphoratus and other medicinal mushrooms play an increasing role in anticancer treatment and in the global market.

TEST QUESTIONS

1. The development of medical mushrooms against cancer is derived from
   a. **Screening of many wild mushrooms for bioactive compounds**
   b. Lignin-decomposing enzymatic activity of wood-rotting fungi
   c. Usage of mushrooms in food fermentation
   d. Usage in ethno- and traditional medicines

2. Why it is not enough to cultivate large quantities of mycelia of medical mushrooms for therapeutics?
   a. Different strains of the same species can differ by their quantities of bioactive compounds
   b. Fruitbodies or sclerotia usually have higher concentrations of bioactive compounds than cultivated mycelia
   c. Cultivation condition influence the composition and amount of bioactive compounds
   d. **All of the above**
3. *Taiwanofungus camphoratus* (*Antrodia cinnamomea*)
   a. **Is an endemic polypore from Taiwan used in ethnomedicine**
   b. Is a widespread mushroom used in Traditional Chinese Medicine
   c. Forms agaric-like fruitbodies with stipe and gills
   d. Is a parasite of caterpillars

4. The immunostimulation activity of *Taiwanofungus camphoratus* (*Antrodia cinnamomea*) is partly based on:
   a. Stimulation of white blood cells by antroquinonol derivatives
   b. **Stimulation of natural killer cells by γ-dodecalactone (γDDL)**
   c. Stimulation of natural killer cells by triterpenoids
   d. Stimulation of white blood cells by cordycepin

5. The aromatic tree *Cinnamomum kanehirae* (Lauraceae) is?
   a. **A tree native to Taiwan**
   b. A tree native to China
   c. A tree native to South America
   d. A tree native to Europe

6. Which of the following statement is correct?
   a. *A. cinnamomea* fruiting bodies grow slowly.
   b. The growth rate of the wild *A. cinnamomea* mushroom is extremely slow.
   c. The genomic and transcriptomic analyses of the medicinal fungus A. *cinnamomea* was performed.
   d. **All the above statements are correct.**

7. Which of the following compounds was not reported as biologically active isolated from *A. cinnamomea*?
   a. Antroquinonol and its derivatives
   b. Triterpenoids
   c. **Fatty acids**
   d. Polysaccharides
   e. Volatile essential oils.

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List of Abbreviations: 20-deoxy salinomycin, SY-1; a strain of white mouse, BALB/c mice; B-cell lymphoma 2, Bcl-2; Bcl-2-associated X protein, Bax; Cluster of Differentiation 69 (a human protein used as marker of early immune activation), CD69; cytotoxic concentration of a substance causing death to 50% of viable cells, CC_{50}; deoxyribonucleic acid, DNA; fluorescein isothiocyanate/ propidium iodide, FITC/PI; □-dodecalactone, □-DDL; gas chromatography–mass spectrometry, GC-MS; half maximum inhibitory concentration, IC_{50}; human breast cancer cell lines, MDA-MB-231 and MCF7; human colon cancer cell line, COLO 205; human glioblastoma cell lines, U87MG and GBM8401; human leukemia cancer cell line, HL-60; human liver carcinoma cell lines, Hep3B, HepG2 and Huh7; human liver cancer cell line marked with Enhanced Green Fluorescent Protein, HepG2-EGFP; human lung cancer cell line, A549; human oral squamous cell carcinoma cell lines, OC-2 and OEC-M; human prostate carcinoma cell lines, DU-145 and LNCaP; interphase arrested at fully grown cell stage, G0/G1 arrest; interphase and mitosis, G2/M phase; interphase (prior to DNA duplication) characterized by DNA fragmentation, sub-G1; messenger ribonucleic acid, mRNA; Michigan Cancer Foundation-7, MCF-7; micro ribonucleic acids, microRNAs; natural killer cells, NK cells; natural killer cells isolated from human peripheral-blood mononuclear cells, hPB-NK; neural cell adhesion molecule, CD56+; Poly (ADP-ribose) polymerase, PARP; selectivity index (proportion of the IC_{50} value of cancer cells relative to that of normal cells), SI; tricarboxylic acid cycle, TCA; terminal deoxynucleotidyl transferase dUTP nick end labeling, TUNEL.

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