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MINI-REVIEW

Diversity of potentially exploitable pharmacological activities of the highly prized edible medicinal fungus *Antrodia camphorata*

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Abstract

Antrodia camphorata, also known as *A. cinnamomea*, is a precious medicinal basidiomycete fungus endemic to Taiwan. This article summarizes the recent advances in research on the multifarious pharmacological effects of *A. camphorata*. The mushroom exhibits anticancer activity toward a large variety of cancers including breast, cervical, ovarian, prostate, bladder, colorectal, pancreatic, liver, and lung cancers; melanoma; leukemia; lymphoma; neuroblastoma; and glioblastoma. Other activities encompass antiinflammatory, antiatopic dermatitis, anticachexia, immunoregulatory, antiobesity, antidiabetic, antihyperlipidemic, antiatherosclerotic, antihypertensive, antiplatelet, antioxidative, antiphotodamaging, hepatoprotective, renoprotective, neuroprotective, testis protecting, antiasthmatic, osteogenic, osteoprotective, antiviral, antibacterial, and wound healing activities. This review aims to provide a reference for further development and utilization of this highly prized mushroom.

Keywords *Antrodia camphorata* · Anticancer · Antiinflammatory · Antileukemia · Hepatoprotective · Neuroprotective

Introduction

Mushrooms produce a spectacular array of enzymes, non-enzymatic proteins, proteins, polysaccharides, and other compounds with a myriad of activities beneficial to health and thus have arrested the attention of many researchers (Hu et al. 2017; Jedinak et al. 2011; Jiang and Sliva 2010; Lavi et al. 2010a,b; Liu et al. 2017a, b; Pan et al. 2013; Schwartz and Hadar 2014; Wasser 2014, 2017; Wong et al. 2010; Zhou et al. 2017, 2018).

Antrodia camphorata, also known as *Antrodia cinnamomea*, or *Taiwanofungus camphoratus* and Niu-chang-chih or Niu-chang-ku in China, which means bull camphor mushroom and stout camphor fungus, is a precious medicinal fungus that belongs to Basidiomycetes. *A. camphorata* grows in areas 450 to 2000 m above the sea level on the mountains of Taiwan, in the hollow interior of the decayed trunk or the moist surface of the lodging trunk of *Cinnamomum kanehirae* tree (bull camphor tree) (Ao et al. 2009; Wu et al. 1997), an endemic native tree species in Taiwan. The mushroom has been used as a traditional remedy and a cancer-preventive herbal supplement in Taiwanese folk medicine. It is well known for its antidotal and antitumor functions and used to treat toxicities caused by food, alcohol, and drugs as well as conditions such as diarrhea, abdominal pain, hypertension, itchy skin, and tumors (Geethangili and Tzeng 2011). It has captured much attention in recent years owing to its multifarious health benefits embracing antiinflammatory, antioxidative, antileukemia, hepatoprotective, detoxifying, neuroprotective, and other effects, particularly its anticancer activity. In this article, the pharmacological effects of *A. camphorata* are presented from the above facets. Its active ingredients and pharmacological effects are summarized in Table 1, with the intent to provide a reference which may be useful for future work exploring the further development and utilization of *A. camphorata*.

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Pharmacological effects of *A. camphorata* demonstrated using purified ingredients

Effect of 4,7-dimethoxy-5-methylbenzo [d][1,3] dioxole and its more polar analogs on some cancer cell lines

The synthetic forms of a secondary metabolite of *A. camphorata*, 4,7-dimethoxy-5-methylbenzo [d][1,3]dioxole, and its more polar analogs weakly suppressed the proliferation of some cancer cell lines in the NCI-60 screen at 10 μM concentration (Yeung and Piggott, 2018).

Effect of antroquinonol on several carcinoma cells

Antroquinonol induced apoptosis in carcinoma cells via impeding activation of Ras and Rho signaling protein. This effect was achieved by downregulating the expression level of isoprenyltransferase (Ho et al. 2014).

Effect of methylantcinate A on oral cancer cells

A triterpenoid compound, methylantcinate A, extracted from the fruiting bodies of *A. camphorata* was investigated for the antiproliferative effect and the mechanism of induction of apoptosis in human oral cancer cell lines OEC-M1 and OC-2. The inhibitory effect on the growth of oral cancer cells was mediated by the Bax-related mitochondrial apoptotic pathway, but the specific mechanism of action needs further study (Tsai et al. 2010).

Effect of 4,7-dimethoxy-5-methyl-1,3-benzodioxole, 1(10 → 6)abeo-ergosta-5,7,9,22-tetraen-3α-ol, citreoanthrasteroid B, dankasterones A, dankasterones B, 4-acetylantroquinonol B, and antroquinonol on colon or colorectal cancer cells

A purified ingredient of fruiting bodies from *A. camphorata*, 4,7-dimethoxy-5-methyl-1,3-benzodioxole, exhibited an inhibitory effect on COLO-205 colon cancer cells in vitro by activating the p27/Kip1 signaling pathway mediated by p53 (Tu et al. 2012).

The effects of seven components from *A. camphorata* were explored. The results indicated that four of these compounds including 1(10 → 6)abeo-ergosta-5,7,9,22-tetraen-3α-ol, citreoanthrasteroid B, dankasterones A, and dankasterones B exhibited a significant inhibitory effect on CT26 colorectal cancer cells and human K562 leukemia cells (Lee et al. 2014b).

4-Acetylantroquinonol B, also extracted from *A. camphorata* mycelia, exerted a suppressive effect on colorectal carcinoma cells. The activity likely involved the STAT3 signaling channel (Chang et al. 2015a). Antroquinonol isolated from *A. camphorata* mycelia impeded the growth, migration, and invasion of colon carcinoma cells, probably by acting on the PI3K/AKT/β signaling pathway (Lin et al. 2017).

4-Acetylantroquinonol B did not affect the viability and proliferation of normal colon cells. In contrast, it diminished proliferation, migration, invasion, clonogenicity, and viability in colorectal cancer HCT116 and DLD1 cells. Re-expression of hsa-miR-324-5p and expression of E-cadherin and BAX2 were stimulated while expression of BcL-xL2, c-Myc, N-cadherin, SOD2, and vimentin was reduced. The expression of hsa-miR-324-5p in colorectal cancer cells was inhibited and demonstrated an inverse relationship with superoxide dismutase SOD2 expression. Enhanced expression of hsa-miR-324-5p in colorectal cancer cells repressed their *in vitro* and in vivo carcinogenicities. 4-Acetylantroquinonol B enhanced the antineoplastic activity of FOLFOX (composed of folinate (leucovorin), fluorouracil, and oxaliplatin) by eliciting the re-expression of SOD2-suppressed hsa-miR-324 and inhibiting SOD2-mediated tumorigenicity (Bamodu et al. 2018).

Effect of antroquinonol, triterpenoids, polysaccharides, and 1,3-β-D-glucan on pancreatic adenocarcinoma cells

Antroquinonol isolated from *A. camphorata* exhibited antiproliferative activity in PANC-1 and AsPC-1 pancreatic cancer cells. The mechanism involved inhibition of PI3-kinase/Akt/mTOR pathways and induction of G1 arrest in the cell cycle and apoptosis (Yu et al. 2012).

The ethanol-soluble and ethyl acetate-soluble compounds (mainly triterpenoids, polysaccharides, and 1,3-β-D-glucan) extracted from *A. camphorata* fruiting bodies manifested a cytotoxic effect on BxPC-3 human pancreatic adenocarcinoma cells but not on normal cells. The extracts of *A. camphorata* hindered proliferation, promoted apoptosis, and suppressed migration of BxPC-3 human pancreatic adenocarcinoma cells. These effects were dependent on the mitochondrial apoptotic pathway. In particular, it was brought about by regulating the bax/bcl-2 ratio of the levels of expression of bax and bcl-2, augmenting the release of cytochrome c, and triggering the activation of caspase-9 and caspase-3 (Lee et al. 2014a).

Effects of 4-acetylantroquinonol B on hepatocellular carcinoma cells

5′AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR) are targets for treatment of liver cancer with chemotherapy. The ranking of potency of antroquinonol against various liver cancer lines was HepG2 > HepG2.2.15 > Mahlavu > PLC/PRF/5 > SK-Hep1 > Hep3B. Antroquinonol curbed the translation but not

transcription of G1 regulator proteins, encompassing Cdk2, Cdk4, cyclin D1, and cyclin E. The assembly of tuberous sclerosis complex (TSC)-1/TSC2 was thwarted, resulting in arrest of protein biosynthesis via suppression of protein

Table 1 Pharmacological effects of some active ingredients isolated from *Antrodia camphorata*

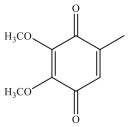
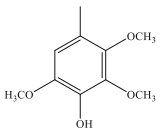
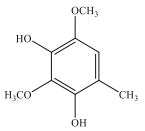
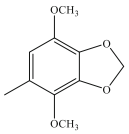
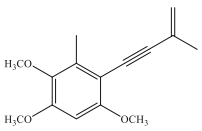
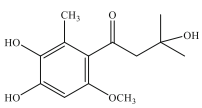
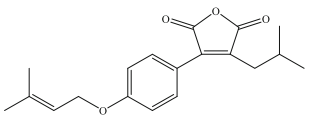
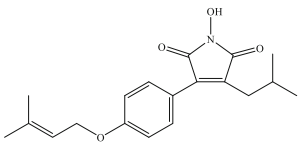
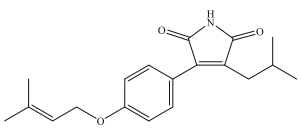
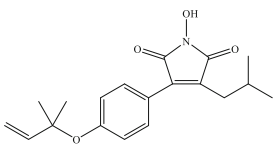
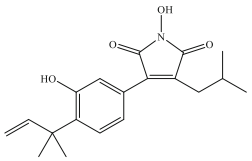
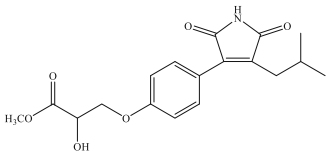
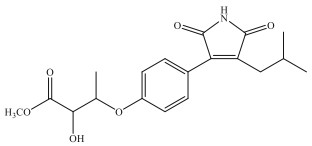
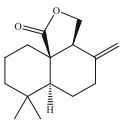
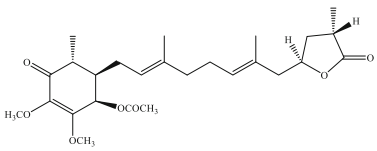
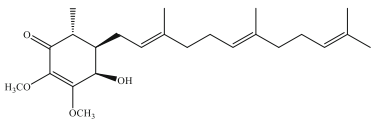
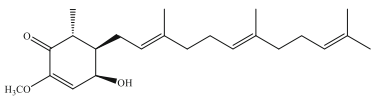
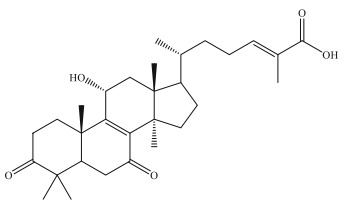
Chemical class	Chemical structure	Compound name	Main pharmacological effects	Reference
Benzoquinone		2,3-Dimethoxy-5-methyl-1,4-benzoquinone	Anti-cancer effect through inducing A549 lung cell apoptosis and mediating ROS production	Chung et al. 2014
Methoxyphenol		2,3,5-Trimethoxy-4-cresol	Suppressing lung carcinoma cells migration/invasion	Lin et al. 2015a
Benzenoid		2,4-Dimethoxy-6-methylbenzene-1,3-diol	Ameliorating atopic dermatitis-like lesion	Yang et al. 2018
Benzenoid		4,7-Dimethoxy-5-methyl-1,3-benzodioxole	Inhibiting COLO-205 colon cancer cells; Inhibiting LPS-induced inflammation in RAW264.7 cells	Tu et al. 2012 Shie et al. 2016
Benzenoid		Antrocamphin A	Inhibitory synthesis and expression of TNF	Buccini et al. 2014
Benzenoid		Antrolone	Inhibiting LPS-induced inflammation in RAW264.7 cells	Yen et al. 2018
Furan-2,5-dione		Antrodin A	Inhibiting replication of herpes simplex virus in Vero cells	He et al. 2016
Pyrrole-2,5-dione		3-Isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]-1H-pyrrol-1-ol-2,5-dione	Inhibiting Lewis lung carcinoma cells	Nakamura et al. 2004
Pyrrole-2,5-dione		3-Isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]-1H-pyrrole-2,5-dione	Inhibiting Lewis lung carcinoma cells Preventing liver fibrosis both *in vitro* and *in vivo* in an early phase	Nakamura et al. 2004 Yang et al. 2017b
Pyrrole-2,5-dione		Antrocinnamomins E	Anti-inflammatory activity by restraining NO generation	Wu et al. 2013

Table 1 (continued)

Pyrrole-2,5-dione		Antrocinnamomins F	Anti-inflammatory activity by restraining NO generation	Wu et al. 2013
Pyrrole-2,5-dione		Antrocinnamomins G	Anti-inflammatory activity by restraining NO generation	Wu et al. 2013
Pyrrole-2,5-dione		Antrocinnamomins H	Anti-inflammatory activity by restraining NO generation	Wu et al. 2013
Sesquiterpene lactone		Antrocin	Thwarting cell proliferation and evoking apoptosis in the lung cancer cells	Yeh et al. 2013
Ubiquinone derivative		4-Acetylantroquinonol B	Inhibiting proliferation of hepatoma carcinoma cells;	Lin et al. 2010b
			Inhibiting colorectal cancer tumorigenesis and suppressing cancer stem-like phenotype	Chang et al. 2015a
Ubiquinone derivative		Antroquinonol	Inhibiting colon cancer stem cell-like cells;	Lin et al. 2017
			Suppressing breast tumor migration/invasion;	Lee et al. 2015a
			Promoting learning and memory of defective mice;	Chang et al. 2015b
			Blocking Ras and Rho signaling via the inhibition of protein isoprenyltransferase;	Ho et al. 2014
			Inhibiting cell proliferation in pancreatic cancer PANC-1 and AsPC-1 cells	Yu et al. 2012
Ubiquinone derivative		Antroquinonol D	Potential DNA demethylatingand anticancer effects	Wang et al. 2014
Lanostanoid		11α-Hydroxy-3,7-dioxolanost-8,24(E)-dien-26-oic acid	Anti-inflammatory activity by inhibiting NO production	Liaw et al. 2013

phosphorylation. AMPK activity was upregulated. AMPK plays a paramount role in the action of antroquinonol since the effects of antroquinonol were abolished by an AMPK inhibitor. Disruption of mitochondrial membrane potential,

Table 1 (continued)

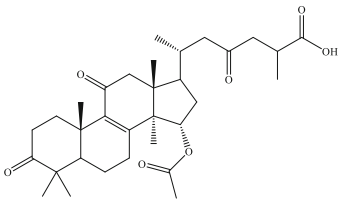
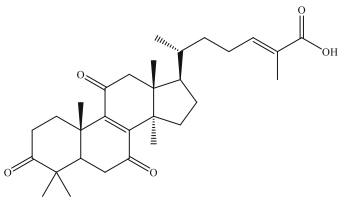
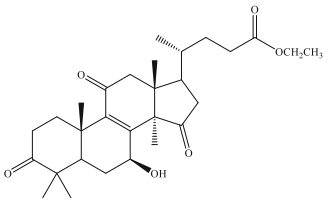
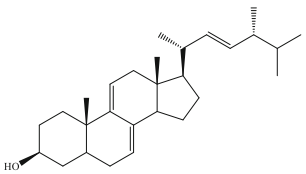
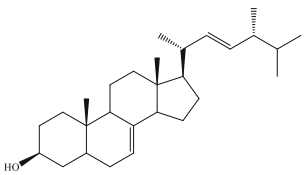
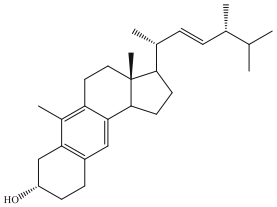
Lanostanoid		15-O-acetylganolucidate A	Anti-inflammatory activity by inhibiting NO production	Liaw et al. 2013
Lanostanoid		3,7,11-Trioxo-5α-lanosta-8,24(E)-dien-26-oic acid	Anti-inflammatory activity by inhibiting NO production	Liaw et al. 2013
Lanostanoid		Ethyl lucidenate A	Anti-inflammatory activity by inhibiting NO production	Liaw et al. 2013
Unsaturated sterol		7,9(11),22-Ergostatrien-3β-ol (Antrosterol)	Antidiabetic activity by regulating the expression levels of GLUT4, phosphenolpyruvate carboxykinase, glucose-6-phosphatase and AMPK phosphorylation;	Kuo et al. 2015b
			Anti-inflammatory effects in a mouse skin ischemia model;	Tsai et al. 2015
			Anti-inflammatory and anti-photodamaging effects;	Kuo et al. 2016b
			Protecting the liver from CCl4-induced damage via enhancing antioxidant and anti-inflammatory capacities	Chang et al. 2017b
			Downregulating expression of the proinflammatory cytokines IL-1β and IL-6	Kao et al. 2018
Unsaturated sterol		7,22-Ergostadien-3β-ol	Downregulating expression of the proinflammatory cytokines IL-1β and IL-6	Kao et al. 2018
Sterol with aromatic ring B		1(10→6)Abeo-ergosta-5,7,9,22-tetraen-3α-ol	Inhibiting CT26 colorectal cancer cells and human K562 leukemia cell line	Lee et al. 2014b

Table 1 (continued)

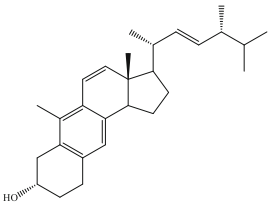
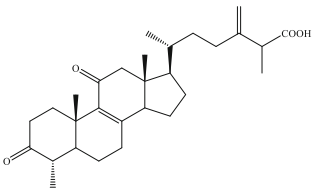
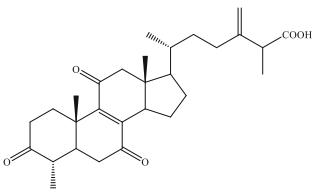
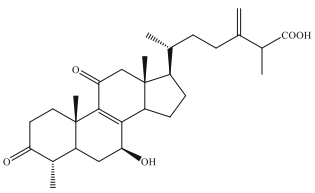
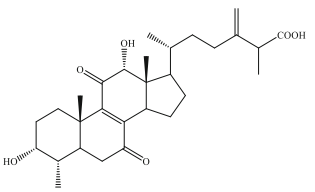
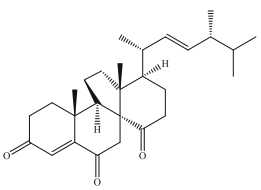
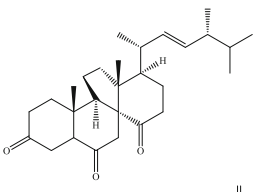
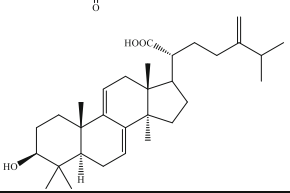
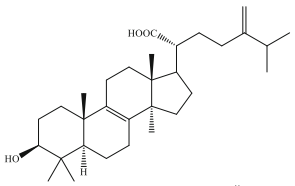
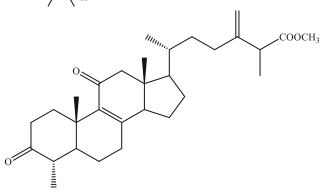
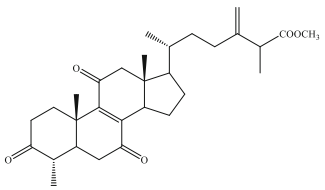
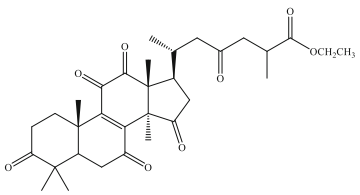
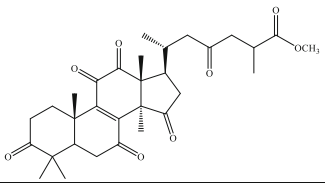
Sterol with aromatic ring B		Citreoanthrasteroid B	Inhibiting CT26 colorectal cancer cells and human K562 leukemia cell line	Lee et al. 2014b
Steroid		Antcin A	Triggering glucocorticoid receptor transfer to the nucleus to restrain inflammation	Chen et al. 2011
Steroid		Antcin B (Zhankuic acid A)	Inhibiting HL 60 leukemia cells	Du et al. 2012
Steroid		Antcin C	Inhibiting HL 60 leukemia cells	Du et al. 2012
Steroid		Antcin H (Zhankuic acid C)	Inhibiting HL 60 leukemia cells Inducing lymphoma cell line apoptosis	Du et al. 2012 Chen et al. 2018f
13(14→8) Abeo-ergostane-type steroid		Dankasterone A	Inhibiting CT26 colorectal cancer cells and human K562 leukemia cell line	Lee et al. 2014b
13(14→8) Abeo-ergostane-type steroid		Dankasterone B	Inhibiting CT26 colorectal cancer cells and human K562 leukemia cell line	Lee et al. 2014b
Triterpenoid		Dehydroeburicoic acid	Inhibiting HL 60 leukemia cells Suppressing inflammatory mediator expression in mice; Hepatoprotective effects in a mouse model	Du et al. 2012 Deng et al. 2013 Huang et al. 2013

Table 1 (continued)

			of acute hepatic injury;	
			Antidiabetic and antihyperlipidemic activities in streptozotocin-induced mice *in vitro*;	Kuo et al. 2015a
			Preventing diabetic and dyslipidemic state in high-fat-fed mice;	Kuo et al. 2016a
Triterpenoid		Eburicoic acid	Suppressing inflammatory mediator expression in mice	Deng et al. 2013
			Hepatoprotective effects in a mouse model of acute hepatic injury	Huang et al. 2013
Triterpenoid		Methylantcinate A	Inducing apoptosis in OEC-M1 and OC-2 human oral cancer cells	Tsai et al. 2010
Triterpenoid		Methylantcinate B	Inhibiting *Helicobacter pylori* cytotoxin-associated gene A -induced pathogenesis	Lin et al. 2013
Lanostane triterpene		Ethyl 3,7,11,12,15,23-hexaoxo-5α-lanost-8-en-26-oate	Anti-inflammatory activity by inhibiting NO production	Liaw et al. 2013
Lanostane triterpene		Methyl 3,7,11,12,15,23-hexaoxo-5α-lanost-8-en-26-oate	Anti-inflammatory activity by inhibiting NO production	Liaw et al. 2013

arrest of the cancer cells at G1 phase of the cell cycle, and ultimately apoptosis were observed (Chiang et al. 2010).

4-Acetylantroquinonol B was the most effective active ingredient in the fermentation broth of cultured *A. camphorata* mycelia which was capable of suppressing proliferation of hepatoma carcinoma cells (Lin et al. 2010b).

4-Acetylantroquinonol B from *A. cinnamomea* mycelia augmented the anticancer action of dendritic cells against liver cancer stem cells and holds promise for the prevention and immunotherapy of hepatoma. 4-Acetylantroquinonol B downregulated epithelial cell adhesion molecule (EpCAM), alpha-fetoprotein (AFP), and related pathways of hepatoma HepG2 cells and suppressed tumorigenicity. It repressed β-catenin expression and liberation of cytokines associated with immune escape and exerted proliferative activity toward immunocytes and enhanced the endocytotic activity of immature dendritic cells. When immature dendritic cells were cultured with EpCAM+ HepG2 cells, MHC class I and II expressions on both types of cells were upregulated by 4-acetylantroquinonol B. The expression of CD80 costimulatory molecules in dendritic cells and cytokines associated with immunostimulation was upregulated (Li and Chiang, 2019).

Effect of 4-acetylantroquinonol B on neuroblastoma and glioblastoma cells

Antroquinonol decreased cell viability in C6 glioma N18 as well as neuroblastoma cell lines and triggered apoptosis of the cancer cells. p53 and other pro-apoptotic proteins were upregulated while antiapoptotic proteins were suppressed. The protein levels of cdc42 FAK, pFAK, Rac1, Src, pSrc, and epithelial-to-mesenchymal-transition proteins were reduced in response to antroquinonol. Antroquinonol exerted an anticancer action in mice bearing xenograft C6 glioma (Thiyagarajan et al. 2015).

4-Acetylantroquinonol B downregulated expression of the following: Sox2 and Oct4 important for keeping the pluripotent embryonic stem cell phenotype; β-catenin, vimentin, and slug involved in epithelial-mesenchymal transition; the oncogene c-Myc and Krüppel-like factor 4 were involved in proliferation, differentiation, and apoptosis. 4-Acetylantroquinonol B suppressed the cancer-promoting catenin/LEF1/Stat3 signaling pathway and decreased viability in U87MG and DBTRG-05MG glioblastoma cells. Invasiveness of the cells and formation of colonies and tumorspheres were abated (Liu et al. 2018a).

Effects of antroquinonol D, antroquinonol, and antrocin on breast cancer cells and action of ergostane-type triterpenoids on breast cancer cells

Antroquinonol D isolated from *A. camphorata* mycelia elicited DNA demethylation, induced cancer cell apoptosis, and suppressed the survival and migration of breast carcinoma cells (Wang et al. 2014). The impact of antroquinonol, (4R,5R,6R)-4-hydroxy-2,3-dimethoxy-6-methyl-5-[(2E,6E)-3,7,11–trimethyldodeca-2,6,10-trien-1-yl] cyclohex-2-en-1-one, a ubiquitin derivative extracted from the solid-state culture of *A. camphorata*, on human breast carcinoma cells including MCF7 and MDA-MB-231 cells, has been investigated. The results demonstrated that antroquinonol manifested a repressive effect on the migration and invasion of MCF7 and MDA-MB-231 cells to different degrees. The mechanism primarily entailed suppressing the expression of EMT protein and matrix metalloproteinase (MMP)-9 protein via mediating the ERK-AP-1 and AKT-NF-κB signaling pathways (Lee et al. 2015a).

Ergostane-type triterpenoids extracted from *A. camphorata* fruiting bodies possessed cytotoxicity against human breast cancer MDA-MB-231 cells (Huang et al. 2014b).

Antrocin suppressed the viability and production of migration colonies and mammospheres. It downregulated the expression of Notch1, Akt, and β-catenin. It is known that β-catenin phosphorylation of AKT enhances invasiveness of cancer cells, elevated expression of Notch 1 is detected in cancer tissue, and that heightened Atk and β-catenin expression is associated with drug resistance and poor prognosis in breast cancer patients. Antrocin synergized with paclitaxel to reduce viability of breast cancer cells in vitro and exhibited an anticancer action in mice bearing breast cancer xenografts. The concurrent application of antrocin and paclitaxel awaits clinical trials (Chen et al. 2019a).

Effect of polysaccharide on cervical cancer cells

A polysaccharide purified from water extraction of *A. cinnamomea* mycelia displayed inhibitory effects on HeLa cervical cancer cells. It induced apoptosis and cell cycle arrest, and the mechanism involved blocking of topoisomerase I/tyrosyl-DNA phosphodiesterase I-mediated DNA repair pathway (Zhang et al. 2018b).

Ameliorative effect of antrodan and antrocin on prostatic hyperplasia

Antrodan extracted from *A. camphorata* mycelia could improve benign prostatic hyperplasia in the Sprague-Dawley rat model. It exerted its action through reducing collagen accumulation and decreasing the expression of sex hormones including testosterone and estradiol (Peng et al. 2015).

Concurrent application of antrocin and ionizing radiation produced synergistic antiproliferative and apoptotic effects in prostate cancer cells resistant to radiation. Antrocin downregulated PI3K/AKT and MAPK signaling pathways as well as suppressed type 1 insulin-like growth factor 1 receptor (IGF-1R)-mediated induction of β-catenin. Antrocin potentiated the efficacy of radiotherapy in mice bearing prostate cancer xenografts (Chen et al. 2019c).

Effect of maleic and succinic acid derivatives, antrocin, 2,3-dimethoxy-5-methyl-1,4-benzoquinone, 2,3,5-trimethoxy-4-cresol, antrodan, antroquinonol, and sulfated glucan on lung carcinoma cells

Five new maleic and succinic acid derivatives were extracted from *A. camphorata* mycelia. It was found that 3-isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]-1H-pyrrole-2,5-dione and 3-isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]-1H-pyrrol-1-ol-2,5-dione displayed cytotoxic activity on Lewis lung carcinoma cells (Nakamura et al. 2004).

Studies have been conducted on the antilung cancer effect and the action mechanism of antrocin, which is 7,7-dimethyl-4-methylidene-3,3a,5,6,6a,8,9,10-octahydro benzo [h][2] benzofuran-1-one, a sesquiterpene lactone extracted from *A. camphorata* on H441 and H1975 non-small-cell lung cancer cells. Antrocin thwarted cell proliferation and evoked apoptosis in the lung cancer cells. Antrocin induced cell apoptosis via enhancing the activity of caspase-3, mediating the expression of apoptosis-related proteins and bringing about downregulation of the JAK2/STAT3 signal pathway (Yeh et al. 2013).

The effect of an ethyl acetate extract of submerged cultivated *A. camphorata* mycelia against A549 human lung cancer cells was investigated. The results indicated that 2,3-dimethoxy-5-methyl-1,4-benzoquinone was the most effective active ingredient in the induction of apoptosis in A549 cells. 2,3-Dimethoxy-5-methyl-1,4-benzoquinone exhibited anticancer effect through inducing apoptosis of A549 cells and mediating ROS production (Chung et al. 2014). Ergostane-type triterpenoids extracted from *A. camphorata* fruiting bodies possessed cytotoxicity against lung carcinoma A549 cells (Huang et al. 2014b).

2,3,5-Trimethoxy-4-cresol obtained from the solid-state cultivation of *A. camphorata* mycelia inhibited the invasion and migration of lung carcinoma cells by mediating the expression levels of some molecules including protein kinase B, MMP-2, MMP-9, E-cadherin, and tissue inhibitor of metalloproteinase (TIMP)-1 (Lin et al. 2015a).

Antrodan isolated from *A. camphorata* mycelia exerted antimetastatic activity in lung carcinoma cells through regulating the expression of MMP-2, MMP-9, TIMP-1, TIMP-2, and nm23-H1 (Fa et al. 2015). Furthermore, antrodan performed well in adjuvant therapy when combined with cisplatin and ameliorated cisplatin-induced kidney dysfunction (Chen et al. 2018c).

In A549 cells, antroquinonol elicited mitochondrial membrane depolarization, increased arrest in Sub-G1 phase of the cell cycle, exerted an antiproliferative effect, increased cell shrinkage, and induced appearance of apoptotic vacuoles, pores, and TUNEL-positive cells. Antroquinonol downregulated cdc2, Bcl2, PI3K, and mTOR but did not affect the expression of pcdc2, pcdc25C cyclin B1, and cdc25C. PARP cleavage and caspase 3 were activated. The levels of expression of miRNAs antroquinonol were altered (Kumar et al. 2011b). In view of the action of antroquinonol on different kinds of cancers such as non-small cell lung cancer, Huang et al. (2017) suggested the use of antroquinonol in conjunction with anticancer drugs in the treatment of advanced and/or refractory solid tumors. Antroquinonol as a therapeutic agent for non-small-cell lung cancer is in phase II clinical trials in Taiwan and USA (Chou et al. 2019). 4-Hydroxybenzoic acid is the ring precursor for antroquinonol but not for 4-acetylantroquinonol B. Endogenous 4-hydroxybenzoic acid is employed by *A. cinnamomea* through the shikimate pathway for the formation of antroquinonol, but exogenous phenylalanine and tyrosine are used instead in the event of glyphosate blockade of the shikimate pathway. The benzoquinone ring of antroquinonol is produced through the polyketide pathway as well as the shikimate pathway whereas 4-acetylantroquinonol B is formed through only the polyketide pathway (Chou et al. 2019).

Sulfated glucan isolated from *A. cinnamomea* exhibited inhibitory activity toward lung cancer cells; it reduced cancer cell viability via inhibition of EGFR and mTOR activity and showed a synergistic effect when administered in conjunction with cisplatin (Lu et al. 2018). The glucan downregulated the TGFβ/FAK/AKT axis and triggered the breakdown of Slug in lung cancer H1975 cells and thus prevented the growth of the lung cancer cells (Lin et al. 2019b).

Antileukemia activity of antcin C, dehydroeburicoic acid, zhankuic acid A, and zhankuic acid C on leukemia cells

The cytotoxicity of active ingredients from the ethanolic extract of *A. camphorata* on leukemia HL 60 cells was studied. The active ingredients were predominantly enriched in the triterpenoid fraction. Four major triterpenoids were isolated from the active components, namely, antcin C ((6R)-6-[(4S,5S,7S,10S,13R,14R,17R)-7-hydroxy-4,10,13-trimethyl-3,11-dioxo-2,4,5,6,7,12,14,15,16,17-decahydro-1H-cyclopenta [a]phenanthren-17-yl]-2-methyl-3-methylideneheptanoic acid), dehydroeburicoic acid ((2R)-2-[(3S,5R,10S,13R,14R,17R)-3-hydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta [a]phenanthren-17-yl]-6-methyl-5-methylideneheptanoic acid), zhankuic acid A ((6R)-2-methyl-3-methylidene-6-[(4S,5S,10S,13R,14R,17R)-4,10,13-trimethyl-3,7,11-trioxo-1,2,4,5,6,12,14,15,16,17-decahydrocyclopenta [a]phenanthren-17-yl] heptanoic acid), and zhankuic acid C ((6R)-6-[(3R,4S,5S,10S,12R,13R,14R,17R)-3,12-dihydroxy-4,10,13-trimethyl-7,11-dioxo-2,3,4,5,6,12,14,15,16,17-decahydro-1H-cyclpoenta [a]phenanthren-17-yl]-2-methyl-3-methylideneheptanoic acid). Dehydroeburicoic acid demonstrated the most potent cytotoxicity through inducing DNA damage and apoptosis. Dehydroeburicoic acid also induced cell cycle (mainly G2/M phase) arrest and suppressed the expression of topoisomerase II (Du et al. 2012).

Effect of antcin H on lymphoma cells

Antcin H inhibited JAK/STAT-related signaling induced by latent membrane protein 1 and induced apoptosis of lymphoma cells. Besides, it enhanced the cytotoxicity of methotrexate against lymphoma cells at a low concentration (Chen et al. 2018f).

Immunomodulatory effect of polysaccharides, antroquinonol, antrodin D, and 2,4-dimethoxy-6-methylbenzene-1,3-diol

Through a series of analyses, it was revealed that the immunomodulatory effect of a hot water extract of fermentation culture obtained from *A. camphorata* mycelia was mainly related to the 10–20 kDa polysaccharides and adenosine (Kuo et al. 2008). The immunomodulatory activity and antiinfective effect of polysaccharides extracted from *A. camphorata* mycelia on *Schistosoma mansoni* were disclosed by studying cytokine expression and immune

function in T1/T2 doubly transgenic mice (Cheng et al. 2008). Polysaccharides derived from *A. camphorata* mycelia could regulate the levels of indices of immune organs (spleen, thymus, and bursa), blood biochemical indices, and T lymphocyte proliferation and manifested an immunomodulatory effect on specific pathogen-free chickens (Song et al. 2014).

Antroquinonol exerted an antiproliferative activity toward $CD8^+$ T cells and inhibited the generation of proinflammatory cytokines interferon-γ and interleukin-2 markers of T cell activation CD137 and CD69 in vitro. Antroquinonol attenuated the decrease in length of hair follicles, cutaneous thickness, and expression of tyrosinase involved in pigment formation and pigmentation caused by damage brought about by hydrogen peroxide in C57BL/6 mice. Antroquinonol downregulated cutaneous $CD8^+$ T cell infiltration, proinflammatory cytokine secretion, and expression of the chemokines CXCL10 and CXCR3 (Guan et al. 2017).

The cold water-soluble galactomannan of *A. cinnamomea* augmented the ability of mouse macrophages to phagocytose and kill *Escherichia coli* and elevate the production of the cytokines IL-6 and TNF-α. The galactomannan exerted its immunoenhancing action through protein kinase C-α and mitogen-activated protein kinases (MAPK) phosphorylation via Toll-like receptor 4 and the endotoxin tolerance-like effect via suppression of NF-κB (Perera et al. 2017, 2018). The ameliorative effects of polysaccharide obtained from *A. cinnamomea* against cyclophosphamide-induced immunosuppression were determined. It was found that polysaccharide administration enhanced the function of T cells and the cytotoxicity of natural killer cells and counteracted the effects induced by cyclophosphamide, including decreased levels of immunoglobulin A, G, and M and interleukin 2, 6, and 12 (Liu et al. 2018b).

Antrodin D and 2,4-dimethoxy-6-methylbenzene-1,3-diol suppressed nitric oxide production in mouse macrophages which had been stimulated by lipopolysaccharide but did not affect their viability, with IC_{50} values of 26.3 and 32.2 μg/mL, respectively. 4-Acetyl-antroquinonol B and antroquinonol B were more potent with IC_{50} values of 14.7 and 16.2 μg/mL, respectively, but cytotoxicity was detectable albeit at much higher concentrations. Slightly less than half of the macrophages were viable after exposure to 2,3-(methylenedioxy)-6-methylbenzene-1,4-diol at a concentration of 16.8 μg/mL (Yang et al. 2009).

Antiinflammatory activity of polysaccharides, antcin A, antrocinnamomins E-H, dehydroeburicoic acid, eburicoic acid, lanostanoids, lactone derivatives, methylantcinate B, antrocamphin A, 4,7-dimethoxy-5-methyl-1,3-benzodioxole, ergostatrien-3β-ol, and antrolone

The antiinflammatory effect of polysaccharides isolated from mycelia and fruiting bodies of *A. camphorata* in septic mice has been explored. The polysaccharides undermined the inflammatory reaction mainly through diminishing the expression levels of proinflammatory cytokines such as IL-6, IL-10, and TNF-α. Polysaccharides extracted from fruiting bodies appeared to be more efficacious than their mycelial counterparts in attenuating the inflammatory reaction (Meng et al. 2012).

The antiinflammatory activity of active constituents including five major antcins (A, B, C, H, and K) isolated from the methanolic extract of *A. camphorata* fruiting bodies was examined. Antcin A (6R)-2-methyl-3-methylidene-6-[(4S,5S,10S,13R,14R,17R)-4,10,13-trimethyl-3,11-dioxo-2,4,5,6,7,12,14,15,16,17-decahydro-1H-cyclopenta [a] phenanthrene-17-yl] heptanoic acid) played a role in triggering glucocorticoid receptor transfer to the nucleus to curb inflammation like glucocorticoids, while antcins B, C, H, and K did not produce similar effects (Chen et al. 2011). As antiinflammatory drugs, however, glucocorticoids exert some short-term side effects. It awaits further research to ascertain whether antcin A exerts an adverse effect on the body.

The ethanol extract of *A. camphorata* mycelia restrained NO generation. The isolated main active ingredients were antrocinnamomins E, antrocinnamomins F, antrocinnamomins G, and antrocinnamomins H, respectively (Wu et al. 2013).

Eburicoic acid ((2R)-2-[(3S,5R,10S,13R,14R,17R)-3-hydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,7,11,12, 15,16,17-decahydro-1H-cyclopenta [a]phenanthren-17-yl]-6-methyl-5-methylideneheptanoic acid) and dehydroeburicoic acid ((2R)-2-[(3S,5R,10S,13R,14R,17R)-3-hydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta [a] phenanthren-17-yl]-6-methyl-5-methylideneheptanoic acid) extracted from the solid culture of *A. camphorata* exhibited analgesic and antiinflammatory activities associated with the reduction of some inflammatory cytokines such as NO, TNF-α, and IL-1β and the augmented activities of some antioxidant enzymes including catalase, superoxide dismutase, and glutathione peroxidase (Deng et al. 2013).

Six lanostanoids and lactone derivatives were isolated from the coculture of mycelia and fruiting bodies of *A. camphorate.* Four known compounds were evaluated for antiinflammatory effect through measuring the level of NO generated by RAW 264.7 cells. It was found that six compounds (ethyl lucidenate A, 15-O-acetylganolucidate A, 11α-hydroxy-3,7-dioxolanost-8,24(E)-dien-26-oic acid, 3,7,11-trioxo-5α-lanosta-8,24(E)-dien-26-oic acid, methyl 3,7,11,12,15,23-hexaoxo-5α-lanost-8-en-26-oate and ethyl 3,7,11,12,15,23-hexaoxo-5α-lanost-8-en-26-oate, respectively) exerted antiinflammatory activity by inhibiting NO production (Liaw et al. 2013).

Methylantcinate B, purified from the chloroform extract of *A. camphorata* fruiting bodies, bridled the inflammatory reaction induced by cytotoxin-associated gene A through mediating some molecules including NF-κB, p65 NF-κB, IκBa, and IL-8 (Lin et al. 2013).

There are numerous reports on the antiinflammatory effects of some active ingredients of *A. camphorata* such as the benzenoid compounds antrocamphin A and 4,7-dimethoxy-5-methyl-1,3-benzodioxole (Buccini et al. 2014; Shie et al. 2016). Antrocamphin A derived from *A. camphorata* had an inhibitory effect on the biosynthesis and expression of TNF. 4,7-Dimethoxy-5-methyl-1,3-benzodioxole exerted an antiinflammatory action on LPS-stimulated RAW264.7 cells by inhibiting the production of pro-inflammatory molecules such as NO, TNF-α, and inter IL-1β mainly through downregulating the NF-κB and TLR4 signaling pathway. In addition, the induction of hemoxygenase-1 in RAW264.7 cells was related to the antiinflammatory effect of 4,7-dimethoxy-5-methyl-1,3-benzodioxole.

A. camphorata in wood culture, *A. camphorata* in solid-state culture, as well as its ingredient ergostatrien-3β-ol, decreased in mice, following skin flap surgery, necrosis, and infiltration of inflammatory cells, in both the epidermis and the sub-dermis of the skin flap. The expression of pro-inflammatory genes such as interleukin-6, inducible nitric oxide synthase, NF-κappaB, and tumor necrosis factor-α was inhibited. The action of *A. camphorata* against inflammation may have application in hydrocolloid dressings (Tsai et al. 2015). Ergostatrien-3β-ol extracted from the submerged culture of *A. camphorata* possessed antiinflammatory and antiphotodamaging attributes. Treatment of hairless mice, topically irradiated with ultraviolet B with ergostatrien-3β-ol, disclosed that ergostatrien-3β-ol played an antiinflammatory role through restraining the expression level of iNOS, IL-6, MMP-1, and NF-κB. Moreover, ergostatrien-3β-ol also defended the hairless murine skin against ultraviolet-induced photodamage (Kuo et al. 2016b). The crude extract of solid-state-cultured mycelia of *A. camphorata* attenuated, in BALB/c mice, mite allergen *Dermatogoides pteronyssinus*-induced airway hyperresponsiveness, suppressed total serum immunoglobulin E levels, and inhibited recruitment of inflammatory cells to the bronchoalveolar lavage fluid through cytokine downregulation and modulation of Th1/Th2/Th17 response. The steroids (7,22-ergostadien-3β-ol and 7,9(11),22-ergostatrien-3β-ol) purified from the crude extract downregulated the expression of the proinflammatory cytokines IL-1β and IL-6 in lung macrophages (Kao et al. 2018).

The antiinflammatory effects of antrolone were determined in murine macrophage RAW264.7 cells. The results showed that antrolone significantly decreased the production of NO, prostaglandin E-2, pro-inflammatory cytokine, keratinocyte chemoattractant, the levels of the proteins inducible NO synthase and cyclooxygenase-2, and increased the level of nuclear factor erythroid-2-related factor 2 (Nrf2) and heme oxygenase-1. Moreover, antrolone inhibited the activation of the NF kappa B, MAPK, and AKT pathways (Yen et al. 2018).

Antiasthmatic activity of polysaccharides from solid-state culture

Polysaccharides extracted from a solid-state culture of *A. camphorata* exhibited the potential for preventing ovalbumin (OVA)-induced asthma. Polysaccharides possessed an immunomodulatory treatment potential against allergic asthma (Liu et al. 2010).

Antidiabetic and antihyperlipidemic activities of dehydroeburicoic acid, ergostatrien-3β-ol, and antroquinonol

A triterpenoid compound, dehydroeburicoic acid, isolated from the mycelia of *A. camphorata,* alleviated diabetes and dyslipidemia in streptozotocin-induced diabetic mice. The antidiabetic effect of dehydroeburicoic acid was associated with regulation of the expression level of glucose transporter 4 (GLUT4) protein and AMP-activated protein kinase (AMPK) phosphorylation and thereby lowering the levels of blood glucose and insulin. Dehydroeburicoic acid also exhibited hypolipidemic activity through mediating the expression of fatty acid synthase, peroxisome proliferator-activated receptor (PPAR)-α, and carnitine palmitoyl transferase Ia (Kuo et al. 2015a). Dehydroeburicoic acid also prevented diabetes and dyslipidemia in high-fat diet-fed mice. The mechanism involved regulating the levels of phosphorylation of GLUT4, PPAR-α, and AMPK (Kuo et al. 2016a).

Treating high-fat-diet fed mice with ergostatrien-3β-ol ((3S,9S,10R,13R,14R,17R)-17-[(E,2R,5R)-5,6-dimethylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,9,11,12,14,15,16,17-decahydro-1H-cyclopenta [a]phenanthren-3-ol) extracted from the submerged culture broth of *A. camphorata* mycelia revealed that ergostatrien-3β-ol effectively reduced the blood levels of glucose and triglyceride. By a series of analysis including body weight, food intake, the blood levels of glucose and glycated hemoglobin, western blotting, and hepatic lipid analysis, the effects of ergostatrien-3β-ol were associated with regulating the expression levels of glucose transporter 4, phosphoenolpyruvate carboxykinase, glucose-6-phosphatase, and AMP-activated protein kinase phosphorylation (Kuo et al. 2015b).

Antroquinonol inhibited dipeptidyl peptidase IV activity as potently as sitagliptin. Antroquinonol and sitagliptin exhibited antihyperglycemic activity in diet-induced obese mice (Hsu et al. 2015). Antroquinonol possessed antidiabetic activity in vitro as well as in vivo (Sulake et al. 2015). Antroquinonol lowered activities ofα-amylase and α-glucosidase (Riyaphan et al. 2018).

Activation of peroxisome proliferator-activated receptor α

Since peroxisome proliferator-activated receptor α (PPARα) is involved in the control of the metabolism of lipids, its agonists like fibrates are therapeutic candidates for hyperlipidemia and other derangements of metabolism. It would be desirable to find agonists with reduced undesirable side effects compared with the existing agonists. Antcins B, H, and K, but not ergostatrien-3β-ol (EK100), are activators of PPARα. His440 and Tyr314 located in the ligand-binding domain of PPARα are necessitated to stabilize helix 12. The PPARα-stimulating activity of antcins depends on binding which requires stabilization of helix 12. Antcins appear to be safe and promising PPARα agonists (Wang et al. 2019).

Ameliorative effects of triterpenoids on reproductive function in diabetic rats

It was reported that administration of nanoencapsulated triterpenoids extracted from petri dish-cultured *A. cinnamomea* ameliorated morphology of testicular seminiferous tubules and sperm morphology and motility in diabetic rats, as well as increased the plasma levels of testosterone, luteinizing hormone, and follicle stimulating hormone (Sudirman et al. 2018).

Hepatoprotective effect of antroquinonol, antcin C, antcin K, dehydroeburicoic acid, eburicoic acid, antrodan, antrosterol, and maleic acid derivative

Antroquinonol inhibited ethanol (100 mM)-induced escalations in activities of alanine and aspartate aminotransferases, reactive oxygen species, nitric oxide, malondialdehyde production, and glutathione reduction in human liver cancer HepG2 cells. Antroquinonol enhanced Nrf-2 activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf-2) and its downstream antioxidant gene heme oxygenase 1 via mitogen-activated protein kinase pathway (Kumar et al. 2011a).

Antcin C exerted a protective action on HepG2 cells against the apoptosis inducing activity of 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH) by attenuating the generation of reactive oxygen species and the pro-apoptotic factors Bax, caspase-3, caspase-4, caspase 9, caspase-12, cytochrome c, and poly ADP ribose polymerase (PARP). In mice, antcin C attenuated the glutathione reduction and diminished the elevations in activities of hepatic aminotransferases and lipid peroxidation brought about by AAPH. Antioxidant genes such asγ-glutamylcysteine synthetase, hemeoxygenase-1, superoxide dismutase, and NAD(P)H: quinone oxidoreductase 1 were induced through stimulation of Nrf2 transcription. Antcin C stimulated nuclear factor (erythroid-derived 2)-like 2 (Nrf2) through upregulation of and phosphatidylinositol 3-kinase (PI3K) and c-Jun N-terminal kinases (JNK1/2) (Gokila Vani et al. 2013). The chief ingredient antcin K displayed a hepatoprotective action on alcohol-intoxicated mice as evidenced by the diminished activities of alanine and aspartate aminotransferases and level of triglyceride (Wu et al. 2019).

Dehydroeburicoic acid and eburicoic acid derived from a solid-state culture of *A. camphorata* fruiting bodies shielded the liver from CCl_4 (carbon tetrachloride)-induced oxidant stress and injury (Huang et al. 2013).

Antrodan, a glycoprotein extracted from *A. camphorata* mycelia, displayed a hepatoprotective effect on the Sprague-Dawley rat model induced by LPS. Low doses of antrodan had a protective effect on liver injury, while high doses produced some side effects (Ker et al. 2014).

Antrosterol extracted from the submerged culture of *A. camphorata* exerted a protective effect on the liver of chronic-alcohol fed mice, which was mainly related to the regulation of alcohol clearance, attenuation of inflammation, and oxidation in addition to lipid balance in the liver (Chang et al. 2017b).

A maleic acid derivative, procured from mycelia of *A. camphorata*, suppressed early hepatic fibrosis brought about by TGF-β, mainly involved the inhibition of ROS, inflammation as well as the activation of hepatic stellate cells (Yang et al. 2017b).

Neuroprotective effect of antroquinonol

Amyloid-β peptide (Aβ) is a fragment cleaved from amyloid precursor protein and a triggering factor for early incidence of Alzheimer's disease. Antroquinonol isolated from *A. camphorata*, a ubiquinone derivative, promoted learning and memory of defective mice and reduced levels of hippocampal Aβ and the degree of astrogliosis, mainly through upregulating the Nrf2 pathway and downregulating the level of histone deacetylase 2 (Chang et al. 2015b).

Renoprotective activity of antroquinonol

Antroquinonol suppressed inflammatory changes of the kidneys and alleviated oxidative stress in a murine renal fibrosis model. It delayed the development of severe kidney damage in mice with induced accelerated and progressive IgA nephropathy. Antroquinonol upregulated the Nrf2 antioxidant pathway, suppressed activation of T cells and NLRP3 inflammasomes, reduced proteinuria and kidney histopathology, and ameliorated kidney function (Yang et al. 2013c).

Antroquinonol suppressed interleukin-1β and tumor necrosis factor-α in RAW 267.4 macrophages stimulated by lipopolysaccharide (Chang et al. 2011). Antroquinonol mitigated urinary protein excretion, kidney dysfunction, and glomerulopathological alterations in glomeruli; alleviated

oxidative stress, infiltration of leukocytes, and expression of renal proteins associated with fibrosis; enhanced glutathione peroxidase activity and renal nuclear factor E2-related factor 2; prevented activation of kidney nuclear factor-κB; and reduced renal and serum transforming growth factor-β1 in a murine model of focal segmental glomerulosclerosis (Tsai et al. 2011).

In (NZB × NZW) F1 mice with experimental accelerated severe lupus nephritis brought about by *Salmonella*-type lipopolysaccharide, antroquinonol reduced urinary excretion of blood and protein, cellular crescent formation, fibrinoid necrosis, T cell activation/proliferation and neutrophil infiltration in the glomerulus, production of interleukin-18, nitric oxide, and reactive oxygen species. Renal inflammation and interstitial inflammation in the vicinity of the glomerulus were inhibited, but Treg cell suppression and Nrf2 activation were increased (Tsai et al. 2012). In rats with Nω-nitro-l-arginine methyl ester-induced hypertension, antroquinonol suppressed the rise of diastolic and systolic blood pressure, serum creatinine, renal malondialdehyde, endothelin-1, angiotensin II, NADPH oxidase heme oxygenase-1, greater nuclear factor erythroid-2, and arteriole thickening (Chen et al. 2018a).

Antiviral activity of antrodin A

Several isolated constituents including antrodin A displayed an inhibitory effect on herpes simplex virus in the presence as well as in the absence of the antiviral drug acyclovir (He et al. 2016).

Ameliorative effect of 2,4-dimethoxy-6-methylbenzene-1,3-diol on atopic dermatitis-like lesion

The ameliorative effects of 2,4-dimethoxy-6-methylbenzene-1,3-diol on atopic dermatitis-like lesion and its associated *Staphylococcus aureus* infection were investigated. The results showed that 2,4-dimethoxy-6-methylbenzene-1,3-diol ameliorated atopic dermatitis-like lesion, reduced chemokines in activated keratinocytes, and inhibited the growth of methicillin-resistant *S. aureus* (Yang et al. 2018).

Safety assessment of *Antrodia camphorata*

Antroquinonol, provided at 50–600 mg daily for 1 month to patients with metastatic non-small-cell lung cancer, was regarded as well tolerated and generally safe, devoid of dose-limiting toxicities or mortality associated with treatment. The most common treatment-related adverse events, nausea, vomiting, and diarrhea, were the side effects (Lee et al. 2015b).

A. cinnamomea β-glucan provided orally at a daily dose of 2 g/kg for 3 months did not produce harmful effects on the eyes, feed intake, weights of different organs, increase in body weight, hematological, serum, and urine parameters. Histopathological examination and tests of mutagenicity and genotoxicity did not disclose toxicity of *A. cinnamomea* (Chen et al. 2018d).

However, as the saying goes, "As long as the body intakes drugs, the body will produce three-tenths of the toxicity," the drugs consumed will undergo hepatic metabolism and may increase the burden on the liver if the drug intake is excessive. After all, if a person is healthy, there is no urgent need to take a lot of medicine. At present, there is no specific statement on the daily safe dose of *A. camphorata*; hence, safe dosages still require further study and clinical validation. At the same time, we need to popularize knowledge about *A. camphorata* as well as human pharmacology to consumers through various channels including newspapers, media, radio, and so on, so that people can acquire a better understanding and relevant knowledge and will not undertake a blind pursuit of the so-called God medicine and fall into the snare and be swindled.

Other activities demonstrated using aqueous extract and alcoholic extract of mycelia or fruiting bodies and fermentation culture broth

In their investigations, some authors preferred to employ purified ingredients whereas others chose to use extracts and fermentation culture medium, probably because the purified ingredients were readily accessible to only some of the researchers. Different assays with dissimilar assay parameters were utilized. Nevertheless, the various investigations yielded different information which individually is useful in its own right. The following information is included because of reasons including (i) the corresponding information on purified ingredients is not available since the purified ingredients have not been assayed and (ii) the information gathered using aqueous extract and alcoholic extract of mycelia or fruiting bodies, and fermentation culture broth, for instance, the apoptotic pathway or proteins affected, is distinct from that collected using purified ingredients. All in all, the following information sheds new light on the activities in *A. camphorata.* This information will, together with the information above on pure compounds, give a more complete picture and enable one to gain a fuller understanding of the multifarious actions of *A. camphorata*.

Effect of extract on oral cancer cells

A. camphorata extracts induced apoptosis in OC-2 human oral cancer cells and also induced the phosphorylation of mitogen activated protein kinases and influenced the regulation of Ca^{2+} ions (Huang et al. 2009).

Effects of methanolic and ethanolic extract of fruiting bodies and mycelia on liver cancer cells

The apoptotic mechanism of the methanolic mycelial extract on HepG2 human hepatoma cells entailed activation of caspase-3 and caspase-8 and upregulation of the expression of Fas protein to transmit the death signal (Song et al. 2005). The ethanolic extract of fruiting bodies hampered the migration of human hepatocellular carcinoma cells, which depends on the ERp57, PGK-1, MAPK, and PI3K/Akt cellular pathways (Chen et al. 2015). The extract also brought about cell cycle arrest in Hep3B and HepJ5 human hepatocellular carcinoma cells through heightening the expression of P21s and P27 and triggering apoptosis via activating the expression of caspase-3. The extract potentiated the chemotherapeutic drugs (cisplatin and doxorubicin) (Lin et al. 2015c) and ginger extract (Chen et al. 2018e) in inhibition of hepatocellular carcinoma cells. An ethanolic extract of mycelia triggered apoptosis, induced loss of cell viability, and inhibited invasiveness in cultured liver cancer HepG2 and SMMC-7721 hepatoma cells. The extract induced apoptosis and suppressed JAK2/STAT3 activation/ phosphorylation in cells as well as tumors. The expression of STAT3-targeted molecules, such as antiapoptotic proteins Bcl-2 and Bcl-xL, and matrix metalloproteinase-2 and matrix metalloproteinase-9, was diminished. The extract suppressed tumor growth but was devoid of toxicity on rats, nude mice, and normal human liver-derived cells (Zhu et al. 2018).

Effects of fermentation culture broth, ethanolic extract of fruiting bodies, and mycelia on breast cancer cells

The fermented culture broth of mycelia exhibited an undermining effect on cell proliferation and an inductive action on cell apoptosis in HER-2/neu-overexpressing MDA-MB-453 and BT-474 breast cancer cells. It did so by elevating the production of reactive oxygen species (ROS) in the cells, downregulating the HER-2/neu signal channel and inhibiting the activation of PI3K/Akt-dependent signaling pathway (Lee et al. 2012). The culture broth suppressed the Twist expression in human breast cancer cells (MDA-MB-231) and inhibited the epithelial-to-mesenchymal transition by downregulating mesenchymal marker proteins. Moreover, it restrained breast cancer metastasis to the lungs (Hseu et al. 2019).

The ethanol extract of fruiting bodies suppressed the growth of MCF-7 and tamoxifen-resistant MCF-7 breast cancer cells and induced their apoptosis. It inhibited the mRNA expression of S-phase kinase-associated protein 2 by increasing the expression of miR-21-5p, miR-26-5p, and miR-30-5p in these breast cancer cells (Lin et al. 2018b).

The ethanolic extract of artificially cultured *A. cinnamomea* exerted an antiproliferative activity toward T47D breast cancer cells. The cells were arrested at G1 phase of the cell cycle. Autophagy of the cells was also observed. Expression of transcription factor FOXO1 and autophagic markers LC3 II and p62 was upregulated, whereas expression of cell-cycle-related proteins was downregulated. The mechanism also involved endoplasmic reticulum stress. The expression of C/EBP homologous protein, glucose regulating protein 78, and inositol-requiring enzyme 1α was enhanced but histone deacetylase activity was inhibited. The extract suppressed tumor growth without undesirable side effects (Chen et al. 2019d).

Effect of extract of fruiting bodies and fermentation culture broth on ovarian cancer cells

The fruiting body extract exerted cytotoxicity and induced apoptosis in SKOV-3 and TOV-21G human ovarian cancer cells by mediating the expression of Bcl-2 family proteins; activating the activity of caspase-3, caspase-8, and caspase-9; and upregulating the release of mitochondrial cytochrome c. The crude extract enhanced the cytotoxicity of paclitaxel to both SKOV-3 and TOV-21G ovarian cancers (Liu et al. 2011). The fermentation culture broth retarded the proliferation and expedited the apoptosis of SKOV-3 human ovarian cancer cells. These effects were associated with the generation of ROS, downregulation of the HER-2/neu signaling pathway, and suppression of the PI3K/Akt cascade, which involved the attenuated expression of some proteins including HER-2/neu protein, β-catenin, cyclin D1, and p27 KIP1 (Yang et al. 2013a).

Effect of extract of fruiting bodies on cervical cancer cells

The crude extract of fruiting body exerted cytotoxicity on HeLa and C-33A human cervical cancer cells and induced apoptosis of these cells, by activating caspase-3, caspase-8, and caspase-9, elevating the release of cytosolic cytochrome c and promoting the expression of the pro-apoptotic proteins Bak, Bim, and Bad (Yang et al. 2013b).

Effect of ethanolic extract of fruiting bodies on lung cancer cells

The ethanolic extract hindered the proliferation of lung cancer cells through initiating endoplasmic reticulum stress and reduced the excretion of galectin-1 which plays a significant role in the survival and apoptosis of the cells (Wu et al. 2006).

The ethanol extract of mycelia exerted a dose-dependent cytotoxic action and apoptotic action in Lewis lung carcinoma cells. It upregulated Bax and p53 expression, caspase-3 and PARP cleavage, inhibited Bcl-2 and survivin expression, ad suppressed JAK2, and phosphorylated STAT3 levels in LLC

cells. Oral treatment of tumor bearing mice with the ethanol extract inhibited tumor growth and metastasis without altering body weight and serum parameters. The treatment upregulated caspase-3 cleavage and downregulated STAT3 phosphorylation in tumors reduced the growth of human tumor xenografts in nude mice (Huang et al., 2019).

Effect of ethanol extract on bladder cancer cells

The ethanol extract induced cell cycle arrest (at G2 and M phase) and prevented migration of T24 human bladder cancer cells (Peng et al. 2006). Testing of the ethanolic extract on bladder cancer cells exhibiting different degrees of invasiveness, including RT4 cells, TSGH-8301 cells, and T24 cells, revealed that the growth of these three types of bladder cancer cells could be inhibited to varying degrees and that the different inhibitory effects of the ethanolic extract were largely related to the degree of cell differentiation. The repressive effect of the ethanol extract on RT4 cells might be attributed to the mechanism of replicative senescence, while the growth inhibiting activity of the ethanolic extract on TSGH-8301 cells and T24 cells was probably dependent on the expression of Cdc2 and cyclin B1 complex (Peng et al. 2007).

Effect of extracts on colorectal cancer cells

A. cinnamomea extracts showed cytotoxicity in colorectal cancer Caco-2, Colo205, HCT116, HT29, and SW480 cells. The mechanism involved autophagy mediated by the CHOP/TRB3/Akt/mTOR pathway (Tsai et al. 2018).

Effect of ethanol extract on leukemia cells

The crude extracts exerted antileukemia activity and expedited immune responses through lengthening the survival rate and precluding the body weight loss in WEHI-3 leukemia bearing BALB/c mice (Lin et al. 2010a).

The ethanol extract derived from wild fruiting bodies of induced HL 60 cells apoptosis, by decreasing histone acetylation via raising the activity of histone deacetyltransferase 1 and lowering the activity of histone acetyltransferase (Lu et al. 2009).

Effect of fermentation culture broth on melanoma cells

The fermented culture broth from *A. camphorata* restrained the proliferation and migration of the B16F1 and B16F10 melanoma cells in vitro. It triggered apoptosis and prevented metastasis of melanoma cells, mainly by regulation of the Wnt/β-catenin signaling pathways (Hseu et al. 2012).

Ameliorative effect of ethanol extract on cachexia symptoms

Administration of the ethanol extract greatly rectified the problems of body weight loss and skeletal muscle atrophy induced by gemcitabine and cisplatin in lung tumor-bearing mice (Chen et al. 2018b).

Immunomodulatory effect of aqueous extract and mycelial powder

When p185neu-overexpressed MBT-2 bladder tumor bearing mice were treated the aqueous extract together with a HER-2/neu DNA vaccine, the inhibitory effect on tumor cell growth was enhanced and the survival of experimental mice was prolonged. These effects were associated with the immunomodulatory activity of the *A. camphorata* extract (Huang et al. 2010).

The mycelial powder exhibited immunomodulatory effects. Oral administration of a health food product containing the mycelial powder could upregulate the immune function of the mouse, as evidenced by increased proliferation of splenic lymphocytes, half value of serum hemolysin, phagocytic activity of macrophages, and cytolytic activity of natural killer cells (Chen et al. 2018g; Lin et al. 2018a). In addition, the mycelial powder increased the levels of IL-2, TNF-α, INF-γ, GM-CSF, serum OVA-IgG, and OVA-IgM (Chen et al. 2018g).

Wound healing activity of ethanol extract

The ethanol extract of *A. camphorata* expedited wound healing in Sprague-Dawley rats through accelerating fibroblast proliferation (Amin et al. 2015).

Antiinflammatory effect of ethanol extract

The antiinflammatory effects of the ethanol extract of *A. camphorata* grown on germinated brown rice against colitis symptoms induced by sodium dextran sulfate were investigated, which were evaluated through diminishing the disease activity index scores and preventing the body weight loss. The results indicated that the ethanol extract impeded the production of some molecules including nitric oxide and prostaglandin E2 in RAW264.7 cells and curtailed the protein level of some enzymes encompassing inducible nitric oxide synthase and cyclooxygenase-2. The expression of tumor necrosis factor (TNF)-α and interleukin (IL)-6 mRNA was also mitigated following exposure of lipopolysaccharide (LPS)-stimulated RAW264.7 cells to the ethanol extract. These antiinflammatory effects of ethanol extract may be attributed to the regulation of the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPK) signaling pathways (Park and Park 2013).

The ethanol extract depressed the expression of some inflammation-related cytokines including TNF-α, IL-1β, and IL-18. These effects were associated with MAPK and NF-κB signal pathways (Huang et al. 2014a).

Antidiabetic activity of ethanolic extract

The ethanolic extract mitigated lipid peroxidation, oxidative stress, insulin resistance, and hyperglycemia in male rats rendered diabetic by streptozotocin and nicotinamide (Johnson et al. 2019).

Antiobesity activity of water extract

Mice fed a high-fat diet and receiving treatment with a water extract for 2 months demonstrated a lower body weight, insulin resistance, serum levels of leptin and triglyceride, as well as inflammation markers (interleukin-1β and interleukin-6 and tumor necrosis factor-α), but higher levels of adipokine than mice fed a high fat diet but without the extract. Treatment with the extract resulted in upregulation, in the small intestine, of the antimicrobial proteins lysozyme C and Reg3g and the intestinal tight junction proteins occludin and zonula occludens-1, giving rise to diminished endotoxin levels in the blood. The Firmicutes/Bacteroidetes ratio was decreased, but the populations of *Akkermansia muciniphila* and other antiinflammatory bacteria were escalated (Chang et al. 2018).

Antiatherosclerotic activity of fermentation culture medium

Fermentation culture medium attenuated the production of ROS induced by cigarette smoke and lowered DNA damage as well as mitigated atherosclerosis in apolipoprotein E- deficient mice (Yang et al. 2017a).

Antihypertensive activity of methanol extract of solid-state culture

The methanol extract of solid-state culture effectively lowered the blood pressure of spontaneously hypertensive rats including diastolic blood pressure and systolic blood pressure by restraining the activity of angiotensin-converting enzyme (Liu et al. 2007).

Ameliorative effects of ethanol extract on reproductive function in diabetic rats

In male rats rendered diabetic by streptozotocin and nicotinamide, the ethanol extract restored seminiferous tubule structure, reduced damage to DNA, and ameliorated mitochondrial membrane potential in spermatozoa (Johnson et al. 2019).

Hepatoprotective effect of mycelia, fruiting body, fermented product, aqueous extract, ethanolic extract, and *n*-hexane extract

The hepatoprotective activity of *A. camphorata* was evaluated after orally treating acute ethanol-induced rats with fermentation mycelia. *A. camphorata* fermentation culture remarkably suppressed the serum levels of alanine aminotransferase, aspartate transaminase, alkaline phosphatase, and bilirubin, which are all related to liver injury (Lu et al. 2007).

Feeding of alcohol-treated rats with *A. camphorata* powder accelerated alcohol clearance, which was associated with raised aldehyde dehydrogenase and catalase enzyme systems. In mice treated with ethanol (5 g/kg), heightened activities of alanine and aspartate aminotransferases in the blood, glutathione reduction, lipid peroxidation, enlargement, and degenerative changes in the liver were observed. Administration of ethanolic extracts of *A. camphorata* mycelia enhanced heme oxygenase-1 and Nrf-2 activation via mitogen-activated protein kinase and attenuated the aforementioned hepatic changes. Thus, the mushroom is useful for the treatment of alcoholic liver diseases (Kumar et al. 2011a). Metalloproteinases upregulated by TNF-α play a part in the development of liver fibrosis, while *A. camphorata* powder reduced the activity of metalloproteinase-9 and serum and lowered the expression of tumor necrosis factor-α, Krüppel-like factor 6, and transforming growth factor-β1; thereby, *A. camphorata* had a certain protective effect on the liver (Wu et al. 2011).

The fermentation culture exerted a hepatoprotective effect on liver damage and fibrosis in fibrotic rats via suppressing the levels of expression of lipid peroxidation, ROS, iNOS, and TNF-α (Wang et al. 2013).

Activation of hepatic stellate cells played a crucial part in liver fibrosis, while transforming growth factor (TGF)-β1 had a central role in the activation of hepatic stellate cells. The *n*-hexane extract of *A. camphorata* inhibited the expression of α-smooth muscle actin, collagen I, collagen III, and fibronectin stimulated by TGF-β1 in CFSC-8B cells (Geng et al. 2014). An aqueous extract of *A. cinnamomea*, CCM111, exhibited a hepatoprotective action against damage produced by carbon tetrachloride. CCM111 lowered the hepatic activities of alanine and aspartate aminotransferase; suppressed STAT3-, TGF-β-, and Wnt-dependent profibrotic and proinflammatory mediators; and minimized collagen deposition and fibrotic changes in the liver (Lin et al. 2019a).

Nephroprotective action of mycelial extract

The mycelial extract reduced urinary protein excretion and blood urea nitrogen levels and thickness of renal glomerular basement membrane in NZB/W F1 mice with a tendency to develop systemic lupus erythematosus (Chang et al. 2011).

Neuroprotective effect of extract and fermentation culture

The neuroprotective effect of *A. camphorata* extract in a rat model of ischemic stroke, induced by middle cerebral artery occlusion, may occur through strengthening of the inhibitory effect on the expression of haem oxygenase-1, followed by conspicuous suppression of the expression of other molecules including Bax, iNOS, and caspase-3. Moreover, the formation of hydroxyl radicals was partly inhibited (Yang et al. 2015). The ability of the culture filtrate of *A. camphorata* to counteract amyloid β-peptide-induced neurotoxicity was augmented via increasing the mycelial secretion of some ingredients (Shi et al. 2016).

Radioprotective action of ethanolic extract

The ethanolic extract removed irradiation-triggered reactive oxygen species by upregulating Nrf2 (a basic leucine zipper protein regulating expression of antioxidant proteins) and the downstream redox system enzymes in normal liver CL48 cells. The extract exerted a protective action on irradiation-induced acute hepatitis in tumor-bearing mice and carbon tetrachloride-induced hepatitis in normal mice (Kuo et al. 2019).

Osteogenic and antiosteoporotic activities of alcohol extract of fruiting bodies

The ability of alcohol extract of fruiting bodies expedited osteogenesis and decreased bone loss in ovariectomized SAMP8 mice (Liu et al. 2016).

Antifatigue activity of combination of *A. camphorata* and *Panax ginseng*

A fixed combination formula of *A. camphorata* and *Panax ginseng*, given orally to male ICR mice for 1 month at the daily dosages of 0.98, 2.95, and 5.90 g/kg, prolonged after a swimming exercise, exhaustive swimming time, enhanced forelimb grip strength, increased serum glucose level, suppressed serum levels of lactate and ammonia, reduced blood urea nitrogen level, and creatine kinase activity (Hsiao et al. 2018).

Antiplatelet activity of crude extracts

The crude extracts largely mediated calcium and protein kinase C cascade reaction and protein kinase B signaling pathway, thereby inhibiting platelet activation and platelet aggregation to prevent thrombosis (Lu et al. 2014).

Antibacterial activity of different extracts and antiviral activity of ethanol extract

The ethyl acetate and chloroform extracts exerted a remarkable inhibitory activity on the growth and adhesion of oral bacteria (*Streptococcus mutans*), while the inhibitory effects of 50% ethanol extract and 95% ethanol extract were only moderate (Lien et al. 2014).

Antioxidant activity of aqueous extract, ethanolic extract, and fermented culture broth

The aqueous mycelial extract inhibited oxidative hemolysis of erythrocytes and lipid or protein peroxidation stimulated by peroxyl radicals as well as attenuated cytoplasmic depletion of the antioxidant tripeptide glutathione (Hseu et al. 2002). Moreover, the aqueous mycelial extract eliminated 2,2-diphenyl-1-picrylhydrozyl free radicals and also exhibited protective activity against DNA damage induced by hydroxyl radicals and antimutagenic effect against direct as well as indirect mutagens (Hsieh et al. 2015). The protective effect of the fermentation culture broth and the aqueous mycelial extract on endothelial cells damage elicited by free radicals was attested to by a decrease of DNA fragmentation, release of cytochrome c, upregulation of caspase-3, and regulation of Bcl-2 and Bax (Hseu et al. 2008).

Supplementing *A. cinnamomea* powder in the diet significantly enhanced the activity of superoxide dismutase and catalase in broiler chicken serum and upregulated the expression of antioxidant genes, including genes of heme oxygenase 1 and glutamate-cysteine ligase catalytic subunit (Lee et al. 2018).

The ethanolic extract removed irradiation-triggered reactive oxygen species by upregulating Nrf2 (a basic leucine zipper protein which regulates expression of antioxidant proteins) and the downstream redox system enzymes in normal liver CL48 cells. The extract exerted a protective action on irradiation-induced acute hepatitis in tumor-bearing mice and carbon tetrachloride-induced hepatitis in normal mice (Kuo et al. 2019).

Antiphotodamaging activity of fermented extract

The fermented extract relieved cytotoxicity induced by radiation. By comparing the cellular viability of immune spleen cells, human colorectal cancer HT-29 cells, and human breast cancer BT-474 cells, it was revealed that the sensitivities of these three kinds of cells to radiation-inducible damage were different (Cheng et al. 2014).

Safety assessment of fermented broth of mycelium and mycelial extract

When experimental rats treated with the fermented broth of mycelium were subjected to the acute toxicity test, the LD_{50} determined exceeded 15 g/kg (Lin et al. 2001). Oral administration of *A. cinnamomea* to mice at 16 mg to 1.6 g/kg body weight for 3 months had no effects on body weight, hematological and serum biochemical parameters, internal organs, and survival (Chang et al. 2013). The *A. cinnamomea* health food product Leader Deluxe *Antrodia cinnamomea* at 0.7–2.8 g/kg/day did not yield anomalous results in the following tests: Ames test, Chinese hamster ovary cells, ratio of immature to total red blood cells and number of micronuclei in immature murine red blood cells, and reproductive and developmental toxicology in pregnant rats and fetuses (Lin et al. 2015b). Oral supplementation of patients with chronic hepatitis C on ribavirin (pegRiba) therapy with *A. cinnamomea* mycelia did not produce a different outcome due to *A. cinnamomea* as evidenced by biochemical data, heavy metals, cytokines, and antioxidant status, immune function, and viral response (Chiu et al. 2017).

Comparison of *A. camphorata* with other medicinal mushrooms

There are a number of medicinal mushrooms other than *A. camphorata.* These mushrooms in the raw form and also in the form of nutraceutical products are available. The literature on some of these medicinal mushrooms is fairly voluminous. da Silva de Souza et al. (2017) reviewed the antimutagenic, anticancer, immunomodulating, antiinflammatory, antioxidant, antidiabetic, hepatoprotective, antimicrobial, and antiparasitic activities of *Agaricus blazei.* Olatunji et al. (2018) and Wong et al. (2018) reviewed the analgesic, antimalarial, antifungal, antibacterial, anti-HIV, cytotoxic, antitumor, immunomodulatory, antiallergic, antiinflammatory, antioxidant, and antidiabetic activities in *Cordyceps.* The antitumor and immunomodulatory activities of *Coriolus versicolor* (Piotrowski et al. 2015; Chang et al. 2017a; Wong et al. 2018), as well as antidiabetic, antioxidative, immunomodulatory, and antitumor activities of *Grifola frondosa* (He et al. 2017, 2018; Rossi et al. 2018) have been reviewed. The diverse activities of *Ganoderma lucidum* comprising anticancer, antiangiogenic, immunomodulatory, antiinflammatory, antiulcer, analgesic, antidiabetic, antihyperlipidemic, antioxidant, antiatherosclerotic, antiarthritic, antifibrotic, hepatoprotective, antiosteoporotic, antiaging, antimicrobial, and antiherpetic activities have been reviewed (Ahmad, 2018; Rossi et al. 2018; Wong et al. 2018). By comparison, *A. camphorata* displays a repertoire of activities which is as impressive if not more impressive than those of the other aforementioned medicinal mushrooms. Hence, *A. camphorata* has enormous potential.

Prospects for the development and utilization of *A. camphorata*

A. camphorata, as a highly prized medicinal fungus, which has tremendous medicinal potential and exploitation value for human health, has been shown in a multitude of studies that it can improve some conditions or treat some diseases, especially cancer. The mushroom demonstrates inhibitory effects on a wide range of cancers. It exerts effects on a variety of organs and produces an array of bioactive molecules with different activities, many of which manifest structural resemblance to steroids. This is reminiscent of the fact that slight variations in the chemical structures of the groups attached to the basic perhydrocyclopentano phenanthrene skeleton typical of cholesterol give rise to different steroid hormones with different activities including the glucocorticoids, mineralocorticoids, progestagens, and sex steroids. Structure function studies may enable the chemists to design potent products. Many mechanisms of its biological actions have been unraveled. Many other exploitable activities of *A. camphorata* await discovery. However, the growth conditions of the wild *A. camphorata* are incredibly harsh and its growth rate is extremely slow. Thus, the wild plant resources are scarce, and hence, the current trend is artificial culture (Chen et al. 2019b; Xia et al. 2019; Zhang et al. 2019). α-Terpineol added to the culture medium of *A. cinnamomea* mycelia increased the yield and modified the composition of triterpenoids. The triterpenoids produced in the presence of α-terpineol exhibited a more potent apoptosis-inducing activity than triterpenoids produced without α-terpineol toward several tumor cell lines. p53, Bax, and caspase-3 in the mitochondrial apoptotic pathway were not affected. However, the production of tyrosyl-DNA phosphodiesterase I and topoisomerase I with a role in DNA repair, at transcriptional as well as translational levels, was downregulated (Zhang et al. 2018a). The optimal conditions for mycelial culture ensuing in an optimal yield await further investigations.

Although the technology of artificial culture has become increasingly mature; nevertheless, there is still some evidence that the content of active ingredients of the cultured *A. camphorata* differs from the wild mushroom and its pharmacological effect is not the same. This is also a problem that calls for solution. The improvement of artificial culture techniques of *A. camphorata* will play a prominent part in future research and development.

Although *A. camphorata* has a diversity of biological activities, the current applications of *A. camphorata* are still mainly focused on the health food products, which are available in the market in the form of capsules of the fruiting body

powder, solution of its extract and fermentation broth, or other dosage forms. Therefore, some of the safety assessments of consumption of *A. camphorata* products and many studies on the biological activity of *A. camphorata* were conducted only at the level of a mixture such as the fermentation broth or an extract. Because research on activity was based on the mixture, the effective components and content have not been elucidated, and consistency in composition of each batch of *A. camphorata* fermentation product cannot be guaranteed. Hence, the quality control and effectiveness of the products may not be assured. Reports on the evaluation of the safety of *A. camphorata* are not comprehensive. If safety evaluation is carried out on a mixture, it may not be easy to draw a firm conclusion because the content of toxic substances may be too low to cause a great impact on the experimental results. In addition, other than the active components of *A. camphorata*, there may be substances non-essential to human, and long-term intake of these will certainly increase the burden on hepatic metabolism and renal excretion. From the above two points of view, the contemporary research on *A. camphorata* still has some limitations. Moreover, although a host of studies have demonstrated that extracts derived from *A. camphorata* fruiting bodies or mycelia exhibited a constellation of effects including anticancer, antileukemia, antiinflammatory, and hepatoprotective activities, most of these experimental findings were derived from in vitro investigations which were not supported by data from clinical trials. Hence, further clinical validation is necessitated if one intends to utilize the active constituents from *A. camphorata* to prevent or treat certain diseases.

In order to create a greater value of *A. camphorata*, the development of its industry is bound to implicate upgrading from the traditional dietary health products to high-end new medications in the future, which will bring along more stringent requirements for the related research on *A. camphorata*. From the traditional health food to the field of medicine, the preliminary research idea is to separate and purify the components from the extract and fermentation broth of *A. camphorata*, determine the specific components and their structures with biological activity, and then pharmacological and toxicological studies of the active constituents will be carried out. Pharmacological research includes pharmacodynamics and pharmacokinetic studies. The former studies should clarify the mechanism of action of the active ingredients of *A. camphorata* and indicate the relationship between efficacy and structure, dose, and time. The latter studies focus on the absorption, metabolism, distribution and excretion of the active ingredient, the effects of different routes of administration on efficacy, and the differences in the efficacy of different species. Toxicological studies emphasize on the toxicity and toxicokinetics of the active ingredients and their metabolites, including acute toxicity, long-term toxicity, reproductive toxicity, genotoxicity, topical toxicity, carcinogenicity, dependence, and immunogenicity. Toxicological studies serve to provide the relationship between the concentration of each active ingredient and its toxicity and determine the target organ of the toxic action and the mechanism of each of its components or its metabolites. From the above, the objective of the preclinical study is to analyze whether the active ingredients of *A. camphorata* have the possibility of new drug development and then it will be followed up by pharmaceutical research and clinical research.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical statement This work does not contain any studies with human participants or animals performed by any of the authors.

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