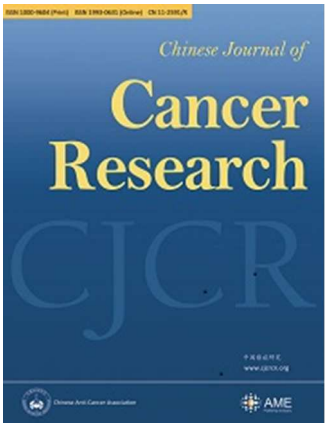

Molecular targets of Antrodia cinnomomea for cancer chemoprevention

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Molecular targets of Antrodia cinnomomea for cancer chemoprevention

Abstract: Antrodia cinnomomea, which is the valuable medicinal fungal, has been identified as potent anti-cancer agents. Extensive in vitro and in vivo studies revealed multiple intracellular targets of Antrodia cinnamomea, which affect cell proliferation, apoptosis, angiogenesis, and invasion and metastasis. These include cell cycle regulators, cyclins, CDKs, Chk1/2, p21, p27; apoptotic and survival regulators, Bax, Bak, Bcl-2, Bcl-XL, PUMA, Akt; tumor suppressors p53 and Rb; metastatic and angiogenic factors, VEGF and matrix metalloproteinase 2/9 and transcription factors NF-κB, AP-1. There is increasing evidence that Antrodia cinnomomea exhibits immunomodulatory which may lead to cell cycle arrest or apoptosis. This review summarizes in vitro and in vivo anti-tumor mechanistic data over the past ten years available for Antrodia cinnomomea.

Keywords: Antrodia cinnamomea; Cancer; Cell cycle regulation; Apoptosis; Transcriptional factors

Introduction

Antrodia cinnamomea, which can be used as medicinal fungal, is a bacterial parasite found on Cinnamomum kanehirai which is uniquely grown in Taiwan. It is a genus of mushrooms belonging to Polyporales in Basidiomycetes. It is highly valued in Taiwan as rich in various bioactive constituents; the mycelium and fruiting body of Antrodia cinnamomea are both edible. Antrodia cinnamomea starting to attract interest due to their abundant bioactive phytocompounds including triterpenoids, flavonoids, polysaccharides, maleic/succinic acid, benzenoids and benzoquinone derivatives. Having extremely high medicinal value, Antrodia cinnamomea has the functions of anti-cancer, liver protection, anti-inflammation, anti-virus, anti-oxidant stress, immunomodulatory, anti-hyperlipidemia and so on[1-5]. Therefore, Antrodia cinnamomea can nourish and build up the body, and support the healthy energy.

In China alone, almost 1 new case of invasive cancer was estimated to occur in 2012 in every 6 minutes (Chinese Cancer Registry Annual Reports, 2012). Comparative and alternative medicine (CAM) agents are among the most promising chemopreventive and treatment options for the management of cancer. Many chemopreventive agents possess the characteristics including inhibiting the neoplastic cells proliferation and promoting their apoptosis through targeting multiple biochemical and biophysical molecular targets and signaling pathways during tumor development [6, 7]. Antrodia cinnamomea is one of the ideal agents, because of its capacity to affect many signaling molecules during the cancer cell survival and tumor growth and low toxicity. The tumor cell microenvironment plays a key role for the survival of cancer cells through inhibiting tumor cells proliferation effects of neighboring normal cells and resisting apoptosis and cell cycle arrest signal, and then promoting tumor cell tissue invasion and metastasis. Many molecules and signaling pathways are involved in tumor development, and dysregulation of them promote the tumorigenesis. These molecules are as follows, the mutation or overexpression of cell cycle regulators Cdks, cyclins, Chk1/2, p21, p27; mutation or overexpression of apoptotic or survival regulators Bax, Bak, Bcl-2, Bcl-XL, PUMA, Akt; mutation or overexpression of metastatic and angiogenic factors VEGF, matrix metallproteinase 2/9; mutation or deletion of tumor suppressor p53, Rb, and PTEN; overexpression of the transcription factors AP-1 and NF-κB; dominant activation of oncogene Ras. Plenty of papers showed that Antrodia cinnamomea regulates many of the cancer molecules and signaling pathways mentioned here, which suppress tumor cell proliferation and promoting apoptosis, inhibiting tissue invasion and metastasis, inhibiting angiogenesis, promoting immunomodulatory, and even plays potentiation effects of chemotherapy and radiotherapy. Till the dates there are more than 400 scientific publications that revealed the therapeutical outcomes of Antrodia cinnamomea and its derived pure compounds. Among them, extensive studies have veried the cancer-preventing properties of Antrodia cinnamomea in various models of human cancer cell lines (Table 1). The present review is focusing on

recently published works on multiple molecular pathways, mechanisms, and clinical trials of Antrodia cinnamomea *in vitro* and *in vivo*. We believe that the outcome of this review will be a potential step forward in understanding the role of Antrodia cinnamomea in cancer management. Figure 1 illustrating the molecular targets modulated by Antrodia cinnamomea.

Table 1. Multiple molecular targets of Antrodia cinnamomea and its pure compounds against various tumor cells and their mechanism

Agents	Mechanism	Molecular targets	Reference
Polysaccharides	Inhibit tummorigenesis	Cytokines activity	Liu et al.2004[8]
Antrodia cinnamomea extracts	Induce apoptosis	Caspase activity	Hseu et al.2004[9]
Antrodia cinnamomea extracts	Induce apoptosis	Fas activity	Song et al.2005[10]
Antrodia cinnamomea extracts	Induce apoptosis	Caspase activity	Song et al. 2005[11]
Polysaccharides	Inhibit angiogenesis	VEGF	Chen et al.2005[12]
Polysaccharides	Inhibit angiogenesis	VEGF	Cheng et al.2005[13]
Antrodia cinnamomea extracts	Induce apoptosis	Caspase activity	Hsu et al.2005[14]
Antrodia cinnamomea extracts	Immunomodulation	Cytokines activity	Meng et al. 2005[15]
Antrodia cinnamomea extracts	Induce apoptosis	Caspase activity	Wu et al.2006[16]
Antrodia cinnamomea extracts	Induce apoptosis	Calpain/Bid/Bax, Ca2+/mitochondrial	Kuo et al.2006[17]
Antrodia cinnamomea extracts	Inhibit proliferation	Cell cycle regulatory proteins	Peng et al.2006[18]
Antrodia cinnamomea extracts	Induce apoptosis	Caspase activity	Yang et al.2006[19]
Antrodia cinnamomea extracts	Inhibit proliferation and inflammation	Cytokines activity	Rao et al.2007[20]
Antrodia cinnamomea extracts	Induce apoptosis	Caspase activity	Hseu et al.2007[21]
Antrodia cinnamomea extracts	Inhibit proliferation	Cell cycle regulatory proteins	Chen et al.2007[22]
Antrodia cinnamomea extracts	Induce senescence	Cell cycle regulatory proteins	Peng et al.2007[23]
Antrodia cinnamomea extracts	Inhibit metastasis	NF-κB	Hsu et al.2007[24]
Antrodia cinnamomea extracts	Induce apoptosis	Ca2+ and MAPK activity	Ho et al.2008[25]
Antrodia cinnamomea extracts	Inhibit tumorigenesis	Cox-2 and MDR1 activity	Chang et al.2008[26]

Antrodia cinnamomea extracts	Inhibit proliferation	Cell cycle regulatory proteins	Hseu et al.2008[27]
Antrodia cinnamomea extracts	Immunomodulation	Cytokines activity	Lu et al.2009[28]
Antrodia cinnamomea extracts	Immunomodulation	Cytokines activity	Chen et al.2008[29]
Antrodia cinnamomea extracts	Induce apoptosis	Ca2+ and MAPK activity	Huang et al.2009[30]
Triterpenoids	Induce apoptosis	Caspase activity	Yeh et al.2009[31]
Antrodia cinnamomea extracts	Inhibit tumorigenesis	Cox-2 and MDR1 activity	Li et al.2009[32]
Antrodia cinnamomea extracts	Immunomodulation	HER-2/neu activity	Huang et al.2010[33]
Antrodia cinnamomea extracts	Immunomodulation	Cytokines activity	Lin et al.2010[34]
Methylantcinate A	Induce apoptosis	Caspase activity	Hseih et al.2010[35]
Methylantcinate A	Induce apoptosis	Caspase activity	Tai et al. 2010[36]
Antroquinonol	Inhibit tummorigenesis	AMPK, mTOR activity	Chiang et al.2010[37]
4-Acetylantroquinonol B	Inhibit tummorigenesis	Cytotoxic effect	Lin et al.2010[38]
Antrodia cinnamomea extracts	Induce apoptosis	Various pathways	Chan et al.2010[39]
Antrodia cinnamomea extracts	Inhibit metastasis	MAPK	Yang et al.2011[40]
Antrodia cinnamomea extracts	Immunomodulation	Cytokines activity	Chang et al.2011[41]
Antroquinonol	Cell cycle arrest	mTOR activity	Kumar et al.2011[42]
Antrocin	Inhibit metastasis	Akt/mTOR activity	Rao et al.2011[43]
4-Acetylantroquinonol B	Cell cycle arrest	p53, p21 and p27	Lin et al. 2011[44]
SY-1	Inhibit proliferation	Cell cycle regulatory proteins	Lien et al.2011[45]
Antrodia cinnamomea extracts	Inhibit tumorigenesis	Various pathways	Chiou et al.2011[46]
Antrodia cinnamomea extracts	Induce apoptosis	Cytotoxic effect	Liu et al.2011[47]
Antrodia cinnamomea extracts	Inhibit tumorigenesis	Cytotoxic effect	Chen et al.2011[48]
Antcin B	Induce apoptosis	Caspase activity	Hsieh et al.2011[49]
Antcin C	Induce apoptosis	Caspase activity, Nrf2/ARE	Gokila Vani et al.2011[50]
Antroquinonol	Inhibit tumorigenesis	various pathways	Yu et al.2012[51]
SY-1	Inhibit apoptosis	p53-mediated p27/Kip1	Tu et al. 2012[52]

Eburicoic Acid	Induce atuophage	Various pathways	Su et al.2012[53]
triterpenoids	Inhibit proliferation	Cytotoxic effect	Du et al.2012[54]
SY-1	Inhibit tummorigenesis	Cytokines activity	Wei et al.2012[55]
Methylantcinate A	Inhibit cancer stem cell activity	NF-kappaB, p53	Peng et al.2013[56]
Antrodia cinnamomea extracts	Inhibit proliferation and cancer stem cell activity	Various pathways	Liu et al.2013[57]
Antrodia cinnamomea extracts	Inhibit proliferation and migration	Cell cycle regulatory proteins, MMP-9	Liu et al.2013[58]
Antrodia cinnamomea extracts	Inhibit tumorigenesis	Cytotoxic effect	Yang et al.2013[59]
YMGKI-1	Inhibit tumorigenesis and cancer stem cell activity	Cytokines activity	Chang et al.2013[60]
Antrocin	Inhibit tumorigenesis	JAK2/STAT3, caspase activity	Yeh et al.2013[61]
Antrodia cinnamomea extracts	Induce tumotogenesis	Various pathways	Chen et al.2013[62]
Antrodia cinnamomea extracts	Inhibit tumorigenesis	β-catenin, cell cycle regulatory proteins	Park et al.2013[63]
Antrodia cinnamomea extracts	Induce apoptosis	Caspase activity	Yang et al.2013[59]
Antrodia cinnamomea extracts	Induce apoptosis	Multiple proteins and the miRNA system	Chen et al.2013[64]
CARI Ⅲ	Inhibit proliferation	Cell cycle regulatory proteins	Park et al.2014[65]
Antroquinonol	Inhibit tumorigenesis	DNA demethylation, multiple tumor suppressor genes	Wang et al.2014[66]
Antrodia cinnamomea extracts	Inhibit proliferation	Cell cycle regulatory proteins	Yang et al.2014[67]
Antroquinonol	Induce apoptosis	Ras, Rho	Ho et al. 2014[68]
Triterpenoids, polysaccharides and 1,3-β-D-glucan	Inhibit tumorigenesis	Caspase activity	Lee et al.2014[69]
Coenzyme Q0	Inhibit tumorigenesis	ROS-mediated apoptosis	Chung et al.2014[70]

4-Acetylantroquinonol B	Inhibit tumorigenesis	mTOR, VEGF, Rho GTPases	Chang et al.2014[71]

1 Antrodia cinnamomea potentiates chemotherapy effects

The use of multiple drugs in cancer therapy increases the efficacy of the potential therapeutic effects. Antrodia cinnamomea potentiates several cancer cell lines to chemotherapy in vitro and in vivo. The solid-state extracts of Antrodia cinnamomea, when combined with anti-tumor agents showed adjuvant anti-proliferative effects on C3A and PLC/PRF/5 liver cancer cells and xenografted cells in tumor-implanted nude mice, extending their median survival days. The inhibition effect was elucidated to be through intervention of MDR gene expression and COX-2-dependent inhibition of p-AKT [26]. In the human RPMI7951 and MG63 cancer cell lines, the solid-state extracts of Antrodia cinnamomea pretreatment followed by amphotericin B (AmB) treatment effectively inhibited cell growth through triggering G2/M arrest and significant apoptosis and increasing level of p21(Cip1/Waf1) and pro-apoptotic protein Bax and reducing level of anti-apoptotic protein Bcl-2[62].

2 Antrodia cinnamomea inhibits tumor cell proliferation

Cell cycle kinase activities are always upregulated in human cancers due to the overexpression of cyclins and CDKs, or inactivation of the CDK inhibitors. In human cancers, deregulation of the cyclinD1-Rb axis is common, as accumulation of cyclin-D1 is found in tumors such as hepatocellular carcinoma, breast cancer, skin cancer, and lung cancer, and affecting the cell cycle regulation becomes one of the extensive studied targets [72]. Methanol extracts of mycelia (MEM) of Antrodia cinnamomea can arrest cell cycle in G0/G1 phase in human HepG2 liver cancer cell [10, 11]. 4-Acetylantroquinonol B isolated from Antrodia cinnamomea can inhibit proliferation of human HepG2 liver cancer cell line through increasing the proportion of G1 phase cells in cell cycle, decreasing the proportion of S phase, reducing CDK2 and CDK4 expression, and elevating CDK inhibitor p53, p21 and p27 protein expression [38, 44].

3 Antrodia cinnamomea induces tumor cell apoptosis

Apoptosis, also known as programmed cell death, is a complex process that includes cell shrinkage, blebbing, nuclear fragmentation, chromatin condensation, chromosoma DNA fragmentation and death. To pharmaceuticals, cell death is an ideal mode, and many cytotoxic chemotherapeutic agents are designed to induce cell apoptosis [73]. Apoptosis mainly occurs in two ways at the molecular level, one is the extrinsic death receptor (DR)-mediated pathway, and the other is the intrinsic mitochondria-mediated pathway [3, 5]. In HL60 cells, the extract of Antrodia cinnamomea and fermented culture broth could trigger apoptosis through upregulating histone hypoacetylation, histone deacetyltransferase 1, and downregulating histone acetyltransferase activities in a dose- and time-dependent manner [28, 67]. Antrodia cinnamomea-induced HL60 cell apoptosis also showed chromatin condensation, internucleosomal DNA fragmentation as well as the release of cytochrome c, activation of caspase-3, specific PARP and Bcl-2 decrease and Bax increase [9]. In human HepG2 liver cancer cells, MEM induced the protein expression of caspase-3, caspase-8 and caspase-9 to 5.3, 6.7 and 2.2 times respectively [11]. The ethylacetate extract of Antrodia cinnamomea (EAC) fruiting bodies induced the apoptosis through increasing the level of Ca2+ in the cytoplasm and activating calpain and caspase-12, initiating the mitochondrial apoptotic pathway by regulation of Bcl-2 expression, release of cytochrome c, and activation of caspase-9, amplifying the interaction of Bid and Bax and Ca2+ translocation in human Hep3B liver cancer cells [17]. The extract compounds antcin A, antcin C and methy antcinate A (MAA) of Antrodia cinnamomea triggered mitochondrial apoptotic pathway through the activation of ROS-dependent Cofilin- and Bax-protein on Huh7, HepG2 and Hep3B liver cancer cells [35]. The triterpenoids methylantcinate B (MAB), antcin B and antcin C induced human HepG2 liver cancer cell cells apoptosis through caspase cascades, mitochondrial disruption, Bax and Bcl-2 expression and NADPH oxidase-provoked oxidative stress [49, 50]. In COLO 205 and HT-29 cells, SY-1 derivative and triterpenes have the

ability to trigger apoptosis by activating caspase-3, -8, -9, Bax, Bcl-2; increasing the levels of p53, p21 and p27; and inducing apoptosis-associated protein poly-(ADP-ribose) polymerase (PARP) cleavage [31, 45, 48].

4 Antrodia cinnamomea inhibits tumor invasion /metastasis

Tumor metastasis is the fact of malignant tumor cells, by way of the lymphatic channel, blood vessels or body cavities, reaching other parts from the primary site and continuing to grow. Enhancing mobility and invasiveness are the two different abilities of cancer cells needed for tumor cell migration. Cadherins and many lysosomal enzymes such as matrix metalloproteinases (MMPs) and urokinase plasminogen activator (uPA) play an important role in tumor invasion and migration [74, 75]. In human MDA-MMB-231 breast cancer cells, the extract of Antrodia cinnamomea suppressed the invasion and migration through inhibition of MMP-9 and uPA activities; the protein content of metastasis-associated proteins including MMP-2, MMP-9, uPA, uPAR, and VEGF were also decreased after Antrodia cinnamomea treatment [40]. EAC showed anti-invasive effect in the human PLC/PRF/5 liver cancer cells and in the nude mice model. Mechanistic studies showed that the inhibition of tumor cell invasion was through decreasing either the level or activity of VEGF, matrix metalloproteinases (MMP-2, MMP-9 and MT1-MMP), and increasing the expression of tissue inhibitors of metalloproteinase (TIMP-1 and TIMP-2) [24]. 4-Acetylantroquinonol B displayed prominent anti-metastatic effects in xenografted human HuH7 liver cancer cells and lung metastasis models through decreasing the production of VEGF and inhibited the activation of GTPase through Rho and Rac1, one of the signaling cascades activated by VEGF, in a concentration-dependent manner [71].

5 Antrodia cinnamomea regulates tumor angiogenesis

Angiogenesis is a complex process including activation, invasion and migration, morphological alternation, amplification and the formation

of new blood vessels from pre-existing ones. Angiogenesis is controlled stringently by a relative balance of angiogenic stimulators and inhibitors, two counteracting factors in normal situation as placentation and would healing [76-78]. Many molecules are angiogenic stimulators, such as angiopoietins, the platelet-derived growth factor (PDGF), the vascular endothelial growth factor (VEGF), the fibroblast growth factor (FGF), the transforming growth factor-beta (TGF-β), and the hepatocyte growth factor (HGF). Angiogenic inhibitors are anti-angiogenic factors like Endostain, Thrombospondin-1/2, Angiostain, Osteopontin, Tissue inhibitors of the metalloproteinase, Platelet-associated platelet factor-4 and Interleukin-12. Many anti-angiogenic drugs including macugen (pegaptanib), lucentis (ranibizumab), and avastin (bevacizumab), have been marketed for cancer treatment, and many other are under investigation. The growth, progression and metastasis of a tumor are always dependent with angiogenesis, especially sprouting angiogenesis [79]. During tumor progression, every cancer cell needs continuous nutrient supply and a way for escaping from the primary site. The development of neovessel can fulfill their needs. Inhibiting the angiogenic process or targeting existing tumor vessels can be used to treat of tumors as an alternative or in parallel with conventional chemotherapy. Different from conventional chemotherapy, anti-angiogenic therapy suppresses cancer indirectly through depriving the nutrients and oxygen of cells. Moreover, overproduction of pro-angiogenic molecules and/or decreasing production of anti-angiogenic molecules leads to abnormalities both in tumor microenvironment and tumor vessels. These factors may interfere with the therapeutic drugs delivery, maintaining tumor cells resistant to both chemotherapy and radiotherapy, induce genetic stability and select for malignant cells which show increased metastatic potential and compromise the immune cells cytotoxic functions [80, 81]. In the endothelial cells and in the tumor cells, anti-angiogenic effect of Antrodia cinnamomea extracts was regulated through suppression VEGF and VEGFR signaling, the binding of VEGF with VEGFR2, VEGFR2 phosphorylation, and VEGF-induced cyclin D1 expression in a dose-dependent manner [12, 13]. The inhibitory effect on angiogenesis were also

studied from the human PLC/PRF/5 and C3A, HA22T/VGH liver cancer cells after treating with extracts of Antrodia cinnamomea, the tumor growth was significantly inhibited and the characteristics of cancer stem cells of EA.hy926 and SVEC4-10 were also inhibited, the biomolecular activity pathway was found to suppress VEGF secretion and down-regulate HIF-1α level [24, 57].

6 Antrodia cinnamomea inhibits transcriptional factors signaling pathway

Nuclear factor-kappaB (NF-κB) is a ubiquitously expressed transcriptional factor, which composes of different family members and regulates more than 500 genes expression involved in inflammatory responses, proliferation, survival, migration, angiogenesis, metastasis and cellular transformation. In addition, NF-κB plays important roles during the development of certain hemopoietic cells, keratinocytes, and lymphoid organ structures. Moreover, NF-κB family members have been implicated in neoplastic progression and the formation of neuronal synapses. A variety of molecules can activate NF-κB through canonical and noncanonical pathways. Canonical pathway involves many steps which including the phosphorylation and degration of the inhibitor of NF-κB (IκBα). IκBα leads to p50-p65 subunit of NF-κB translocation into the nucleus and further p65 phosphorylation, acetylation, methylation, DNA binding and transcription. The agents that can inhibit phosphatases, proteasomes, protein kinases, unbiquitination, acetylation, methylation and DNA binding can be used as inhibitors of NF-κB signaling [82]. The fermented culture broth extracts of Antrodia cinnamomea inhibit invasive behavior of MDA-MB-231 breast cancer cells through the suppression of NF-κB binding and activation in a dose-dependent manner [40]. In the human PLC/PRF/5 liver cancer cell, EAC inhibited constitutively activated and inducible NF-κB in both its DNA-binding activity and transcriptional activity; EAC also inhibited the TNF-α-activated NF-κB-dependent reporter gene expression of VEGF and MMP-9 [24].

Activated protein-1 (AP-1) is another transcription factor that regulates the expression of several genes involved in cell differentiation,

transformation, survival and proliferation. Functional activation of the AP-1 transcription complex is implicated in tumor promotion as well as malignant transformation. This complex consists of either homo or heterodimers of the members of the Jun(c-Jun, JunB, JunD) and Fos(c-Fos, FosB, Fra1 and Fra2) family of proteins. c-Jun is the most potent transcriptional activator in its group, whose transcriptional activity is attenuated and sometimes antagonized by JunB. The Fos proteins, which cannot homodimerize, form stable heterodimers with Jun proteins and thereby enhance their DNA binding activity. Several stimulis like serum and growth factors potently induce AP-1 through phosphorylation of the extracellular-signal-regulated kinase (ERK) subgroup of MAPKs, whose members translocate to the nucleus and phosphorylate, and thereby potentiate, the transcriptional activity of ternary complex factors (TCFs) that bind to fos promoters [83]. Similar with NF-κB, AP-1/MAPK inhibitory activity of Antrodia cinnamomea was observed in various cancers and activated cell lines as summarized in previous review papers [1-5]. However, the inhibitory effect of Antrodia cinnmomea on AP-1transcriptional activation is still yet to be understood.

7 Antrodia cinnamomea regulates immunomodualoty

Another mechanism of action of the anti-cancer effects of Antrodia cinnamomea is adjustment of the body's immune response. Anti-tumor effects using various extracts of Antrodia cinnamomea and immunomodulation of RAW 264.7 macrophages were observed through increasing mRNA expression of TNF-α and IL-β of the macrophages in human hepatoma cancer cells [15, 41]. Oral administration of Antrodia cinnamomea fruiting bodies significantly increased the life span of ATCC BNL IMEA.7R.1 hepatoma-bearing mice through increasing cytotoxicity against hepatoma cells, increasing serum levels of tumor-specific IgG and increasing tumor-specific proliferation with upregulating production of IFN-γ, IL-2, and TNF-α [29].

Conclusion

As a rare medicinal fungus in Taiwan, Antrodia cinnamomea has been paid high attention for only 20 years since it is found in the 1990s. The extracts or singe active compound are widely used for the treatment of liver protection, anti-inflammation, anti-virus, immunoregulation and antioxidation. The anti-tumor activity of the extracts or single pure compound of Antrodia cinnamomea *in vitro* and in various tumor-bearing animal models has been investigated for years, and many findings showed that the extracts or single pure compound of Antrodia cinnamomea are a promising agents in anti-tumor therapy. However, clinical evidence is relatively limited as far as we know. Antroquinonol, one of the compounds of Antrodia cinnamomea are currently being investigated in early clinical phase Ⅱ trials, but the anti-tumor effect and mechanism of the extracts and single pure compound of Antrodia cinnamomea need to be further elucidated. The present results and data might provide new insights into the possible therapeutic uses of mushrooms and helpful suggestions for the design of anti-tumor drugs from mushrooms in combating cancer.

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Abbreviations

Akt1: v-Akt murine thymoma viral oncogene homolog-1; **AMPK:** AMP-activated protein kinase; **AP-1:** activator protein 1; **BAK:** Bcl2 antagonist/killer; **BAX:** Bcl2 associated X protein; **BID:** BH3 interacting domain death agonist; **Bcl2:** B-cell CLL/lymphoma-2; **Bcl2-xL:** BCL2-like 1 isoform 1; **CDK:** cyclin dependent kinase; **Chk1/2:** checkpoint kinase1/2; **COX:** cyclooxygenase; **EAC:** ethylacetate extract from Anrodia cinnamomea fruiting bodies; **EC:** endothelial cell; **ERK1/2:** extracellular signal-regulated kinase 1/2; **HIF-1α:** hypoxia inducible factor-1 alpha; **IFN-γ:** interferon-gama; **Jak2:** Janus kinase 2; **JNK:** c-Jun NH2-terminal kinases; **MAPKs:** mitogen activated protein kinases; **MDR1:** multidrug resistance; **MEM:** methanol extract of mycelia of Antrodia cinnamomea; **MMP1:** matrix metalloproteinase-1; **mTOR:** mammalian target of rapamycin; **NF-κB:** Nuclear factor kappa B; **PI3K:** phosphoinositide-3-kinase; **PTEN:** phosphatase and tensin homolog deleted on chromosome-10; **PUMA:** p53-upregulated modulator of apoptosis; **Rip1:** the kinases receptor-interacting protein 1; **Rb:** retinoblastoma protein; **ROS:** reactive oxygen species; **STAT3:** signal transduction and activator of transcription 3; **TIMP:** tissue inhibitor of matrix metalloproteinase; **TNF-α:** tumor nerosis factor- alpha; **VEGF:** vascular endothelial growth factor;

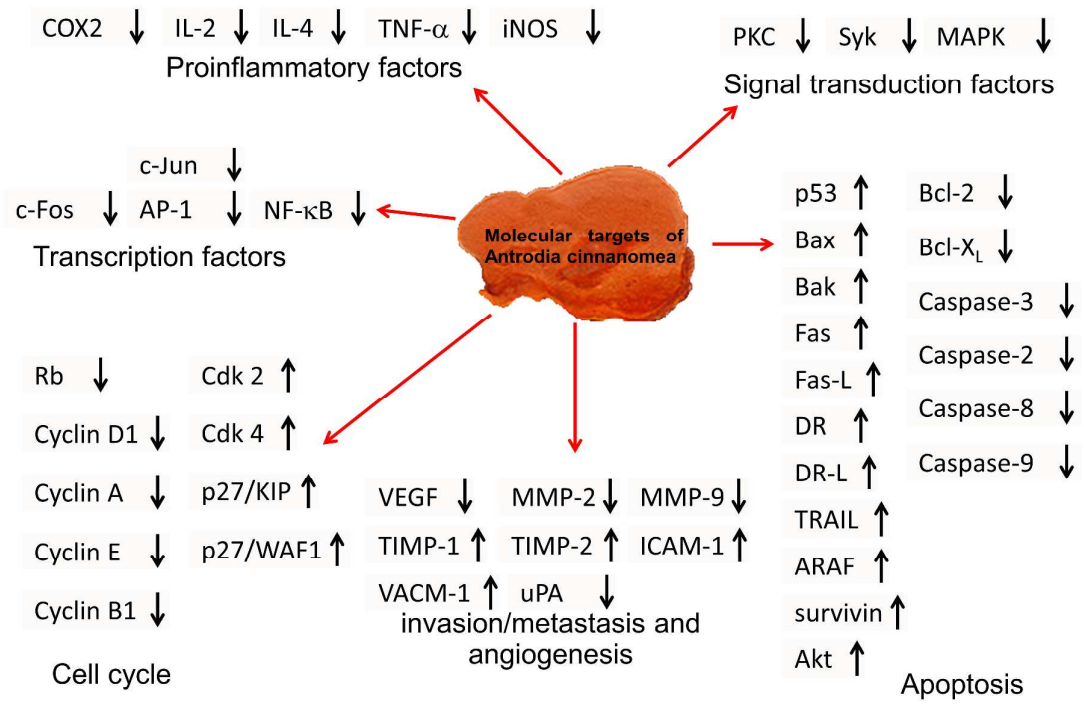

Figure 1. Identification of molecular targets of Antrodia cinnanomea