Supplementary Table S1 Anticancer properties of selected plant/mushroom bioactives *in vitro,* in preclinical animal models, and in clinical trials.

Plant/Component	Bioactives	Doses	Cell line/Animal models/Trial details	Mechanism	Comments	Reference
In vitro studies						
Astragalus membranaceous	APS (*Astragalus* Polysaccharide)	800 ug/mL 10 mM	MCF7, MDA-MB-231	APS inhibits Wnt/β-catenin signalling pathway (Lithium Chloride used to identify Wnt pathway)	0, 25, 50, 100, 200, 400, 800 or 1,600 μg/ml APS treated for 24 hours; MTT Assay	[1]
Astragalus membranaceous	APS	50 ug/mL	A549 cells co-cultivated with mesenchymal stem cells	Reduced cell proliferation and improved cell morphology	Effects regulated by MAPK-NFkB pathway	[2]
Astragalus membranaceous	Astragaloside- IV	(10 – 160) ug/ml	Hepatocellular carcinoma cell lines – SMMC-7721 and huh - 7	Decreased expression for long non-coding RNA (Lnc RNA) and inactivated signalling of IL-11/STAT 3		[3]
Astragalus membranaceous	Astragaloside- IV	(10 – 40)umol/L	Human gastric carcinoma BGC-823 cell line	Significant increase in microRNA-214 expression and decrease in microRNA-301a expression that led to subsequent decrease in expression of SOX2 and NANOG		[4]
Astragalus membranaceous	Astragaloside- IV	0.1 mM	5-fluorouracil resistant human lung cancer cells (Bel-7402/FU)	Significant decrease in expression of multi-drug resistant gene (MDR1) by downregulating the JNK/c-Jun/AP-1 signalling pathway		[5]
Astragalus membranaceous	APS extracted at 4 and 90 ^{0}C	(25 – 800) ug/ml	MGC-803, A549 and HepG2 cells	APS4 showed higher content of (1→2,6)-α-d-Glcp compared to APS4-90 and APS90, which indicated that higher branched degree would be responsible for the stronger in vitro antitumor activity in APS4		[6]
Lentinus edodes	β-glucans fractions	1, 0.33 and 0.11 mg/mL	A549 (NSCLC), MDA-MB-231 (breast cancer cells)	Cell viability assayed – reduced by 20% at 0.11 mg/mL, 95% at 0.33 mg/mL	6 fractions from ultrafiltration process	[7]

				and 100% at 1 mg/mL (breast cancer cells) Induced apoptosis at 1 mg/mL	
Lentinus edodes	Treated (with formic acid, lactic acid and boiled at 100^0C) and non-treated water soluble *lentinula edodes* polysaccharides (LEPs)	(25 – 250) ug/ml	Human breast cancer cell lines (MCF-7 and T47D)	Non-treated LEPs showed high anti-proliferative activities in MCF-7 and T47D compared to treated LEPs	[8]
Lentinus edodes	LEPs (triple helix structure) and LEPs (single flexible chain)	(5 – 500) ug/ml	Sarcoma-180 tumor cells	LEPs with triple helix structure had higher inhibition of tumor growth compared to the single flexible chain LEPs	[9]
AHCC and Wasbi combination (L edodes and Wasabia japonica)	Glucans and 6-methyl-sulfinyl-hexyl isothiocyanate	(7.5 – 500) ug/ml	MCF7, Panc02, Adenocarcinoma cell lines	Significant increase in G(0)/G(1) together with marked percentage of apoptotic cells, BAIC reduced the size and number of mamosphere formation from the stem cells	[10]
Lentinus edodes	Lacriptin – 4 domain		HepG2 cells	Inhibit growth of human HepG2 cells	[11]
Lentinus edodes	Lacriptin – 11 domain	(6.25 – 200) ug/ml	U937 (lymphoma)	Induce apoptosis	[12]
Lentinus edodes	Lacriptin – 1 domain	0 to 120 ug/mL	SGC-7901, BGC-823, SKOV-3, HepG-2, MDA-MB-231, MCF7	IC50 of 31.5 and 40.7 ug/mL for SGC-7901 and BGC-823	[13]
Lentinus edodes	LSMS-1 & LSMS-2 (polysaccharide from crude extract)	25, 50, 100, 200, 400 ug/mL	A549, SGC7901, MCF7, U937, MG63	Inhibition was maximum at 400 ug/mL	[14]
Lentinus edodes	Water extract CP	0.2, 0.5, 1.0, 2.0, 5.0 mg/mL	Hep-2 cells and MRC-5 (normal cells)	IC50 = ~1 mg/mL Early apoptosis at 1 mg/mL and late apoptotic event 2 mg/mL	[15]
A. bisporus, brown A. bisporus Lentinus edodes	b-glucan	0-100 ug/mL	PC3	No significant changes in cell viability observed, dose dependent cell proliferation inhibition obtained. Ethanolic extractions reduced IL-8 production and a trend in	[16]

				VEGF secretion at higher concentration.		
Lycium barbarum	Arabinogalactan Purified fractions of *L. barabarum* crude polysaccharides (LBP-1)	50, 100, 200, 400, 800 ug/mL for 24 hours	Hepatoma cells (SMMC-7721 and HepG2), cervical cancer cells (HeLa), gastric carcinoma cells (SGC 7901), Human breast cancer cells (MCF7) and normal human liver cells (L02)	Affected cell viability in a tissue specific manner. The inhibition of growth was mediated through cell cycle arrest and apoptosis.		[17]
L. edodes	LEP-1 and LEP-2	0.056, 0.112, 0.224, 0.448, 0.896, 1.792 mg/mL for 72 hours	HCT116 HeLa cells			[18]
A. membranaceous in combination with quercetin, dithiodipropionic acid, folic acid and curcumin (Cur)	Quercetin-3'3-dithiodipropionic acid-*Astragalus* polysaccharides-Folic acid (QDAF)@Cur	(0.5 – 20) ug/ml of Cur	MCF7 (Breast cancer cell line)	Increased intracellular uptake, tumour inhibition and apoptosis in ER-α positive cell lines		[19]
Astragalus membranaceous	Astragaloside IV	(100 – 400) uM	HCC (SK-Hep1 & Hep38 cells)	Induce extrinsic /intrinsic apoptosis, trigger G (1) arrest		[20]
Astragalus membranaceous	APS	50,100,200, 500, 1000 ug/mL and CM (Conditioned medium from macrophages)	4T1 cells	APS treated macrophages suppressed 4T1 by mitochondrial apoptotic pathway		[21]
Astragalus membranaceous	APS	5 mg/mL APS time dependent inhibition (48h)	Prostate cancer cells (PC3 and DU145 cells)	miR-138-5p/SIRT1/SREBP1 pathway in PCa	*In-vitro* and *In-vivo* Inhibited proliferation and invasion of PCa cells	[22]
Astragalus membranaceous	APS	0.25,0.5,0.75,1 and 2 mg/mL incubated for 24, 48, 72 and 96 hours	MCF7, MDA-MB-231 cells	Cell viability, migration and invasion assays demonstrates that APS interferes growth of MCF and MDA-MB-231 cells in a dose dependent manner. Mechanistically APS downregulated the expression of CCNB1 and CDC6 and		[23]

				upregulate the tumour suppressor gene p53.		
Lentinus edodes	β-glucans fractions		MDA-MB-231			[24]
Desert truffles *Terfezia boudieri*	Aqueous/methanolic extract	0.78 to 25 mg/mL incubated for 48h	T47D, MCF7, MDA-MB-231, HCT116, HeLa, Vero (normal)			[25]
Preclinical animal studies						
Astragalus membranaceous in combination with rhubarb and *Curcumae longae*	Astraagalus:rhubarb:rhihoma *Curcumae longae* (3:1:1) crude decoction in combination with small interfering RNAs (siRNAs)	6.4g/kg	Female Nude Mouse (xenograft with MCF7)	Increase the expression of Nrf2 and Suppress the expression of PI3K/AKT/mTOR signalling pathway		[26]
Astragalus membranaceous	Astragaloside - IV	160 ug/ml 80 ug/ml	Female C57BL/6 mice (xenograft with 3LL-luc cells)	Significant increase in expression of cytotoxic T lymphocytes while decreased expression for T regulatory cells		[27]
Astragalus membranaceous	*Astragalus* saponins (AST)	0.02,0.04, 0.08, 0.16, 0.2 mg/mL (0,12, 24,48,72h) 2% DSS (n=8, positive control), 0.1 mg/g AST (n=8, negative control) and 0.1 mg/g AST treatment combined with 2% DSS in drinking water (n=8)	Invitro (HT29, SW620) and in-vivo (DSS induced colitis mouse model – c57BL/6J mice)	IC50 for HT-29 and SW620 were 35 and 46 ug/mL AST inhibits cell proliferation in a dose dependent manner and induces apoptosis (decreases Bcl2, PARP and pro-caspase-3 and increases Bax, Bak and Bad)	AST could inhibit growth and glycolysis metabolism in CRC cells *in vitro*, and attenuate the inflammatory response and tumor-like aerobic glycolysis in the DSS-induced mouse model. The findings indicated that AST may have the capacity to resist tumor-associated inflammation and maintain normal glucose homeostasis, suggesting that AST could be a novel therapeutic strategy in CRC treatment.	[28]

Mushroom mix *Agaricus blazei, Ophiocordyceps sinensis, Ganoderma lucidum, Grifola frondosa, and Lentinula edodes*	Micotherapy U-care	The blend contains 20% each of the 5 mushrooms. 16 mice received 4 mg of supplement per day – 4 healthy controls and 14 untreated	8 wk old BALB/c Syngene mice (4T1 triple negative mouse breast cancer model)	Reduced pulmonary metastasis density, decreased fibrotic response and reduced IL-6, NOS and COX2 expression		[29]
Astragalus membranaceous	APS 5FU APS+5FU	Blank, negative (0.9% NS), APS (100 & 200 ug/Kg), 5FU (20 mg/Kg), Combined (200 mg/Kg APS + 20 mg/Kg 5FU)	Female BALB/c mice	Anticancer activity by restoring immune organs, increased cytokine release, induced phagocytosis	Along with 5FU - Immune adjuvant for chemotherapy	[21]
Astragalus membranaceous	APS	NC, LD-APS (50 mg/Kg), HD-APS (100 mg/Kg) OD – PO for 14 days	Nude mouse	Reduced tumour size and fatty acid		[22]
water extract of ginseng and *Astragalus* (WEGA)	WEGA	0,5,10,20 mg/mL – cell culture and 0, 30, 60 and 120 mg/Kg bwt for animal experimentation	A549 cells and Tumour Associated macrophages			[30]
Clinical trials						
Astragalus mongholicus and *Semen Cuscutae* or placebo			N – of – 1 with gastric cancer	Randomized double blind and controlled treatment	Symptoms improved in two patients	[31]
Antrodia cinnamomea	2.1g PS, 172 mg triterpenoids and 2.6875 g g-aminobutyric acid	2.1g PS, 172 mg triterpenoids and 2.6875 g g-aminobutyric acid	37 patients with gastric, liver, breast and crc	Double blind randomized clinical trial – 30-ay trial	No significant improvement in the combination therapy	[32]

		SD rat (toxicity)			
Ganoderma lucidum				Cochraine database – systemic review	[33]
Agaricus bisporus (white button mushroom)	6 doses from 4g/day until 14g/day		36 patients – prostate cancer	Phase-I study	[34]

Supplementary Table S2 Anticancer properties of plant and mushroom based bioactives in combination with standard chemotherapeutic agents in *in-vitro* studies, animal models, and clinical trials.

Plant/Component	Bioactive	Dose	Cell line/Animal models/Trial details	Mechanism	Comments	Reference
In vitro studies						
Astragalus membranaceous + Cisplatin	Astragaloside- IV	(10 – 40) ng/ml	Human non-small cell lung cancer cells (A549, NCI-H1299 and HCC827)	Significant increase in chemo sensitivity of cisplatin to lung cancer cells by inhibiting mRNA and B7-H3 proteins		[35]
Astragalus membranaceous Adriamycin	APS	APS (50-200 ug/mL) Adriamycin (0.1 ug/ml)	SGC-7901, SGC-7901/ADR, GES-1	APS inhibit gastric carcinoma by signalling AMPK pathway	APS 50 to 200 ug/mL plus or minus Adriamycin (0.1ug/mL)	[36]
Lentinula edodes Oxaliplatin	Lentinan Oxaliplatin	20 uM (Oxaliplatin) 800ug/ml (lentinan)	Hepatocellular carcinoma (HepG2) cells	Enhanced caspase-3 activation and reduced the expression for NF-κB and survivin		[37]
Astragalus membranaceous Taxol	AS-IV	10 – 90 uM (AS-IV) + 1-70 uM (Taxol)	MCF7, MDA-MB-231	Enhance chemosensitivity of Taxol by reversing caveolin-1 expression induced by taxol.	MTT/CFU assays	[38]
Astragalus Apatinib	APS	Apatinib 40 uM + 50, 100, 200 and 400 APS	Pancreatic cell lines, ASPC-1 and PANC-1	Inhibited cell proliferation in a dose dependent manner, increased apoptotic percentage, significantly enhanced downregulation of AKT, ERK and MMP9		[39]
Preclinical animal studies						
Astragalus membranaceous	Astragaloside IV	NS (control), Cis (3mg/Kg every 2 days PO for 14 days) or Cis+AS IV (3mg/Kg Cis + 50 mg/mL) or AS IV (50 mg/Kg IV).	BALB/c mice	Downregulated MRP2 expression in tumour cells, but not in HepG2 cells	AS IV co-administration increased chemosensitivity of Cisplatin	[40]

Lentinus edodes Oxaliplatin	Lentinan Oxaliplatin	Lentinan (25 mg/kg, i.p injection) Oxaliplatin (10mg/kg, i.p injection)	Hepatocellular carcinoma (H22) cells	Downregulated the expression of survivin, Stat3, p-Stat3 and NF-Kb (p65)	[37]
Clinical trials					
Lentinus edodes	S-1 based chemotherapy Lentinan	2 mg/Kg bwt	Chemotherapy (n=37) Chemo+Immuno (n=31)		[41]

Supplementary Table S3 Immunomodulating functions of plant and mushroom based bioactives in *in-vitro* studies, animal models, and clinical trials.

Plant/Component	Bioactive	Dose	Cell line/Animal models/Trial details	Mechanism	Comments	Reference
In vitro studies						
Astragalus membranaceous	RAP	30, 100, 300 ug/mL RAP or 1ug/mL LPS	RAW264.7 and 4T1 BMDMs (with IL-4 or LPS) BALB/c	RAP induce M1 (produced high iNOS, IL-6, TNF-a and CXL10) and skewed M2 to M1 phenotype (downregulated CD206 and upregulated CD86). Activates Notch signalling.	Reduced tumour size in mice received 4T1 grafts and Macrophages treated with RAP	[42]
Shiitake	b-glucan	100 ug/mL	PMA differentiated THP-1	Immunomodulation observed – expression of inflammation-related genes – IL-10 was highest expressed after 24 h of b-glucan.	No effect in phagocytosis index noticed except for pure Lentinan.	[43]
Astragalus membranaceous	APS in combination with cisplatin	APS- 8 and 16 mg/ml	H441, H1299, H1437 (human lung cancer cell) and LLC1 (Lewis lung cancer cell)	PBMCs from lung cancer patients (n=17)		[44]
Astragalus membranaceous	PG2 (APS)	10 ug/mL	Breast - 4T1 &colorectal - CT26. Murine WEHI-3 leukemia or murine EL4 lymphoblasts	PG2 reduced PD-L1 production which was associated with downregulation of AKT/mTOR/p7056K pathway. AKT/mTOR signal increased in murine lymphocytes when co-cultivated with PG2 treated 4T1 or CT26.		[45]
Astragalus membranaceous	APS	200 to 1000 ug/mL	RAW264.7 MCF7	Increased NO and TNF-a from macrophages and inhibited proliferation, G1 phase arrest and regulated apoptotic genes (13 fold increase in Bax/Bcl-2)	Increased NO and TNF-a expression directly blocked MCF7 cells	[6]
Preclinical animal studies						
Astragalus membranaceous	APS	50,100,200, 500, 1000 ug/mL and CM (Conditioned	4T1 cells	APS treated macrophages suppressed 4T1 by		[21]

		medium from macrophages)		mitochondrial apoptotic pathway		
Desert truffles *Terfezia boudieri*	Aqueous/methanolic extract	0.78 to 25 mg/mL incubated for 48h				
Grifola frondosa and *Lentinula edodes*	MTG404, Shiitake extract or AHCC	61.5 ug/day MaitakeGold 404, 820 ug/mL Shiitake, 820 ug Shiitake and 61.5 ug Maitake Gold 404 or 100 ug AHCC, PBS for 14 days	Female 8 wk old BALB/c mice	Phagocytic activity of peritoneal monocytes and neutrophils increased for combination, Maitake, Shiitake and AHCC in that order. Maitake and Shiitake or Maitake alone activated NK cells.		[46]
Astraalus membranaceous	Polysaccharide powder		6-8 wk old C57BL/6 mice (n=15)	PBMCs from lung cancer patients (n=17)		[44]
Clinical trials						
Lentinula edodes	Mycelia extract (LEM) – hot water extract	1.8 g/day for 4 weeks	Cancer patients	Improved quality of life, NK cell activity and immunosuppressive additive protein levels		[47]
Whole mushroom		5g (n=26) and 10 g (n=25) ODI for 4 weeks	Healthy volunteers (66 males – 21-41 years of age) Randomized parallel group study	The expression of CD69 on γδ-T cells increased in post treated cells than baseline cells when stimulated with a mitogen for 24 hrs.	Blood drawn before (baseline) and after 4wks of consumption – PBMC and Serum	[48]
Lentinula edodes	Lentinan b-1,3; 1.6-glucan Lentinex	2.5 mg/day	Healthy elderly individuals (42) Double blind cross over placebo controlled study	Increased circulatory B cells but no change in Ig	No change in immunoglobulins, complement proteins or cytokines	[49]
Lentinula edodes and Anthracycline based chemotherapy	*Lentinula edodes* mycelial crude extract (LEM) in combination with chemo drugs (5-FU/ cyclophosphamide/ doxorubicin/pirarubicin/ epirubicin)	LEM - 1800 mg/day for 3 wks for a total of 6 wks	Randomized double blind study (47 breast cancer patient)	QOL better for LEM group than placebo group Treg reduced for LEM group and increased for placebo group		[50]
Astraalus membranaceous	Polysaccharide powder			PBMCs from lung cancer patients (n=17)		[44]
Lentinula edodes	Mycelial extract (LEM)	1800 mg/day for 4 wks	10 patients who received DC vaccine therapy or CAT therapy	Improved QoL and increased IFN-g secretion from PBMCs (Increased FOX3P/CD4+		[51]

		expression and TGF-b excretion) (n=10)

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