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Review

Immunopotentiating significance of conventionally used plant adaptogens as modulators in biochemical and molecular signalling pathways in cell mediated processes

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ABSTRACT

Natural products are of great surge in the identification of chemopreventive agents and biologically active molecules for the development of new promising therapeutic agents. These agents influence the cascade of biochemical and molecular signalling pathways involved in numerous physiological and pathological processes. The natural agents combat the dogma associated with the most dreaded, unconquered health concern and a multigenic disease- cancer. A category of plants known as adaptogens maintain perturbed homoeostasis, augment adaptations to noxious stimuli (exposure to cold, heat, pain, general stress, infectious organisms) and offer endurance to attenuate several disorders in human beings. The well known adaptogens and immunomodulators such as *Rhodiola rosea, Withania somnifera, Tinospora cordifolia, Bacopa monnieri, Emblica officinalis, Glycyrrhiza glabra, Asparagus racemosus*, *Ocimum sanctum* and *Panax notoginseng* claimed to have significant antioxidant and anticarcinogenic properties due to the presence of various biologically active chemical compounds. Their immunopotentiating activity is mediated through the modulation of T-cell immunity biochemical factors, transcription factors, some genes and factors associated with tumor development and progression. The combinatory formulation of active immunostimulating constituents from these plants may provide better homeostasis. These immunostimulant factors suggest their potential therapeutic significance in adjuvant or supportive therapy in cancer treatment.

1. Introduction

Significant immunity variations in a healthy human being can be greatly driven by the non-inheritable environmental influences. The impact of these influences exaggerates with exposure to the pathogens and microbes as age increases [1]. The immune system is chronically impaired by rigorous infections (bacterial, viral), toxic environmental agents (pollutants, pesticides, allergens), undernourishment, psychic anxiety, endogenic autoimmune reactions, cancer and prolonged chemotherapy or radiotherapy [2]. Globally among these factors, cancer is one of the top causes of deaths in recent years [3]. Cancer is characterized as the disease which is self sustained in upgrading proliferative signals, silent to anti-growth signals, escape programmed cell death, possess inexhaustible replication potential, upregulate angiogenesis, facilitate tissue invasion and metastasis [4,5]. Nature has been the revolutionary basis of traditional medicinal system for millennia and the plant derived agents have been the key precursors in cancer chemotherapy. It has been a source of novel active agents that may serve as the leads in developing efficacious drugs for a multitude of disease indications [6]. The universal research on drug development through molecular approaches spotlights the targeted therapy employing natural bioactive molecules [7–9]. There are numerous studies indicating the intervention of natural products with this prolific disease. The plant derived bioactive components, such as stilbenes, anthocyanins, procyanidins, epicatechin, gallocatechin gallate, acetogenins, isorhamnetin, 4-methylsulfanyl-3-butenyl glucosinolate, sulforaphane, allyl isothiocyanate, hemagglutinin, lycopene, tomatine, lectin, suchasalliin, allicin, diallyldisulfide, allyl mercaptan, S-allylcysteine, curcumin, 6-shogaol and 6-gingerol, targets the biochemical and molecular signalling pathways associated with cancer [10].

The anticancer medicines like vinblastine, vincristine, paclitaxel, docetaxel, cabazitaxel, etoposide, sorafenib, topotecan and irinotecan are some well known plant derived clinically active drugs [11,12]. However, these and other chemotherapeutic agents are known to cause

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Table 1
Biomodulatory significance of nine conventionally used plant adaptogens with mechanism of action.

Plant adaptogen	Part used/source	Active extract/fraction/component	Cell line/Animal model	Bioactivity	Mechanism of biomodulatory action	Reference
Rhodiola rosea						
	Rhizome	Ethanolic extract	HL-60 (Promielotic leukemia cell line)	Antiproliferative and cytostatic	- Prophase accumulation of HL-60 cells - Induction of apoptosis from G2/M phase	[32]
	Root	Tincture extract	Carrageenan-induced paw oedema, formaldehyde-induced arthritis and nystatin-induced paw oedema in male wistar rats	Anti-inflammatory	- Repression of COX-1, COX-2 and phospholipase A2 - Inhibition of arachidonic acid release from cell membranes - Lysosomal membrane stabilization	[33]
	Swedish Herbal Institute (Göteborg, Sweden)	SHR-5 extract/Salidroside	UMUC3 (Human urinary bladder cancer cell line)	Anticancer	- Dephosphorylation of 4E-BP1 and increased binding of 4E-BP1 to m7 GTP - Reticence of translational initiation *via* AMPK α activation - Inhibition of p53 defective cells *via* arresting mTOR pathway	[35]
	Root	Ethanolic extract/Total glycosides	TIPE2-deficient male BALB/c mice, caecal ligation and puncture (CLP) induced sepsis	Immune regulation, Protection against sepsis	- Suppression of overexpressed TIPE2, Fas, FasL, and T-lymphocyte apoptosis - Elevation of Bcl-2, thymus T-lymphocytes along with sub-sets $CD3^+$, $CD4^+$, $CD8^+$, and Th1 cytokines, IFNγ, IL-2 and IL-12	[38]
	Source not mentioned in the study	Salidroside (phenylpropanoid glycoside)	SW1116 (Human colon carcinoma cell line)	Anticancer	- Cell cycle arrest at G0/G1 phase - Reduced expression of p-JAK2 and p-STAT3 - Down-regulation of MMP-2, MMP-9, VEGF and VEGFR-2 expression	[39]
	Source not mentioned in the study	Salidroside	Middle cerebral artery occlusion (MCAO) in male sprague dawley rats (ischemia-reperfusion injury) and CoCl2-treated PC12 (rat adrenal pheochromocytoma) cells	Neuroprotective	- Inhibition of group of genes linked with inflammation such as CD14, CD44, C1s, CCR5, A2m - Induction of genes correlated with synaptic plasticity *viz.*, Egr1, Egr2, Egr4, Arc - Abolished Bax/Bcl-xl associated apoptosis pathway	[40]
Withania somnifera						
	Root	Total extract and alkaloid-free polar fraction	Ascitic sarcoma in BALB/c male mice	Myeloprotection and immunoprotection	- Augmentation in the levels of IFNγ, IL-2, granulocyte macrophage colony-stimulating factor - Reduced expression of tumor necrosis factor alpha	[42]
	Leaf	Methanol: water (3:7) extract (TLC separated portion)/flavonoids and phenolic acid	Stainless steel implant induced inflammation in adult zebrafish	Anti-inflammatory	- Diminution in TNF-α mRNA level	[43]
	Calbiochem (La Jolla, CA, USA)	Withaferin A	CaSki (Human cervical cancer cell line) and SK-Hep-1 (Human hepatoma cell line)	Anti-invasive and anti-migratory	- Inhibition of TGFβ-induced phosphorylation of Akt - Down regulation of MMP-9 mRNA expression	[45]
	Sigma (St. Louis, MO, USA)	Withaferin A	U2OS, SaOS-2, MG-63 (Human osteosarcoma cell lines)	Antitumor	- Cell cycle arrest at G2/M phase - Inactivation of Notch-1, Hes-1, Hey-1, Hey-2 and cyclin D1 - Suppressed expression of MMP-2 and MMP-9 mRNA and protein level	[46]
	Source not mentioned in the study	Withaferin A	Human and mouse islet culture, syngeneic C57BL/6 mouse islet transplant model	Anti-inflammatory	- Prevention of IκB degradation, NF-κB nuclear translocation and its binding to DNA transcription sites - Inhibition of TNF-α, iNOS and IP-10 caused by IKKβ specific inhibitor BMS-345541	[49]

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Table 1 (*continued*)

Plant adaptogen	Part used/source	Active extract/fraction/component	Cell line/Animal model	Bioactivity	Mechanism of biomodulatory action	Reference
	Now Foods, Bloomingdale, IL, USA)	Endotoxin-free aqueous soluble extract/ Total withanolides	NRK-52E cells (Rat renal proximal tubular cell line)	Anti-inflammatory	- Declination in gene expression of CCL2 and CCL5 stimulated by TNF-α and LPS - Inhibition of NF-κB expression	[50]
Tinospora cordifolia						
	Stem	G1-4A (arabinogalactan polysaccharide)	EL-4 murine lymphoma model/EL4 (murine lymphoma cell line), B16F10 (murine melanoma cell line), A549 (human lung adenocarcinoma cell line), MCF7 and MDA-MB-231 (human breast cancer cell lines)	Immunomodulatory	- Phenotypic maturation of bone marrow derived dendritic cells and splenic dendritic cells - Enhanced surface expression of CD40, CD80, CD86, MHCII, allostimulatory activity and activation of cytotoxic T-cells - Increased secretion of nitric oxide and generation of peroxynitrite	[52,53]
	Sigma (St. Louis, MO, USA)	Berberine (isoquinoline alkaloid	Azoxymethane induced colon cancer in male albino wistar rats	Antioxidant, antitumor and anti-neoplastic	- Modulation of glycoprotein component and abolition of lipid peroxidation - Increased level of superoxide dismutase, catalase, glutathione perxidase, glutathione-s-tranferase,vitamin C and vitamin E - Topoisomerase poisoning by DNA intercalation	[54,55]
	Stem	Hexane fraction	Ehrlich ascites tumor (EAT) bearing swiss albino female mice	Apoptotic	- Amplified expression of Bax - Abrogated Bcl-2 expression - Stimulation of characteristic apoptotic features related with the constitutive expression of caspase activated DNase in nucleus and cytoplasm	[56]
	Stem	Octacosanol (aliphatic alcohol)	Human umbilical vein endothelial cells, ehrlich ascites tumor bearing swiss albino mice	Anti-angiogenic and antimetastatic	- Decline in geletinolytic activity of MMP-2 and MMP-9 - Inhibition of NF-κB directing reduction in VEGF gene expression	[57]
	Stem	Aqueous ethanolic extract	IMR-32 (human neuroblastoma cell line)	Antiproliferative and antimetastatic	- Modulation in expression of PCNA and cyclin D1 - Stimulated expression of mortalin and Rel A subunit of NF- κB - Downregulation of Bcl-xl, neural cell adhesion molecule polysialylation and secretion of MMPs	[58]
Bacopa monnieri						
	Whole plant	n-Butanol fraction/Bacopaside E and bacopaside VII	MDA-MB-231 (human breast cancer cell line), SHG-44 (human glioma cell line), HCT-8 (human ileocecal adenocarcinoma cell line), A-549 (human lung adenocarcinoma cell line) and PC-3M (human prostate cancer cell line) and Sarcoma S180 implanted in mouse	Antitumor	- Cytotoxicity - Prohibition of adhesion, migration and matrigel invasion	[60]
	Aerial parts	Bacoside rich extract	Sodium nitroprusside (SNP) induced apoptosis in L132 (human embryonic lung epithelial cell line)	Anti-apoptotic	- Hampered iNOS expression - Modulation in expressions of Bax, cytochrome c and caspase 3	[61]
	Nivaran Herbal Pvt. Ltd., Chennai, India	Purified Bacoside A from crude extract	N-nitrosodiethylamine induced hepatocellular carcinoma in male albino wistar rats	Antimetastatic	- Diminution of MMP-2 and MMP-9 expression	[62]
	Aerial parts	Stigmasterol	Ehrlich ascites carcinoma (EAC) in swiss albino mice	Antitumor	- Reduction in lipid peroxidation and membrane microviscosity - Increased levels of glutathione, superoxide dismutase and catalase	[63]

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Table 1 (*continued*)

Plant adaptogen	Part used/source	Active extract/fraction/component	Cell line/Animal model	Bioactivity	Mechanism of biomodulatory action	Reference
					- Stimulated expression of protein phosphatase 2A intended for inducing apoptosis	
	Whole plant	Aqueous extract/15 kDa protein	Ehrlich ascites carcinoma (EAC) in swiss albino mice	Antitumor and anti-angiogenic	- Deactivation of peritoneal endothelial cells - Reduction in Bcl-2 expression and VEGF secretion - Activation of caspase-activated DNase (CAD) and Bax gene expression	[64]
	Whole plant	Ethanolic extract	S-180 (murine sarcoma cells)	Cytotoxici and apoptotic	- Reduction in glutathione content in cytosol - Alterations in the Ca^{2+} transport	[65]
	Whole plant	Methanolic extract and Bacoside fractions	Carrageenan-induced paw edema in male wistar rats	Anti-inflammatory	- Abrogation of COX-2, 5-LOX and 15-LOX activities - Down regulation of TNF-α	[66]
	Whole plant	Betulinic acid	Human peripheral blood mononuclear cells	Anti-inflammatory	- Vetoed IL-6 expression and p65 level - Inhibition of p65 NF-κB nuclear translocation *via* involvement of PD98059 and SB203580 (p38 and ERK MAPK inhibitors)	[67]
	Keen Health Pvt. Ltd, Rozelle, NSW, Australia	Ethanolic extract/Bacoside A and B	Murine RAW 264.7 macrophage cells, human whole blood cells	Anti-inflammatory	- Suppression of nitrous oxide, TNF-α and IFNγ - Upstream inhibition of COX-2 - Regularization of Th1-polarised immune response	[68]
	Whole plant	Tea, infusion, alkaloid extract and Bacoside A	N9 (Microglial cells)	Anti-neuroinflammatory	- Abolition of TNF-α and IL-6 release - Inhibition of MMP-3, Caspase 1 and 3 expression	[69]
Emblica officinalis						
	Fruit	Unfractionated extract and n-butanolic extract	K562 (Human erythroleukemia), B lymphoid Raji and T lymphoid Jurkat cell lines	Inhibitory action against transcription factors	- Inhibition of NF-κB/DNA and GATA-1/DNA interactions	[72,73]
	Fruit	Hydroalcoholic extract	Carrageenan-induced hind paw edema, autacoids-induced hind paw edema, and cotton pellet-induced granuloma in wistar albino rats	Anti-inflammatory	- Increase in glutathione, superoxide dismutase, and catalase activity - Reduction in lipid peroxidation and malondialdehyde - Inhibition of NF-κB activation - Quenching of inducible nitric oxide synthase (iNOS) - Reduced expression of COX-2 enzyme levels	[76]
	Fruit	Aqueous extract	L929/Daltons lymphoma ascites cells and Ehrlich ascites cells xenograft in Swiss albino mice	Antitumor	- Diminution of Cdc2 kinase and Cdc25 phosphatase over-expression	[77]
	Fruit pulp	Aqueous extract	SiHa and HeLa (Human cervical cancer cell lines) positive for HPV16 and HPV18, respectively	Anticancer	- Inhibition of ERK1/2 and JNK - Downregulation of c-Jun, JunB, JunD and c-Fos - Inhibition of HPV transcription	[78]
	Fruit	Aqueous extract	HT1080 (Human fibrosarcoma cell line)	Antimetastatic	- Reduction in MMP-2 and MMP-9 mRNA levels	[79]
Glycyrrhiza glabra						
	Root	β-hydroxy-DHP [1-(2,4-dihydroxyphenyl)-3-hydroxy-3-(4′-hydroxyphenyl) 1-propanone]	T47D, MCF-7 (Breast cancer), HL-60 (Leukemia cancer), DUPro-1 (Prostate cancer) cell lines	Apoptotic	- Stimulated phosphorylation of Bcl-2 - G2/M cell cycle arrest	[82]
	Root	Licochalcone-A	Androgen-independent p53-null PC-3 (Prostate cancer) cells	Antitumor	- Arrested cells in G2/M phase - Suppression of cyclin B1, cdc2, cyclin D1, CDK 4, CDK 6 and E2F	[83]

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Table 1 (*continued*)

Plant adaptogen	Part used/source	Active extract/fraction/component	Cell line/Animal model	Bioactivity	Mechanism of biomodulatory action	Reference
					- Inhibition of Rb/pRb (S780) phosphorylation - Amplification in cyclin E expression	
	Calbiochem (La Jolla, CA, USA)	Licochalcone A	Lipopolysaccharide stimulated RAW 264.7 (Murine macrophage cell line)/LPS-exposed male BALB/c mice	Anti-inflammatory	- Abated expression of COX-2, iNOS, (PG)E2, IL-1β and IL-6 - Suppression of NF-κB and AP-1 activation	[84]
	Tianjin Zhongxin Pharmaceutical Group Co., Ltd. (Tianjin, China)	Licochalcone A	T24 (Human bladder cancer cell line)	Apoptotic	- Induced mitochondrial dysfunction, caspase 3 activation and PARP cleavage - Alleviated expression of UPR central regulator GRP78, UPR transcription factor GADD153/CHOP and caspase 12	[85]
	Root	Licochalcone A	BGC-823 (Human gastric cancer cell line), SiHa and HeLa (Human cervical cancer cell lines)/SiHa xenograft in BALB/c female athymic mice	Apoptotic	- Activation of ERK, JNK, p38 MAPK and inhibition of PI3K/Akt/mTOR signalling	[86,87]
	Root	Methanolic and aqueous extract/ Licocoumarone	Ehrlich ascites tumor xenograft in swiss albino mice	Anti-angiogenic and antitumor	- Repressed expression of VEGF cytokine	[88]
	Root	Herbal tincture	16 human subjects (3 male; 13 female)	Immunostimulatory	- Stimulation of CD4 and CD8T cells	[89]
	Sigma-Aldrich, USA	Glycyrrhizin	Bovine aortic endothelial cells/B16-F10 (Melanoma cells) xenograft in C57BL/6 mice	Anticancer	- Inhibition of HMGB1 protein activity - Enhanced competence of necrosis-inducing CAMEL peptide	[90]
	Root	Glabridin	MDA-MB-231 and Hs-578T (Human breast cancer cell lines)/MDA-MB-231 xenograft in nude BALB/c mice		- Upregulated miR148a expresision - Decreased expressions of DNMT1 and DNMT3a - Suppression of TGFβ/SMAD2 signalling	[91]
Asparagus racemosus						
	Underground part	Sarsasapogenin glycoside (immunoside)	Immunoside adjuvanted with HBsAg (hepatitis B surface antigen)	Immunoadjuvant	- Augmentation of Th1/Th2 response - Increased synthesis of IL-12, IFNγ and production of NO	[95]
	Harbin University of Commerce (Harbin, China)	Saponins	HepG2 (Human hepatoma cell line)	Apoptotic	- Increased intracellular reactive oxygen species, intracellular Ca^{2+} and intracellular Cyt-c - Activated caspase 3, caspase 9 and Bax expression - Reduced Bcl-2 expression	[96]
	Root	Aqueous extract	Recombinant human CYP3A4 isoenzyme	Adjuvant	- Inhibition of CYP3A4	[97]
	Root	Ethanolic extract	*Drosophila melanogaster*	Longevity	- Elevation in glucose-6-phosphate dehydrogenase activity - Raised synthesis of NADPH - Promote resistance against oxidative stress	[99]
Ocimum sanctum						
	Leaves	Ethanolic extract	A549 (Human nonsmall cell lung carcinoma) cells/ Lewis lung carcinoma (LLC) in C57BL6 mice	Apoptotic and antitumor	- Poly(ADP-ribose)polymerase (PARP) cleavage - Release of cytochrome c into cytosol leading to the activation of caspase 9 and caspase 3 - Increased Bax/Bcl-2 ratio - inhibited phosphorylation of Akt and ERK in cancer cells	[103]
	Leaves	Ethanolic extract	Mouse Lewis lung carcinoma (LLC) cells/LLC in C57BL/6 mice	Anti-oxidative and antimetastatic	- Amplified activities of superoxide dismutase, catalase and glutathione peroxidase - Downregulation of proteolytic enzyme MMP-9	[104]
	Leaves	Ethanolic extract, aqueous extract and essential oil		Antitumor		[105]

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Table 1 (*continued*)

Plant adaptogen	Part used/source	Active extract/fraction/component	Cell line/Animal model	Bioactivity	Mechanism of biomodulatory action	Reference
			AsPC-1, MiaPaCa, Capan-1 and CD18/HPAF (Human pancreatic cell lines)/AsPC-1 xenograft in female athymic mice		- Downregulation of ERK-(1/2) and Focal Adhesion Kinase (FAK), Bcl-2, Bcl-xl, AURKA, Chk 1 and Survivin - Upregulation of E-cadherin and BAD	
	Leaves	Essential oil	Lipopolysaccharide induced inflammatory cells (lymphocytes)/MCF-7 (Breast cancer cell line)	Anti-inflammatory and antimetastatic	- Down-regulated expression of MMP-9	[102]
	Leaves	Ethanolic extract	Osteopontin activated NCI-H460 (non-small cell lung cancer) cells	Antimetastatic	- Censored osteopontin and CD44 expression - Weakened PI3K and COX-2 expression and phosphorylation of Akt - Attenuated expression of uPA and its receptor uPAR, EGFR, VEGF and MMP-9	[106]
	Leaves	Ethanolic extract	LNCaP (Prostate cancer cells)	Apoptotic	- Decreased expression of Bcl-2 accompained by activation of caspase 3 and caspase 9 - PARP cleavage	[107]
Panax notoginseng						
	Root	Ginsenoside Rd (1)	HeLa (Human cervical cancer cell line)	Cytotoxic and apoptotic	- Declined Bcl-2 expression - Up-regulation of Bax protein level - Triggered caspase 3 pathway	[110]
	Flower	Methanolic extract	RAW 264.7 (Mouse peritoneal macrophage cell line)	Anti-inflammatory	- Impeded release of nitric oxide, PGE2, TNF-α and IL-1β - Restrained expression of iNOS and COX-2 - Attenuation of IκBα degradation in cytosol - Inhibition of p65 NF-κB nuclear translocation	[111]
	Leaves	PPD25 (20(S)-25-OCH3-PPD)	LS174, SW620 and SW480 (Human colorectal adenocarcinoma cancer cell lines), A549 (Human lung cancer cell line)	Anticancer	- Suppressed action of β-catenin, cyclin D1, c-Myc and CDK 4 - Blocking of Wnt/β-catenin signalling pathway - Inhibition of transcriptional activity	[112]
	Root	Aqueous extract	A549 and NCI-H460 (Human lung carcinoma cell lines)	Anticancer	- Increased Bax and lowered Bcl-2 expression - Proteolytic cleavage of poly(ADP ribose) polymerase (PARP) protein - Caspase 3 activation - Downregulation of PI3K/Akt signalling pathway	[113]
	BioAsia International Life Science Research Limited (Shanghai, China)	Ginsenosides (Rb1, Rg1 and Rd) and Notoginsenoside (R1 and Rh1)	4T1 (Mouse mammary carcinoma cell line)/4T1 metastasis in female Balb/c mice	Antimetastatic	- Upregulation of E-cadherin expression - Downregulated vimentin coupled with the increased expression of Brms 1, Mtss 1, Timp 2 - Decreased expression of MMP-3 and MMP-9	[114]
	Shanghai R & D centre for standardization of Chinese medicines (Shanghai, China)	Notoginsenoside Ft1	SH-SY5Y (Human neuroblastoma cell line)	Pro-apoptotic	- Cell cycle arrest at S and/or G_2M phase - Raised cyclin B1 expression, activation of p38 MAPK and ERK1/2 pathways - Suppression of JAK2 and PI3K pathways - Downregulation of caspase 3, p53, p21 and Bcl-2 expression	[115]
	Leaves	F2 (Ginsenoside)	SGC7901 (Human gastric adenocarcinoma cell line)/ SGC7901 cells xenograft mouse (female athymic nude BALB/c, nu/nu) model	Anticancer	- Decreased mitochondrial transmembrane potential - Declined cytochrome c and Bcl-2 - Activated ASK-1/JNK (apoptosis signal-regulated kinase-1/c-Jun N-terminal protein kinase) signalling pathway	[116]
	Ambo Institute (Daejeon, Korea)	Rc (Gensinoside)	Lipopolysaccharide activated RAW 264.7 (Murine macrophage cells), TNF-α/IFNγ induced synovial	Anti-inflammatory and anti-arthritic	- Blocked the expression of TNF-α and interleukin-1b	[117]

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Table 1 (*continued*)

Plant adaptogen	Part used/source	Active extract/fraction/component	Cell line/Animal model	Bioactivity	Mechanism of biomodulatory action	Reference
			cells, and HEK293 (human embryonic kidney cells) transfected with inducers of inflammation		- Suppression of TANK-binding kinase 1/IkB kinase ε/Interferon regulatory factor-3 and p38/ATF-2 proteins	
	Flower	RN1 (arabinogalactan polysaccharide)	HMEC-1 (Human microvascular endothelial cell line) and BxPC- 3 (Human pancreatic cancer cell line)/ BxPC-3 xenograft tumor in female athymic nude (nu/nu) mice	Anti-angiogenic	- Decrease in phosphorylation of Smad1/5/8 - Downregulation of Id-1gene expression leading to subdued BMP2 signalling	[119]
	BioAsia International Life Science Research LTD (Shanghai, China)	Ginsenoside (Rg1and Rb1) and notoginsenoside R1	LLC (Lewis lung carcinoma) xenograft tumor in C56BL/6J male mice and myocardial ischemia	Bidirectional regulation of angiogenesis	- Declined expression of CD34 and vWF (vascular markers) in tumor and their increased expression in heart - Abridged expression of miR-18a in tumor and its upregulation in heart	[120]
	Wanfang Natural Pharmaceutical Company (China)	PNS (Total saponins), PDS (protopanaxadiol type saponin), PTS (protopanaxatriol type saponin), Rg1 and Rb1 (Ginsenoside)	Recombinant human TNF-α induced human coronary artery endothelial cells/high cholesterol diet fed male sprague-dawley rats	Anti-atherogenic	- Suppression of NF-κB activation and mRNA expressions of ICAM-1 and VCAM-1	[121]

hepatotoxicity, recurrence, drug resistance, toxicity to normal tissues, and influence immunosuppression. Thus, immunotherapy with natural substances has been a new approach which is being explored in carcinogenesis. This treatment may help in the up-regulation of the immune system to combat the side effects of chemotherapy [13]. Immunostimulating plant based studies showed that oral or intravenous administration of plant adaptogens proffers the prospect to reinstate immune competency during such immune allied alterations and immunocompromised conditions [2,14]. Their immunosurveillance action engross the regulation of macrophages, polymorphonuclear cells, natural killer cells, T and B lymphocytes, antigen-specific immunoglobulins, tumor necrosis factor-α, interleukins. [15–18].

The present review provides an insight to understand the immunopotentiating significance of *Rhodiola rosea, Withania somnifera, Tinospora cordifolia, Bacopa monnieri, Emblica officinalis, Glycyrrhiza glabra, Asparagus racemosus*, *Ocimum sanctum* and *Panax notoginseng* and development of protective agents from these phytoadaptogens that could be used as co-chemotherapeutic agents or as supportive or adjuvant therapy affirming healthier results compared to chemotherapeutic agents alone.

2. Chasing the term 'Phytoadaptogen'

The term 'adaptogen' was coined by N. V. Lazarev (Russian physician and scientist) in 1947. He carried out the experiments intended to stimulate non-specific resistance in human subjects exploring the adaptogenic potential of an arterial dilator, dibazol (2-benzyl-benzimidazol) [19]. During the golden age of research of adaptogens, Brekhman [20] outlined the term adaptogen as: **Non-specific action:** This provides stimulance against physical, chemical or biological lethal agents. The non-specific protective outcome of phytoadaptogens enhanced the resistance of *Lymnaea stagnalis* larvae irrespective of stress conditions like: (i) Physical stress: heat shock of 43 °C for 4 min (ii) Oxidative stress: superoxide radicals induced stress by menadione at concentration of 600 μM for 2 h and iii) Heavy metal stress: copper induced stress at concentration of 150 μM for 1 h and cadmium induced stress at concentration of 20 μM for 1 h. Furthermore, the observed preventive action against environmental induced stress conditions appeared to be independent of nature of extract (aqueous or ethanolic) [21]. Similarly, in humans the immunobiological screening of a phytoadaptogenic preparation exerted non-specific immunomodulatory and interferonogenic potential on immunological phenotype of lymphocytes of patients suffering with ovarian cancer at different stages [22]. **Normalizing influence:** Autonomous of the nature of any human abnormalities, phytoadaptogens are key mediators in regulating neuroendocrine and immune system, refraining stress induced neurobehavioural and neuropathological dysfunctions and hence providing homeostasis [23]. The phytoadaptogen preparation reflected the adhesiogenic potency against hepatocarcinoma by stimulating expression of leukocyte integrins LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) on immunity effectors. It also normalized urodynamics, levelled imbalanced sex hormones, and reduced the size of prostate gland with geroprotectiveness correcting other clinical and immunobiological parameters in patients suffering with benign prostatic hyperplasia [22,24]. **Innocuous function:** Its administration has non-influential effects on normal body functions. Use of phytoadaptogens restores natural homeostasis with no side effects, unlike traditional stimulants that pose addiction and hypersomnolence. The single-dose administration activates corticosteroid formation and long term usuage normalizes the levels of stress hormones, such as adrenocorticotropic hormone. [25,26]. These have been observed to reinforce stress resistance, longevity, repair and maintenance. The molecular mechanism behind this is that phytoadaptogens induce translocation of DAF-16 (transcription factor) into the nucleus which leads to initiation of transcription of large number of genes involved in metabolism and oxidative stress resistance alongwith chaperones and detoxifying

proteins [27]. Hence, phytoadaptogens are defined as metabolic regulators that boost the state of non-specific resistance of an organism compromised by stress, environmental assaults and emotional trauma [28–30].

3. Conventionally used phytoadaptogens as immunopotentiators

The immunopotentiating significance of some selected traditional plant adaptogens is described below. Table 1 represents an abridged description of their possible mechanism.

3.1. Rhodiola rosea

Rhodiola rosea commonly known as golden root or arctic root belongs to the family Crassulaceae. In traditional medicine, it has been reported to enhance physical endurance, offer resistance to high altitude sickness, cure depression and mitigate swellings, gastrointestinal and nervous system disorders [31]. The plant roots have been a main component in traditional supplements or medicines. Majewska et al. [32] suggested the use of *R. rosea* rhizome extract in supplementary chemotherapy by analysing its antiproliferative and cytostatic effect on HL-60 cells with conclusion that extract inhibited cell division and led to induction of apoptosis and necrosis in HL-60 cells with no chromosomal aberrations. The study demonstrates bioprotective potential of rhizome extract against promielotic leukemia cell line with no corresponding genotoxicity. The extract treatment caused cell cycle arrest in HL-60 cells, *via* prophase cell accumulation, causing apoptotic action from G2/M phase. The study proposes the immune response of extract *via* cytotoxic killing which may have been regulated by family of Bcl-2 proteins. In another study, the tincture extract from *R. rosea* roots was evaluated for anti-inflammatory activity by Pooja and co-workers [33]. The enzymes related to inflammation *viz*., cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and phospholipase A2 (PLA2) were observed. The extract moderately inhibited COX-1 (housekeeping enzyme) and significantly inhibited COX-2 enzyme expression. The extract also repressed the phospholipase A2 and prevented the release of arachidonic acid from cell membranes thereby, rendering membrane stabilization. The study offered biomodulatory effects of *R. rosea* on prostaglandin-endoperoxide synthase and anti-inflammatory mediators. Some clinical evidences on *R. rosea* supplements, in improvement of physical and mental fatigue, have conflicting inconclusive results due to methodological flaws, thereby limiting the accurate evaluation of its efficacy [34]. However, more unbiased studies with proper population size can rectify the prevailing paradox, enabling determination of robust biomodulatory end results. Moreover, these extract based studies assisted the establishment of further exploration of *R. rosea* roots with identification of active principles in it, to observe biochemical modulatory effects. Liu et al. [35] conducted experiments on various bladder cancer cell lines (RT4, T24, UMUC3 and J82) and suggested that the *R. rosea* root extract (SHR-5) and its active principle, salidroside (a phenylpropanoid glycoside) inhibited growth of bladder cancer cell lines and p53 defective cells *via* inhibition of mTOR pathway. It led to the conversion of hyperphosphorylated gamma form to the hypo- or nonphosphorylated alpha form, which allowed 4E-BP1 to sequester eIF4G from its binding to eIF4E, and blocked cap-dependent translation, thus halted mTOR pathway. The mTOR regulates translation initiation by phosphorylation of its downstream targets whose deregulation leads to devastating human pathologies [36]. It has a significant role in regulation of innate immunity responses [37]. Liu et al. [38] reported the presence of glycosides in ethanolic root extract. The extract suppressed the overexpression of TIPE2, apoptosis-promoting proteins (Fas and FasL), inhibited T-lymphocyte apoptosis and elevated the expression of apoptosis-inhibiting protein (Bcl-2), T lymphocytes along with sub-sets $CD3^+$, $CD4^+$, $CD8^+$ and Th1 cytokines (IFNγ, IL-2 and IL-12), thus, boosted the host's resistance. The treatment of salidroside [2-(4-hydroxyphenyl) ethyl b-D-glucopyranoside] extracted from *R. rosea* to colon cancer SW1116 cells has been demonstrated to increase the percentage of cells in G0/G1 phase. Hence, leads to cell cycle arrest. Furthermore, it also inhibited the phosphorylation of JAK2, down-regulated STAT3 target proteins (MMP-2 and MMP-9) and VEGF expression [39]. Microarray analysis also revealed the protective effect of salidroside treatment against inflammation by inhibiting the group of genes linked with inflammation such as CD14, CD44, C1s, CCR5, and A2m [40]. The root system of *R. rosea* may offer potential immunopotentiating, anti-inflammatory and anticancer ability of its extracts and active principles in adjuvant therapy.

3.2. Withania somnifera

Withania somnifera Dunal, also known as Ashwagandha (Solanaceae) is a store house of ashwagandhine, choline, cuscohygrine, isopelletierine, anaferine anhygrine, tropine, sitoindosides, withanolides, withananine, withanamides and glycowithanolides [41]. Diwanay et al. [42] observed that treatment of *W. somnifera* root extract raised the levels of IFNγ, IL-2, granulocyte macrophage colony-stimulating factor (GM-CSF) and lowered TNF-α in mice administered with cyclophosphamide. The myelo-, immunoprotective ability of polar alkaloid free root extract of *W. somnifera* was attributed to increased white blood cells and antibody (HA and HL) titers. The alkaloid free polar extract of plant was found to be more effective than non-polar one, without interference to the chemotherapeutic effect of cyclophosphamide. In an anti-inflammatory study, Sivamani et al. [43] proposed that the *W. somnifera* could drop off the risk of implant rejection. The research group evaluated the anti-inflammatory propensity of leaf extract against stainless steel implant induced inflammation in adult zebrafish and uncovered the reduction in TNF-α mRNA levels. In the study, anti-inflammatory property of leaf extract was viewed as more effective than commonly used non-steroidal anti-inflammatory drugs (NSAIDs) against stainless steel implant induced inflammation. The study proposes the presence of phenolic acids and flavonoids in leaf extract. The *W. somnifera* leaves contains compound withaferin A, as one of the major active component [44]. In subsequent studies on withaferin A, a cell permeable and low molecular weight steroid lactone isolated from *W. somnifera*, ceased invasiveness and metastasis in a dose dependent manner in CaSki and SK-Hep-1 cell lines by inhibiting TGFβ induced phosphorylation of Akt, which further down regulated MMP-9 mRNA expression and activity [45]. In cancer development, the chief concern of metastasis progression is overexpression of MMPs in cancer cells. The study articulates the potential action of withaferin A with effective transcriptional regulation of TGFβ and PMA-induced overexpression of MMP-9 in cancer cells. In a study, Chen et al. [46] reported the upregulation of Notch-1 pathway and its target genes Hes-1, Hey-1 and Hey-2 under metastatic conditions. The Notch-1 signalling pathway helps in the regulation of NF-κB, Bcl-xl, p21, p27 and various developmental steps of B and T cells in immune system [47,48]. Administration of withaferin A inactivated Notch-1 signalling pathway and its downstream target genes MMPs in osteosarcoma cell lines U2OS and MG-63. In another study, withaferin A also afforded the protection to pancreatic islets against inflammatory damage in islet transplants in diabetic mice [49]. It directed the prevention of IκB degradation, NF-κB nuclear translocation and NF-κB binding to DNA transcription sites, inhibition of TNF-α, iNOS and IP-10, caused by IKKβ specific inhibitor BMS-345541. The study proposed that withaferin A treatment inhibited the negative act of pro-inflammatory cytokines on implanted islets cell mass. The compound also inhibited the post-transplant inflammatory response due to blood-mediated inflammatory reaction (IBMIR) thereby improving survival of transplanted grafts. All these and many more studies demonstrate the potent anti-inflammatory activity of withaferin A. However, an *in vitro* study on *W. somnifera* study proposed that withaferin A from *W. somnifera* cannot be considered exclusively as anti-inflammatory due to low water solubility of compound and cytotoxic effects [50]. The study elucidates that commercial water soluble

extract of plant prevented the renal chronic inflammatory response by reduction in gene expression of CCL2 and CCL5 in response to TNF-α intervened by inhibition of NF-κB activity in NRK-52E cells. Thus, more elaborated research and development may be focused especially on the immunopotentiating response of different combinations of active principles from this plant.

3.3. Tinospora cordifolia

Tinospora cordifolia belongs to the family Menispermaceae and is an ayurvedic herb. In Ayurveda, the plant has been reported to have many pharmacological effects like hepatoprotective, anti-inflammatory, antipyretic, anti-allergic, antimalarial, anti-diabetic, anti-arthritic, antispasmodic, anti-neoplastic, antioxidant, anti-stress, anti-leprotic and immunomodulatory activities [51]. Immunomodulatory experiments conducted by the Indian research group [52,53] validated that an arabinogalactan polysaccharide (G1-4A) isolated from *T. cordifolia* raised the phenotypic and functional maturation of bone marrow derived dendritic cells (BMDCs) leading to activation of cytotoxic T-cells. The killer phenotype of BMDC matured with G1-4A released nitric oxide which further generated peroxynitrite that killed syngeneic and xenogenic tumors. The killing of tumorigenic cells was abrogated by inducible nitric oxide synthase (iNOS) inhibitor and NADPH oxidase inhibitor (apocyanin). Thus, experiment highlighted the utilization of this natural product as an adjuvant in tumor related immunotherapy. The active principle Berberine (isoquinoline alkaloid) acts as a colon cancer preventive agent by obstructing the neoplastic invasion. This potency of berberine is attributed to its modulatory effect on glycoprotein component and lipid peroxidation with enhanced anti-oxidative defence status [54]. It also causes topoisomerase poisoning in malignant cells by intercalating with DNA [55]. The plant extract has been found to be apoptotic inducer in cancer cells. In a study against Ehrlich ascites tumor, the administration of hexane fraction of *T. cordifolia* amplified Bax, reduced Bcl-2 expression and stimulated characteristic apoptotic features related with constitutive expression of caspase activated DNase in nucleus and cytoplasm [56]. In another study, octacosanol (aliphatic alcohol) isolated from *T. cordifolia* exhibited angio-inhibitory and antimetastatic effects [57]. The mechanism reflected decline in the activity of transcription factors and inhibition of NF-κB from cytoplasm to nucleus directing reduction in VEGF gene expression and hence, suppressed sprouting of new blood vessels. A recent study suggested the potential of this plant in differential therapy against neuroblastoma [58]. The study demonstrates that aqueous ethanolic extract of *T. cordifolia* has potential to restrain neuroblastoma cell proliferation *via* modulated expression of PCNA and cyclin D1, stimulated expression of mortalin and Rel A subunit of NF-κB with down-regulation of Bcl-xl, neural cell adhesion molecule polysialylation and secretion of MMPs. Study showed the differentiation of neuroblastoma cells *via* translocation of growth-associated protein 43 (GAP-43) in the direction of cytoplasm and surface of cells. Hence, studies on *T. cordifolia* propose the immense potential of this plant and its active principles in immunomodulatory therapeutic treatments.

3.4. Bacopa monnieri

Bacopa monnieri L. belongs to the family Scrophulariaceae and its active components *viz*., bacosides, bacopasides I–XII, monnierasides I–III, plantainoside B, brahmine, herpestine suggests its protective approach in mitigating several dysfunctions [59]. Peng et al. [60] reported that bacopaside E and bacopaside VII (dammarane triterpene saponins) isolated from n-butanol fraction of *B. monnieri* displayed prominent cytotoxic activity against MDA-MB-231, SHG-44, HCT-8, A-549 and PC-3M cell lines. These isolated compounds also prohibited adhesion, migration and matrigel invasion of MDA-MB-231 cells. *B. monnieri* extract afforded protection against sodium nitroprusside induced toxicity in L132 cells *via* reinstating the damaged cells, nucleus and mitochondria by hampering iNOS expression, boosting antioxidant enzymatic machinery, modulating Bax, cytochrome c and caspase 3 expressions [61]. Bacoside A, a triterpenoid saponin, purified from *B. monnieri* has been accounted to exert antimetastatic effect against hepatocellular carcinoma impelled by N-nitrosodiethylamine. The results of gelatin zymography unveiled the diminished MMP-2 and MMP-9 expression [62]. In another study aerial part of the plant was used for extraction and isolation of stigmasterol and this phytosterol was administered to Ehrlich Ascites Carcinoma (EAC) bearing Swiss albino mice. The research revealed that survival life span of the host mice was increased while murine tumor size was decreased considerably. The antitumor activity was thought to be attributed by the ceramide stimulated expression of protein phosphatase 2A intended for inducing apoptosis [63]. Aqueous extract treatment of *B. monnieri* to Ehrlich ascites tumor cells transplanted Swiss albino mice restrained the proliferation of diseased cells. It deactivated peritoneal endothelial cells that reduced vasculature, inhibited VEGF secretion, activated an endogenous endonuclease referred as caspase-activated DNase (CAD) requisite for endonuclease plasmid degradation and fragmentation in cancer cells, decreased Bcl-2 and increased Bax gene expression. The bioassay-guided purification attributed the protective propensity of *B. monnieri* against mouse mammary carcinoma cells to a 15 kDa protein [64]. The ethanolic extract reduced glutathione content in cytosol, escorted alterations in Ca^{2+} transport and eventually promoted apoptosis of S-180 cells as observed under electron microscope. The investigators advocated the phyto-constituents to be responsible for such action of the extract [65]. The bacoside rich extract and fractions have also been depicted to freeze COX-2, 5-LOX and 15-LOX activities with down regulation of TNF-α projecting inflammation abolishment [66]. Viji et al. [67] extracted betulinic acid from *B. monnieri* extract and provided an insight to the cross talks between MAPK and NF-κB signalling pathways. The isolated compound along with ERK MAPK inhibitors (PD98059 and SB203580) vetoed IL-6 expression by inhibiting nuclear translocation of p65 NF-κB *via* involvement of p38 and ERK MAPKs as the cross talks commenced among MAPK and NF-κB pathways. An experimental study conducted by Williams et al. [68] used cell based models to regularize Th1-polarised immune response indicating suppression of nitrous oxide and TNF-α in cultured cells and IFNγ in lymphocytes. Nemetchek et al. [69] extended their study to N9 microglial cells and strongly confirmed its anti-neuroinflammatory potency by demonstrating the inhibition of TNF-α, MMP-3 and caspase 1, 3.

3.5. Emblica officinalis

Emblica officinalis (syn. *Phyllanthus emblica* L.), commonly known as Amla in Ayurveda is a rich source of vitamin C and has manifold pharmacological actions [70,71]. The experiments conducted by Lampronti et al. [72] employing electrophoretic mobility shift assay (EMSA) and filter-binding assay using [γ-^{32}P] 5-end-labeled oligonucleotides as target DNA confirmed the inhibitory activity of *E. officinalis* extracts against NF- κB/DNA and GATA-1/DNA interactions. This inhibition of molecular interaction between DNA and transcription factor leads to alteration of gene transcription and could be a meritocratic strategy for the development of chemotherapeutic agent for different human pathologies [73]. The inflammatory gene activation is directly linked to cancer cascade and has been proposed as the hallmark of cancer [74,75]. The hydroalcoholic fruit extract has been found to suppress the inflammatory insult induced by carrageenan, histamine, serotonin, prostaglandin E2 and cotton pellet granuloma. The extract exhibited potent anti-inflammatory activity by rising glutathione, superoxide dismutase, and catalase content with diminution in lipid peroxidation and malondialdehyde level. The possible mechanism could be attributed to the inhibition of NF-κB activation, quenching of inducible nitric oxide synthase (iNOS) and reduced expression of COX-2 enzyme levels [76]. Jose et al. [77] also documented that the aqueous fruit extract of

E. officinalis inhibited over-expression of Cdc2 kinase and Cdc25 phosphatase. These cyclin dependent kinases control p34cdc2/cyclin B activation which is required for G2/M transition during cell division. *E. officinalis* targeted the cell cycle check points and controlled cell cycle regulation, which accounts for its anticancer activity and suggesting its use as an adjuvant in cancer chemotherapy. Mahata et al. [78] reported the strong anticancer activity of aqueous fruit pulp extract against SiHa and HeLa representing HPV16 and HPV18 positive cervical cancer cells, respectively. The extract targeted the transcription of viral oncogenes responsible for progression of cervical cancer. The three possible mechanisms for its anticancer activity proposed are, 1) alteration of redox sensitivity of cells; 2) inhibition of ERK1/2 and JNK; and 3) down-regulation of AP-1 family proteins c-Jun, JunB, JunD and c-Fos. Thus, suggesting *E. officinalis* as a prospective utility for treatment of human papilloma virus-induced cervical cancers. The aqueous fruit extract was also evaluated to possess antimetastatic activity against fibrosarcoma cell line, HT1080. The mechanism underlying antimetastatic activity was assessed using RT-PCR assay and has been linked to the reduction of matrix metalloproteinases, MMP-2 and MMP-9 [79].

3.6. Glycyrrhiza glabra

Glycyrrhiza glabra (Fabaceae) commonly known as liquorice is considered to possess carminative, antimicrobial, hypolipidemic, anti-antherscleroticc, antiviral, antiulcerogenic, hepatoprotective, cardio-protective, immunomodulatory, antimutagenic, anti-pyretic, anti-inflammatory activities [80]. *Glycyrrhiza* species have been recognized by the National Cancer Institute for their peculiar defensive potential against cancer. The constituents present in different species include glabridin, glycyrrhizin, glycyrrhetinic acid alongwith liquiritin, liquiritigin, isoliquiritigin, isoliquiritin and licochalcones. These constituents aggravate apoptosis in malignant cells and act as lipoxygenase, cyclooxygenase, and protein kinase C inhibitors with repression of epidermal growth factor receptor [81]. A polyphenol, 1-(2,4-dihydroxyphenyl)-3-hydroxy-3-(4′-hydroxyphenyl) 1-propanone (β-hydroxy-DHP), purified and isolated from *G. glabra* roots by Rafi et al. [82] stimulated Bcl-2 phosphorylation, apoptosis, G2/M cell cycle arrest and altered microtubule structure in T47D, MCF-7, HL-60 and DUPro-1 cell lines suggesting the development of potent lead molecules with improved therapeutic efficacy. Fu et al. [83] carried out the studies in androgen-independent p53-null PC-3 prostate cancer cells and manifested that Licochalcone-A extracted from *G. glabra* roots arrested cells in G2/M, suppressed cyclin B1, cdc2 accompanied by inhibited phosphorylation of Rb/pRb (S780) with no alteration in T821 status, reduced expression of cyclin D1, CDK 4, CDK 6 and amplified cyclin E expression. Licochalcone A has also been recognized to abate the expression of COX-2, iNOS, (PG)E2, IL-1β and IL-6 induced by lipopolysaccharide in RAW 264.7 cells *via* suppression of NF-κB and AP-1 activation [84]. It also induced mitochondrial dysfunction, caspase 3 activation and poly-ADP-ribose polymerase (PARP) cleavage. Furthermore, it elicited endoplasmic reticulum (ER) stress that alleviated the expression of UPR central regulator GRP78, UPR transcription factor GADD153/CHOP, and apoptotic ER stress response caspase 12 to trigger apoptosis in T24 cells [85]. The other underlying mechanisms involved in the antitumor activity of this compound are activation of ERK, JNK, p38 MAPK and inhibition of PI3K/Akt/mTOR signalling [86,87]. Sheela et al. [88] delineated that presence of licocoumarone in *G. glabra* root extract decreased VEGF production and repressed neovascularization, thereby elicited anti-angiogenic and antitumor potential. The stimulation of various immune cells has been revealed by the ingestion of *Glycyrrhiza* herbal tincture for seven days as quantified by CD69 expression on CD4 and CD8T cells [89]. A polish research group explored that the glycyrrhizin administration successfully encumbered the progression, relocation of cells, angiogenesis and TNF-α level induced by mobility group box 1 (HMGB1) protein and enhanced anticancer competence of necrosis-inducing CAMEL peptide [90]. Glabridin isolated from *G. glabra* decreased the formation of mammospheres and anchorage independent growth, attenuated epithelial features and adhesive capability of MDA-MB-231 cells. It also upregulated miR148a by decreasing expressions of DNMT1 and DNMT3a, that suppressed the TGFβ/SMAD2 signalling [91].

3.7. Asparagus racemosus

Asparagus racemosus Linn. (Shatavari), family Liliaceae belonging to the category of ayurvedic rasayana possesses adaptogenic, anaphylactic, anticancer, antifungal, anti-leishmanial and radioprotective properties [92,93]. The roots of plant have been reported to contain array of bioactive constituents like saponins, alkaloids, flavonoids, sterols and terpenes. Hayes et al. [94] isolated and characterized shatavarin I, IV, V, shatavarin VI–X, schidigerasaponin D5 and immunoside from the roots of *A. racemosus*. Sarsasapogenin glycoside isolated from *A. racemosus* elicited immunoadjuvant potential against HBsAg (hepatitis B surface antigen) thereby augmenting Th1/Th2 response [95]. The saponins isolated from this plant have also been observed to possess potent apoptotic action against human hepatoma cell line, HepG2 [96]. The treatment increased intracellular reactive oxygen species, intracellular Ca^{2+}, intracellular Cytc, activated caspase 3, caspase 9 and Bax expression along with reduced intracellular pH and Bcl-2 expression. Patil et al. [97] monitored that no significant CYP3A4 inhibition was observed by the treatment of *A. racemosus*, *W. somnifera* and *T. cordifolia* extracts. Hence, these could be safely used as adjuvant concomitantly with cancer chemotherapeutic agents coupled to CYP3A4 substrates. The *in-silico* screening studies conducted by Asthana et al. [98] conveyed the clue that exploration of asparagamine A (a polycyclic alkaloid) through molecular docking exhibited prominent affinity towards computationally isolated critical proteins targeted to combat cancer, osteoporosis, malaria, tuberculosis, HIV, leishmmaniasis and trypanosomiasis. The research group [99] educed that the supplementation of *A. racemosus* ethanolic extract elevated glucose-6-phosphate dehydrogenase activity which further raised the synthesis of NADPH and thus enhanced resistance against oxidative stress as well as extended the life span by 41% in *Drosophila melanogaster*.

3.8. Ocimum sanctum

Ocimum sanctum (L.) also known as *Ocimum tenifluorum* (holy basil or tulsi) belongs to the family Lamiaceae. *O. sanctum* is considered as ‘the elixir of life’ and its leaves are classified as functional foods possessing anti-inflammatory, analgesic, anti-pyretic, anti-asthmatic, anti-emetic, antimicrobial, anti-diabetic, hepatoprotective, hypotensive, anti-coagulant, anti-cataract, radioprotective and immunomodulatory actions. Leaves have been reported to contain eugenol, methyl eugenol, carvacrol, caryophyllene, cirsilineol, circimaritin, isothymusin, apigenin, rosmeric acid, orientin vicenin, ursolic acid, apigenin, luteolin, apigenin-7-*O*-glucuronide, luteolin-7-*O*-glucuronide, molludistin, bornyl acetate, α-elemene, neral, myrtenal, α-pinene, β-pinene, camphene, campesterol, stigmasterol and β-sitosterol [100–102]. The findings of Magesh et al. [103] suggested *O. sanctum* as a potent chemopreventive candidate against lung cancer. The experiments exposed that ethanolic extract exerted cytotoxicity against lung cancer cells, augmented the sub-G1 population, cleaved poly(ADP-ribose)polymerase (PARP), released cytochrome c into cytosol leading to the activation of caspase 9 and caspase 3, increased the ratio of Bax/Bcl-2 and inhibited phosphorylation of Akt and ERK in cancer cells. Kim et al. [104] also reported the antimetastatic action of ethanolic leaf extract of *O. sanctum* against mouse Lewis lung carcinoma cells. The extract significantly amplified anti-oxidative enzymatic machinery, barred cell adhesion and cell invasion. Also, the gelatin zymography revealed the down-regulation of proteolytic enzyme MMP-9. These findings suggested its use as antimetastatic drug for lung cancer. Shimizu et al. [105] provided the evidence that ethanolic leaf extract and essential oil

of *O. sanctum* inhibited cell migration and cell invasion of pancreatic cells *in vitro* in association with the downregulation of ERK-(1/2) and focal adhesion kinase (FAK). It resulted in the upregulation of E-cadherin (metastasis inhibiting gene) and BAD (apoptosis inducing gene) with down regulation of Bcl-2 and Bcl-xl (anti-apoptotic genes), AURKA, Chk 1 and Survivin (chemo/radiation resistance genes) in malignant tissues. The study conducted by Manaharan et al. [102] advocated that the essential oil of *O. sanctum* inhibited cancer cell motility and down-regulated the expression of MMP-9 in a dose dependent manner exerting antimetastatic and anti-inflammatory potential. Kwak et al. [106] visualized the antimetastatic mechanism of ethanolic extract employing NCI-H460 cells. The extract productively censored cell invasion of tumor cells, osteopontin (glycoprotein, molecular target of cancer) and CD44 expression. Further, it weakened PI3K and COX-2 expression, suppressed phosphorylation of Akt, attenuated expression of uPA and its receptors uPAR, EGFR, VEGF and MMP-9. Dhandayuthapan et al. [107] uncovered the molecular mechanism of apoptosis induced by ethanolic extract of *O. sanctum* in prostate cancer cells (LNCaP). The experiments showed the progressive loss of mitochondrial integrity with the decreased expression of Bcl-2 accompained by activation of caspases. The active caspase 3 and caspase 9 further cleaved the PARP and consequently led to cell death.

3.9. Panax notoginseng

Panax notoginseng (Burk.) FH Chen (Radix Notoginseng or Sanchi) is a well-known traditional Chinese materia medica belonging to family Araliaceae. It has been most commonly used for its remarkable immunoregulatory action. The prime bioactive constituents are dammarane-type triterpene saponins which include notoginsenosides, ginsenosides, and gypenosides. *P. notoginseng* saponins (PNS) mainly contain ginsenoside Rg1, ginsenoside Rb1, and notoginsenoside R1. These constituents render anticancer, anti-hypertensive, antioxidant, anti-thrombotic, anti-atherosclerotic, hepatoprotective and neuroprotective properties [108,109]. Numerous research studies reveal preclinical reports that justify the inclusion of *P. notoginseng* as a promising tactic in cancer chemotherapy or as adjuvant to chemotherapeutics. The immunohistochemical evaluation of HeLa cells treated with the saponin, ginsenoside Rd1, isolated from *P. notoginseng* resulted in declined Bcl-2/Bax ratio which is influential in deciding the fate of the cells [110]. In another study, Jung et al. [111] utilized mouse peritoneal macrophage cell line (RAW 264.7) and indicated the potential of *P. notoginseng* flower extract against many inflammatory diseases by suppressing the lipopolysaccharide-activated inflammatory mediators and hence blocking NF- κB signal transduction. Bi et al. [112] reported the strong dose-dependent antiproliferative effect of PPD25 (20(S)-25-OCH3-PPD), a dammarane-type triterpene sapogenin in colorectal and lung cancer cell lines. This natural compound isolated from the leaves of *P. notoginseng* inhibited transcriptional activity and downregulated protein expression *via* suppressing β-catenin alongwith cyclin D1, c-Myc and CDK 4. Thus, it blocked the Wnt/β-catenin signalling pathway that may serve as potential target for therapeutic agents. Park et al. [113] elucidated the anticancer activity of *P. notoginseng* aqueous extract in A549 and NCI-H460 cells with the underlying mechanisms that treatment of extract increased Bax and lowered Bcl-2 expression, induced mitochondrial damage, proteolytic cleavage of poly(ADP ribose) polymerase, caspase 3 activation and downregulation of the PI3K/Akt signalling pathway. The experiments conducted by Wang et al.[114] delineated the inhibitory effect of *P. notoginseng* saponins (ginsenosides Rb1, Rg1, Rd, notoginsenoside R1 and Rh1) on the cell migration and invasion of mammary carcinoma cell line (4T1) through modulation of epithelial-to-mesenchymal transition (EMT) markers. The treatment of saponins to 4T1 cells upregulated the expression of E-cadherin, downregulated vimentin coupled with the increased expression of tumor suppressing genes (Brms 1, Mtss 1, Timp 2) and decreased expression of metastasis promoters (MMP-3 and MMP-9). Gao et al. [115] disclosed that notoginsenoside Ft1 triggered apoptosis in neuroblastoma (SH-SY5Y) cells and may have therapeutic importance in neuroblastoma therapy. The targets underlying strong antiproliferative effect of Ft1 includes cell cycle arrest at S and/or G_2M phase leading to raised cyclin B1 expression, activation of p38 MAPK and ERK1/2 pathways, suppression of JAK2 and PI3K pathways with downstream regulation of caspase 3, p53, p21 and Bcl-2 expression. Mao et al. [116] investigated the anticancer activity of ginsenoside F2 using human gastric adenocarcinoma cell line (SGC790) and human gastric adenocarcinoma cancer xenograft mouse model. The research group accumulated evidences that ginsenoside F2 provoked accumulation of reactive oxygen species, lowered mitochondrial transmembrane potential which in turn declined cytochrome c, activated ASK-1/JNK (apoptosis signal-regulated kinase-1/c-Jun N-terminal protein kinase) signalling pathway and finally lead to the apoptosis. The anti-inflammatory, immuno stiumulant properties of *P. notoginseng* could be used as adjuvant therapy with cancer chemotherapy. Ginsenoside Rc has been documented to block the expression of TNF-α in splenic lymphocytes *via* targeting TBK1/IRF-3 and p38/ATF-2 proteins [117]. The administration of *P. notoginseng* to RAW 264.7 macrophages fortified cell viability thereby lowering expressions of Toll-like receptor 4 (TLR4), TNF-α and enhanced the expression of phosphoinositide 3-kinase (PI3K) and Akt kinase [118]. RN1, arabinogalactan polysaccharide, isolated from flowers of *P. notoginseng* blocked angiogenic signalling both *in vitro* and *in vivo*. RN1 repressed microvessel formation *via* decreasing phosphorylation of Smad1/5/8 which downregulated Id-1 gene expression leading to subdued BMP2 signalling [119]. Another study in China demonstrated that PNS comprising Rg1, Rb1 and R1 abrogated tumor progression and concurrently attenuated myocardial ischemia. PNS treatment reflected bidirectional efficacy by declining expression of CD34 and vWF (vascular markers) in tumor and increasing their expression in heart. It also led to the abridged expression of miR-18a in tumor and its upregulation in heart [120]. A research group [121] examined the protective effect of three saponin fractions (total saponins, protopanaxadiol type saponin and protopanaxatriol type saponin) including two individual ginsenosides (ginsenoside Rg1 and Rb1) against vascular inflammation at mRNA and protein level which may be attributed to the suppression of TNF-α induced NF-κB activation. Since, the chronic inflammation and cancer is strictly coupled to vascular remodelling, the anti-vascular inflammatory activity of *P. notoginseng* could be an influential approach in regressing the degeneration.

4. Discussion

The anticancer drugs are linked with the multidirectional cytotoxic adversities jeopardizing quality of life, imposing dose reductions, dose delays and negatively hamper response treatment and outcome. Gemcitabine and docetaxel combination therapy to human subject leads to uveal effusions and outer retinal disruption. Other complications related with docetaxel include canalicular and nasolacrimal duct obstruction, erosive conjunctivitis, cystoid macular edema, febrile neutropenia, fluid retention, acral erythema, hyperkeratosis, interstitial pneumonitis, hypothyroidism, epiphora and lacrimal duct stenosis [122,123]. Sleurs et al. [124] reported in their review study that chemotherapeutic agents (methotrexate, ifosfamide, cyclophosphamide, cisplatin and vincristine) are associated with neurotoxic symptoms like encephalopathy, hemiparesis, aphasia, hemiplegia, hallucinations, delirium, cortical blindness, peripheral and sensory neuropathy, diplopia, nerve paralysis and absence of peripheral reflexes. Vincristine has also been reported to exert toxic sensory and motor neurotoxicity in patients suffering with acute lymphoblastic leukemia [125]. It has been reported in a case study that vincristine treatment to a human subject of 21 years suffering with pre-B acute lymphoblastic leukemia resulted in the lack of CYP3A5 expression with reduced CYP3A4/5 activity augmenting neuropathic pain [126]. Another review report [127] illustrated the dose-limited administration of doxorubicin and fatal incidences which

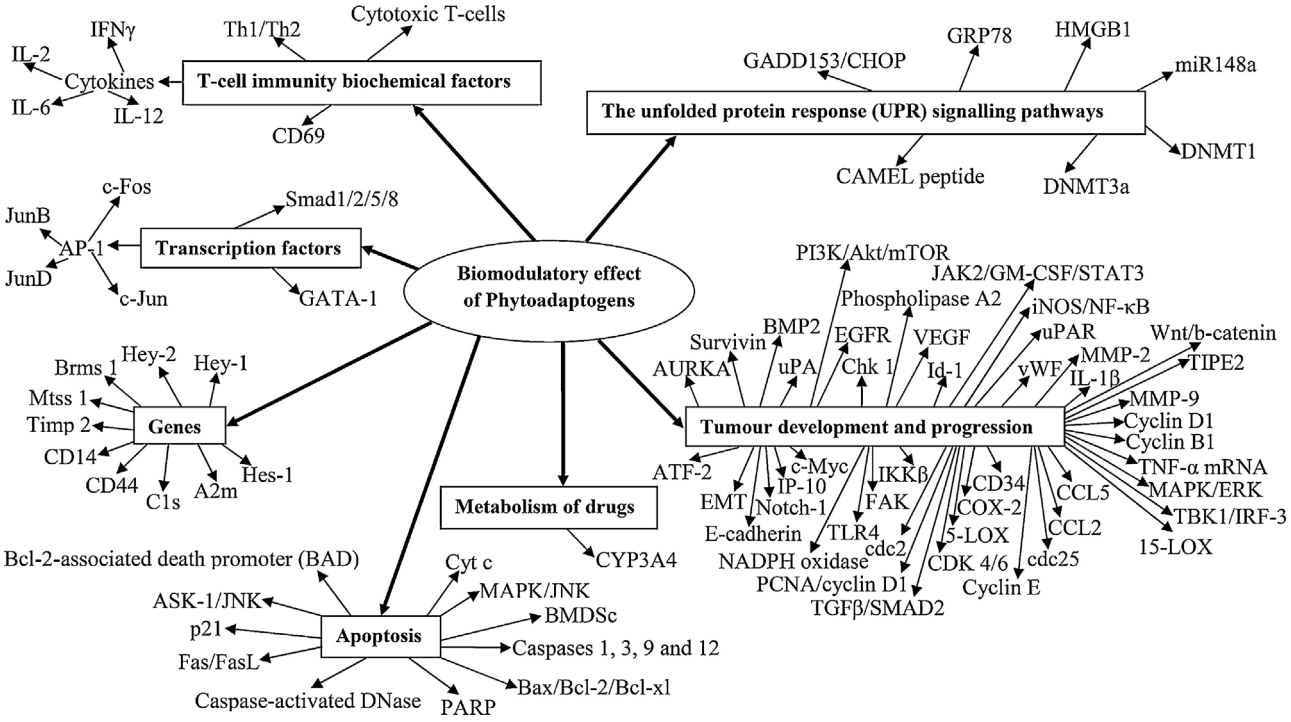

Fig. 1. Biomodulatory effects of phytoadaptogens in cellular signalling processes.

include structural alterations of the cardiomyocytes, cognitive impairment, nephropathy, proteinuria, hyperpigmentation, alopecia, photosensitivity, urticaria, anaphylaxis, mucositis ulceration, necrosis and chronic infections in the colon and caecum. The repeated cycles of paclitaxel treatment in some cases exerted tumor resistance [128]. Irinotecan produced haemotological, intestinal and systemic maladies causing myelosuppression [129]. A population-based epidemiological study monitored that pre-operative cancer chemotherapy period aggravated insomnia and impaired circadian rhythms [130]. Such wide range of pernicious toxicities could be rectified by the usage of chemotherapeutic agents along with the supportive therapy availing plant adaptogens. The combined relevance of plant adaptogens *viz*., *Rhodiola rosea, Withania somnifera, Tinospora cordifolia, Bacopa monnieri, Emblica officinalis, Glycyrrhiza glabra, Asparagus racemosus*, *Ocimum sanctum* and *Panax notoginseng* in biomodulatory assistance in cell-mediated, innate and adaptive immunity, signalling processes can be deduced as shown in Fig. 1. The possible combined potential of immune stimulant constituents from these phytoadaptogens in formulations to facilitate the induction of innate and adaptive immunity cannot be overlooked in adjuvant therapies. These adaptogens may exert protective and immuno-stimulatory potential by proffering the resistance against stress leading to accelerated performance, endurance and enhanced longevity which is correlated with sustenance of homeostasis. The key mechanisms behind the action of adaptogens are coupled to hypothalamic-pituitary-adrenal axis and the regulation of stress-sensor protein (Hsp70), stress-activated c-Jun N-terminal protein kinase (JNK1), Forkhead Box O transcription factor DAF-16, cortisol and nitric oxide (NO). Adaptogens promote Hsp70, which hinders the expression of NO synthase II gene and intervene with glucocorticoid receptors *via* JNK1 and DAF-16-mediated pathways [131,132]. Adaptogens slow down the action of enzymes accountable for degradation of monoamines: monoamine oxidase and catechol-O-methyltransferase. This leads to reduction of norepinephrine and dopamine with elevation of serotonin in the cerebral cortex and brain stem and vice-versa in hypothalamus [133]. Adaptogens may regulate tissue glycogen and enzymes associated with energy metabolism (hexokinase, phosphofructokinase, citrate synthase and glucose-6-phosphate dehydrogenase) reallocating the anaerobic metabolism to aerobic metabolism [134]. Thus, these phytoadaptogens may helps in maintenance of perturbed homeostasis in adjuvant or supportive therapy in cancer treatment.

5. Conclusion

The body of knowledge on the role of phytodaptogens in moderating biological and molecular processes against carcinogenic cells is increasing with a prospect of fascinating possibilities. This review/account therefore strongly supports the view that the beneficial properties of plant adaptogens should be contemplated as an adjuvant since it holds so much potential in the fight against cancer with its ability in orchestrating molecular mechanisms in restoring homeostasis in the body system. These promising results should further be substantiated by clinical trials.

Conflict of interest

The authors declare no conflict of interest.

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