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Review

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

Pardeep Kaur[a], Robin[a], Victor O. Makanjuola[c], Rohit Arora[a], Balbir Singh[b], Saroj Arora[a,*]

[a] Department of Botanical & Environmental Sciences, Guru Nanak Dev University, Amritsar, Punjab, 143005, India
[b] Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, 143005, India
[c] Department of Anatomy, Bingham University, Karu, Nasarawa State, Nigeria

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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

* Corresponding author.
E-mail address: sarojarora.gndu@gmail.com (S. Arora).

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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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