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***Corresponding author:**
Dr. Rohit Sharma
Research Officer, Central Ayurveda Research Institute for Drug Development, CCRAS, Ministry of AYUSH, Government of India, Bidhannagar, Kolkata-700091, India
Email: dhanvantari86[at]mail.com

Molecular targets of common Ayurvedic herbal antioxidants

Rohit Sharma[1], Hetal Amin[1], Galib R[2], PK Prajapati[3]

1 *Research Officer, Central Ayurveda Research Institute for Drug Development, CCRAS, Ministry of AYUSH, Government of India, Bidhannagar, Kolkata-700091, India*

2 *Assistant Professor, Department of Rasashastra & Bhaishajya Kalpana, I.P.G.T. & R.A., Gujarat Ayurved University, Jamnagar, Gujarat-361008, India*

3 *Professor and HOD, Department of Rasashastra & Bhaishajya Kalpana, All India Institute of Ayurveda, New Delhi, Delhi- 110076, India*

ABSTRACT

In recent times, holistic and herbal solutions from Ayurveda are being searched that prevent oxidative stress-linked tissue damage and provide significant antioxidant defenses to promote longevity and rejuvenation. Understanding of pharmacokinetic-dynamic of botanicals is very intricate, though essential in the field of biomedicine and drug development. Researchers have identified some of the molecular targets of commonly used herbal antioxidants and rejuvenators, used as *Rasayana*. Present report attempts to share insights on the concepts behind the application of herbal antioxidants to promote longevity, in light of scientific underlying molecular mechanisms.

Keywords: *Rasayana, Ayurveda*, Antioxidant, Oxidative stress, Herbs.

INTRODUCTION

Increased life expectancy in present century and significant increase in the aging population poses a huge challenge to maintain a healthy old age. Compelling evidence implicates the causal role of ROS, free radicals, oxidative and nitroxidative stress in metabolic derangements, progressive tissue damage and early aging.[1,2] In view of complexity of the aging process and associated degenerative processes, comprehensive solutions are being searched from complementary and alternative medicine to provide holistic approach to reverse, arrest, delay or repair the progressive deterioration of the aging cells. Ayurvedic *Rasayana* herbs are being used in Indian system of medicine since centuries to revitalize and rejuvenate the whole functional dynamics of the body system. *Rasayana* herbs exert multidimentional health benefits and generally possess strong antioxidant activity, though only a few have been scientifically investigated in detail. Present commentary attempts to share insights on the concepts behind the application of herbal antioxidants to promote longevity, in light of scientific underlying molecular mechanisms. Common *Rasayana* herbs which are used in practice have been investigated to prepare present report.

Methodology

The approach consisted to search several resources, including Books, Theses, Technical Reports, Conference proceedings, web-based scientific databases such as publications on PubMed, Science direct, Springer, ACS, Scielo, PROTA, Google, Google scholar, MEDSCAPE, BMC, MEDLINE, Pubmed, SCOPEMED, and other allied databases covering fields of pharmacology and biomedicine. The search criterion was aimed to probe molecular targets of common Ayurvedic herbal antioxidants, in light of published experimental and clinical reports. Searches were not limited by date or place of publications but to publications available in English. Present report examined the available literature up to December 2016.

Results

Triphala (dried fruits of *Terminalia chebula*, *Terminalia bellirica* and *Emblica officinalis*, the three myrobalans, in equal parts), is a renowned polyherbal *Rasayana*. Apart from wide array of biological activities and therapeutic credentials, *Triphala* and its constituents are highly acknowledged for their significant antioxidant or anti-aging potential[3-6] and nitric oxide scavenging activity.[7] Activation of ERK and p53 were reported to mediate the growth inhibitory effects of *Triphala* in pancreatic tumor cells.[8]

Apart from this, the anti-cancer,[9-11] immunomodulatory[12] and anti-inflammatory[13] activities of *Triphala* of together contribute to directly target the aging-related health problems. *Triphala* has shown selective cytotoxic and apoptotic activity on cancer cells while sparing the adjacent normal cells[14] further strengthens its compelling role as a dietary supplement to promote longevity. It is also noteworthy that *Triphala* is found in maximum *Lauha kalpa* (iron based formulations). *Triphala* mainly consists of tannin, gallic acid, ascorbic acid, and phenolics. Ascorbic acid increases the bioavailability of iron by converting Fe^{3+} to Fe^{2+}, while phenolics can reduce the iron by binding to it, thus preventing too much iron absorption.[15] Chebulagic acid isolated from *Terminalia chebula* has been reported to inhibit COX-2/5-LOX.[16] Emblicanin A, emblicanin B, punigluconin and pedunculagin, contents of *Emblica officinalis* induced an increase in both frontal cortical and striatal SOD, CAT and GSH-px activity, with concomitant decrease in LPO in brain areas.[17] Fresh *Emblica* fruits juice increased the activities of cardiac SOD, CAT and GSH-px, with a concomitant decrease of LPO in Ischemia-reperfusion-induced rats.[18] Besides, *Emblica* also showed cytoprotective and broad-spectrum antioxidant activity.[19] Terminalia chebula fruits exerted strong antioxidant effects, superoxide scavenging, inhibited LPO, hydoxyl radicals, and TBARS formation.[20,21]

Ashwagandha (*Withania somnifera*) has been observed to mediate its multi-faceted biological activities via several signaling molecules. The anti-cancer activity of *Ashwagandha* has been attributed to suppression of NF-κB[22] and inhibition of notch-1 signaling[23] by Withaferin (an active constituent in *Ashwagandha*). Withaferin-A has been shown to cause FOXO3a- and Bim-dependent apoptosis and inhibits growth of human breast cancer cells *in vivo*,[24] induce apoptosis in human leukemia U937 cells through down-regulation of Akt phosphorylation,[25] and inhibit Hsp90 chaperone activity in pancreatic cancer cells.[26] Anti-inflammatory activity of *Ashwagandha* has been attributed to the inhibition of nitric oxide production, iNOS expression and subsequent downregulation of NF-κB.[25] Sominone alkaloid of *Ashwagandha* have been reported to enhance neurite outgrowth and spatial memory mediated by the neurotrophic factor receptor, RET.[27] Deceleration of senescence has been reported in normal human fibroblasts by withanone extracted from *Ashwagandha* leaves.[28] Active glycowithanolides, sitoindosides VII-X and withaferin A of *Ashwagandha* induced a dose-related increase in SOD, CAT and GSH-px activity, where glycowithanolides also exerted antistress adaptogen effects.[29,30] Such a broad spectrum of biological effects suggests that a common systemic mechanism regulated by the antioxidant effect of *Ashwagandha* underlies its adaptogenic activity in promoting a healthy aging.

Tulsi (*Ocimum sanctum*) has been reported to show its antioxidant activity by attenuation of stress-induced changes in antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase and endogenous antioxidants such as reduced glutathione.[31] In addition, *Tulsi* was found effective in scavenging the DPPH, superoxide, nitric oxide, hydroxyl and ABTS radicals in a dose dependent manner.[32] The interruption of the free-radical chain of oxidation by the hydrogen donated from the phenolic compound's hydroxyl groups, thereby forming stable free radicals, which do not initiate or propagate further oxidation of lipids, is probably responsible for the antioxidant property of *Tulsi*. The anti-oxidant property of *Tulsi* has also been confirmed by other reports.[32] Furthermore, flavonoids are useful exogenous agents in protecting the aging brain, other organs and tissues of the body against free-radical induced damage. It appears that the phenolic and flavonoid contents of *Tulsi* are responsible for the attenuation of oxidative damage. *Tulsi* treatment attenuated noise-induced changes in levels of neurotransmitters such as dopamine and serotonin in brain.[33] *Tulsi* has also been reported to normalize the stress induced membrane changes in the hippocampus and sensorimotor cortex.[34] These reports indicate that *Tulsi* is a non-specific anti-stressor. Apart from these, treatment with *Tulsi* extract decreased the expression of PCNA, GST-pi, Bcl-2, CK and VEGF, and increased the expression of Bax, cytochrome C, and caspase 3 in gastric carcinoma,[35] suggesting that these molecules may be potential targets that mediate the pharmacological effects of *Tulsi*. Ethanol extract of *Tulsi* exerts anti-metastatic activity through inactivation of matrix metalloproteinase-9 and enhancement of anti-oxidant enzymes.[36]

In *Ardraka* (*Zingiber officinale*), the active principles zingerone, 6-gingerol, 8-gingerol, 10-gingerol, and 6 shogaol demonstrated significant free radical scavenging activity particularly against DPPH radical, superoxide radical and hydroxyl radical in in-vitro assays.[37] Moreover, dietary treatment with *Ardraka* protected from oxidative-cellular damage by the attenuation of lindane-induced lipid peroxidation, and modulation of reduced glutathione (GSH), glutathione peroxidase (Gpx), glutathione reductase (GR), and glutathione-S-transferase (GST).[38] 6-shogaol component was found to downregulate iNOS and COX-2 gene expression by inhibiting the activation of NF-κB.[39] Zingerone, another major active compound of *Ardraka*, modulate age-related NF-κB activation through the MAPK signaling pathway.[36] 6-gingerol compound has been reported to inhibit NO synthesis and protect against peroxynitrite-mediated damage.[40] Several anti-cancer investigations have reported the involvement of signaling molecules such as NF-κB, TNF-‡, AKT, ERK1/2, p38 MAPK, MMP-2 and MMP-9 in mediating the cellular responses to various phytochemicals of *Ardraka.*[41-44]

The biological effects of the active principles present in *Nimba* (*Azardirachta indica*) are regulated through various signaling molecules. Ethanolic extract of *Nimba* leaves augmented the expression levels of HMOX1, AKR1C2, AKR1C3, and AKR1B10 in prostate cancer cells.[45] Inhibition of PC-3 cell proliferation and Bcl-2 expression was observed after *Nimba* treatment.[46] Methanolic extract of *Nimba* leaves inhibited NF-κB activity in cultured human leukemia cells.[47] Azadirachtin constituent of *Nimba* has been found to activate transcription factors like CREB, Sp1, NF-κB.[48] The viability of human cervical cancer HeLa cells were suppressed by azadirachtin and nimbolide by p53-dependent p21 accumulation and down-regulation of cell cycle regulatory proteins cyclin B, cyclin D1 and PCNA.[49] In addition, the antioxidant potential of *Nimba* leaves was demonstrated by the reduction of DPPH, ABTS, superoxide, hydroxyl, and nitric oxide radicals by different extracts of *Nimba* leaves.[50] *Nimba* leaf extracts decreased LPO, enhanced the antioxidant enzymes like SOD, CAT, GSH-px and GST, and protected against MNNG-induced genotoxicity and oxidative stress in male rats.[51-52]

8-C-β-D-[2-*O*-(E)-Coumaroyl]glucopyranosyl-2-[2-hydroxy]-propyl-7-metho-xy-5-methylchromone, a potent antioxidative compound has been isolated from a methanolic extract of *Kumari* (*Aloe vera*).[53] Aloesin derivatives isorabaichromone together with feruloylaloesin and p-coumaroylaloesin from *Kumari* showed potent DPPH radical and superoxide anion scavenging activities. Electron spin resonance (ESR) using the spin trapping method suggested that the potent superoxide anion scavenging activity of isorabaichromone may have been due to its caffeoyl group.[54] Polysaccharides and flavonoids fractions along with aloe extracts showed significant antioxidant activity.[55] Treatment with *Kumari* reduced the MDA in tissues and ameliorated SOD and CAT activities.[56]

Kalmegh (*Andrographis paniculata*) showed protective effect in the activity of SOD, CAT, GSH-px, GSH-R and GSH levels,[57] and the decreased activity of lipid peroxidise, LDL and MDA.[58]

The polysaccharides fraction and crude extract of *Shatavari* (*Asparagus racemosus*) showed pronounced reduction in LPO, as assessed by TBARS formation, inhibiting protein oxidation, and improvement in the activity of SOD, CAT, GSH-px, and GSH levels.[59,60] Antioxidant

compound racemofuran, isolated from *Shatavari*, showed activity against DPPH with IC50 value of 130µM.[61]

Brahmi (*Bacopa monnieri*) extract induced a dose-dependent free radical scavenging capacity, protective effect on DNA damage in human non-immortalized fibroblasts,[62] and increase in SOD, CAT and GSH-px activities in rat brain.[63]

Shalparni (*Desmodium gangeticum*) extract also showed scavenging abilities observed against DPPH, nitric oxide, ferryl-bipyridyl and hypochlorous acid and LPO activity.[64]

Yashtimadhu (*Glycyrrhiza glabra*) roots reduced CAT activity and LDL levels in animal models and possess several antioxidant constituents namely hispaglabridin A, hispaglabridin B, glabridin, 4′-*O*-methylglabridin, isoprenylchalcone derivative, isoliquiritigenin, and formononetin.[65,66]

In *Kutki* (*Picrorhiza kurroa*) roots, picroliv, picroside-I and kutkoside contents scavenge the superoxide anions and possess the properties of antioxidants which appear to be mediated through activity like that of SOD, metal ion chelation and xanthine oxidase inhibition.[67]

In *Bakuchi* (*Psoralea corylifolia*) seeds, the bakuchiol, bavachinin, bavachin, isobavachin and isobavachalcone contents showed broad antioxidative activities, inhibited NADPH-, ascorbate-, *t*-BuOH- and LPO in rat liver microsomes and mitochondria.[68]

Bhallataka (*Semecarpus anacardium*) nut extracts increased the level of non-enzymatic antioxidants (GSH, Vitamin E, Vitamin C) and enzymatic antioxidants (CAT and GSH-px except SOD) to near normal levels in arthritic rats,[69] elevated antioxidant levels and cytochrome P450 contents in hepatocellular carcinoma, and protected against lipid peroxidation. Mechanism of action may be through metal chelation or activation of endogenous antioxidant enzymes.[70,71]

Guduchi (*Tinospora cordifolia*) extracts exerted strong antioxidant effects, inhibited LPO, TBARS, increased GSH, CAT and SOD, demonstrated free radical scavenging activity particularly against DPPH, superoxide and hydroxyl radicals.[72,73] *Guduchi* was found effective in effective in expression of the gamma-glutamylcysteine ligase and Cu–Zn SOD genes and also exhibited strong scavenging properties against ROS and RNS.[74] Furthermore, aqueous extract inhibited the formation of ferryl–bipiridyl complex by chelating Fe^{2+} ions.[75]

Many other *Rasayana* plants are also scrutinized, though in limited studies, nevertheless valuable in ascertaining the acting mechanisms. The ethyl acetate extract of *Vacha* (*Acorus calamus*) was found to be potent antioxidant by inhibition of DPPH free radical.[76] *Kokilaaksha* (*Hygrophila auriculata*) showed significant radical scavenging activity against DPPH with moderate scavenging activity against nitric oxide, hydroxyl radical, ferryl bipyridyl complex and LPO.[77] Alcohol extract of the seeds of *Kapikacchu* (*Mucuna pruriens*) demonstrated antilipid peroxidation property, mediated through the removal of superoxides and hydroxyl radicals.[78] Plants such as *Maricha* (*Piper nigrum*), *Pippali* (*Piper longum*), *Chitraka* (*Plumbago zeylanica*), *Bala* (*Sida cordifolia*), *Vishnukraanti* (*Evolvulus alsinoides*), and *Durva* (*Cynodon dactylon*) also showed radical scavenging and LPO inhibitory activities in animal models.[79-81]

CONCLUSION

Available reports suggests that Ayurvedic herbs possess a rich array of a diverse spectrum of bio-active compounds (viz. flavonoids, phenolics, carotenoids etc.) with multiple pharmacological effects, which may help to reduce the oxidative milieu, enhance antioxidant defences and promote rejuvenation. Several distinct signaling pathways (primarily NF-κB pathway), chelating mechanisms, and cytoprotective effects mediates the biological effects of the herbal rejuvenators. The potential antioxidant contributions of Ayurvedic Rasayana herbs are indubitable and unstoppable, though the available reports are limited to portray the exact mechanistic pathways of action of these botanicals. Nevertheless, further detailed *in vitro* and *in vivo* investigations are warranted to isolate active principles and their pharmacological validation, analyze herb-drug interactions, safety evaluations and to explore those aspects that remain untouched.

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Conflict of interest – None declared.

Abbreviations: CAT: catalase; DPPH: 1,1-diphenyl-2-picrylhydrazyl; NADPH: nicotinamide adenine dinucleotide phosphate; GSH: glutathione; GSH-px: glutathione peroxidase; GSH-R: glutathione reductase; GST: glutathione S-transferase; LDL: low density lipoproteins; LPO: lipid peroxidation; MDA: malondialdehyde; RNS: reactive nitrogen species; ROS: reactive oxygen species; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances, MNNG: *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine.

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