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Herbal Antioxidants as Rejuvenators in Alternative Medicine

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1. Introduction

Life expectancy has nearly doubled during the 20th century. This dramatic increase in the aging population presents with an enormous challenge to maintain a healthy old age. A comprehensive solution to address this important problem is compounded by a multitude of factors that contribute to the accumulation of damage to macromolecules, cells, tissues and organs during aging. The rejuvenation strategies, currently being employed with a targeted approach, to reverse or repair the damage associated with aging have only yielded partial benefits. The complexity of the aging process highlights the need for a holistic approach, as recommended by the alternative systems of medicine, to prevent the progressive deterioration of the aging cells. Herbal antioxidants have been successfully employed as rejuvenators, for several centuries in the Indian systems of alternative medicine. This chapter describes the concepts behind the application of herbal antioxidants to promote longevity and scientifically validate their potential by highlighting the molecular mechanisms underlying the biological activity of the phytochemicals in these herbs.

2. Oxidative and nitroxidative stress – major etiological factors in aging phenomenon

Oxidative stress is widely recognized to play a causal role in the aging phenomenon. Every day metabolic activities including breathing could lead to the exposure of cells to biochemical substances such as free radicals and the gradual accumulation of free radicals can induce cellular damage. According to the free radical theory of aging, which is based on Harman's hypothesis, continued creation of free radicals influenced by a multitude of factors associated with routine life style is responsible for the aging process (Harman, 1972). Normally, the antioxidant mechanism fails either due to overproduction of free radicals or insufficient activities of scavenging enzymes, or both causing lipid peroxidation. Since lipid peroxidation is a self-propagating chain reaction the initial oxidation of only a few lipid molecules can result in significant tissue damage and disease.

Moreover, it has already been established that superoxide radicals that are generated during normal cellular respiration could eventually lead to nitration of proteins (Figure 1). Nitration of tyrosine, a posttranslational modification of immense functional importance, occurs by the substitution of a nitro group in place of hydrogen on carbon 3 in the phenolic

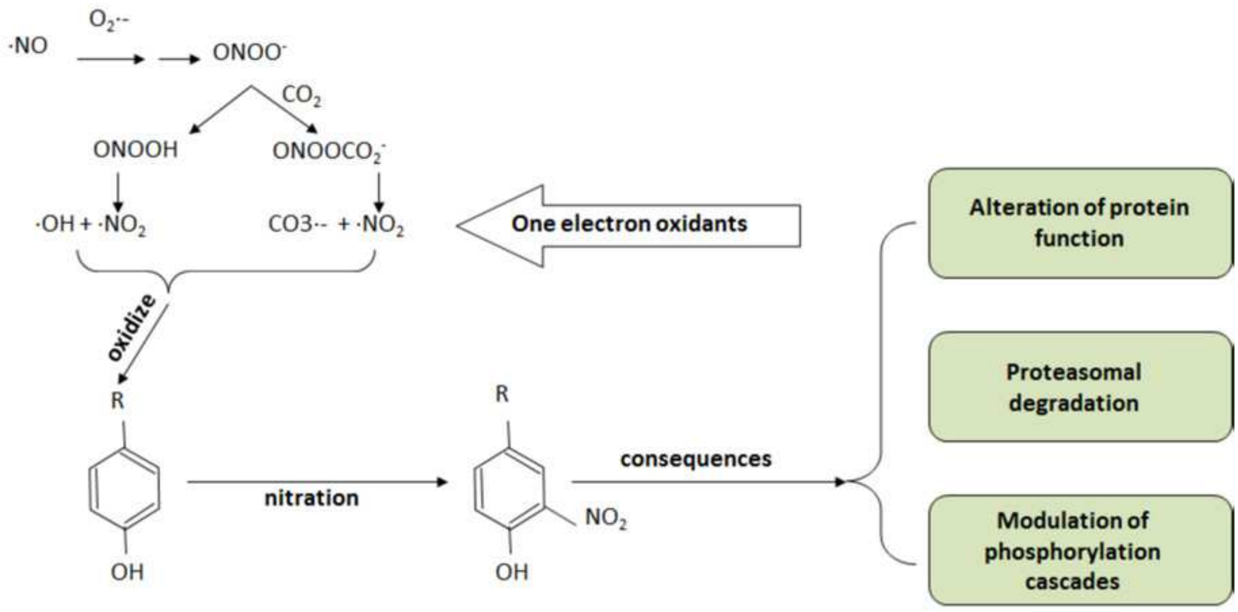

Fig. 1. Protein nitration and its consequences

ring of a tyrosine residue (Radi, 2004). In vivo nitration mostly depends on superoxide (O_2·-) and nitric oxide (NO) radicals, generated during routine cellular activity, as they react to form peroxynitrite (ONOO-). Peroxynitrite eventually leads to the formation of one-electron oxidants (CO3·-, ·OH, NO_2) which can oxidize the phenolic ring of tyrosine to yield the tyrosyl radical (Tyr·). The addition of NO_2 to Tyr· in a radical–radical termination reaction results in tyrosine nitration.

Although the nitration of tyrosine occurs at relatively low levels compared to tyrosine phosphorylation, protein nitration can result in serious biological consequences as it can modulate phosphorylation cascades. Nitrated proteins are often targets of proteasomal degradation. Age-related increase in nitrotyrosine has been reported in the hippocampus, which is responsible for spatial memory, in humans with mild cognitive impairment (Butterfield et al., 2007). As the metabolic activity of brain is relatively high, the aberrant electron transfers result in additional free radical formation and subsequent protein nitration in aged brain tissue. Therefore, protein nitration is generally considered as a biomarker for age-related neurodegeneration (Butterfield et al., 2006; Chung and David, 2010). Moreover, nitroxidative damage of neurons can also contribute to age-related deficits in memory function. Thus, oxidative and nitroxidative stress are crucial factors responsible for the aging process.

3. Alternative medicine concepts in promoting longevity

Herbal antioxidants are widely used as dietary supplements for promoting longevity in alternative medicine systems of Ayurveda and Siddha, which originate from India (Table 1). These traditional systems of medicine are based on the concept of tridosha theory, according to which vatha, pitha and kapha are the three humors that govern the physiological function of the body. When the normal balance of the three humors is deranged they are known as doshas which ultimately results in pathological consequences during the aging process. A set of applications known as “Kaya Karpam”, which literally means transforming the body from its fragile state to a stable stone like state, are used to attenuate vatha, pitha or kapha rationalizing their extensive use in complementary and alternative medicines for promoting health and wellness.

S. No.	Common name	Botanical name	Part used
1.	Aloe	Aloe vera	Succulent leaf
2.	Ashwagandha	Withania somnifera	Root
3.	Black nightshade	Solanum nigrum	Fruits and leaves
4.	Cardamom	Elateria cardamom	Fruit
5.	Chaste tree	Vitex negundo	Leaves
6.	Clearing nut	Strychnos potatorum	Seed
7.	Country green	Amaranthus gangeticus	Leaves
8.	Cumin	Cuminum cyminum	Seed
9.	False daisy	Eclipta alba	Leaves
10.	Ginger	Zingiber officinale	Rhizome
11.	Indian acalypha	Acalypha indica	Leaves
12.	Indian Sarsaparilla	Hemidesmus indicus	Root
13.	Indian sorrel	Oxalis corniculata	Leaves
14.	Lemon	Citrus medica	Fruit
15.	Neem	Azardirachta indica	Leaves
16.	Nut grass	Cyperus rotundus	Tuberous root
17.	Red spiderling	Boerhaavia diffusa	Whole plant
18.	Sessile joyweed	Alternanthera sessilis	Leaves
19.	Stonebreaker	Phyllanthus niruri	Whole plant
20.	Triphala	Terminalia chebula	Dried fruit
		Terminalia bellerica	Dried fruit
		Emblica officinalis	Dried fruit
21.	Tulsi / Holy basil	Ocimun sanctum	Leaves

Table 1. Medicinal herbs used as rejuvenators in Indian system of alternative medicine

This concept is similar to one of the central theories of aging which suggests that every day metabolic activities including breathing could lead to the exposure of cells to biochemical substances such as free radicals and antioxidants can be employed to prevent the gradual accumulation of free radical induced cellular damage during aging. Several studies have shown that the life span of an organism can be extended by diminishing oxidative stress (Finkel and Holbrook, 2000). Consistent with this notion, the "Kaya Karpam" herbs extensively used to promote longevity in alternative medicine systems have been found to have significant antioxidant properties. Some of the current research findings also substantiate the use of medicinal herbs, because phytochemicals such as resveratrol, sulforaphanes and curcumin, are considered to possess neurohormetic property because of their ability to protect neurons against injury and disease by stimulating the production of antioxidant enzymes, neurotrophic factors, protein chaperones and other proteins that help cells to withstand stress (Mattson and Cheng, 2006). The subsequent sections describes the mechanism underlying the prophylactic as well as therapeutic effects of some common herbal antioxidants employed in Indian systems of alternative medicine to promote longevity.

4. Common herbal antioxidants used in Indian system of alternative medicine

Triphala, ashwagandha, tulsi, ginger and neem are extensively used in Indian systems of alternative medicine, as they are considered to possess significant rejuvenating properties.

4.1 Triphala

Triphala is an herbal formula consisting of dried fruits from A) *Terminalia chebula,* B) *Terminalia bellirica* and C) *Emblica officinalis*, the three myrobalans, in equal parts (Figure 2). The chebulic and belleric myrobalans belong to the family Combretaceae, while the emblic myrobalan, commonly known as amlaki, belongs to the family Phyllanthaceae. Triphala is widely used as a dietary supplement for promoting longevity in alternative medicine systems of Ayurveda and Siddha (Jagetia et al., 2002). Triphala is classified as a kaya karpam and has already been reported for its significant antioxidant activity (Naik et al., 2005; Hazra et al., 2010). The constituents of triphala were reported to enhance the antioxidant status in aging animal models (Yokozawa et al., 2007; Mahesh et al., 2009). In addition, triphala has been reported to possess several other important medicinal properties (Srikumar et al., 2005; Rasool and Sabina, 2007; Shi et al., 2008) that strengthen its potential to deal with multiple problems associated with aging. Such a multi-faceted activity of triphala is consistent with the complementary and alternative medicine concepts of a holistic approach to restore the normal balance of the three humors and supports its potential to rejuvenate the aging cells.

Fig. 2. Constituents of triphala

4.2 Ashwagandha

Ashwagndha *(Withania somnifera,* Figure 3*)* belongs to Solanaceae family and has been used for centuries in Indian systems of alternative medicine to treat various ailments. It is commonly known as Indian Ginseng because of its comparable medicinal value to ginseng which is acclaimed for its adaptogenic activity in alleviating stress induced illness. The medicinal properties of ashwagandha are mostly attributed to its tuberous roots whose extracts are widely marketed as an over the counter herbal supplement. Adaptogens, like ashwagandha, are believed to facilitate the maintenance of homeostasis by normalizing physiological as well as biochemical changes induced by stress. The anti-inflammatory (Maitra et al., 2009), anti-cancer (Ichikawa et al., 2006) and immunomodulatory (Bhattacharya and Muruganandam, 2003) activities of ashwagandha rationalize its extensive use in promoting longevity. Ashwagandha's antioxidant activity (Udayakumar et al., 2010) suggests that a common molecular mechanism may be responsible for its diverse biological effects.

Fig. 3. Ashwagandha herb

4.3 Tulsi

Tulsi (*Ocimum sanctum,* Figure 4), a medicinal herb classified as a kaaya karpam, is cultivated in India for medicinal as well as religious purposes. It is commonly known as "holy basil". It is an aromatic plant which belongs to the family Lamiaceae. Due to its immense medicinal value it is extensively used in Indian systems of alternative medicines to heal a number of ailments. Several studies have reported the significant antioxidant activity of tulsi (Kelm et al., 2000; Yanpallewar et al., 2004; Samson et al., 2007). Tulsi treatment enhanced the antioxidant status in discrete regions of brain (Samson et al., 2007) and the phytochemical contents of tulsi have been suggested to be responsible for this effect. The stress alleviating potential of Ocimum sanctum extract is also reflected by its efficacy in attenuating the immunological changes induced by noise exposure (Archana and Namasivayam, 2000). In addition, tulsi has been reported to possess several other important medicinal properties (Singh et al., 1996; Mediratta et al., 2002; Adhvaryu et al., 2007; Kim et al., 2010) that strengthen its potential to deal with aging and oxidative stress. Thus, Tulsi is capable of promoting a healthy aging due to its multiple but complimentary and synergistic medicinal properties which can combat a diverse spectrum of disorders associated with aging.

Fig. 4. Fresh and shade dried tulsi

4.4 Ginger

Ginger (Figure 5) is a widely used herbal supplement, often used in a number of culinary preparations all around the world. It is a rhizome of the herb *Zingiber officinale*, which belongs to the family Zingiberaceae. Due to its diverse healing properties it is extensively used in alternative medicines such as Chinese medicine, Ayurveda, Siddha and Unani. The Indian systems of medicines recommend the use of ginger as a kaya karpam or rejuvenator. It is used both in fresh and dried form to treat nausea and vomiting (Jewell, 2003; Borrelli et al., 2005; Chaiyakunapruk et al., 2006), osteo and rheumatoid arthritis (Srivastava and Mustafa, 1992; Bliddal et al., 2000; Altman and Marcussen, 2001), diabetes mellitus (Sekiya et al., 2004; Goyal and Kadnur, 2006; Heimes et al., 2009), indigestion and some cardiovascular disorders (Jiang et al., 2005; Nicoll and Henein, 2009). Various studies have demonstrated the anti-oxidant (Kabuto et al., 2005; Ahmed et al., 2008; Pan et al., 2008; Dugasani et al., 2010), anti-inflammatory (Young et al., 2005), anti-cancer (Jiang et al., 2005; Rhode et al., 2007; Shukla and Singh, 2007) and anti-microbial (Park et al., 2008; Singh et al., 2008b) properties of ginger. These multiple biological properties of ginger support its clinical application as an herbal rejuvenator.

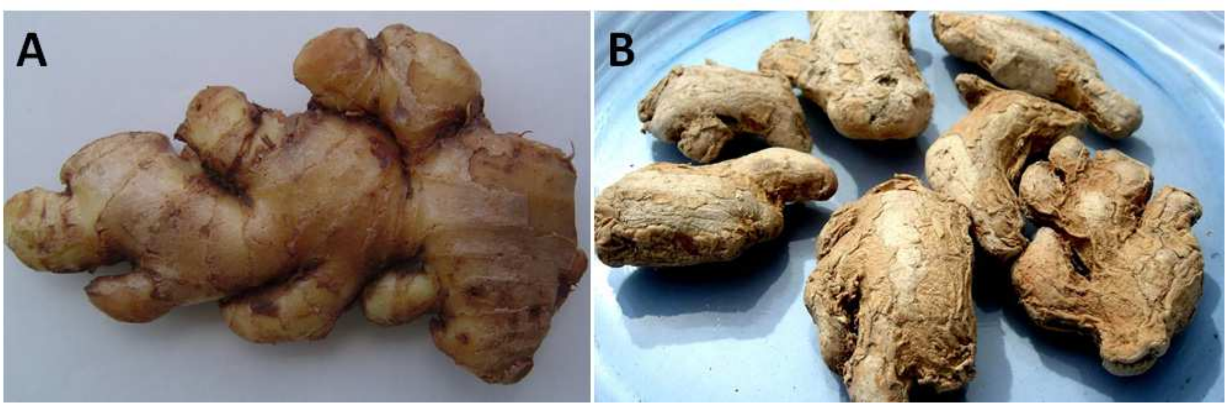

Fig. 5. Fresh and dried ginger

4.5 Neem

Azardirachta indica, commonly known as neem, belongs to the family Meliaceae, is a large ever green tree with immense medicinal applications. Various parts of the neem tree such as leaves (Figure 6), flowers, seeds, roots and bark are used as traditional remedies for a number of ailments in the Indian systems of alternative medicine. However, the wide ranging medicinal value of the neem leaves stands out in comparison with other parts of the tree. Various studies have indicated that the neem leaves have anti-microbial (Wolinsky et al., 1996; Thakurta et al., 2007; Zhang et al., 2010), anti-inflammatory (Okpanyi and Ezeukwu, 1981; Thoh et al., 2010), analgesic (Khattak et al., 1985), anti-diabetic (van der Nat et al., 1991), immunomodulatory (Ray et al., 1996), anti-oxidant (Arivazhagan et al., 2000) and anti-cancer (Miller et al., 1992; Akudugu et al., 2001) properties. Due to its numerous pharmacological activities neem leaves are used as a kaya karpam to promote longevity.

Fig. 6. Neem leaves

5. Phytochemicals responsible for the therapeutic effects of herbal antioxidants

Triphala has been used for centuries in Indian systems of alternative medicine as a dietary supplement for rejuvenation due to its prophylactic and therapeutic properties (Jagetia et al., 2002). The three constituents of triphala have distinct as well as common phytochemicals that are considered to complement each other and act in a synergistic manner. *Terminalia chebula* is reported to contain ascorbic acid, gallic acid, tannic acid, syringic acid and epicatechin while *Terminalia bellerica* has gallic acid, tannic acid and ascorbic acid (Singh et al., 2008a). *Emblica officinalis* is a rich source of vitamin C and also has flavanoids, kaempferol, ellagic acid and gallic acid (Singh et al., 2008a).

Several active compounds of ashwagandha, especially steroidal lactones, have been isolated, in the quest to identify the constituent(s) responsible for its wide ranging clinical application in alternative medicine. A HPLC analysis demonstrated the presence of Withanolide-A, withanone, withaferine-A, withastramonolide, 27-hydroxywithanone, withanoside, physagulin (Dhar et al., 2006). Although active compounds like withaferin A and withanasoide D are considered as major players, it is still not clear whether any one of these compounds are responsible for the biological activities of ashwagandha or whether they exert a synergistic action when administered in their natural form.

Basils contain a wide range of essential oils rich in phenolic compounds (Phippen and Simon, 2000) and a wide array of other natural products including polyphenols such as flavonoids and anthocyanins. Epidemiological studies have suggested positive associations between the consumption of phenolic-rich foods or beverages and the prevention of disease (Scalbert and Williamson, 2000). These effects have been attributed to antioxidant components such as plant phenolics, including flavonoids and phenylpropanoids among others. One of the widely used medicinal herb among the basils is Ocimum sanctum Linn, which is commonly known as holy basil or ''Tulsi''. Ocimum sanctum has been reported to exhibit several medicinal properties and the active principles present in Ocimum species such as rosmarinic acid, lithospermic acid, eugenol, methyleugenol, urosolic acid, h-caryophyllene, methylchavicol, linalool, 1,8-cineole phenolics and flavonoids such as orientin, vicenin etc have been attributed to be responsible for its diverse medicinal activities (Hase et al., 1997; Kelm et al., 2000).

Ginger has a rich array of useful bio-active compounds. The antioxidant property of ginger can be attributed to the phytochemicals present in ginger which includes volatile compounds such as sesquiterpenes (curcumene β-phellandrene, geraniol, 1,8-cineole, citral, terpineol, borneol, linalool, neral) and monoterpenoid hydrocarbons (α-zingiberene, β-sesquiphellandrene, α-farnesene, β-bisabolene, α-curcumene) and non-volatile compounds like gingerols, shogaols, paradols, and zingerone (Gong et al., 2004; Jolad et al., 2004).

A large number of medicinally useful phytochemicals have been isolated and identified from the neem leaves. They include azadirachtanin, azadirachtanin-A, β-sitosterol, hyperoside, isoazadirolide, nimbaflavone, nimbandiol, nimbinene, nimbolide, quercetin, quercitrin, rutin, vilasanin, 3-acetyl-7-tigloyl-lactone-vilasinin (Akhila and Rani, 1999; Siddiqui et al., 2004). These wide ranging bio-active compounds of neem leaves can be considered to be responsible for its multiple biological / medicinal applications.

6. Signaling molecules that mediate the biological effects of herbal antioxidants

Recent studies have identified some of the molecular targets of triphala. Activation of ERK and p53 were found to mediate the growth inhibitory effects of triphala in pancreatic cancer (Shi et al., 2008). Chebulagic acid isolated from Terminalia chebula has been reported to inhibit COX-2/5-LOX (Reddy et al., 2010). Apart from this, triphala has been shown to possess significant antioxidant (Naik et al., 2005; Mahesh et al., 2009; Hazra et al., 2010) and nitric oxide scavenging activity (Jagetia et al., 2004). In addition, the anti-cancer (Deep et al., 2005; Sandhya and Mishra, 2006; Shi et al., 2008), immunomodulatory (Srikumar et al., 2005) and anti-inflammatory (Rasool and Sabina, 2007) activity of triphala directly targets the common health problems associated with aging. The selective cytotoxic and apoptotic activity of triphala on cancer cells while sparing the adjacent normal cells (Shi et al., 2008) further strengthens its compelling role as a dietary supplement to promote longevity.

The biological effects of ashwagandha have been shown to be mediated by several signaling molecules. The anti-cancer activity of ashwagandha has been attributed to suppression of NF-κB (Kaileh et al., 2007) and inhibition of notch-1 signaling (Koduru et al., 2010). Withaferin A, an active principle in ashwagandha, has been reported to cause FOXO3a- and Bim-dependent apoptosis in breast cancer cells (Stan et al., 2008) and inhibit Hsp90 chaperone activity in pancreatic cancer cells (Yu et al., 2010). Ashwagandha's anti-inflammatory activity has been attributed to the inhibition of nitric oxide production and iNOS expression and subsequent downregulation of NF-κB (Oh et al., 2008). Alkaloids of ashwagandha have been reported to enhance neurite outgrowth and spatial memory (Tohda and Joyashiki, 2009). Deceleration of senescence has been reported in fibroblasts (Widodo et al., 2009). Such a broad spectrum of biological effects suggests that a common systemic mechanism regulated by the antioxidant property of ashwagandha underlies its adaptogenic activity in promoting a healthy aging.

The antioxidant activity of tulsi has been demonstrated by its attenuation of stress-induced changes in antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase and endogenous antioxidants such as reduced glutathione (Samson et al., 2007). Moreover, Ocimum sanctum was effective in scavenging the DPPH, superoxide, nitric oxide, hydroxyl and ABTS radicals in a dose dependent manner (Samson et al., 2007). 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 Ocimum sanctum has also been confirmed by other reports (Devi and Ganasoundari, 1999). 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 Ocimum sanctum are responsible for the attenuation of oxidative damage. Ocimum sanctum treatment attenuated noise-induced changes in levels of neurotransmitters such as dopamine and serotonin in brain (Samson et al., 2006). Ocimum sanctum has also been reported to normalize the stress induced membrane changes in the hippocampus and sensorimotor cortex (Sen et al., 1992). These reports indicate that Ocimum sanctum is a non-specific anti-stressor. Apart from these, treatment with Ocimum sanctum 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 (Manikandan et al., 2007), suggesting that these molecules may be potential targets that mediate the pharmacological effects of Ocimum sanctum.

The active principles of ginger such as 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 (Dugasani et al., 2010). Moreover, the efficacy of ginger in protecting the cells from oxidative stress was indicated 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) after dietary treatment with ginger (Ahmed et al., 2008). The active compound 6-shogaol was found to downregulate iNOS and COX-2 gene expression by inhibiting the activation of NF-κB (Pan et al., 2008). Zingerone, another major active compound of ginger, has been reported to modulate age-related NF-κB activation through the MAPK signaling pathway (Kim et al., 2010). Another study indicated that 6-gingerol has been reported to inhibit NO synthesis and protect against peroxynitrite-mediated damage (Ippoushi et al., 2003). Apart from these, several studies investigating the anti-cancer potential of ginger have reported the involvement of signaling molecules such as NF-κB, TNF-α, AKT, ERK1/2, p38 MAPK, MMP-2 and MMP-9 in mediating the cellular responses to various phytochemicals of ginger (Rhode et al., 2007; Habib et al., 2008; Hung et al., 2009; Yodkeeree et al., 2009; Kim et al., 2010).

The biological effects of the active principles present in neem are regulated through various signaling molecules. Increase in expression levels of HMOX1, AKR1C2, AKR1C3, and AKR1B10 was observed in prostate cancer cells after treatment with an ethanolic extract of neem leaves (Mahapatra et al., 2011). Inhibition of PC-3 cell proliferation and Bcl-2 expression was observed after neem treatment (Priyadarsini et al., 2009). A methanolic extract of neem leaves inhibited NF-κB activity in cultured human leukemia cells (Schumacher et al., 2011). Azadirachtin, an active principle of neem, has been reported to activate transcription factors like CREB, Sp1, NF-κB (Thoh et al., 2011). 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 (Priyadarsini et al., 2010). Apart from this, the antioxidant potential of neem leaves were demonstrated by the reduction of DPPH, ABTS, superoxide, hydroxyl, and nitric oxide radicals by different extracts of neem leaves (Manikandan et al., 2009).

7. Conclusion

Emerging studies on herbs employed as rejuvenators, for centuries in Indian system of alternative medicine, validates their clinical application by highlighting the mechanistic principle underlying the biological effects of these herbs. Analytical reports on triphala, ashwagandha, tulsi, ginger and neem suggest that these medicinal herbs have a rich array of a diverse spectrum of bio-active compounds. The abundance of phytochemicals with antioxidant properties, such as phenolics, flavonoids and carotenoids, may be held responsible for the rejuvenating activity of these medicinal herbs. The molecular targets of major phytochemicals identified in each of the herbal antioxidants discussed in this chapter suggest that NF-κB signaling pathway plays an important role in regulating the biological activity of the herbal rejuvenators. In addition, it is also evident that several other signaling pathways, which differ for each of these herbs, also mediate their biological effects. Thus, the medicinal herbs employed to promote longevity in Indian systems of alternative medicine have multiple pharmacological effects. However, the antioxidant property of these herbs seems to have a major role in determining their rejuvenating potential.

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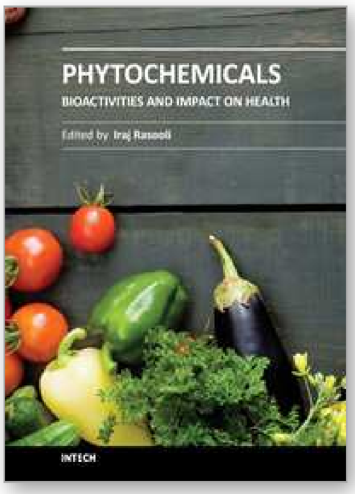

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Among the thousands of naturally occurring constituents so far identified in plants and exhibiting a long history of safe use, there are none that pose - or reasonably might be expected to pose - a significant risk to human health at current low levels of intake when used as flavoring substances. Due to their natural origin, environmental and genetic factors will influence the chemical composition of the plant essential oils. Factors such as species and subspecies, geographical location, harvest time, plant part used and method of isolation all affect chemical composition of the crude material separated from the plant. The screening of plant extracts and natural products for antioxidative and antimicrobial activity has revealed the potential of higher plants as a source of new agents, to serve the processing of natural products.

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