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# Prospect of Indian herbs as sources of antioxidants in combating oxidative stress

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**Abstract:** Oxidative stress is a state that reflects imbalance between reactive oxygen species (ROS) production and their elimination by enzymatic and non-enzymatic antioxidants. Excessive production of ROS causes potential biological damage resulting in many forms of cancer, atherosclerosis, cataracts, neurodegenerative diseases and a plethora of other diseases, as well as premature aging. Medicinal herbs as a rich source of natural antioxidants are enjoying a high profile at present. Several phytochemicals, herbal extracts and food additives are blessed with multifaceted therapeutic benefits through a cascade of molecular events. In this review article, we explore the potential of five Indian herbs viz. tulsi, giloy, turmeric, ashwagandha and aloe vera as sources of antioxidants to combat the ever-increasing oxidative stress by increasing the levels of antioxidant molecules and scavenging free radicals in the body for holistic development. Antioxidants mediated cellular response has also been attributed to modulation of transcription factors, inflammatory cytokines, interleukins, iNOS, COX-2, LOX, growth factors, protein kinases as well as arrest of cell cycle and apoptosis of cancer cells.

**Keywords:** Oxidative stress, Tulsi (*Ocimum sanctum Linn*), Giloy (*Tinospora cordifolia*), Turmeric (*Curcuma longa*), Ashwagandha (*Withania somnifera*), Aloe vera (*Aloe barbadensis*), Antioxidants

**Abbreviations:** ABTS: azinobis-(3-ethylbenzothiazoline-6-sulphonic acid), AP-1: activator protein 1, Bax: B-cell lymphoma 2 (Bcl-2)-associated X protein, CAT: catalase, CDK4: cyclin-dependent kinase 4, COX: cyclooxygenase, CXCL1: C-X-C motif chemokine ligand 1**,** DR5: death receptor-5, DPPH: 2,2-diphenyl-1-picrylhydrazyl, EGFR: epidermal growth factor receptor, ERK: extracellular signal regulated kinase, FAK: focal adhesion kinase, GPx: glutathione peroxidise, GSH: glutathione, GST: glutathione-S-transferase, HO-1: heme oxygenase-1, HIF-1α: hypoxia-inducible factor 1α, ICAM-1: intercellular adhesion molecule 1, IKK: IκB kinase, IL: interleukin, JAK: Janus Kinase, JNK: c-Jun amino-terminal kinases, LOX: lipoxygenase, MAPKs: mitogen-activated protein kinases, miRNAs: microRNAs, MMPs: matrix metalloproteinases, mTOR: mammalian target of repamycin, NF-κB: nuclear factor kappa B, iNOS: inducible nitric oxide synthase, Nrf-2: nuclear factor erythroid 2-related factor 2, PCNA: Proliferating cell nuclear antigen, PGE2: Prostaglandin E2, PKC: protein kinase C, PPAR-γ: peroxisome proliferator activated receptor-gamma, QR: quinone reductase, ROS: reactive oxygen species, SOD: superoxide dismutase, STAT3: signal transducer and activator of transcription-3, TNF: tumor necrosis factor, VEGF: vascular endothelial cell growth factor

## 1. Introduction

In today's competitive life, several factors associated with modern life style *viz.* environmental, social, nutritional, sedentary work, stress, anxiety and depression are detrimental to human health [1]. During normal cellular metabolism, a number of ROS (free radical or non-radical) generated are superoxide radical, hydroxyl radical, hydrogen peroxide, peroxyl radical, nitric oxide radical and peroxynitrite [2]. However, excessive generation of free radicals, which induces oxidative stress, can occur due to endogenous factors [2-5] such as cellular mitochondrial dysfunction, xenobiotics, or exogenous factors, for instance, air pollution, smog, cigarette smoke, alcohol consumption, toxic wastes, ionizing and ultra violet radiations, certain foods and additives, drugs and infections and excessive exercise [6,7]. Deregulation of ROS results in many forms of cancer, diabetes, arthritis, myocardial infarction, Alzheimer's disease, Parkinson's disease, lung diseases, cataracts, male infertility, aging and a plethora of other diseases [3,4,8]. Adverse effects of several allopathic medicines, lack of curative treatment for several chronic diseases, high outlay of new drugs, microbial resistance and emergence of new diseases have led to increased prominence on the use of ayurvedic herbal medicines which are based on the premise that plants have natural phytochemicals that can promote health and alleviate illness [9,10]. The quest for natural antioxidants for use in preventive medicine, cosmetics and food industry has become a major challenge in industrial and scientific research. Indian herbs *viz.* tulsi, giloy, turmeric, ashwagandha and *aloe vera* possess a rich array of antioxidants with wider therapeutic potentials to reduce oxidative stress and related damage due to their adaptogenic and synergistic properties.

## 2. Oxidative stress and its consequences

Though, ROS are crucial for origin of life, evolution, genome plasticity besides normal physiological functions like detoxification, maintaining redox homeostasis, control of gene expression, intracellular signaling and immune function, [2,11] increased ROS and imbalanced metabolism may result in devastating effects. Oxidative stress is a consequence of disturbances in the normal redox state, ineffective repair systems, and/or insufficient activities of antioxidants defense mechanisms of the body, resulting in overproduction of ROS that promotes cellular aging and tissue damage as a primary or secondary causative factor in many diseases (Figure 1) [3,12]. This imbalance leads to lipid peroxidation, protein fragmentation, DNA damage, modulation of genomic expression, calcium influx, inactivation of many metabolic enzymes, mitochondrial swelling and lysis, age-related diseases, genomic instability and cell death [8,13-15].

## 3. Need for antioxidants to counteract oxidative stress

Antioxidants (enzymatic and non-enzymatic) neutralize the harmful free radicals or repair the resulting damage causing lethal consequences by one or more of the mechanisms like reducing activity, scavenging ROS or their precursors, inhibiting formation of ROS by blocking the initiation or propagation of oxidizing chain reactions, chelating metal ions and quenching of singlet oxygen [12,16]. Many synthetic antioxidants like butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), used in processed foods have some adverse effects and are carcinogenic [17]. Therefore, search of suitable alternative natural antioxidants and synthesis of novel antioxidant analogues is a vivid area to identify and develop more potent and safe antioxidants [10]. It is viable to reduce the ROS-mediated pathogenesis by either enhancing the body's natural antioxidant defenses or supplementing dietary antioxidants

[18]. We hereby are exploring the prospects of five Indian herbs *viz.* tulsi, giloy, turmeric, ashwagandha and *aloe vera* as a promising source of antioxidants for maintaining integrity and functionality of body. However, a comprehensive review of their antioxidant effects and cellular mechanisms is outside the scope of this article.

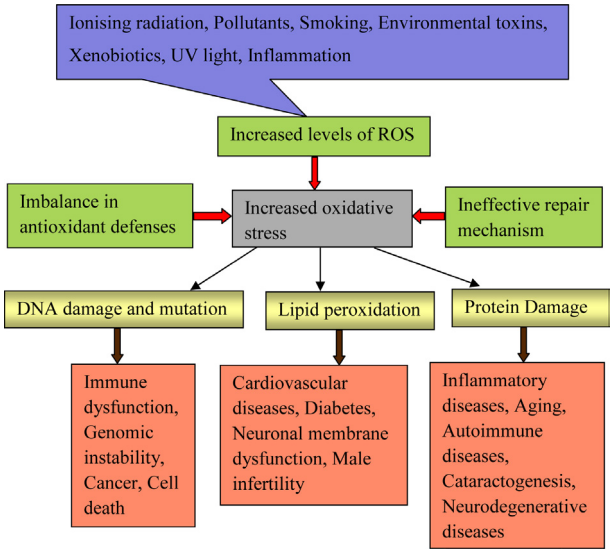



**Figure 1.** Causes and pathophysiological role of oxidative stress.

## 4. Tulsi (*Ocimum sanctum* Linn.)

### *4.1 Active components*

Tulsi or Holy basil, a sacred and traditional medicinal plant of India, well-documented in Ayurveda as the 'elixir of life' curing many ailments such as headache, cough, flu, dysentery, diarrhea, gastric ulcer, sore throat, hepatic diseases, skin diseases, arthritis, eye diseases, insect bites and malaria fever [19]. Biochemically active constituents like eugenol, carvacrol, linalool, ursolic acid, β-caryophyllene, α-pinene, β-pinene, rosmarinic acid, gallic acid, linoleic acid, ocimarin, glycosides, flavonoids (apigenin, orientin, vicenin, luteolin, cirsilineol, cirsimaritin, isothymusin, isothymonin), saponins and tannins etc are responsible for physiological functions of tulsi (Figure 2) [20,21].

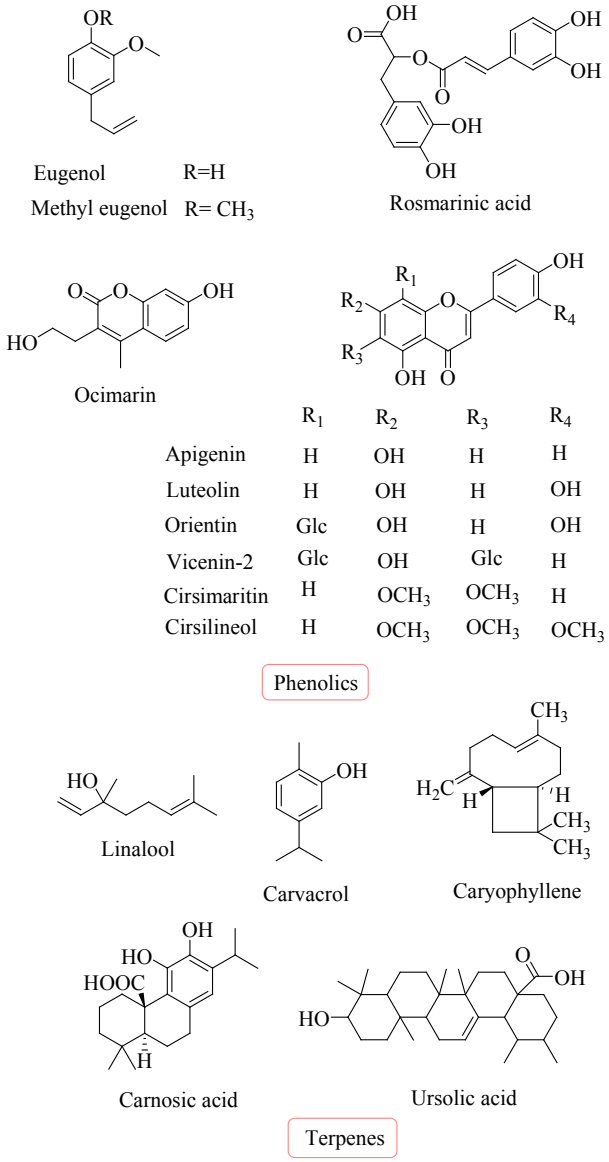



**Figure 2.** Some active components of tulsi (*Ocimum sanctum)*.

### *4.2 Pharmacological profile*

Different parts of plant like leaves, flowers, stem and seeds are used as antidiabetic, memory booster, antiasthmatic, cardioprotective, antifertility, antiseptic and analgesic agent. Tulsi strengthens the immune response by enhancing both cellular and humoral immunity. A premier adaptogen, tulsi can address physical, chemical,

metabolic and psychological stress through a unique combination of pharmacological actions which include normalization of the stress induced membrane changes in the hippocampus and sensorimotor cortex [22,23]. Its ability to decrease glucose levels, enhance insulin secretion, improve blood pressure and lipid profiles has been reported in normal, glucose-fed hyperglycemic and streptozotocin-induced diabetic rats which may help in reducing the complications of diabetes such as cataract, retinopathy [24].

Tulsi contains β-carotene, ascorbic acid and Vitamin A which can be a rich source of antioxidants. High phenolic and flavonoid contents of tulsi are accountable for the attenuation of oxidative damage *via* interruption of the free-radical chain of oxidation at initiation or propagation step, probably by donation of a phenolic hydrogen atom to the free radical [25]. Flavanoids orientin and vicenin exhibit radioprotective effects *via* scavenging radiation-induced free radicals [23]. The extract of tulsi has been reported to decrease the formation of lipid peroxidation products, inactivate MMP-9 and increase the body's levels of antioxidant molecules such as GSH and antioxidant enzymes SOD, CAT, GPx, GST, which protect cellular organelles and membranes by mopping up damaging free radicals [22,24,26]. In addition, it has been reported to scavenge the DPPH, superoxide, hydrogen peroxide, nitric oxide, hydroxyl, ABTS radicals, chelate ferrous iron, and reduce ferric ion in a dose dependent manner [20, 27-28].

Extract of tulsi resulted in concentration-dependent cytotoxic effects against human fibrosarcoma cells, reduction in tumor volume of the Sarcoma-180 bearing animals and inducton of apoptosis in human A549 lung cancer cells through down-regulation of Akt (protein kinase B) and ERK phosphorylation, up-regulation of cytochrome C levels in the cytosol, and supressing the expression of antiapoptotic protein Bcl-2 [29,30]. Preclinical studies have also shown that tulsi and some of its phytochemicals eugenol, rosmarinic acid, apigenin, luteolin, β-sitosterol and carnosic acid have therapeutic efficacy in the prevention of chemical-induced skin, liver, oral, and lung cancers by increasing the antioxidant activity, altering the gene expressions, inducing apoptosis (by increasing the proapoptotic proteins Bax, cytochrome *c*, and caspase-3 and enhancing the activity of carcinogens detoxification enzymes such as cytochrome P450 enzymes and cytochrome b5), inhibiting angiogenesis (by decreasing VEGF) and metastasis [26,29]. Eugenol attributes to its anticancer property by inhibiting NF-κB, decreasing the expression of iNOS and COX-2, the levels of proinflammatory cytokines (IL-6, TNF-*α*, and PGE2) to reduce the expression of c-Myc, H-ras, and Bcl-2 [31]. Molecular mechanism of anticancer potential of vicenin-2 in carcinoma of prostate cells (PC-3, DU-145, and LNCaP) is revealed by inhibition of EGFR/Akt/mTOR/p70S6k pathway and thereby decreasing the cMyc, cyclin D, cyclin B1, CDK4 and PCNA [32].

Oxidative stress and inflammation play vital role in the development of myocardial infarction. Anti-inflammatory activity of linolenic acid is due to inhibition of COX and LOX pathways of arachidonic acid metabolism. The high phenolic content of methanolic extract of tulsi leaves is responsible for its cardioprotective effect [33,34]. The complimentary and synergistic medicinal properties of tulsi can combat a diverse spectrum of disorders associated with aging. Recently, CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP), Lucknow, has published first report of complete genome sequence of tulsi [35]. The availability of whole genome sequence is the first move to understand and unravel the secrets of metabolic and therapeutic potential of this revered plant which is the 'mother of all herbs' and hence

to identify the genes implicated in producing therapeutic molecules and for their *in vitro* production.

## 5. Giloy (*Tinospora cordifolia*)

### *5.1 Active components*

The pharmaceutical credentials of giloy or amrita is mainly because the leaves, stem, bark and roots contain bioactive compounds *viz.* alkaloids (berberine, palmatine, tetrahydropalmatine, tembetarine, jatrorrhizine, magnoflorine), diterpenoid lactones (furanolactone, tinosporide, columbin), glycosides (cordifolioside A, B, C, D, E, tinocordifolioside, syringin), sesquiterpenoid, steroids (ecdysterone, makisterone A, β-sitosterol), polysaccharides, amritosides A, B, C and aliphatic compounds (Figure 3) [36,37].

### *5.2 Pharmacological profile*

Scientific studies have shown giloy to possess the properties like anthelmenthic, anti-inflammatory, aphrodisiac, hepatoprotective, brain tonic, blood purifier, immunomodulatory, anti-neoplastic, antioxidant, antituberculosis, antipyretic, anti-osteoporotic, anti-allergic and side effects prevention of the cancer chemotherapy [37-38]. It strengthens the immunity of body by increasing cytotoxic T cells and B cells differentiation, antibody, level of cytokines like IL-2, IL-10 and TNF-α, therefore, this rejuvenating herb is used as an important ingredient in 'Chyawanprash'. Anti-HIV activity of root extract revealed reduction in eosinophil count and stimulation of B lymphocytes and macrophages [39].

Antidiabetic potential of giloy is due to presence of alpha-glucosidase inhibitor characterized as saponarin and mediated through ameliorating oxidative stress and inhibiting gluconeogenesis and glycogenolysis [36]. Oral administration of stem extract (500 mg/kg bw p.o.) in alloxan induced diabetic rats has been found to exhibit antidyslipidemic activity. Stem extract (50-500 μg) inhibited the generation of superoxide anions and hydroxyl radicals in both enzymic and non-enzymic systems *in vitro* [40]. Several alkaloids present in root extract are responsible for its protective action on lipid peroxidation and ability to normalize the concentration of reduced GSH and activity of CAT and SOD [41].

The aqueous or alcoholic extracts of stem, leaves, barks and roots are endowed with natural antioxidants or nutraceuticals which reduce oxidative stress, modulates LOX, COX-2, iNOS, ICAM-1, and pJNK, pro-inflammatory cytokines IL-4 and TNF-α with consequent health benefits and may protect against mutagenesis [38, 42-44]. Giloy has strong free radical scavenging properties as revealed by electron paramagnetic resonance spectroscopy, DPPH assay, ABTS assay, nitric oxide assay, hydroxyl radical scavenging assay, total reducing power assay, $H_2O_2$ scavenging activity assay, metal chelation, and diminishing the expression of iNOS gene, therefore, attenuating oxidative stress mediated cell injury [45, 46]. Hence it may be an effective therapeutic tool against ischemic brain damage [47]. Its antioxidant activity and amelioration of cyclophosphamide-induced toxicity has been reported [48]. Synergetic action of bioactive constituents present in root extract such as quercetin, gallic acid, flavonoids and alkaloids reduces the deleterious effects of gamma radiations in mammals [49]. The anti-cancer potential of aqueous and alcoholic stem extracts of giloy is well established through *in vitro* and *in vivo* studies using different cell lines (HeLa cells, human breast cancer cell lines namely T47-D, MDA-MB-231 and MCF-7) and animal models (C57 Bl mice, Swiss albino mice and Dalton's lymphoma bearing mice) [46,50-52]. Alcoholic extract stimulates macrophage functions like phagocytosis, antigen-presenting

ability and secretion of IL-1, TNF-α as well as induces apoptosis in cancerous cells by activating caspase-3 and Bax and inhibiting Bcl-2, thereby, reducing tumor growth and enhancing survival. Overexploitation due to immense therapeutic implications poses a serious threat to this plant and plant tissue culture techniques may be suitable means for its conservation.

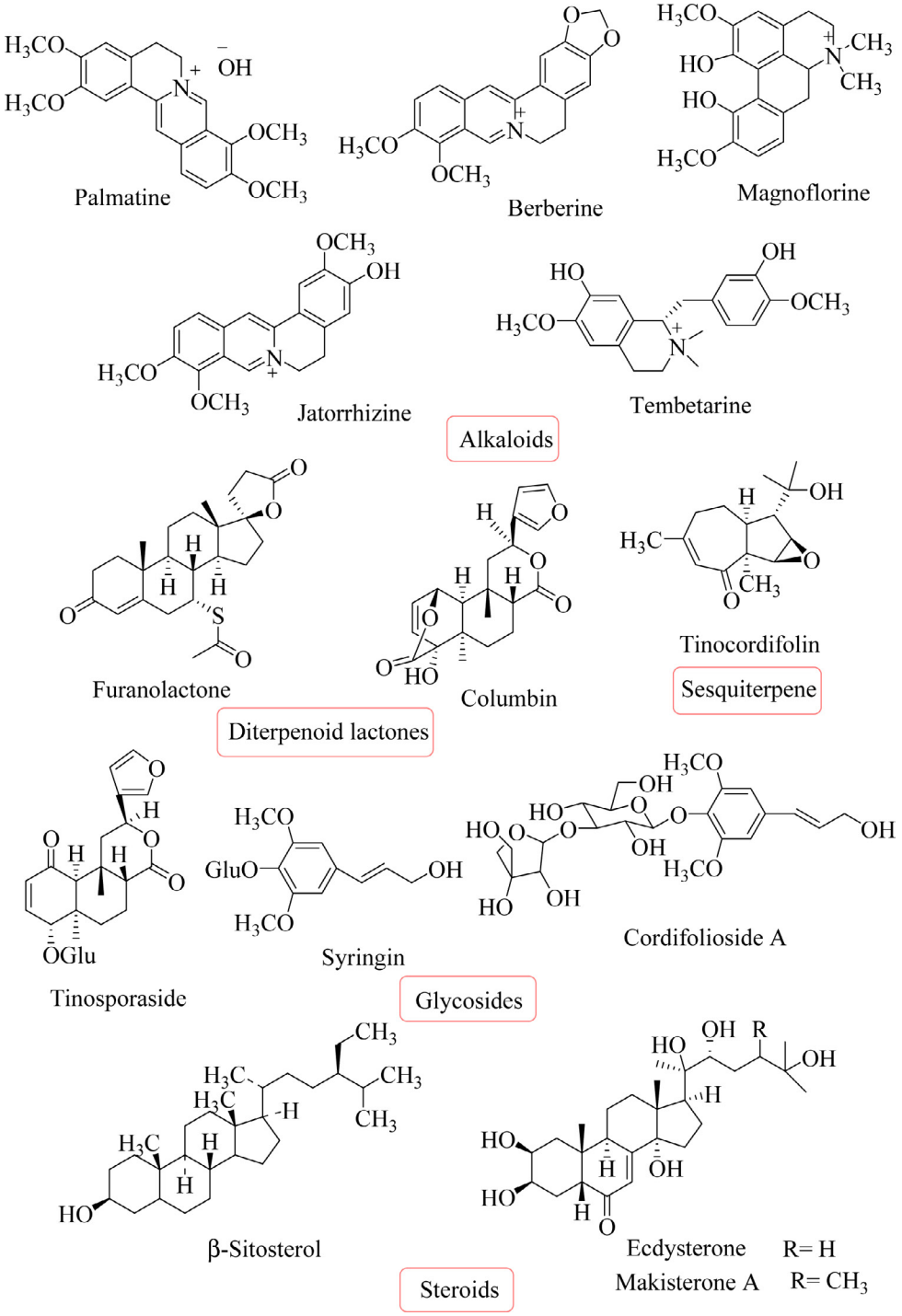



**Figure 3.** Some active components of giloy (*Tinospora cordifolia*).

## 6. Turmeric (*Curcuma longa* Linn.)

### *6.1 Active components*

Turmeric, a common condiment, food preservative and colouring agent, is a perennial herb native to India. Turmeric contains several active ingredients like curcuminoids, essential oils, sugars, proteins like turmerin, alkaloids, steroids, polysaccharides, tannins, saponins, and resins (Figure 4) [53,54].

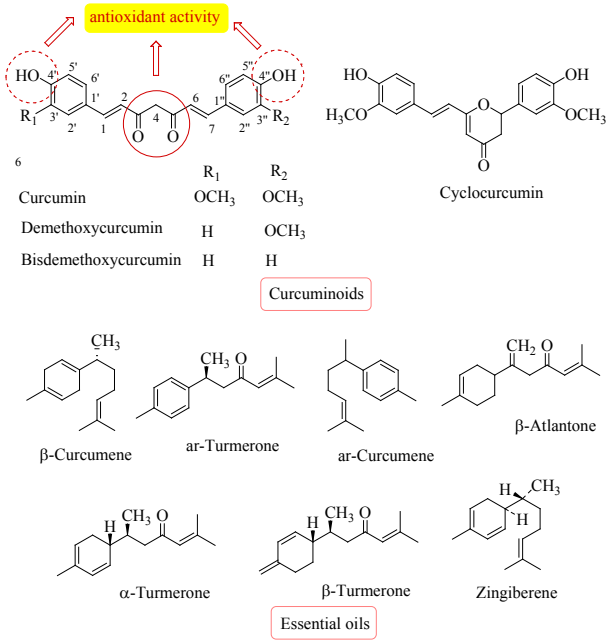



**Figure 4.** Some active components of turmeric (*Curcoma longa*).

### *6.2 Pharmacological profile*

Turmeric is used as a household remedy for inflammatory conditions, skin protection, hepatic disorders, cough, sinusitis, anorexia, rheumatism, biliary disorders, swelling due to injury and wound dressing [54]. *o*-Coumaric acid, protocatechuic acid, syringic acid, vanillic acid present in leaves and essential oils from leaves and rhizomes act as antioxidants and free radicals scavengers in addition to their anti-inflammatory and antimicrobial activities [55-56]. Further, the extracts of *Curcuma longa* also exhibited significant protection to DNA against oxidative damage and act as a free radical scavenger [56]. The compounds isolated from the alcohol extract of turmeric include apigenin-7-*O*-rhamnoside 4′-*O*-glucoside, 7-methoxyapigenin-6-*C*-glucoside and *N*-(3-methoxyphenyl)acetamide and the extract ameliorated the serum glucose, nitric oxide and cytokine levels (IL-6, TNF-α, and IL-1β) in diabetic infected rats with *S. aureus* [57].

Curcumin, a hydrophobic polyphenol, is an extremely pleiotropic molecule capable of interacting with numerous molecular targets [58]. Curcumin mediates anti-inflammatory activity by inducing the expression and production of IL-10 which has ability to reduce PGE2, inhibit the production of pro inflammatory cytokines, angiogenesis and stimulate B cell function [53]. Curcumin is a free radical scavenger and hydrogen donor, which exhibits concentration and chemical environment dependent pro- and antioxidant activities. The antioxidant potential of curcumin is attributed to its ability to donate H-atom from central methylene group flanked by two highly activated carbonyl groups as well as from phenolic hydroxyl group on the phenyl rings to oxidizing free radicals, thereby quenching them [59]. In a study, chain-breaking antioxidant mechanism of curcumin against the oxidation of ethyl linoleate was proposed, which engrosses an oxidative coupling reaction at position-3' of curcumin (Figure 4) with the lipid radical and a subsequent intramolecular Diels-Alder reaction. Moreover, a relatively high concentration of curcumin furnished curcumin dimmers as radical termination product at position-2 of curcumin besides the coupling products between curcumin and the lipid hydroperoxide [60-61]. Antioxidant potential of curcuminoids extracted from rhizomes is revealed by ABTS, FRAP assay, and linoleic acid peroxidation method [62].

The significant hypoglycemic, hepatoprotective,

cardioprotective, antiarthritic, anti-inflammatory, antiangoigenic, antimetastatic and antioxidant activities of turmeric and curcumin may be attributed to their inhibitory effect on activity of transcription factors and their signalling pathways (NF-κB, c-Jun/AP-1 and STAT3) and TNF-α, inflammatory cytokines (CXCL1, CXCL2, IL-1β, IL-2,-6,-8,-12), various kinases (PKC, EGFR kinase, IκB kinase, Akt, MAPKs, FAK), regulation of miRNAs (miR21, miR181b), $Ca^{2+}$ influx, growth factors (such as VEGF), lipid peroxidation, COX-2, 5-LOX, cyclin D1, expression of iNOS gene, overexpression of MMPs and oncogenes [63-65]. Curcumin induced down-regulation of NF-κB activation is mediated through suppression of phosphorylation and degradation of IκB*α* resulting in maintaining bonding of NF-κB with IκB (inhibitor of NF-κB). Inactivated NF-κB /IκB complex is kept in the cytoplasm and not able to enter the nucleus for regulating the expression of a host of genes involved in tumorigenesis, cell proliferation, invasion and angiogenesis.

The anticarcinogenic effects of curcumin in a number of cancer types, including oral, colorectal, pancreatic, gastric, prostate, breast cancers, and leukemia, are due to free-radical scavenging properties, suppression of mutagens *via* suppression of specific cytochrome P450 isozymes, as well as its ability to indirectly increase GSH levels, activate PPAR-γ and up-regulate Nrf-2 for maintaining the activities of phase II antioxidant enzymes (GST, QR, SOD, CAT and GPx) at higher levels, thereby, suppressing cell proliferation and inducing apoptosis [54,64]. Curcumin mediates cytotoxicity in tumor cells *via* induction of apoptosis through regulating various signaling pathways (mitochondria-mediated pathway/ upregulation of caspase cascade/ DR pathways/ JAK-STAT signalling/ PI3K/AKT/PTEN/ FOXO pathway/ NF-κB pathway) and/or arresting tumor cell cycle at the G2/M phase in human melanoma cells, lung cancer cells lines A549 and H460, hepatocellular carcinoma J5, Hep G2, Hep3B, HL-7702, and WCH-17, brain glioblastoma multiforme (GBM) 8401 cells, and monocytic leukemia SHI-1 cells [66-71]. Curcumin induced cell cycle arrest at G2/M phase by downregulation of cyclin B1 and Cdc2 and inhibited colony formation in MCF-7 wt cells [72]. It also stimulates the expression of p53, pro-apoptotic Bax, and procaspases-3, -8, and -9 and decreases the expression of anti-apoptotic Bcl-2.

Various preclinical cell culture and animal studies suggested a potential therapeutic role for curcumin as a mediator of chemoresistance and radioresistance, chemopreventive agent (in azoxymethane (AOM)-induced colon carcinogenesis, 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted skin tumor formation) and therapeutic agent in inflammatory bowel disease, diabetes, neurodegenerative diseases, cardiovascular disease, pulmonary disease and arthritis [73]. Moreover, curcumin in combination with ellagic acid has been reported to synergistically restore p53, induce ROS formation and DNA damage leading to apoptotic cell death in HeLa cervical carcinoma cells [74]. Curcumin in combination with 5-fluorouracil and oxaliplatin act synergistically in human gastric cancer cell line BGC-823 both *in vitro* and *in vivo* by inducing apoptosis *via* Bcl/Bax-caspase 8,9-caspase 3 pathway [75]. *In silico* analysis demonstrated that curcumin, by interacting with six amino acids has stronger binding affinity than bis-demethoxycurcumin to transthyretin protein whose dissociation is involved in the Alzheimer's disease progression, could be lead molecule for the treatment of Alheimer's disease [76]. Owing to safety property of curcumin even at high doses (12g/day) assessed by clinical trials in human, it was used as a potential lead compound to design the new anticancer agents with modified and increased anticancer activities through the

synthesis of its various novel derivatives [77]. Recent advances are focused on complexing curcumin with other substance, formulations (liposomes, micelles, curcumin nanoconjugates with metal and metal oxide) to increase its bioavailability and some of these formulations have promising potential in nanomedicine.

## 7. Ashwagandha (*Withania somnifera* (L.) Dunal)

### *7.1 Active components*

Ashwagandha, popularly known as Indian Ginseng, is the most valued herb in Ayurveda and indigenous system of medicine for over 3000 years for its adaptogenic, potent aphrodisiac, rejuvenative, life prolonging properties and also for the treatment of arthritis and menstrual disorders [78]. It is endowed with alkaloids (somniferine, visamine, hygrine, choline, scopoletin, withanine, somnine, tropine, cuscohygrine, withananine, anaferine, anahygrine, pseudotropine, 3α-tigloyloxytropane, ashwagandhine, pseudowithanine), steroidal lactones (withanolide-A, withanone, withaferine-A, ashwagandhanolide, 27-hydroxywithanone, withanolide D, physagulin), amino acids, phenolic compounds, flavonoids, tannins and saponins containing an additional acyl group (sitoindoside VII and VIII), withanolide glycosides (sitoindoside IX and X), glycowithanolides (sitoindoside VII to X) etc (Figure 5) [79-80]. 2,3-Dihydrowithaferin A-3β-*O*-sulfate is one of the unusual withanolides present in soil-less aeroponically grown ashwagandha leaves and twigs [81].

### *7.2 Pharmacological profile*

The herb is said to have diverse biological activities *viz.*, antitumor, antioxidant, anti-inflammatory, anti-stress (reducing cortisol), cognition-facilitating, sedative, antimicrobial, immunomodulatory, anti-epileptic, thyrotropic, anti-aging, anticarcinogenic and neuroprotective activities [82]. Its effectiveness as an immunoregulatory and chemoprotective agent is due to enhancement of white blood cells and platelet counts. The antioxidant and anti-apoptotic properties of ashwagandha may contribute to its cardioprotective effects in ischemia and reperfusion injury by upregulating the expression of anti-apoptotic protein, Bcl-2 and downregulating Bax [83]. It acts as a useful adjuvant for irradiation therapy and chemotherapy for cancer patients due to its chemopreventive properties.

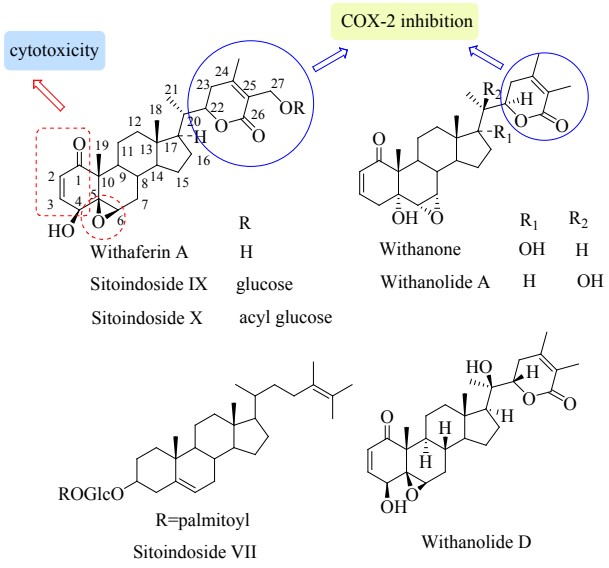



**Figure 5.** Some active components of ashwagandha (*Withania somnifera*).

Ashwagandha extract exhibited cytotoxicity in prostate cancer cell line (PC3) with $IC_{50}$ value of 10 µg/mL and irreversibly arrested the cell cycle in G2/M phase besides inhibiting the expression of IL-8 and COX-2 [84]. Withaferin A, one of the foremost active constituent present in roots and leaves of ashwagandha, acts as pro-apoptotic, anti-invasive (through suppression of MMP9 expression in cervical cancer (Caski) cells and hepatic adenocarcinoma (SK-Hep1) cells) [85] and anti-angiogenic agent [86], which highlights

the potential use of this natural product and its analogues for cancer treatment or prevention. The anticancer activity of ashwagandha has been attributed to suppression of NF-κB by direct binding to key cysteine residues of IKKβ [87], intercellular TNF, down-regulation of Akt phosphorylation [85], inhibition of STAT3 [88], notch-1 signaling [89], stabilization of p53 [88], and covalently modifying the cysteine residue of intermediate filament protein vimentin [90]. Withaferin A showed antiproliferative activity against human umbilical vein endothelial cell (HUVEC) *via* ubiquitin-mediated proteasome pathway [86], against head and neck carcinoma cell (MC3 and HN22) lines by inducing apoptosis accompanied by upregulation of Bim, t-Bid, caspase-8, and DR5 [91], against cervical cancer cells Caski ($IC_{50}$ 0.45 ± 0.05 *m*M) *in vitro* and in athymic nude mice (8 mg/kg WA, i.p. treatment for 6 wks resulted in 70% reduction in tumor volume compared to controls) *in vivo* by repression of HPV E6 and E7 oncoproteins and HCT116 cells xenograft tumors in nude mice by suppressing the STAT3 transcriptional activity [88] and against human breast cancer cells (MDA-MB-231 and MCF-7) *in vitro* by inducing ROS mediated paraptosis (cytoplasmic vacuolation-mediated cell death) [92], by modulating the epigenetic events of gene silencing [93] and *in vivo* by inducing apoptosis (4 mg/kg WA, i.p. 5 times treatment for 2 wks resulted in reduction in tumor weight in nude mice compared to controls) [94].

Ashwagandhanolide, a dimeric thiowithanolide, exhibited growth inhibitory effect on CNS cell line SF-268 along with colon (HCT-116), lung (NCI-H460), human gastric (AGS), breast (MCF-7) cell lines, with $IC_{50}$ values in the range 0.43-1.48 μg/mL [95]. Structure-activity relationship analysis of withanolides revealed that 2-en-1-one in ring A and 5β, 6β-epoxide moiety in ring B are essential for withanolides to remain biologically active (Figure 5) [96,97]. Conversion of epoxide rings into thiiranes, amino alcohols and alcohols resulted in moderate reduction in the cytotoxicity of withaferin A type against cancer cell lines. On the contrary, alcohol derivatives of withanones have shown some improvements in cytotoxicity, which were otherwise inactive [97]. Its pleiotropic therapeutic effects in signaling pathways implicated in oncogenic processes may be due to presence of α,β-unsaturated carbonyl moieties in its structure which can act as a Michael acceptor to inhibit kinases *via* electrophilic covalent targeting of cysteine residues.

Bioinformatics-based molecular docking analyses also demonstrated that withaferin-A strongly binds p53 and its target gene product p21, thereby accounting for tumor cell apoptosis [98]. A computational approach predicted that withanone present in alcoholic extract of leaves elicits anticancer activity by blocking the intermolecular hydrophobic interactions between TPX2 and Aurora A**.** In the same report, withanone has been reported to inhibit cancer cell division by inactivating the oncogenic Aurora A-TPX2 kinase complex and disrupting the mitotic spindle formation [99].

The significant anti-inflammatory and antioxidant effect of ashwagandha may be ascribed to presence of withanolides and its inhibitory effect on the lipid peroxidation, nitric oxide and COX-2 expression (due to presence of double bond in α,β-unsaturated δ-lactone moiety in ring E, Figure 5), iNOS gene expression, downregulation of IL-6, IL-1β, stimulation of Nrf-2/HO-1 pathway and subsequent downregulation of NF-κB [80,100]. A recent study reported that leaf water extract of ashwagandha and one of its active chloroform fractions suppressed the proliferation of activated microglia by causing cell cycle arrest at Go/G1 and G2/M phase [101]. Its effectiveness in MB-PQ induced mouse model of Parkinson's disease is due to increase in dopamine levels in

the substantia nigra and modulation of oxidative stress [102].

The roots of ashwagandha are good source of nonenzymatic (phenolic acids, flavonoids, alkaloids, ascorbic acid, tocopherol and GSH) and enzymatic antioxidant components. Administration of active principles of ashwagandha such as glycowithanolides and equimolar concentrations of sitoindosides VII-X and withaferin A, were found to increase the levels of SOD, CAT and GPx in rat brain [103,104]. Oral administration of a semi-purified extract of root having withanolides and withanosides predominantly reversed behavioral deficits, plaque pathology, accumulation of Aβ and oligomers in the brains of middle-aged and old APP/PS1 Alzheimer's disease transgenic mice [105]. Different parts of ashwagandha were evaluated for their antioxidant potential using different antioxidant assays such as ABTS, DPPH radical scavenging assay, reducing power assay and metal ion chelating activities [106]. Availability of the transcriptomes from ashwagandha provides a framework for future research in proteomics and evolutionary genomics in the withanolide biosynthesis [107].

## 8. Aloe vera (*Aloe barbadensis* Miller)

### *8.1 Active components*

*Aloe vera*, the healing plant, has been used in Indian traditional medicine for its health, medicinal and skin care properties since times immemorial and currently as tissue engineering material, cosmeceuticals and nutraceuticals [108,109]. The marvelous medicinal properties are due to over 200 pharmacologically active ingredients which are concentrated in both the gel and rind of the aloe vera leaves [110]. These include anthraquinones (aloin/ barbaloin, isobarbaloin, *aloe*-emodin, emodin, aloetic acid, anthranol, ester of cinnamic acid, chrysophanic acid), chromones (aloesin, 8-*C*-glucosyl-7-*O*-methylaloediol A, 8-*C*-glucosyl-noreugenin, isoaloeresin-D, iso-rabaichromone, neoaloesin-A), glucoside aloenin, lignin (capacity of penetrating the human skin), saponins (antiseptic property), minerals (calcium, zinc, selenium), vitamins (Vit A, C, E, B1, B2, B6, B12 and choline), amino acids, enzymes (oxidases, catalase, bradykinase, lipase, cellulase, carbxypeptidase, amylase, alkaline phosphatase), flavonoids, terpenoids, proteins (lectins), fatty acids, mono and polysaccharides (pectins, hemicelluloses, glucomannan, acemannan, polymannans and mannose derivatives), complex mucopolysaccharides, tannins, sterols (lupeol, campesterol, β-sitosterol), salicylic acid and organic acids (Figure 6) [108].

### *8.2 Pharmacological profile*

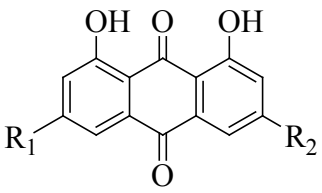
Apart from anticancer and anti-inflammatory activities, aloin exhibits antiviral activity against several viruses such as herpes simplex, varicella zoster and influenza [111]. *Aloe*-emodin (5-20 μmol) protects RIN-5F cell from glucotoxicity by decreasing ROS generation and significantly improved cell viability in a dose and time dependent manner by decreasing apoptotic genes (Bax and caspase-3) and increasing Bcl-2 expression [112]. *Aloe*-emodin, a natural hydroxyanthraquinone compound, exhibited immunomodulatory activity through GM-CSF and IFN-γ production and anticancer activity in BRAF-mutated human melanoma cells [113]. *Aloe*-emodin is inhibitor of angiogenesis and its potential as a photosensitizer in photodynamic therapy (PDT) has been delineated *via* apoptosis in breast cancer MCF-7 cells [114] and also in human gastric cancer cells (SGC-7901) where it exhibited inhibitory effect on the proliferation of SGC-7901 in dose-dependent and energy-dependent manners [115]. It also inhibited colon cancer cell migration by downregulating MMP-2/9 and inhibiting ras a homolog family

member B and VEGF *via* reducing DNA binding activity of NF-κB [116]. *Aloe*-emodin possesses remarkable anticancer activity against T24 human bladder cancer cells through the p53 dependent apoptotic pathway [117]. Emodin has been reported to induce apoptosis in human tongue squamous cancer SCC-4 cells through ROS and mitochondria-dependent pathways [118] and suppress breast cancer cell proliferation through estrogen receptor-α inhibition [119].

Role of *aloe vera* as anti-inflammatory agent is due to its inhibitory effect on COX pathway and PGE2 production [111]. Lupeol, is effective in reducing inflammation in a dose dependent manner. Enzyme bradykinase stimulates immune system, acts as analgesic and decrease inflammation and swelling. Glucomannan and acemannan can accelerate wound healing (by reducing inflammation and promoting the proliferation of fibroblasts and collagen), activate macrophages, stimulate the synthesis and release TNF-α, increase T cells and exhibit antitumor, antioxidant, antiviral and immune stimulating effects [120]. A report revealed that polysaccharides isolated from aloe vera gel exhibited a protective effect against 2,2'-azobis(2-amidinopropane) dihydrochloride-induced oxidative stress and cell death in kidney epithelial cells (Vero cells) as well as in an *in vivo* zebrafish model [121]. Furthermore, the antioxidant potential of *aloe vera*'s polysaccharides is dependent upon the concentration of the molecule and the degree of acetylation of the monomeric units [122]. High polysaccharide concentrations (>8 mg/mL) and increased acetylation enhances its antioxidant potential. Phytosterols are the source for *aloe*'s effectiveness in treating all kinds of internal and external inflammations and type 2 diabetes mellitus [123].

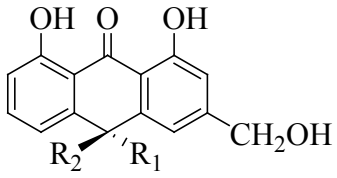
Traditionally, *aloe vera* gel is used topically (remedy against a variety of skin disorders such as skin exposure to UV, gamma and x-rays, cuts, burns, eczema, psoriasis, sunburn, acne and dermatitis) and internally to treat most digestive problems, including constipation, colitis, irritable bowel syndrome as well as ulcers, jaundice, diabetes, headaches, coughs, fever, arthritis and immune-system deficiencies [124]. It acts as a natural fighter against all sorts of infection and effective in vitiated conditions of pitta, rheumatism pain, asthma, cancer and fighting acquired immune deficiency syndrome (AIDS). Leaf exudates and mucilaginous gel of *aloe vera* possesses anti-inflammatory, antitumor, moisturizing, antimicrobial, antiviral (against herpes simplex virus type 2 strain), antioxidant, antidiabetic, antihyperlipidemic, cytoprotective, cardiac stimulatory, anti-aging activities [125]. Immunomodulatory activity of gel is attributed to downregulation of lipopolysaccharide-induced inflammatory cytokine production and expression of NLRP3 (NACHT, LRR, and PYD domain-containing protein 3) inflammasome in human macrophages [126]. Gel also accounted to have a potential anti-parkinson effect in mice [127]. Gel and whole leaf extract possess the ability to improve the drug absorption and bioavailability of co-administered vitamins in human subjects [128].

Phytochemical analysis of aloe vera extract by HPTLC indicated that the plant extract are rich in phenol, flavonoids, berberine and gallic acid implying their importance to human health [129]. *Aloe vera* leaf extract possesses antioxidant and cardioprotective activity, which may be attributed to its protective action on lipid peroxidation and to the enhancing effect on cellular antioxidant defense contributing to the reduction of azoxymethane-induced oxidative stress and reduction of oxidative stress in streptozocin induced diabetic rats [130-132]. A noteworthy rise in reduced GSH, SOD, GPx and GST in the liver of the treated rat was observed [132]. *Aloe vera* gel has a concentration



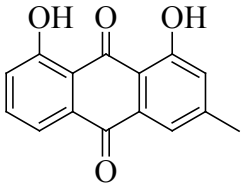

Aloe-emodin $R_1$=H, $R_2$=$CH_2OH$

Emodin $R_1$=$CH_3$, $R_2$=OH

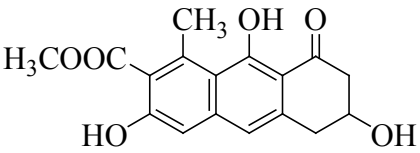



Aloin A $R_1$= H, $R_2$= C-glc

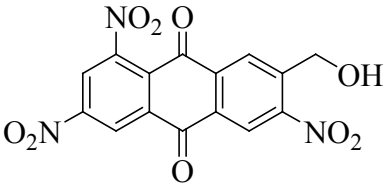
Aloin B $R_1$= C-glc, $R_2$= H




Chrysophanic acid (Chrysophanol)

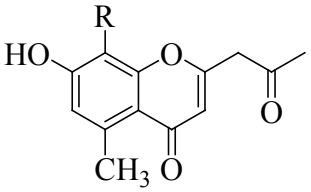



Aloesaponol I (Anthranol)




Aloetic acid

Anthraquinones/ anthrones

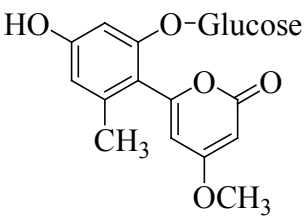



Aloesone R= H

Aloesin R= Glucose

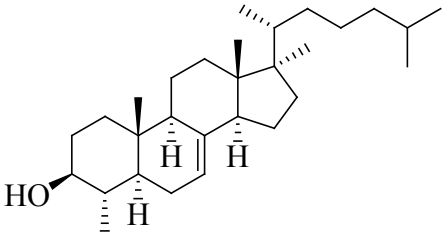
Aloresin A R= Glucose-O-*p*-coumaroyl

Chromones

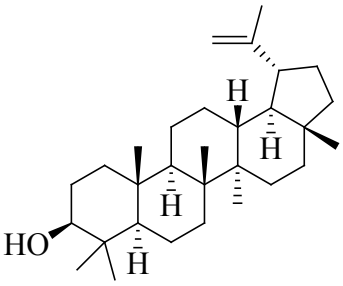



Aloenin

Glucoside




Lophenol




Lupeol

Sterols

**Figure 6.** Some active components of aloe vera (*Aloe barbadensis*).

dependent antioxidant effect as seen in an *in vitro* study of its radioprotective efficacy [133]. This observation demonstrates the prooxidant property in addition to its antioxidant property [134]. *Aloe*-emodin exhibits antioxidant action at lower concentrations, however, acts as a prooxidant at high concentrations. In contrast, aloin has an antioxidant effect at higher concentrations, however, a prooxidant effect at low concentrations. Aloin has been optimized by using natural amino acids to produce Schiff's base and modifying it into its corresponding aglycons to enhance the utility of this compound. The synthetic glycoside derivative disclosed significant enhancement of antioxidant and cytotoxic efficacy compared to that of the parent compound, aloin, showing potential for application in cancer treatment [135]. The antioxidative properties of extracts of *aloe vera* gel were revealed by DPPH radical, ABTS radical, nitric oxide, superoxide anion radicals scavenging, metal ion chelation, reducing power, hydroxyl radicals scavenging and total antioxidant activity [136].

The antioxidant/prooxidant activities of many of *aloe vera*'s phytochemicals are dependent not only on their individual levels, but also on the ratios of various components, and on their individual redox states [137]. Some reports also illustrate adverse effects and carcinogenicity of *aloe vera* whole leaf extract, gel and latex [138].

## 9. Conclusion

Indian herbs *viz.* tulsi, giloy, turmeric, ashwagandha and *aloe vera* as sources of inherent antioxidants play a vital role in combating oxidative stress by limiting the ROS formation to maintain redox balance and cellular integrity. Growth constraints, variation in biochemical composition, extraction techniques and solvent employed are the key players for the disparities in result regarding their therapeutic claims. Due emphasis has to be given to scientific approaches in screening bioactive components, studying pharmacokinetic-dynamics, efficacy and potency testing, docking and molecular dynamics simulations to probe binding interaction on the molecular targets, scientific validation using various innovative experimental models and clinical trials to understand mechanism of action for exploring immense potential of herbs. Furthermore, future perspective with a vision to counter the emerging antimicrobial resistance and to find promising leads for the discovery of potent antioxidants that can universally have therapeutic and dietary uses, we should promote and popularize herbs to ensure a step towards a clean and green earth.

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