Herbal Remedies for Improving Cancer Treatment Through Modulation of Redox Balance

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Abstract

The redox modulation induced by oxidative stress is one of the major cause of the metabolic and inflammatory disorders including cancer. The reactive oxygen species (ROS) produced by various sources in the cell shift the redox homeostasis of cells towards more oxidizing or acidic environment. This shift results in the alterations of normal physiologic functioning of biomolecules as well as causes damage to these biomolecules (proteins, lipids, and DNA/RNA). The excessive ROS and redox modulation are the key factors that support growth, progression, and survival of cancer cells. ROS-induced redox modulation further activates pro-tumorigenic cellular pathways for e.g., PI3K/AKT, HIF-1, and MAPK signaling pathways as well as hinders epigenetic signaling. Increasing evidences demonstrate that long-term side effects of anti-cancer chemotherapy are major concern of medical sciences although modern treatments are quite effective. The combination of various herbal formulations with anti-cancer therapy

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S. Chakraborti (ed.), *Handbook of Oxidative Stress in Cancer: Therapeutic Aspects*,
https://doi.org/10.1007/978-981-16-5422-0_270

shows improvement in treatment effectiveness in cancer patients. Bioactive compounds present in herbal formulations possess antioxidant and anti-cancer properties that help in the regulation of redox status of cancer cells. The synergetic effects of herbal remedies along with conventional treatment are proven as novel therapeutics in cancer progression management. Clinical studies have shown that broad range of herbs and bioactive compounds from various plants having antioxidant, anti-inflammatory properties can suppress the carcinogenesis. In this chapter we will discuss the role of various plants such as *Glycyrrhiza glabra*, *Picrorhiza kurroa*, *Tinospora cordifolia*, *Curcuma longa, Ocimum sanctum, Viola odorata,* and bioactive compound ferulic acid found in various cereals. The chapter will also focus on various mechanisms involved in the modulation of chemo-toxicity and improvement of efficacy of conventional anti-cancer therapies by these plants.

Keywords

Cancer · Oxidative stress · Redox modulation · Herbal formulations

Introduction

In current times, cancer is considered as toughest challenge in medical sciences and is accountable for nearly 10 million deaths worldwide with the detection of nearly 19.3 million new cases per year (Sung et al. 2021). It is crucial to understand the causes as well as mechanism of drug resistance for effective treatment. The regulation of redox homeostasis is anticipated as an important factor to manage characteristics of cancer such as migration, invasion, metastasis, and colonization. The increased production of free radicals, i.e., superoxide ions, hydroxyl ions induces the proliferation signals in cancer cells which results in increased growth of cancer cells (Kumari et al. 2018). The cancer cells use internal microenvironment to sustain their development by activating the sources of free radical production. NADPH oxidases (NOX) are highly expressed in various types of cancers and NADPH oxidase induced ROS production is linked with release of inflammatory molecules and a condition of chronic inflammation in cancer cells (Lu et al. 2020). Further NADPH oxidases derived oxidative stress causes damage to proteins, lipids, and DNA/RNA (Weyemi et al. 2013). Cancer cells also target glucose metabolic pathways and increase its uptake by aerobic glycolysis making them more resistant to tumor suppression and apoptosis. Aerobic glycolysis also contributes to drug resistance during anti-cancer therapy (Lin et al. 2019).

Redox Status in Normal Healthy Cells

The redox status of the cell varies with cell to cell, is simplified by comparing the state of the normal healthy cell with the early and advanced stage of a cancer cell

based on antioxidant and oxidative stress levels. The levels of antioxidants continuously diminish as progress from early to the advanced stage of cancer occurs and the oxidative stress keeps on increasing (Miao et al. 2014). Glutathione, thioredoxin reductase/thioredoxin (TR/TRX), superoxide dismutase, catalase as well as other extrinsic factors like Vitamin C, carotenoids, and selenium neutralize the ROS and maintain the redox homeostasis. Glutathione is the most abundant thiol compound which protects the cell from oxidative damage. It is found in both oxidized and reduced forms, the reduced form of glutathione acts as an antioxidant which counteracts the effect of ROS-induced oxidative stress and gets converted into oxidized form which drives the cell toward normal condition. In a healthy cell, the glutathione reductase enzyme is upregulated which recycles the reduced glutathione from used oxidized glutathione (Gibson et al. 2012). Glutathione not only protects the cell from ROS but also eliminates the detoxified oxidative products from the cell. In the presence of abundant free radicals, thioredoxin (TRX), an important redox protein gets activated and translocates to the nucleus to switch on the nuclear redox-signaling pathway Ref-1 which further initiate the activation of genes to protect the cell from oxidative stress and nullify mutation in both glutathione reductase and thioredoxin reductase gene leads to accumulation of chronic oxidative damage (McLoughlin et al. 2019).

The crucial metalloenzyme which acts as a first-line defense against the ROS-mediated cell damage is superoxide dismutase (SOD) which has three forms, Copper/zinc-containing members, CuZnSOD (SOD1), extracellular SOD (EcSOD) and Manganese-SOD (MnSOD). CuZnSOD also known as SOD1 that is present inside the cytosol, mitochondrial inner membrane space, and nucleus; MnSOD also known as SOD2 is found predominately in the mitochondrial matrix, and EcSOD also known as SOD3 is localized in extracellular space (Griess et al. 2017). These enzymes catalyze the conversion of superoxide anion free radicals ($O_2^{\cdot -}$) which otherwise can damage the cell (Yasui and Baba 2006).

Catalase is a heme-containing homo-tetrameric enzyme which protects the cell from H_2O_2 mediated cellular injury by converting it into water and oxygen. In mitochondria, both ROS production and its elimination are tightly regulated by the above-mentioned proteins. The mitochondrial inner membrane contains multi-subunit protein complexes which transfer electrons from NADH (via complex-1) and $FADH_2$ (via complex-2) to complex-4 through complex-3 where these electrons helps combing hydrogen ion (H^+) and molecular oxygen to form water. Under stress conditions, premature electron leakage produces superoxide further leakage of electrons from complex-1 and 2 moves superoxide toward the mitochondrial matrix, but complex-3 drives it towards both inter membrane space and mitochondrial matrix. The superoxide is then converted into hydrogen peroxides by SOD1 and SOD2 in inter-membrane space and mitochondrial matrix, respectively. The superoxide which reaches cytosol from inter-membrane space via voltage-dependent anion-selective channels (VDAC) is also converted into H_2O_2 by SOD1 in the cytosol. Further, H_2O_2 is detoxified by catalase and glutathione peroxidase into water and oxygen in the cytosol and mitochondrial matrix, respectively. Hence,

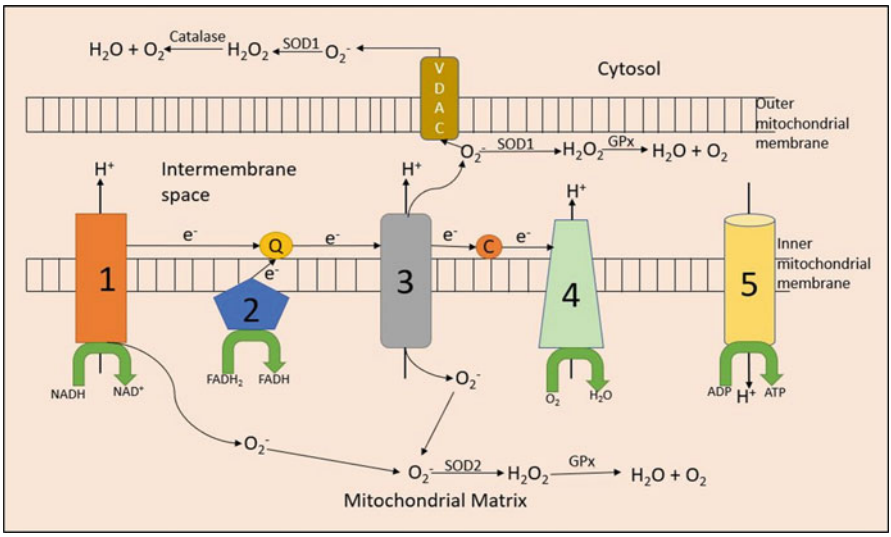

Fig. 1 Role of intracellular antioxidants in maintaining redox homeostasis

the antioxidants work in collaboration to maintain the redox status of the cell (Fig. 1).

Apart from the internal factors, some extrinsic factors also alleviate the oxidative stress in healthy cells where the free radicals in presence of radicals' scavengers gets stabilized. Water-soluble Vitamin C acts as a strong antioxidant by donating its electrons to free radicals to deactivate their reactivity. Vitamin C protects the DNA damage induced by ROS and also combats the oxidative damage caused by pesticides and heavy metals. Carotenoid also acts as an antioxidant in a normal cell, but can also be pro-oxidant in the cancer cell and enhance ROS-mediated cell death in the cancer cell. The treatment of ROS-inducing cytotoxic drugs, i.e., anthracycline along with carotenoids reduces the effect of the cytotoxic drug on normal cells (Shin et al. 2020).

Redox Modulation in Cancer Cells

An imbalanced redox status of a cell creates a cancerous microenvironment inside the cell. The mitochondrial ROS play a beneficial role in cancer progression by the activating transcription factor hypoxia-inducible factor 1 (HIF1) which helps cancer cell to survive under low oxygen condition (Fig. 2) (Ivanova et al. 2013). HIF1 further activates vascular endothelial growth factor-A (VEGF-A) which provides the blood supply to the metastatic cancer cell (Verma et al. 2021). The angiogenic factor IL-8 and collagenase MMP-1 enhance the angiogenic growth within the tumor microenvironment (Ushio-Fukai and Nakamura 2008). ROS produced by NADPH oxidases (NOX) which has seven subunits ranging from NOX1–5, DUOX1, and

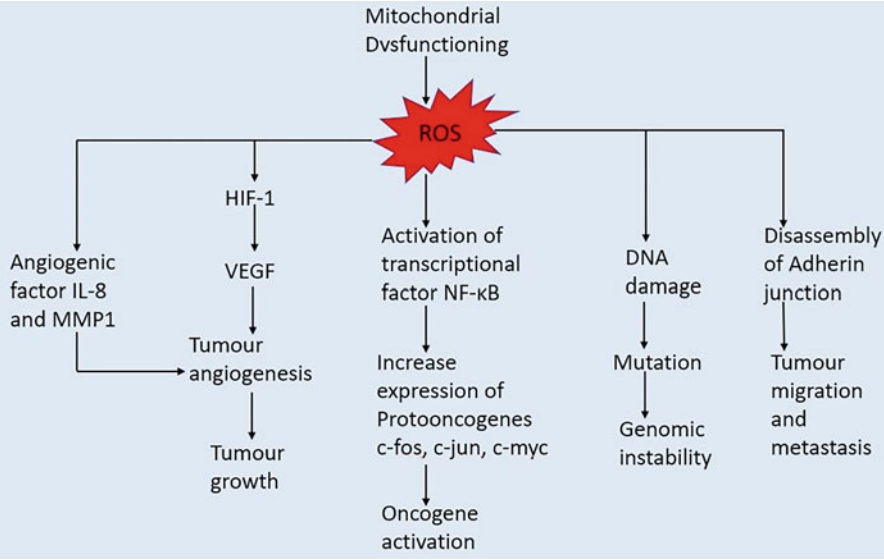

Fig. 2 Mitochondrial dysfunction in imbalanced redox status

DUOX2 is involved in tumor progression. The role of NOX 1–3 and 5 is in the production of superoxide, whereas NOX4 and DUOX 1 and 2 are involved in the formation of H_2O_2 by transferring the electrons from NADPH to reduce oxygen to form superoxide anion and hydrogen peroxide.

ROS activate transcription factor NF-κB by intracellular signaling pathways and enhance the expression of proto-oncogenes such as c-fos, c-jun, and c-myc (Fig. 2). In cancer cell, ROS are involved in metastasizing the cancer cell to the peripheral parts of the body. ROS production in cancer cell occurs by interaction of cell surface receptor with growth factor or by integrin assembly via modulating mitochondrial metabolic function or by NOX activation. ROS disintegrate adherin junction which further helps in cell migration and metastasis (Lee and Kang 2013). The ROS hence produced are involved in the oxidation of lipids, proteins, DNA, and RNA to cause genomic instability, mutation, oncogenic activation and finally cause carcinogenesis (Skonieczna et al. 2017).

It is also reported that ROS are involved in the oxidation of DNA, especially at adenine and guanine to form 8-oxo-A and 8-oxo-G, respectively. The oxidation of DNA by ROS at guanine in cancer cell is 30–50% more than that of normal cell and 8-oxo-G pair up with adenine instead of cytosine which causes the transversion of GT suggesting ROS-mediated mutagenesis and tumorigenesis. ROS leads to the leakage of Ca^{2+} from the mitochondria via lipid peroxidation that in turn stimulates protein kinase C (PKC) required for cancer cell proliferation, differentiation, survival and metastasis via affecting/inducing activation of HIF-1alpha that further regulates cancer progression genes (Perillo et al. 2020) (Fig. 3).

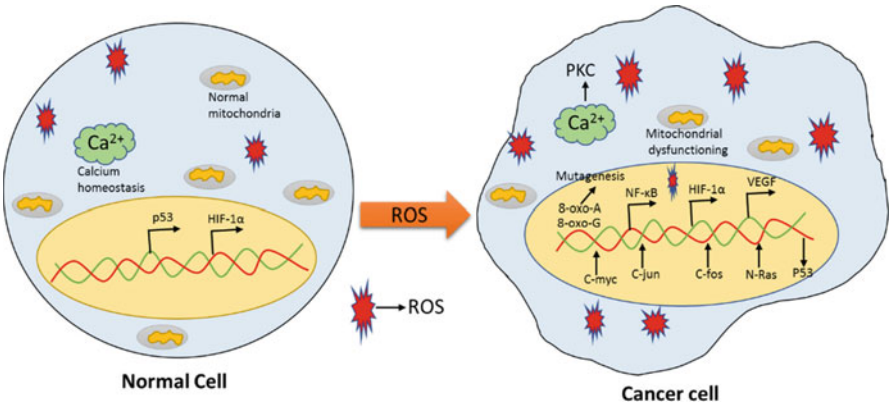

Fig. 3 Transformation of normal cell to cancer cell

Cancer Treatment

Till late 1960, surgery was the only treatment option for cancer and then radiation/chemotherapy was introduced to control the cancer progression. The effectiveness of treatments (surgery and chemo/radiation therapy) is not specific and is associated with numerous side effects to the normal cells and tissues. Considerably, these therapies target the cancer cells as well as healthy cells and result in consequent side effects such as loss of hair, acidosis, nausea, etc. (Falzone et al. 2018). The conventional treatment also makes the patient immune compromised more prone to infections. Chemotherapeutic drugs for, e.g., doxorubicin, cisplatin, crizotinib, and docetaxel, are widely used for cancer treatment and these drugs develop resistance against cancer which is another major limitation of chemotherapy. These drugs also induce toxicity in kidneys, liver, and heart which may result in other serious ailments (Upadhyay et al. 2021). Nowadays the biological and immune mediated interventions are being practiced to treat cancer effectively; these are quite promising therapies which lowers the risk of mortality. In recent times, naturally occurring herbs and phytochemicals have been presented as potential adjuvant therapies against cancer cell proliferation (Pucci et al. 2019).

Herbal Remedies as Adjuvants in Cancer Treatment Therapy

The possibilities of reoccurrence of cancer, toxicity, and drug resistance are key challenges of anti-cancer therapies due to which other promising anti-cancer treatment interventions with enhanced efficacy and low side effects are required.

Literature indicates that herbal remedies or formulations are effective in cancer prevention. The mode of action of these herbal remedies in the regulation of redox-signaling pathways plays crucial role in cancer growth and progression. These plant based remedies particularly improve the antioxidant status of the cancer cells, inhibit

proliferation by enhancing apoptotic cell death, and normalize the triggered inflammatory responses.

Some ancient herbs such as curcumin, tulsi, and mulethi are few most common in Indian Ayurveda system due to their tremendous novel properties. Curcumin (*Curcuma longa*) also known as Indian saffron is an ancient herb which is being used in India from 4000 years as a traditional medicine and culinary spice (Nair 2019). Tulsi (*Ocimum sanctum*) is considered as holy plant in India and being used in Ayurvedic system for more than 3000 years. Tulsi possesses healing properties to treat numerous complex health conditions (Jamshidi and Cohen 2017). Mulethi (*Glycyrrhiza glabra*) is also more than 4000 old herb and known as grandfather of herbs due its revaluating properties (Pastorino et al. 2018). Beside these three major ancient herbs, kutki (*Picrorhiza kurroa*) and Viola (*Viola odorata* or sweet violet) are quite famous herbs in Indian Ayurveda system for their curative assets since past times (Fazeenah and Quamri 2020; Raina et al. 2021). Another herb, Guduchi (*Tinospora cordifolia*) has scared place in Hindu mythology and commonly known as elixir of heaven is used to treat fever and common infections. A phytoconstituent, Ferulic acid, is chiefly found in pulses, vegetables, fruits, and coffee beans; known to be effective in modulating neurodegenerative diseases and cancer (Kaur et al. 2018). The detailed possible mode of actions of these herbs in cancer cells will be discussed in the present chapter.

Curcumin (*Curcuma longa*)

C. longa is an indigenous plant of south-eastern and southern tropical areas and root is the major part of this plant used as turmeric that belongs to the Zingiberaceae family. Turmeric is vastly used in food preservation, flavoring, and coloring in daily activities; apart from this, turmeric is also used as an ancient traditional medicine for pain-relieving and wound healing (Kong et al. 2021). It is hydrophobic in nature and is soluble in alcohol, oil, and acetone. Curcumin also termed diferuloylmethane which is a low molecular weight polyphenol that is a major component of turmeric. Curcumin restores the antioxidant status and attenuates the oxidative stress responses in pesticide induced neurotoxicity in neurodegenerative diseases (Sarkar et al. 2017).

It is crucial to understand the molecular alteration that plays a vital role in cancer development and progression is important for cancer prevention and treatment. Several strategies can target specific tumor cells and inhibit their progression without any severe side effects. Curcumin and its derivatives have potential as an effective anti-cancer therapy due to their multifunctional properties, while curcumin is naturally derived, but its derivatives can be produced through chemical reactions.

Dimethylcurcumin is a derivative that enhances the degradation of androgen receptors thus can be used to treat prostate cancer. The scanning of 50 curcumin analogue showed that changing seven carbon linker to five carbon linker improves the anti-androgenic activity, curcumin mainly exhibits its mechanism of action by inducing apoptosis and inhibiting the invasion and proliferation of tumor by suppressing a variety of signaling pathways (Tomeh et al. 2019).

MCF-7 and MDA-MB-468 breast cancer cells when treated with curcumin, the Ras-association domain family one isoform A (RASSF1A) was increased and prevents tumorigenesis and promotes apoptosis. It was also found that curcumin treatment upregulates the Bax level that can induce apoptosis. Autophagy or type II cell death is another path of cell death that is associated with curcumin. Mechanistic target of rapamycin (mTOR) activation controls autophagy in cancer cells and curcumin deactivates this regulation by deactivation of phosphoinositide 3-kinase/AKT/mTOR pathway that is extensively demonstrated in multiple cell culture model (Willenbacher et al. 2019).

The Wnt/β-catenin signaling pathway has an important role in the pathogenesis of various human diseases. Dysregulation of the Wnt/β-catenin pathway accumulates β-catenin in the nucleus and increases the expression of multiple oncogenes, including cyclin D1 and c-myc. Curcumin has inhibitory effect on Wnt/β-catenin signaling, it reduces glycipan 3 (GPC-3) expression which further inhibits the expression of cyclin D1, c-myc, and β-catenin. The silencing of GPC-3 also induces curcumin-induced apoptosis and growth inhibition in hepatocellular carcinoma (HCC) cells (Hu et al. 2019).

MicroRNA (miRNA) are small non-coding RNA that plays a pivotal role in physiological conditions, including growth, differentiation, angiogenesis, and apoptosis. Dysregulation of these miRNA can modulate several molecular or cellular targets that can lead to cancer progression. There are compelling evidences that suggests that curcumin shows its anti-cancer properties by targeting different miRNAs such as miR-181B, miR-203, miR-9, miR-19, miR-203, and miR-208 expression. Curcumin upregulates miR expression level in thyroid cancer. Curcumin inhibits the NF-kb pathway in many cancer cells such as adenoid cystic carcinoma, breast cancer, human oral squamous carcinoma, cutaneous T-cell lymphoma, gastric cancer, ovarian cancer, colorectal cancer, Hodgkin's lymphoma, prostate carcinoma, pancreatic cancer, thyroid carcinoma, and lymphoma, hence reduces the associated complications during carcinogenesis (Ghasemi et al. 2019).

The use of chemotherapeutic agents against cancer has significantly increased the survival rate but the associated undesirable side effects, such as cognitive impairment, fatigue, neuropathy, and motivational deficit are few concerns (Yi et al. 2020). There is clear clinical evidence that suggests that combination therapies show high efficacy without enhancing toxicity. The treatment of chemotherapeutic drug docetaxel and curcumin inhibits the proliferation and induces apoptosis in prostate cancer cells. Doxorubicin is another active single-agent drug that is vastly used to treat cancers including ovarian, breast, brain, lung, and prostate. However, critical cardiotoxicity and multiple drug resistance are the significant side effects shown by the clinical use of doxorubicin. Substantial evidence suggests that doxorubicin shows better efficacy with curcumin due to the efflux inhibitory effect of curcumin. Doxorubicin and curcumin exhibit a reduction in proliferation of Hodgkin lymphoma (Guorgui et al. 2018). Hence, turmeric potentially acts as anti-cancer, anti-inflammatory, antioxidant, nephroprotective, cardioprotective, and hepatoprotective against chemotherapeutic mediated toxicity due to the presence of vast source of

phytochemicals such as curcumin, volatile oil which have overwhelming pharmacological properties.

Tulsi (*Ocimum sanctum*)

Tulsi is an aromatic perennial plant of the Lamiaceae family. It is also commonly referred to as holy basil in English and tulsi in Hindi, indigenous to the Indian subcontinent and widespread as a cultivated plant throughout the Southeast Asian tropics. *O. sanctum* is cultivated for medicinal, religious, and culinary purposes. *O. sanctum* is cultivated at low altitudes (up to 900 m) with high humidity and relatively high rainfall. The different parts of *O. sanctum* such as leaves, stem, flower, root, and seeds are used in European and Asian countries for the treatment of common cold, bronchitis, urinary tract infection, skin infection, headache, inflammation, heart disease, and various forms of deadly infection like scorpion sting and snake bite since ancient times (Gupta et al. 2021).

Flavonoids and phenolic compounds such as rosmarinic acid, cirsilineol, cirsimaritin, and isothymonin are present in the leaves and stem of *O. sanctum*. Various essential oils that possess anti-inflammatory, anti-microbial, anti-diabetic, and anti-ulcer properties are prepared from *O. sanctum*. The role of *O. sanctum* in cancer inhibition has been demonstrated when aqueous, and ethanolic extract of *O. sanctum* is given to mice bearing sarcoma-180 solid tumors. It arbitrated that there is an apparent reduction in tumor and increase in lifespan that suggest its anti-cancer role. The anti-cancer properties of *O. tenuiflorum* against human breast cancer line (MCF-7) show reduced cell viability (Lam et al. 2018).

Vicenin-2, a component of *O. sanctum* has an anti-proliferative effect on human colon cancer cells. It is a flavonoid from basil which shows substantial cell cycle arrest at the G2M phase. Additionally, vicenin-2 treatment induced the expression of caspases-3, cytochrome C, and Bax and decreased the expression of Bcl-2. The efficacy of docetaxel in combination with vicenin-2 shows anti-angiogenic, anti-proliferative as well as anti-apoptotic activities; hence, synergistically inhibit prostate tumor growth (Nagaprashantha et al. 2011).

The essential oil of *O. sanctum* suppresses matrix metallopeptidase 9 (MM9) activities in lipopolysaccharide-induced inflammatory cells. Studies have shown that an aqueous suspension and methanol extract of *O. sanctum* inhibit acute and chronic inflammation. *O. sanctum* also has radiation protective properties, majorly showed by two isolated flavonoids, namely orientin and vicenin. Studies investigated the radio-protectant activity of *O. sanctum* by exposing salivary glands of mice with radioiodine, and its effect is compared against a well-known radio-protectant, amifostine (Singh et al. 2012).

The ethanol extract of *O. sanctum* (EEOS) has shown a significant role in carcinogen metabolizing enzymes, including cytochrome b5, cytochrome P450, and aryl hydrocarbon hydroxylase. A549 cells when treated with EEOS show cell detachment in a dose-dependent manner and cell death via DNA fragmentation and cell shrinkage (Wihadmadyatami et al. 2019) hence, signifies to the therapeutic significance of tulsi in management of different type of cancers.

Licorice (*Glycyrrhiza glabra*)

Licorice or *Glycyrrhiza glabra* is one of the commonly used herbal remedies in ancient medicine. It is frequently used in food products to enhance flavor and sweetness. The herb belongs to family Leguminosae and is commonly known as mulethi in India and rhizomes and roots are two major parts of licorice being used. The key bioactive components of licorice are glycyrrhizin, glycyrrhizic acid and various polyphenols, and polysaccharides. Studies demonstrate pharmaceutical properties of licorice such as antioxidant, anti-inflammatory, antivirus, anti-ulcer, and anti-carcinogenesis. Licorice is known for its protective role against DNA damage and also inhibits the enzymes involved in carcinogenesis such as lipoxygenase and cyclooxygenase. Protein kinase C and epidermal growth factor receptor are also the potential targets of this versatile herb. Licorice shows tremendous role in neuroprotection against neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and used as brain tonic and memory enhancer (Sharma et al. 2021).

In breast cancer, increased levels of cytochrome P450 1 B1 and A1 (CYP1B1 and CYP1A1) develop the resistance against anti-cancer drug cisplatin and interfere in the treatment of breast cancer. In vitro studies reveal that licorice extract treatment to breast cancer cells efficaciously inhibits CYP1B1 and CYP1A1 enzymes and enhances the efficacy of cisplatin. Licorice shows anti-proliferative properties in prostate cancer by targeting autophagy and apoptosis and its co-administration with adriamycin significantly enhances the recovery rate in prostate cancer. The secondary metabolites present in the indigenous species of licorice (*G. iconica*) show cytotoxic and anti-tumor activity against liver cancer, breast, and colorectal cancer *in vitro* via activating caspases and p53 expression (Çevik et al. 2019).

Chemotherapy induced anemia and low white blood cell count are key side effects in the cancer patients. Chemotherapy also affects the kidney functioning by increased levels of creatinine hence poor recovery of cancer patients (Schwameis et al. 2019). Anti-cancer drug crizotinib causes nephrotoxicity and formation of renal cysts. The 3 month adjuvant therapy with licorice and gudchi (*Tinospora cordifolia*) to the patients receiving chemotherapy significantly helped in managing the various side effects of chemotherapy and remarkably improves the levels of Hb, TLC, and creatinine (Beriwal et al. 2019).

The breast cancer cell when treated with a synthetic derivative of licorice (soloxolone) effectively kills them by inducing endoplasmic reticulum (ER) stress. Soloxolone induced ER stress activates apoptotic machinery (IRE1-α, Bip, CHOP markers) and declines cell viability in dose/time dependent manner (Alper et al. 2021).

Hepatic cancer is characterized by rapid progression and low survival due to which the treatment strategies are challenging. Studies showed that the combination of conventional medicines with herbal medications including licorice effectively aids healing liver cancer patients. The ethanol extract of licorice showed anti-cancer properties in HT-292 cancer cell line by downregulating the HSP90 gene which

further downregulates anti-apoptotic gene Bcl-w and apoptosis (Nourazarian et al. 2016).

High Mobility Group Box1 (HMGB1) is a chromosomal protein that play crucial role in formation of nucleosome and transcription during cancer progression in several types of cancers. The elevated levels of HMGB1 are known to be linked with migration and invasion of cancer cells and increased serum HMGB1 is considered as prospective clinical biomarker for lung cancer. The glycyrrhizin an active component of licorice downregulates the levels of HMBG1 in non-small cell lung cancer cell line by affecting JAK/STAT signaling via blocking phosphorylation of Jak2 and Stat3 (Wu et al. 2018).

The treatment of aqueous extract of licorice in breast and colon cancer cell lines (MCF7 and HT 29) proficiently reduces the cell viability and increases apoptosis in these cell lines suggesting that licorice can be effective anti-cancer agent and dietary supplementation can expand the recovery rate in cancer patients (Nazmi et al. 2018).

The oral mucositis is characterized by redness of mucosal membranes due to increased blood flow and development of ulcers/lesions in oral mucosal membrane. Oral mucositis is a side effect in patients undergoing radiotherapy especially in case of head and neck cancer. The aqueous extract of licorice reduces the wound size and mucosal irritation in patient suffering with head and neck cancer. Chemotherapy induced heart damage, i.e., cardiomyopathy is one the deleterious effects of anti-cancer therapy. Doxorubicin, an anti-cancer drug causes oxidative damage and weakens heat muscle proteins in cardiomyocytes which ultimately affects heart functioning and results in heart attack. *In vitro* research also reported the positive effect of *G. glabra* against doxorubicin induced cardiocytoxicity. It regulates the expression of SIRT-1 and PPAR-α/γ which are important proteins for cardiac function and lipid metabolism (Upadhyay et al. 2020).

The synergistic approach to use *G. glabra* in combination with chemotherapeutic drugs reduces the drug resistance and cytotoxicity to normal cells which suggested that *G. glabra* can act as adjunct contestant in combinational treatment strategies against cancer.

Picrorhiza (*Picrorhiza kurroa*)

Picrorhiza kurroa is a famous medicinal plant that belongs to family Plantaginaceae. This perennial herb commonly known as Kutki and found in mainly in north-western Himalayas. The rhizome and root part of this herb are being used to treat hepatic and respiratory disorders. *P. kurroa* is excellent source antioxidants and also has anti-inflammatory, anti-allergic, and anti-cancerous activities. The active constituents of *P. kurroa* are monoterpene, iridoid glycosides. The commonly present iridoid glycosides are kutkin, kutkoside, picroside, pikuroside, and bartsioside (Soni and Grover 2019).

The methanolic and aqueous extracts of *P. kurroa* were studied to check antioxidant and anti-neoplastic activities in breast, hepatic, and prostate cancer cell lines (Rajkumar et al. 2011). Another active component of *P. kurroa*, Picroside II shows anti-metastatic and anti-angiogenic properties. MDA-MB-231 breast cancer cell line

when treated with Picroside II shows downregulation of MMP-9 and CD31. The MMP-9 is an important marker of tumor metastasis that stimulates circulation of cancer cells to colonize in various organs, whereas CD31 is an angiogenic marker which increases formation of new blood vessels and blood supply in cancer cells (Owyong et al. 2019).

The combination 10 herbs including *P. kurroa* known as HC9 is prescribed by Ayurvedic specialists to lactating women to clean and detoxify breast milk. The effect of HC9 herbal formulation was also verified in breast cancer in vitro. HC9 significantly alters the progression cancer in breast cancer cell lines (MCF-7 and MDA MB-231). It upregulates the expression of p53 and p21, ultimately cell cycle is blocked at S stage and G1 phase in MCF-7 and MDA MB-231, respectively, whereas the expression of ppRb is decreased. HC9 also affects the cell migration and invasion by targeting metastatic factors such as MMP-9 and VEGF (Suryavanshi et al. 2019).

Giloy (*Tinospora cordifolia*)

Tinospora cordifolia also known as "Guduchi" or "Giloy" for its involvement in the treatment of numerous diseases in the field of traditional system of medicines in India. It belongs to family Menispermaceae that found mostly at higher altitudes (Saha and Ghosh 2012). The fresh leaves, stem, root, and whole plant of *T. cordifolia* have been used to treat numerous ailments. The key active compounds present in *T. cordifolia* are phenolics, alkaloids, lactones, glycosides, steroids, aliphatic compounds as well as polysaccharides (Mishra and Kaur 2013). It has been reported that the cyclin D1 protein which plays a crucial role in cell cycle progression by allowing transition from G0/G1 to S phase was shown to get downregulated in C6 cells after treatment of ethanolic extract of *T. cordifolia*. Ethanolic extract of *T. cordifolia* was observed to reduce the expression of Bcl-xl which makes cancer cell resistant toward chemotherapy-mediated apoptosis. In MCF7 and MDA MB 21, the cytotoxic and apoptotic effects of ethanolic extract of *T. cordifolia* were observed, but aqueous extract of *T. cordifolia* was unable to induce sufficient cytotoxicity in breast cancer. The ethanolic extract of *T. cordifolia* studied in HaCaT, i.e., non-cancerous cell line which shows its less cytotoxicity toward human non-cancerous cells. Similarly, after treating HCA-7 (Human colon adenocarcinoma) cells with *T. cordifolia* decreases the expression of CALD1 (Ca2+/Calmodulin-dependent proteins) which is involved in the process of invasion, migration and proliferation of several types of cancer including colorectal cancer (Palmieri et al. 2019). *T. cordifolia* affects multiple pathways involved in cancer progression hence can act as an effective drug to improve cancer treatment therapies.

Sweet Violet (*Viola odorata*)

Viola odorata belongs to the family Violaceae which mostly used in Iranian traditional medicine. Fresh leaves of *V. odorata* have been used to treat cancer and cyclotide and flavonoid like key active compounds obtained from *V. odorata* have been reported as anti-carcinogenic, antioxidant, anti-inflammatory, anti-pyretic, and anti-bacterial (Burman et al. 2010). In recent reports, hydro-alcoholic extracts of

V. odorata were considered to have cytotoxic, antioxidant, and anti-metastatic properties against 4T1 breast cancer model (Alipanah et al. 2018). The hydro-alcoholic extract also enhances the activity of caspase-3 in glioblastoma multiforme-derived cells (fast growing astrocytoma) which makes glioblastoma cells more prone toward apoptosis. Data suggest that the alcoholic extract of *V. odorata* exerts anti-cancerous effects on the growth of breast cancer cell line, namely MCF7 and SKBR3, but it does not harm non-cancerous cell (Yousefnia et al. 2020). Furthermore, active component of *V. odorata* that is anthocyanin activates apoptosis pathway via enhancing the activity of caspases-3, apoptotic induction factor (AIF) as well as endonuclease G (pro-apoptotic factor). It also causes the cell cycle arrest at G0/G1 and G2/M by decreasing the expression of cyclin A and B. The cytotoxic and anti-proliferative effect of *V. odorata* on T47-D cell (breast cancer cell) was also examined suggesting it to be a promising drug in combination with chemotherapeutics to treat cancer effectively (Zeinoddini et al. 2019).

Ferulic Acid (FA)

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a phenolic phytochemical present in grains, fruits, vegetables, and some beverages such as beer and coffee. It was first isolated in1866 from the *Ferula foetida* plant. FA is identified in Chinese medicine herbs such as *Cimicifuga heracleifolia, Ligusticum chuanxiong, and Angelica sinensis.* FA possesses various pharmacological effects, including anti-cancer, antioxidant, anti-inflammatory, anti-thrombotic, and anti-microbial. The anti-cancer effect of ferulic acid is vastly demonstrated in multiple cancer cell lines through its potential to generate cytotoxic and pro-apoptotic effects (Eroglu et al. 2018). The apoptotic effects of FA were determined in renal carcinoma cell line (ACHN) by Annexin V/PI assay by using flow cytometry via elevating the expression of Bax genes. Studies showed that FA in combination with aspirin decreases cell viability, migration, and cell proliferation in human pancreatic cancer cells (MIA PaCa-2). FA was also shown to induce apoptosis in liver and breast cancer cell lines via activating caspase 8 and caspase 9 pathways (ElKhazendar et al. 2019).

To assess the anti-cancer role of ferulic acid on the human prostate cancer cell line, Eroğlu et al. treated androgen-independent PC3, and androgen-dependent LNCaP prostate cancer cell lines with FA and it was found to inhibit the proliferation of PC3 cells and LNCaP cells in a time dependent and dose-dependent manner. The decrease in proliferation was found to be associated with increase in gene expression of ATR, ATM, TP53, BIK, BAX, CASP1, CASP2, and CYCS and decrease in gene expression levels of CCND1, CCND2, CCND3, CDK2, CDK4, CDK6, and BCL2. FA also reduced cell viability of Hela and Caski cells via causing nuclear DNA condensation and activation of caspase 3, caspase 8, and caspase 9 pathways, thus suggesting the cytotoxic role of FA. Many studies have revealed that FA and its derivatives inhibit i-NOS, COX and caspase-1 function/expression, and activation of NF-κB pathway to decrease the levels of pro-inflammatory cytokines as reviewed (Kaur et al. 2018).

Cisplatin can cause excessive ROS production resulting in cell death in the cochlea that is the major reason behind ototoxicity. However, antioxidant

phytochemicals, curcumin, and FA protect human cancer cells against cisplatin induced ototoxicity via upregulating translocation of NRF-2 to nucleus, thus inducing the adaptive stress responses and attenuate hearing threshold elevation. Antioxidant properties of FA inhibit p53 phosphorylation and decrease the outer hair cell death, thus protecting the hair cell population from the adverse effects of cisplatin chemotherapy (Paciello et al. 2020). Additionally, in cervical cancer cells FA arrest the cells in G0/G1 phase of cell cycle. It also increases the expression of p53, p21, whereas decreases the expression of Cyclin D1 and Cyclin E, thus pointing out the role of FA in inhibiting/regulating cell cycle (Gao et al. 2018). Taken together, FA show cytotoxic effects to various cancer cells at higher concentrations via modulating cell cycle, inflammatory pathways, oxidative/antioxidant signaling, apoptosis pathway, and cell morphology. Hence it can be utilized along with chemotherapy for better approach towards cancer treatment.

Conclusion

The conventional cancer treatment approaches such as radiotherapy and chemotherapy are always linked with poor prognosis and survival rate in cancer patients. Simultaneously, these approaches come with severe side effects such as organ specific toxicity (renal/hepatic) and gastrointestinal complications. There is a prodigious necessity to determine new possible agents that helps to increase the efficacy of conventional treatment strategies to kill cancer cells as well as can reduce the harmful effects of these strategies in normal cells.

Growing evidence recommends that herbal plants have multidimensional roles in different cancer cell lines *in vitro* including anti-proliferation, apoptosis inducers, and anti-metastatic, thus hindering the growth of cancer cells. In addition, the antioxidant property of these herbal compounds minimizes the possibility of posing deleterious effects on normal cells. Thus, by maintaining the redox balance in cancer cells, these herbal compounds inhibit metastasis as well as help maintain homeostasis in normal cells. Further, these herbs are quite attractive due to their low cost and easy availability. Complementing herbal remedies to available cancer therapies can eliminate the associated side effects as well as can improve the efficacy of the treatment strategies. Based on existing ancient knowledge, innovative investigations should be focused to understand the mechanistic action of ancient herbal remedies and further clinical evaluations should be made to confirm the effectiveness of herbal remedies in the prevention and treatment of various types of cancer.

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