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Phytotherapeutic Molecules & Antioxidants: A Novel & Secure Approach of Cancer Prevention

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Authors' contributions

This work was carried out in collaboration between all authors. Author VS designed the study, wrote the protocol and interpreted the data. Author AK anchored the field study, gathered the initial data and performed preliminary data analysis. Authors VS, AK and RCA managed the literature searches and produced the initial draft. All authors read and approved the final manuscript.

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ABSTRACT

Cancer is the second leading cause of death worldwide. Although great advancements have been made in the treatment and control of cancer progression, significant deficiencies and room for improvement remain. A number of undesired side effects such as vomiting, hair loss, immunosupression, free radical formation etc. occur during chemotherapy. Free radicals are the cause of oxidative stress, which may causes injury to cells, gene mutation, and may lead to cancer. Oxidative stress can also causes cancer, by the interaction with intracellular signal transduction and transcription factors, directly or indirectly. An antioxidant is any substance that delays, prevents or removes oxidative damage to a target molecule. This can be achieved by the entrance of substances such as phytotherapeutic molecules, oxidation inhibitors, vitamins, minerals, in the body from different natural sources. These compounds neutralize the free radicals and prevent from excessive production of harmful elements in the body. Phytotherapeutic molecules are the secondary metabolites which hold the promise to design new drugs in drug development process for treatment of lot of diseases such as cancer. This review is attempt to screen and explore the

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role of phytotherapeutic molecules and oxidative inhibitors as novel and secures approach of anticancer and chemo-preventive agents. There are lots of natural therapies available in traditional medicine system such as phytotherapy, immunotherapy etc. to prevent and sometimes cure the cancer. The herbs, spices, vegetables & fruits are the rich source of phytotherapeutic molecules and antioxidants which are strongly active against carcinogenesis.

Keywords: Antioxidants; cancer; chemotherapy; herbs; oxidative stress; phytochemicals; traditional medicine.

1. INTRODUCTION

Cancers are a large family of diseases which involve abnormal cell growth with the potential to invade or spread to other parts of the body. Six characteristics of cancer have been proposed: a) self-sufficiency in growth signaling, b) insensitivity to anti-growth signals, c) evasion of apoptosis, d) enabling of a limitless replicative potential, e) induction and sustainment of angiogenesis, f) activation of metastasis and invasion of tissue [1]. The progression from normal cells to cells that can form a discernible mass to outright cancer involves multiple steps known as malignant progression [2]. Cancer development is understood to be a multistep process as described in Fig. 1. The concept of multi-stage carcinogenesis was first proposed by Beremblum and Schubik in 1947 and supported by later studies [3]. Present day oncology recognizes three main phases: initiation, promotion and progression.

As the tumor progression advances, the cells lose their adherence property, detach from the tumor mass and invade the neighboring tissues. The detached cells also enter the circulating blood and lymph and are transported to other organs/tissues away from the site of the primary growth and develop into secondary tumors at the new sites. These form the distant metastases, resulting in widely spread cancers. Cancer metastasis consists of a number of steps; the main steps are common for all tumors. The progress of the neoplastic disease depends on metastatic changes that facilitate: (a) invasion of local normal tissues, (b) entry and transit of neoplastic cells in the blood and lymphatic systems, and (c) the subsequent establishment of secondary tumor growth at distant sites [4,5]. The behavior of tumor is influenced by the cell adhesion molecules, one of the most important of which is cadherins [6]. Animal studies have shown that a down-regulation of E-cadherin expression, resulting in lower levels, correlated with metastatic behavior *in vivo*, suggesting that cadherins function as invasion suppressor gene products [7].

Chemoprevention refers to the administration of herbal or phytochemical agents to prevent the initiational and promotional events that occur during the process of neoplastic development. Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care.

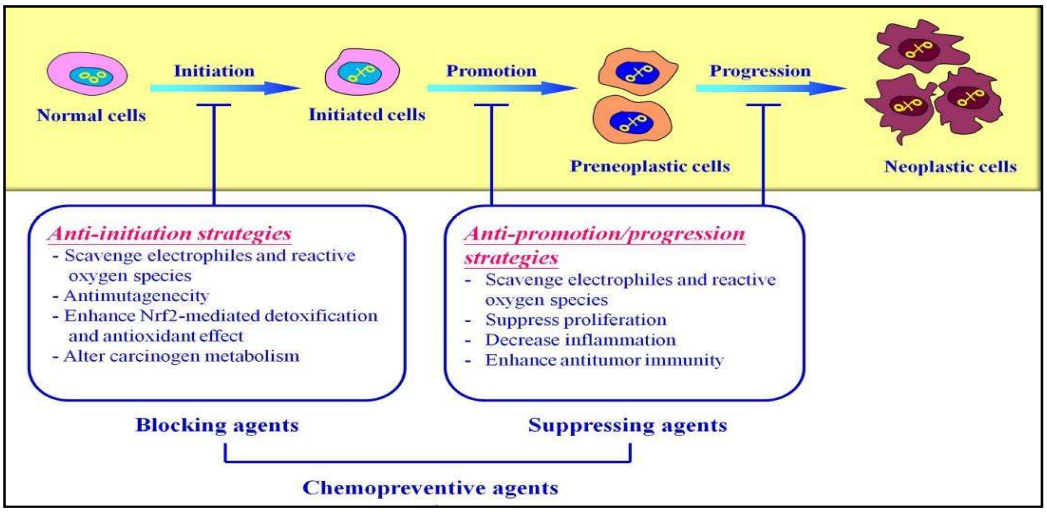

Fig. 1. Showing stages of neoplasia and stage specific chemo-preventive agents

They have stood the test of time for their safety, efficacy, cultural acceptability and lesser side effects. The chemical constituents present in them are a part of the physiological functions of living flora and hence they are believed to have better compatibility with the human body [8]. Epidemiological studies have suggested that diets rich in vegetables and fruits reduce the risk of certain cancers [9]. Fruits and vegetables are rich sources of chemopreventive chemicals. These include inhibitors of carcinogen formation, blocking agents (block conversion of procarcinogens to carcinogens), stimulators of detoxifying system, trapping agents (trap and eliminate potential carcinogens) and suppressing agents (suppress the different steps of the metabolic pathway leading to cancer) [10]. Chemopreventions with Herbal phytochemicals such as Flavonoids, Triterpenoids, Steroids, Saponins, Glycosides etc. are currently regarded as one of the most important strategies for cancer control.

2. PHYTOTHERAPEUTIC MOLECULES: AS CHEMOPREVENTIVE AGENTS

The conventional radiotherapy and chemotherapy with synthetic drugs used in treating cancer evoke severe side effects such as immunosuppression, organ failure and infectious diseases which causes the death of patient after recovery from cancer [11]. Thus from this point of view, induction of apoptosis in a neoplastic cell line without damaging the healthy cells of the body with phytochemical chemopreventive agents seems to be the best strategy in cancer management and treatment [12]. Phytochemicals are found as a substance responsible for the health promoting properties of varieties of natural and functional foods due to their ability to alter cell communication, and DNA repair and influence cell processes that can cause development of cancer and other disease [13]. These compounds are divided into two main groups as earlier stated: the blocking agents such as ellagic acid, indole-3-carbinol, sulphoraphane and flavonoids which prevent cancer causing substances from getting to their target sites through many actions such as enhancement of carcinogen detoxification, modification of carcinogen uptake and metabolism, elimination of ROS and enhancement of DNA repair [14]. Suppressing agents like beta-carotene, genistein, capsaicin, curcumin, gingerol and resveratrol suppress promotion and progression of cancer after stimulation of preneoplastic cells through their influence on cell differentiation, proliferation and apoptosis [15].

All plants produce chemical compounds as part of their normal metabolic activities. Some of the phytochemicals that can be useful as plant based drugs are discussed;

2.1 Carbohydrates

Carbohydrates have several roles in living organisms, including energy transportation, as well as being structural components of plants and arthropods. The lowering amount of CHOs in the diet can have direct beneficial effects on the prevention and treatment of malignant diseases [16].

2.2 Protein

Proteins perform a vast array of functions within living organisms, including catalyzing metabolic reactions, replicating DNA, responding to stimuli, and transporting molecules from one location to another. Lactoferrin acts by induction of apoptosis, inhibition of angiogenesis, and modulation of carcinogen metabolizing enzymes and perhaps acting as an iron scavenger. Supplementing cows with selenium increases the content of seleno-proteins in milk, which on isolation inhibited colon tumorigenesis in rats [17].

2.3 Alkaloids

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. This group also includes some related compounds with neutral and even weakly acidic properties [18]. Some synthetic compounds of similar structure are also attributed to alkaloids [19]. Many alkaloids have dramatic effects on the central nervous system.

2.4 Flavonoids

Flavonoids help to maintain the health of small blood vessels and connective tissue, and some are under study as possible treatments of cancer. Physiological processing of unwanted flavonoid compounds induces so-called Phase II enzymes that also help to eliminate mutagens and carcinogens, and therefore may be of value in cancer prevention. Flavonoids could also induce mechanisms that may kill cancer cells and inhibit tumor invasion [20].

2.5 Terpenoids

Plant terpenoids are used extensively for their aromatic qualities. More than 40000 individual terpenoids are known to exist in nature with new compounds being discovered every year. A large number of terpenoids exhibit cytotoxicity against a variety of tumor cells and cancer preventive as well as anticancer efficacy in preclinical animal models [21].

2.6 Phenols

Natural phenolic compounds play an important role in cancer prevention and treatment. Various bioactivities of phenolic compounds are responsible for their chemopreventive properties (e.g., antioxidant, anticarcinogenic, or antimutagenic and anti-inflammatory effects) and also contribute to their inducing apoptosis by arresting cell cycle, regulating carcinogen metabolism and oncogenesis expression, inhibiting DNA binding and cell adhesion, migration, proliferation or differentiation, and blocking signaling pathways [22].

2.7 Glycosides

New findings within the past five years have revealed these compounds to be involved in complex cell-signal transduction mechanisms, resulting in selective control of human tumor but not normal cellular proliferation. As such, they represent a promising form of targeted cancer chemotherapy. New clinical studies of their anticancer potential as single or adjuvant treatments may provide insight into these potentially valuable therapeutic options [23].

2.8 Steroids

A steroid is a type of organic compound that contains a characteristic arrangement of four cycloalkane rings that are joined to each other. Among the steroid substrate analogs, *formestane* and *examestane* have been shown to be effective in breast cancer patients with advanced disease [24].

2.9 Saponins

Saponins consist of a polycyclic aglycones attached to one or more sugar side chains. The foaming ability of saponins is caused by the combination of a hydrophobic (fat-soluble) sapogenin and a hydrophilic (water-soluble) sugar part. Soy saponin may be effective in preventing colon cancer by affecting cell morphology, cell proliferation enzymes, and cell growth [25].

2.10 Tannins

Many tannin molecules have been reported to reduce the mutagenicity of a number of mutagens. Tannins were also reported to have anticarcinogenic activity. The growth of fungi, bacteria, and viruses has been inhibited by tannins. Tannins in food plants serve as a natural defence mechanism against microbial infections. Thus, tannins can theoretically serve as natural regulators of the microbial population in different habitats including the human gastrointestinal tract [26].

2.11 Anthraquinones

Anthraquinone is a compound of yellow crystalline solid used in the manufacture of dyes, esp anthraquinone dyes, which have excellent colour properties. Formula: $C_6H_4(CO)_2C_6H_4$. Rhubarb has been used as a traditional Chinese medicine since ancient times and today it is still present in various herbal preparations. The most abundant anthraquinone of rhubarb, emodin, was capable of inhibiting cellular proliferation, induction of apoptosis, and prevention of metastasis [27].

3. OXIDATIVE STRESS & CANCER

An imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage, is termed 'oxidative stress'. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling. Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. ROS form as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis [28]. Oxidative stress has been implicated in chronic fatigue syndrome [29]. Oxidative stress is likely to be involved in age-related development of cancer. The reactive species produced in oxidative stress can cause direct damage to the DNA and are therefore mutagenic, and it may also suppress apoptosis and promote proliferation, invasiveness and metastasis [30]. Infection by *Helicobacter pylori* which increases the production of reactive oxygen and nitrogen species in human stomach is also thought to be important in the development of gastric cancer [31].

3.1 Lipid Peroxidation

Lipid peroxidation often affects polyunsaturated fatty acids, because they contain multiple double bonds in between which lie methylene bridges ($-CH_2-$) that possess especially reactive hydrogen's. As with any radical reaction, the reaction consists of three major steps: initiation, propagation, and termination. In addition, end-products of lipid per-oxidation may be mutagenic and carcinogenic. For instance, the end-product malondialdehyde reacts with deoxyadenosine and deoxyguanosine in DNA, forming DNA adducts to them, primarily M_1G[32].

4. ANTIOXIDANTS (OXIDATION INHIBITOR): HEALTH PROMOTING ELEMENTS & GENERAL PREVENTIVE MECHANISM OF ACTION

An antioxidant is simply a molecule that prevents another molecule from oxidizing. Fig. 2 Showing herbs, spices, vegetables, fruits and their active ingredients as free radical/hydroxyl radical scavengers and also mode of action of antioxidants. Since there are many processes in the body which result in oxidation, the intake of antioxidants is essential to counteract some of the negative results of the buildup of too many oxidized molecules in the body. Antioxidants can be divided into two groups: a) Preventive antioxidants, b) Chain-breaking antioxidants. The first group comprises metal chelators such as metallothionein, neuromelanin, transferin and other proteins involved in transition metal transport and storage and antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase etc.

4.1 Glutathione

Glutathione (GSH, g-glutamylcysteinylglycine), the primary non-protein sulfhydryl in aerobic organisms is synthesized in most cells. The ubiquitous tripeptide is formed by the ATP dependent condensation of glutamic acid and cysteine, catalyzed by g-glutamylcysteinyl synthetase. Glycine is then added by glutathione synthetase to form GSH. It is a potent antioxidant, it protects against damage from chemicals, free radicals (particularly peroxides), smoke, radiation, and other toxins.

4.2 Catalase

Catalase has one of the highest turnover numbers of all enzymes; one catalase molecule can convert millions of molecules of hydrogen peroxide to water and oxygen each second [33]. Catalase play an essential role in p53-mediated ROS regulation and it is found that the p53/p53R2-catalase and p53/PIG3-catalase pathways are critically involved in intracellular ROS regulation under physiological conditions and during the response to DNA damage, respectively [34].

Free-radical scavengers pertain to the second group. They scavenge free radicals and stop the propagation of free radical chain reactions. Most significant chain-breaking antioxidants are vitamins C and E, carotenoids and polyphenols [35]. Flavonoids are a class of secondary plant metabolites that are thought to exert beneficial health effects through their antioxidant and chelating properties being the major contributor to the antioxidant capacity of vegetables [36,37]. Vitamin C has an antioxidant activity when it reduces oxidizing substances such as hydrogen peroxide [38], however, it will also reduce metal ions that generate free radicals. Research indicates several possible mechanisms of action for herbal medicines, or their bioactive components, may act alone or in concert to reduce cancer risk through their anti-oxidant [39], and anti-tumorigenic properties, as well as their direct suppressive effect on carcinogen bioactivities.

5. HERBS, SPICES, VEGETABLES & FRUITS: VERSATILE SOURCE OF PHYTOTHERAPEUTIC & ANTIOXI-DANT MOLECULES

Nature is an attractive source of new therapeutic candidate compounds as a tremendous chemical diversity is found in millions of species of plants, animals, marine organisms and microorganisms as potential anti-cancer agent. Natural products have been a prime source for the treatment of many forms of cancer, many of which are consumed daily with the diet. They provide significant protection against various cancers and many other diseases. There are lot of herbal plants, spices, vegetables & fruits present in nature those having phytotherapeutic molecules and oxidative stress inhibitors which are able to prevent kind of diseases including cancer. Some examples discussed in Table no. 1.

Table 1. Representing spices, herbs, fruits & vegetables are rich source of chemopreventive agents studied having anticancer activity

S. no.	Botanical name (family)	Common name	Reported phytotherapeutic molecules	Reported medicinal activities	Action against specific cancers
1.	*Allium sativum* (*Liliaceae*)	Garlic	Carbohydrates, reducing sugars, lipids, flavonoids, ketones, alkaloids, steroids and triterpenes. (Allin, allicin, allicnase, s-allylc cysteine, diallyl disulphide, methylallyl trisulphide) [40].	Antithrombotic, hypolipidemic, hypoglycemic, antiarthritic, antimicrobial and extract from aged garlic has high free radical scavenging activity.	Oral cavity, pharynx, esophageal cancer, colorectal cancer and laryngeal cancer, Carcinoma of mammary gland, Hepato carcinoma [40].
2.	*Allium cepa* (*Liliaceae*)	Onion	Carbohydrates, glycosides, proteins, alkaloids, saponins, acid compounds, reducing sugars, oils Flavonoids. (Quercetin & kaempferol, fructans and organosulfurs) [41].	Anthelmintic, antioxidant, antiseptic carminative, diuretic, expectorant, febrifuge and vulnerary properties.	Significantly reduces the risk of colorectal and melanoma Cancer [42].
3.	*Zingiber officinale* (*Zingiberaceae*)	Ginger	Alkaloids, carbohydrates, glycosides, proteins, saponins, steroids, flavonoids and terpenoids. (Gingerenone A, gingeols, Zingerone, Oleoresin) [40].	Motion sickness, morning sickness, colic, upset stomach, gas, diarrhea, nausea, pain relief from arthritis or muscle soreness, menstrual pain, upper respiratory tract infections, cough, bronchitis, chest pain, low back pain.	Ethanolic extract of ginger exhibits chemopreventive effects in the SENCAR mice, Leukemia, Skin cancer [40].
4.	*Piper nigrum* (*Piperaceae*)	Black pepper	Alkaloids, Steroids, Phenols, glycosides, carbohydrats, saponins, vitamin-C and vitamin-A Flavonoids (Piperine, Purpurogallin) [43].	Antioxidant activity, anti-inflammatory, carminative, anti-flatulent.	Suppress tumor incursion and migration, possible process involved in HT-1080 cell line [44].
5.	*Curcuma longa* (*Zinziberaceae*)	Turmeric	Carbohyrates, Glycosides, Anthroquinone, Phlobatannin, Phenols, Anthocyanin, saponins, tannins, Alkaloids, Flavonoids (Tumerone, Curcumine) [45].	Anti-inflammatory, antimicrobial, anti-fertility, anticancer, anti-diabetic, antioxidant, hypolipidemic, anti-venom, anti hepato-toxic, nephroprotective, anticoagulant.	Inhibit oncologial incidences of skin, fore stomach, colon, lungs and oral cavity and protect from several carcinogens and mutagens [46].
6.	*Cinnamomum cassia* (*Lauracease*)	Cinnamon	Alkaloids, phenols, flavonoids, terpenoids, steroids, tannins. (Cinnamaldehyde and eugenol).	Antioxidant, anti-inflammatory, antimicrobial, antitumor, cholesterol lowering, and immunomodulatory [47].	Cervical cancer [48], promyelocytic leukemia [49], Melanoma caner [50].
7.	*Crocus sativus* (*Iridaceae*)	Saffron	Anthocyanins, flavonoids, vitamins (riboflavin and thiamine) amino acids, proteins, starch, mineral matte,gums, carotenoids (Crocetin and crocin).	Antioxidant, anti-alzheimer's, anti-tussive, hypolipidemic, anti-convulsant, anti-inflammatory, cardioprotection.	Carcinomas of colon, skin and soft tissue, fibrosarcoma, cervical epithelioid carcinoma, and breast carcinoma [51].
8.	*Taxus baccata* (*Taxaceae*)	Yew tree	lignans, flavonoids, glycosides, sterols, sugars, amino acids and triterpenoids [52], (Taxanes, Taxol, Cepholomannine) [53].	Antiulcer, antimicrobial, antipletlet activity, antioxidant, enzyme inhibitory.	Leukemia, Breast cancer, Sarcoma, Cancer of larynx, ovary and colon [54].
9.	*Withania somnifera* (*Solanaceae*)	Ashwagandha	Alkaloids, amino acids, steroids, volatile oil, starch, reducing sugars, glycosides, hentriacontane, dulcitol (Withanolides,	Antiinflammatory, antibiotic, immunomodulatory, antistress, Anti-hyperglycaemic, Musculotropic, Hepatoprotective, antioxidant, antiageing etc [55].	Antitumor and Radio sensitizing effect, Ehrlich ascites carcinoma, Sarcoma 180, Sarcoma Black (SBL),

S. no.	Botanical name (family)	Common name	Reported phytotherapeutic molecules	Reported medicinal activities	Action against specific cancers
			Withaniferin).		and E 0771 [55].
10.	*Plumbago indica* (*Plumbginaceae*)	Lal chitrak	Steroids, alkaloids, saponins, tannins, phenols, flavonoids, glycosides (Plumbagin, Apigenin).	Antioxidants, effective in skin diseases, leukoderma, leprosy, opthalmia, scabies etc.	Prostate cancer [56].
11.	*Glycyrrhiza galbra* (*Leguminaceae*)	Mulethi	Alkaloids, flavonoids, tannins, steroids, saponins, terpenoids, glycosides (Glycyrrhizin)[57].	Antioxidants, hepatoprotective [58], Antimutagenic [59], Antiinflammatory, immunomodulatory, expectorant etc. [60].	Promyelotic leukemia, Stomach cancer, Prostate cancer [54].
12.	*Linum usitatissimum* (*Linaceae*)	Atasi	Carbohydrats, glycosides, flavonoids, steroids, terpenoids, Lignans etc. [61].	Effective against skin disorders, constipations, respiratory disorders, ganito urinary ailments etc.	Breast cancer [61].
13.	*Bacopa monnieri* (*Scropularaciae*)	Brahmi	Tannins, terpenoids, flavonoids, steroids, phytosterols, saponins etc. (Mannitol, Hersaponin, Monerin) [62].	Anti-anxiety, antidepression, antioxidants, effective on epilepsy, asthma, gastrointestinal disorders etc.	Carcinosarcoma [62].
14.	*Tinospora cardifolia* (*Menispermiaceae*)	Amrita	Carbohydrates, glycosides, alkaloids, phytosterol, tannins, saponins, tannins (Tinosporin) [63].	Antipyretic, antiinflammatory, Immunomodulatory, anti-leprotic, antibacterial, analgesic etc. [63].	Breast cancer, leukemia and cervical cancer [62].
15.	*Ocimum sanctum* (*Laminaceae*)	Tulsi	Tannins, alkaloids, saponins, steroids, terpenoids, flavonoids etc. (Orientin & Vicenin) [62].	Antioxidants, hepatoprotective, antihelminthic, antidiabetic, immunomodulatory etc.	Radioprotective antioxidant [62].
16.	*Vitex negundo* (*Verbanaceae*)	Nirkundi	Carbohydrats, alkaloids, steroids, terpenoids, Anthraquinones, phenols, etc. (Chrysoplenetin) [64].	Antioxidants, Anti-inflammatory, analgesic, Enzyme-inhibitory, effect on reproductive potential etc.	Human pancreatic cancer. Effective against myelo suppression and anaemia during chemotherapy [65].
17.	*Emblica officinalis* (*Euphorbiaceae*)	Amla	Alkaloids, sugras, polyphenols, flavones ,tannins, saponins, glycosides etc. (emblicanin A&B, puniglucanin, pedunculagin, Vitamin C, glutamic acid, proline, aspartic acid) [65].	Hypocholestrolemic, effective against vomiting, hemorrhage, fever, coughs, eye inflammation, ulceration, anorexia, scurvy, diabetes, jaundice, menorrhagia, leucorrhoea and toxicosis etc.	Lymphoma, Anti metastatic activity, melanoma [65].
18.	*Catharanthus roseus* (*Apocynaceae*)	Madagascar periwinkle	Carbohydrates, saponins, flavonoids, anthraquinone alkaloids (Vincristein, Vinblastin)	Diuretic, Antidysenteric, Hemorrhagic, Antiseptic, Antidiabetic etc.	Leukemia, Lymphomas, Testicular Cancer, Breast & Lung Cancers, Kaposi's Sarcoma.
19.	*Semecarpus anacardium (Anacardiaceae)*	Marking Nut	Steroids, anthraquinones, phenols Semicarpin, anacardin [66].	Antibacterial, anti-inflammatory, antiarthritic, anthelmentic, antioxidative, skin diseases, neurological disorders, ulcers etc. [67].	Leukemia, Melanoma, Glioma, Hepato carcinoma [66].
20.	*Andrographis paniculata* (*Acanthaceae*)	Kalmegh	Steroids, terpenoids, flavonoids, phenols (Andrographiolide, Andrographiside) [68].	Antimicrobial, antiulcerogenic, antityphoid, anti snake venom, antimalerial, antifertility, anti-inflammatory, antihypoglycemic etc.	Squamous cell carcinoma of nasopharynx, Lymphatic leukemia [68].
21.	*Albezia lebbek*	Benth	Carbohydrates, steroids, glycosides, saponins,	Antimicrobial, antiasthmetic, antiproliferative,	Sarcoma, Human epidermal

S. no.	Botanical name (family)	Common name	Reported phytotherapeutic molecules	Reported medicinal activities	Action against specific cancers
	(*Mimosaceae*)		tannins, alkalois, terpenoids, flavonoids etc. (Budmunchiamine) [66].	antidiarrheal, antifungul, hemolytic, antioxidant etc.	carcinoma of nasopharynx [66].
22.	*Rubia cordifolia* (*Rubiaceae*)	Manjishtha	Carbohydrates, tannins, phenols, alkaloids etc. (Rubiadin) [69].	Antitussive, useful in chronic low fevers, tuberculosis, antiulcerogenic, effective on hyperpigmentation, scabies, acne and allergies, edema and oozing.	Melanoma, Sarcoma, Lung carcinoma, Lymphatic leukemia [40].
23.	*Momordica charantia (Cucurbitaceae)*	Karela	Glycosides, saponins, reducing sugars, resins, phenols, alkaloids, (Charantin, sitosterol, Ascorbigin) [40].	Effective on constipation, digestion, demulcent, dermatosis, hepatitis, hypoglycemic, inflammation etc.	Breast Cancer, Skin cancer, Colon cancer, Leukemia [40].
24.	*Azadirachta indica* (*Meliaceae*)	Neem	Carbohydrates, proteins, terpenoids, tannins, polyphenolics, glycosides, flavonoids, (Nimbidin, azadirachtin) [70].	Antioxidant, anti-inflammatory, antimicrobial, antipyretic, antimalarial, antitumor, immunomodulatory etc. [70].	Oral squamous cell Carcinoma, Oral Mucosa [70].
25.	*Camellia sinensis* (*Theaceae*)	Black & Green tea	Carbohydrates, alkaloids, flavonoids, volatile oils, lipids etc. (Catechin and theaflavins) [71].	antioxidant, anti-inflammatory, antiallergic, anti microbial, hepatoprotective, antigenotoxic, antidiabetic etc. [71].	Rectal, Pancreatic, colon, breast, ovarian, prostate, and lung cancers [71].
26.	*Citrus aurantium* (*Rutaceae*)	Orange	Alkaloids, polyphenols, flavonoids, volatile oils, Rich in Vitamin C, E etc. (Hesperidin, Synephrine) [72].	Antioxidant, antiobesity, hepatoprotective, antitumor, anti-inflammatory, antiseptic, effective on cardiovascular and skin diseases [72].	Cancers of the stomach, colon, esophagus, bladder, breast, and cervix [72].
27.	*Vitis vinifera* (*Vitaceae*)	Grapes	Phenolic acids, flavonoids, anthocyanins, proanthocyanidins, sugars, sterols, amino acids, and Minerals (Resveratrol) [73].	Analgesic, anti-inflamantory, antipyretic, hepatocurative, diuretic and antioxidant etc.	Breast cancer, Prostate cancer, Non–hodgkins, Lymphoma [74].
28.	*Cucurbita moschata* (*Cucurbitaceae*)	Pumpkin	Carbohydrates, proteins, saponins, glycosides, phytosterols, tannins, flavonoids, fixed oils etc. (β-Carotene)	Hepatoprotection, anti-diabetes, anti-cancer, anti-obesity, antioxidant, antimicrobial	pancreatic cancer and myeloid leukemia [75].
29.	*Daucus carota sativus* (*Apiaceae/umbelliferae*)	Carrot	Volatile oils, flavonoids, sugars, pectins, vitamins, minerals etc. (β-Carotene).	Effective on intestinal parasites, persistent diarrhea, different digestive problems, high cholesterol, heart strokes etc.	Breast cancer [76].
30.	*Lycopersicon esculentum* (*Solanaceae*)	Tomato	Phenols, flavonoids, phytosterols, folic acids, vitamins, beta-caretenoids, (Lycopene, Lutein, Kaempferol).	Antioxidant, hepatoprotective, effective on cardiovascular and skin diseases, antimicrobial etc.	lung, stomach, prostate gland, cervix, breast, oral cavity, pancreas, colorectum, and esophagus etc [77].

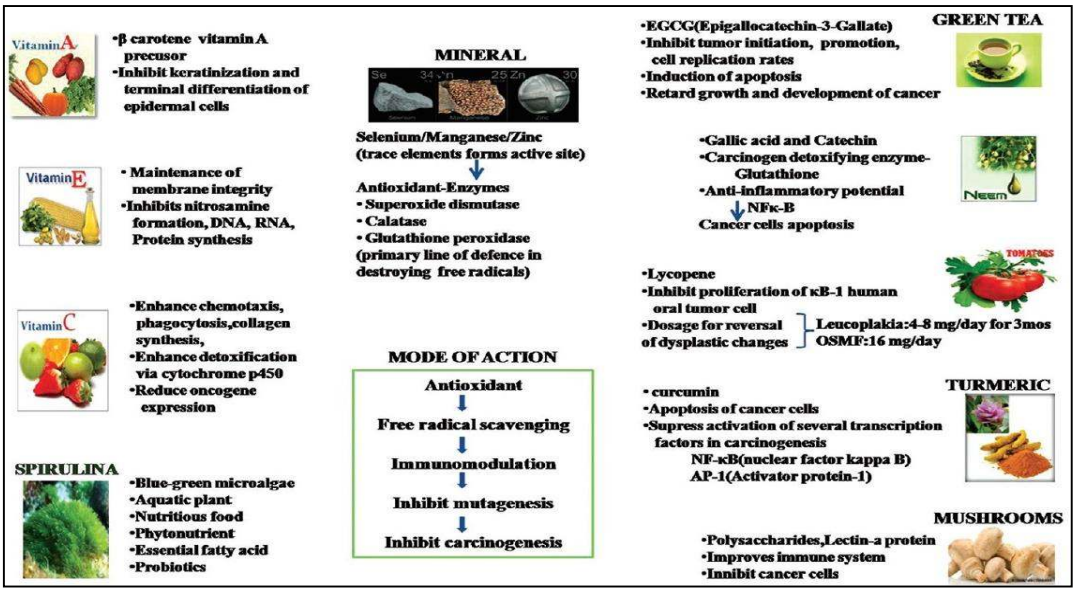

Fig. 2. Showing herbs, spices, vegetables, fruits and their active ingredients as free radical/hydroxyl radical scavengers

6. CONCLUSION

Cancer is one of the most challenging health problems in the entire world today. Herbs, spices, vegetables and fruits based phytotherapeutic molecules and oxidative stress inhibitors are becoming popular as antiproliferative agent, cancer cell growth suppressors and angiogenesis inhibitor thus strengthened their futuristic chemopreventive behavior. Phytochemicals in cancer chemoprevention are considered as the cheapest option without any side effects even immunostimulatory effects. Several studies have shown that plant derived antioxidant scavenge free radicals and modulate oxidative stress. This review has summarized role of phytotherapeutic molecules and antioxidants against cancer and also depicted some of the herbs, spices, vegetables and fruits possessing anticancer activity which is attributed due to presence of phytotherapeutic molecules.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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