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Review Article

Biophenols for cancer treatment: Current perspective and future potential

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ABSTRACT

Vegetable and natural product utilization are conversely connected with diminished malignant growth rate and mortality. Fruit antioxidants have been extensively studied for their ability to scavenge free radicals, preventing to develop the chronic degenerative diseases. As antiproliferative agents, mixtures of biophenols were more effective than individual biophenols. The tyrosol and hydroxytyrosol are major biophenol exist in olive samples. The other biophenol present in olive samples include lignans, verbascoside and flavonoids possessing anticancer properties. The Hydroxychavicol extracted from leaf of *Piper betel* also have chemotherapeutic and chemo preventive properties. Additionally, Curcumin also exhibited strong antit-tumor characteristics against a different type of cancers, including blood, breast, skin, colon, blood and prostrate.

1. Introduction

1.1. Cancer in 21st century

Cancer is a common term employed for a group of disorders that are categorized by the uncontrollable growth of abnormal cells that can enter adjoining parts of body or may spread as well as to other parts. Cancer may also be termed as malignant tumours and neoplasms. It is not limited to any body part as it can affect almost any part of the body and do have various molecular and anatomic subtypes that each type requires specific strategy to manage it.[1] Globally, cancer is becoming a bigger problem for public health and is the second foremost cause of mortality after cardiac diseases. Lung, prostate, oral, stomach, and liver cancer are the most common types of cancer in men. On the other hand, breast, uterine, cervix, stomach, and uterine cancer are the most common types of cancer in women.[2]

WHO has stated that in 2005, from total of 58 million of deaths worldwide, 13% deaths were due to cancer. In 2012, about 15.2 million new cancer cases and 9.3 million mortality due to cancer occurred worldwide as per GLOBOCAN estimates.[3] In year 2015, 8.3 million deaths were due to cancer. Worldwide, currently more than 10 million cancer cases each year. In 2016 it was estimated that 11,323 children from birth to age of 15 years will be suffered with cancer and 1315 will be decease from cancer.[4] By the year 2025 cancer deaths are anticipated to surge considerably upto 17 million globally.[3,5]

Various cancer-causing agents i.e. carcinogens are known. They may be physiological or biochemical such as tobacco and asbestos smoke, ultraviolet radiation, ionizing radiations,[6] several infections by bacteria (e.g., Helicobacter pylori cause gastric cancer),[7] virus (cervical cancer due to human papilloma virus and liver cancer due to hepatitis B virus),[8,9] parasites (e.g., schistosomiasis

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cause bladder cancer)[10] and mycotoxins contaminate food (aflatoxins cause liver cancer).[11] Whereas many kind of cancers are caused because of oxygen centered free radicals and other ROS as their overproduction may cause oxidative damage to biomolecules which includes lipids and proteins etc.[2]

By interfering the cancer cell modulation steps such as initiation and progression, carcinogenesis can be affected. Anti-cancer drugs are effective to treat many cancers but for most of the cancer still there are no extremely effective drugs. Anti-cancer drugs do have several adverse and toxic effects.[12] There is a necessity of novel drugs that are highly effective with minimal side effects and toxicity, and also do have minor environmental impact. Plant derived products offers an approach for innovation in new drug discovery. Biophenols among plant derived products play an imperative role in prevention and cancer therapy with minimal toxicity. Infact a considerable number of clinically used anti-tumour agents are of natural origin. Between 1940s and 2006 more than half of all anti-cancer prescription drugs were belongs to natural products or their derivative, such as biophenols, tannins, alkaloids, etc.[13]

The National Cancer Institute of America, during 1960s started to examine plant extracts with anti-tumour and anti-cancer activity. Since then, natural compounds obtained from medicinal plants have attracted the researchers interest for anti-cancer effects.[14] Many investigations have reported anti-tumour, anti-proliferation, anti-mutagenic effects of plant metabolites specially biophenols. Earlier investigations showed that diet was responsible for 35% of all cancer-related deaths on average.[15] On the other side it is also found that sufficient consumption of biophenols and other plant metabolites in daily diet can prevent and even cure cancer and various other diseases. Therefore, biophenols based drugs would also be extremely effective for most of the cancers. Different clinical trials based on modified diets and plant based nutritional supplements or the cancer prevention.[16]

Dietary plants including vegetables, fruits, leaves, cereals, spices, roots etc. containing noteworthy bioactive compounds levels may offer number of human health aids other than its basic nutritional values. They may also diminish the many chronic diseases risk which include cancer too. The anti-cancer properties of biophenols are believed due to its mechanism to induce cellular defense systems which include detoxifying and anti-oxidant enzymes system, inhibition of anti-inflammatory and anti-proliferation.[2]

2. Treating Cancer Using Synthetic and Plant-based Drugs: Difference and Perspectives

After the cardiovascular diseases, cancer which is multi-step illness starting from a clonal cell with a transformed DNA sequences is the most prominent disease affecting human beings. After the uncontrolled growth of these abnormal cells there occur second mutation that leads to aberrant stage.[17] The cancer instigation and development depend upon both the factors, external i.e., environmental factors (infectious organisms, radiation, tobacco, etc.) and internal factors i.e., within the cells (mutation, immune conditions and hormones). These factors result in atypical behavior and disproportionate proliferation. As a outcome cell mass raise and inflate affecting nearby healthy tissues and may reach to other parts of the body.[18]

The normal frequency of DNA mutations per gene and cell division is one in twenty million. Normally cells divide at fixed rate and controlled manner. For instance, the cells lining the gut are replaced completely every 36 hours, skin cells every few days, and red blood corpuscles every few weeks. When mitosis occurs in these tissues at abnormal rates and uncontrolled manner, this abnormal growth may lead to development of tumour which can further progress into cancer. Tumour development can be described as clonal expansion occurring at naturally selected site, resulting in monoclonal tumours which originate from the progeny of a single cell. During clonal selection, rapidly growing cells accumulate at particular site.[19] The American Cancer Society has projected 1,799,560 new cancer cases and 710,850 deaths from cancer in the USA. In fact, men have a 25 percent higher cancer incidence rate and a 47 percent higher death rate than women do.[20]

When we talk about the treatment strategies for cancer, during chemotherapy, a number of undesirable side effects can occasionally occur. A common chemotherapeutic agent like 5-fluorouracil, for instance, is known to cause cardiotoxicity and myelotoxicity as well as to act as a vaso-spastic agent in a few isolated but documented instances.[21] Doxorubicin, a common chemotherapeutic agent, has cardiac, renal, and myelotoxicity effects. Similarly, the pulmonary toxicity of bleomycin, a well-known chemotherapeutic agent, is well-known. Additionally, bleomycin is toxic to the skin. Cyclophosphamide, which is used to treat a variety of cancers, has been shown to cause hemorrhagic cystitis in the bladder, immunosuppression, alopecia, and cardiotoxicity at high doses.[22]

Natural treatments, like using products made from plants to treat cancer, may reduce side effects. Plants have always had a noteworthy role to play in the folklore of ancient cultures. The plants have been employed as medications for more than 5500 years, in addition to being used as food and spices. In developing nations, it is believed that 75–90% of the populace still uses traditional medicines today.[23] At the beginning of the 19^{th} century, a novel drift that focused on the isolation of plant active compounds began. Plant-derived active compounds were discovered as a result of this trend. In recent eras, an growing number of new plant-derived substances, including those with anti-cancer activity, have been approved and subscribed as medicines.[24] In the

USA, it is assessed that complementary and alternative medicine (CAM) agents derived from various plant parts or nutrients are used by 60-70% of cancer patients either alone or in conjunction with conventional treatments like chemotherapy and/or radiation therapy.[25]

3. Plant Based Drugs: Important Constituents to Fight Against Cancer

Plant based drugs have been known for their beneficial roles. Phytochemical compounds from plants responsible for the pharmacological properties are phenols/polyphenols, alkaloids, tannins, terpenoids, glycosides, carbohydrates, etc. among which plant-based phenols i.e. biophenols have been recognized to diminish the morbidity, and decline the progression of various disorders including cancer. Vegetables, fresh fruits and certain processed plant foods are the good source of biophenols.[26]

It is well-established that phytochemical compounds such as hydroxytyrosol from virgin olive oil, vitamin E obtained from plant oil, phytoestrogens obtained from soybean and EGCG from green tea are effective against cancer.[27] Moreover, many investigations have put focus on plants chemoprotective properties such as Abrus precatorius anti-carcinogenic properties on Yoshida sarcoma in rats, fibrosarcoma in mice and ascites tumour cells.[28] Other than anti-oxidant potential biophenols also possess medicinal properties through, receptor binding, gene expression, enzyme modulation, epigenetic regulation and metabolic interference.[29]

4. Biophenols in Cancer Treatment: Types, Properties and Mechanism

Biophenols are the phenolic compounds of plant origin including curcuminoids, alkaloids, coumarins, quinones, lignans, etc. that have been stated to have antit-tumor, anti-mutagenic, anti-oxidant, cardiovascular, gastrointestinal, immunomodulatory, anti-microbial and chemo preventive properties.[30]

Moreover, biophenols are also documented to affect different body systems, modify immunity and defense mechanism against pathogens, and affect memory, mood, behavior and cognition. Plants with known anti-carcinogenic effects in cancer animal models which include betel, garlic, turmeric, ginger, olive, clove, neem, saffron, aloe vera, etc.[31]

Bioactivities of biophenols are exerted by receptor binding, enzyme modulation, gene expression, epigenetic regulation, metabolic interference. Specifically, cytoprotective effects are exerted by oxidative stress production which induce anti-oxidant defense system, encouraging apoptosis due to cell cycle arrest, carcinogen metabolism regulation and ontogenesis expression, DNA binding and cell adhesion inhibition and blocking signal pathways.[32]

Phenolic phytochemicals activate the ROS-mediated signaling and give rise to the two offensive responses; potential xenohormetic response produces chemo preventive benefits that fortifies the anti-oxidant defense system in premalignant cells, and induction of apoptosis produces chemotherapeutic efficacy by declining the cellular ROS content. Additionally biophenols act as reducing agents and metal chelators to produce anti-oxidant effects.[31]

Anti-oxidant effects of Biophenols was reported in-vitro (in cell lines by upregulating the endogenous anti-oxidation enzymes like catalase, glutathione S-transferase, γ-glutamylcysteine synthetase and glutathione peroxidase. The enhancement of hydroxyl groups and conjugation of double bonds increases the anti-oxidant activity of biophenols.[30]

Oral bioavailability of biophenols is good whereas plasma concentration is low due to extensive first pass mechanism.[33] Cell cycle basically cell growth, activation, proliferation and cell death require redox balance significantly. On occurrence of oxidative stress, cells respond to it. These cellular responses involve the changes in mitochondria and endoplasmic reticulum and results in number of cell deaths that ultimately makes a spectrum from programmed cell death to premature cell death with autophagy. Biophenols induce apoptosis and/or inhibit proliferation by various diverse mechanisms and thus, control cell growth at different stages of carcinogenesis.[34]

5. Plants Containing Anti-cancer Biophenols: Critical Discussion

5.1. HC from piper betle (Betel)

Betel is obtained from Piper betle belonging to family Piperaceae constituting phenols (chavicol, HC, chavibetol, eugenol, cadinene), terpenes, alkaloids, tannins, sugars, diastases, catalase, amino acids, volatile oils, calcium, iron, etc. Betel leaf have been mentioned to hold medicinal characetristics such as anti-microbial, anti-mutagenic, chemopreventive, anti-platelete, immunomodulatory, radioprotective, anti-diabetic, anti-inflammatory, anti-hyperglycemic, etc.[35]

HC is a phenolic compound exist at about 30% in leaves of betel which is stated to have inhibiting effect in prostate cancer, blocks the cell cycle growth in prostate cancer cells and carcinoma cells in oral KB,[36] act as an anti-ulcerogenic agent, lessen stomach ulceration induced by indomethacin that may lead to gastrointestinal cancer,[37] act as an anti-mutagenic agent, effectively inhibit cyclooxygenase (COX) , and production of thromboxane B2,[38] inhibit inflammatory response molecules (COX-2) that increases the growth of tumour by NF-Kb pathway downregulation, oxidative properties, HC high

concentration induces oxidative impairment in cancer cells of liver and thus provokes its pro-oxidant behavior, in oral KB carcinoma act as potent anti-oxidant at lower doses and its high dose increases the level of ROS that induces apoptosis.[36] Chavibetol along with HC possess immunomodulatory, radioprotective.[39]

Chang and his researchers showed in their study that HC encouraged cell cycle arrest at late S and G2/m phase and led to apoptosis of oral KB carcinoma cells. They found HC prevented PUC18 plasmid DNA breaks induced by hydroxyl radicals, suppressed lucigenin chemiluminescence induced by H_2O_2, HC was able to trap superoxide radicals. Results from this study concluded anti-cancer properties of HC. The HC suppressed the KB cells growth, inhibits long term colony formation, KB cell cycle progression. The Attachment of type I collagen to KB cells was inhibited by pretreatment with HC.[36]

In a study, Chakraborty and his researchers exhibited that HC from Piper betle was very effectual against primary cells taken from patient of CML (chronic myeloid leukemia) and leukemic cells expressing mutated Bcr-Abl. The anti CML activity was exhibited by HC in dose dependent fashion. In a xenograft model, BaF3 cells transfected with either T315I or BCR-ABL wild type inhibited tumor growth.[40]

In Another work,Vinsuri et al examined the antitumor activity of HC extracted from P. betle by performing in silico and cytotoxicity investigations. The results of molecular docking proved that HC acted on all sixteen cancer targets tested. The anticancer activity of HC in cell lines of bone cancer (MG63) was also revealed by an in vitro MTT assay, representing the need to develop the molecule as a treatment for various tumors.[41]

Zamakshshari and his researchers also evaluated the anti-cancer effect of HC against the MCF-7 cell lines. After boiling with water, the chloroform extract (M2) contained the highest percentage of HC, according to the HPLC analysis. Except for A549, pure HC and M2 effectively diminished all five studied cell lines. The M2 had better inhibition activity against MCF 7 with IC50 value of 1.94 ug/mL.[42]

Gundala et al., exhibited that HC, obtained from Piper betle leaves, potentially impedes development and propagation through generation of ROS against human prostate cancer cell lines (PC-3). HC altered the progression and kinetics of the cell cycle, diminished clonogenicity, and mediated cytotoxicity through ROS-induced DNA damage that activated a number of pro-apoptotic molecules. The outcomes revealed significant decline in prostate tumour xenografts (75%) with HC oral administration (daily150 mg/kg) demonstrated by measuring quantitative tumour volume and real-time bioluminescent imaging.[43]

5.2. Quercetin from Azadirachta indica (Neem)

Azadiracta indicacommonly known as Neem, belonging to family Meliaceae possess many therapeutic properties such as anti-malarial, anti-cancer, anti-tumourogenic, anti-mutagenic, etc. Neem consists of number of phenolic compounds including quercetin, ß-sitosterol and, limonoids among which quercetin and ß-sitosterol are accountable for its anti-cancer property and limonoids for anti-mutagenic property. Some studies reported diminishing effects of neem on the growth of malignant cells by different molecular pathways such as tumour suppressor gene, apoptosis, modulation of cellular proliferation, etc.[44]

Nimbolide possess anticancer effect against the human chorio carcinoma cells (BeWo) in a study which caused in dose and time dependent decline in BeWo cells growth with IC_{50} values of 3.02 and 1.52 μM for 7 and 24 h, respectively. Quercitin, azadirachtin, limonoids and nimbolide together inhibit the growth of HBP carcinomas induced by DMBA by controlling different mechanisms such as (i) upregulation of anti-oxidant and carcinogen detoxification enzymes, (ii) procarcinogen activation and oxidative DNA damage prevention, and (iii) inhibition of tumour invasion and angiogenesis (possess chemopreventive potential).[45]

Active constituents of neem play crucial role in diverse cell signaling pathways modulation and prevention cancer development and progression. They activates apoptosis, tumour suppressor genes, cyclooxygenase pathway and suppression of signaling of NF- κB, and inactivate several genes such as NF-κB and PI3K/Akt which play important role in development and progression of cancer.[46]

Avila and his colleagues exhibited that quercetin has the capacity to diminish the p53 expression i.e., tumour suppressor protein which is key protein in apoptosis. With this mechanism it inhibited cells of human breast cancer in their study.[47]

Vijayababu and his researchers investigated the quercetin impact on cell cycle arrest and proliferation of cell in prostate cancer cell lines (PC-3). They found that quercetin showed anti-tumour and anti-oxidant effects on PC-3 cancer cells by persuading apoptosis, arrest of cell cycle at G2-M phase, peak at sub G1, inhibiting PC-3 cells growth and increasing hypophosphorylated form of pRb.[48]

Sharma et al., showed the neem anti-proliferative properties chemo preventive agent. The researchers exhibited that neem ethanolic extract diminished the MCF-7 cells and HeLa cells growth which was dose dependent. The neem extracts with 50, 200, and 500 μg/mL against MCF-7 cells and HeLa cells exhibited programmed cell death (apoptosis) characterized with distinctive features such as shrinking of cell, rounding off and detachment of cell from the matrix. The cancer cells' nuclear morphology also displayed apparent variations like nuclear condensation, marginalization, apoptotic body formation, and fragmentation.[46]

5.3. Charvacrol from Ocimum basilicum (Basil)

Charvacrol is obtained from Osimum basilicum (basil), family Lamiaceae which is well known for its anti-cancer activity. Basil contain phenolic compounds and various other chemical constituents due to which it possess anti-microbial, anti-tumor, anti-mutagenic, anti-tumorigenic, anti-mutagenic properties and antagonistic activity against bacteria.[49]

Dasgupta et al., shown that basil lower the oxidative damage in animal models. When mice were feeded with a basil leaves hydroalcoholic extract 200 and 400 mg/kg for 2 weeks, they found marked enhance in glutathione (GSH) reductase (2 fold), GPx (1.5), superoxide dismutase (1.3 fold) and catalase (1.56-1.58 fold) and change in these enzymes leads to the decreased lipid peroxidation.[50]

Dragan et al., found improvement in the breast cancer patients in their research. The researchers investigated the effects of soups and salads containing balsamic vinegar-enriched extracts from rosemary and basil on oxidative stress and quality of life in breast cancer patients in stages III and IV and found the decrease in oxidative stress leading towards improvement.[51]

Jeurissen and his colleagues demonstrated the basil extract anti-mutagenic effect on human hepatoma (HepG2) cell line. The researchers discovered that a 50 g/mL concentration of basil prevented DNA adduct formation in the HepG2 cell line caused by 1′-hydroxyestragole by promoting phase II enzymes and conjugation and eliminating carcinogens. The study provides evidence the basil capability to decline the aflatoxin B_1 and benzo(a)pyrene (B(a)P) mutagenicity. The basil extract based on hexane (1 mg/plate) and basil extract based on methanol-chloroform (0.5 mg/plate) inhibited mutagenicity of AFB_1 by >30% whereas methanol-chloroform basil extract (1-2 mg/plate) hindered the mutagenicity of B(a)P.[52]

Basil is also found to decrease DMBA-induced carcinogenesis. Researchers found decrease in -i skin tumors induced by DMBA (13.7% decline for lower dose and 19% decline for higher dose) and lowered tumor burden in Swiss mice provided with diet 150/300 mg/kg body weight of extract of basil. The control group's tumor burden was 2.5 times lower in the low dose basil group and 4.8 times lower in the high dose basil group when it was compared with average number of tumors per mouse.[53]

Kathirvel and his colleagues examined the anti-cancer activity of chemical composition of Ocimum basilicum essential oil in vitro. The researchers measured HeLa, HEp-2 and NIH 3T3 viability with various O. basilicum essential oil concentrations by comparing with etoposide (anti-cancer agent kept as standard) and found that oil diverse concentrations affected HeLa, Hep-2 and NIH 3T3 cells viability in a dose dependent manner and IC50 values were calculated as 91.2, 95.9 and 121.5 $mgmL^{-1}$, respectively.[54]

5.4. Curcumin from curcuma longa (Turmeric)

Turmeric is the source of curcumin., Curcuma longa belonging to family Zingiberaceae. Turmeric contains curcumin, demethoxycurcumin, bisdemethoxycurcumin, tumerone, germacrone, atlantone and zingeberene among which curcumin is the major component and have been stated for its anti-tumor effects in breast cancer, colon cancer, lung metastases and anti-tumour effects in brain tumour.[55] Curcumin inhibit mTOR complex I, and dissociate raptor from mTOR and hence can also be called mTOR inhibitor.[56] Curcumin, an anti-tumor agent, regulates a variety of cell signaling pathways include caspase-3, 8, and 9, pathway of cell proliferation such as cyclin D1, p21 and cell survival pathway such as Bcl-x, cFLIP protein kinase pathway inlcude Akt, and AMPK,to control the growth of tumor cells[57] and attenuates the p65 and cell invasion by EGFR gene expression suppression and Akt/mTOR signaling modulation, downregulating the MMP-2 expression and COX-2 and cell growth inhibition.[58]

In an investigation Wang and his researchers exhibited that in mouse melanoma B16BL6 curcumin exerted anticancer effect by diminishing cell adhesion and growth by PRL-3 regulation. The PRL-3 mRNA of B16BL6 was diminished by curcumin which was dose dependent. In other cell lines too curcumin inhibited PRL-3 expressions but had negligible impact on PRL-1 and PRL-2 expression.[59]

Wang and his colleagues found curcumin have an anti-tumor effect on cells of breast cancer by diminishing cell proliferation through the miR-21/PTEN/Akt pathway. Their investigation exhibited that curcumin encourages cell apoptosis, apoptotic morphology in cells, cytotoxicity, caspase-3/9 activities, regulates PTEN/Akt and mi-21 expression.[60]

Akt/mammalian target of rapamycin (mTOR) signaling is dysregulated in many tumors, particularly metastatic prostate cancers, plays a significant role in tumorigenesis. By inhibiting this cancer can be inhibited. Yu and his researchers have investigated the curcumin anti-cancer effect in prostate cancer in vivo in which they have exhibited that curcumin effectually prevent and hinder prostate cancer by inhibiting protein synthesis, cell proliferation, Akt phosphorylation in PC-3 cells. Curcumin also activated mitogen-activated protein kinases and 5'-AMP-activated protein kinases. Curcumin inhibited Akt/mTOR signaling through protein phosphatase-dependent dephosphorylation triggered by calyculin A.[61]

Inhibition of DNA and protein synthesis is followed by inhibition of cell proliferation which was concentration dependent.[61]

Saffron is obtained from the Crocus sativus flowers belonging to family Iridaceae. It contains volatile and non-volatile components from which volatile are the aroma yielding components and non-volatile include crocin, α-crocin, carotenoids (lycopene), zeaxanthine, α- and β-

carotenes, crocetin, and picrocrocin which are accountable for different properties of saffron like color, flavor, mass and therapeutic values.[62]

Saffron is reported to have anti-oxidant, anti-inflammatory, anti-nociceptive, anti-tumor, properties. Other than these properties saffron is also reported to improve learning behavior, neuronal cell death and management of psoriasis. Anti-cancer, anti-tumorigenic, properties of saffron are owed to crocin and crocetin.[63]

Some studies show evidence to the capability of saffron to attenuate cancer by different pathways. It is found that aqueous preparation of saffron hinder skin carcinogenesis induced by chemicals.[64] It is known that changes in the bioactivity of carcinogens and the growth of tumors can happen.[65]

Crocin conquers proliferation in neoplastic cells to a larger extent as compared to normal cells and reduces cell viability in a time and concentration dependent manner. According to Dhar and his researchers these responses are not just limited to in-vitro results as they found that pacncreatic xenografts were also influenced by saffron at dose of 4 mg/kg diet for one month in their research.[66]

Samarghandian et al., investigated the caspase-dependent pathways that were responsible for the A549 cells' activation of saffron-induced apoptosis. The researchers observed that saffron demonstrated good cytotoxicity against the A549 cells because of its specific cytotoxic behavior toward A549 cells. The A549 cells' proliferation was reduced by dose and time dependent saffron treatment.

The apoptotic cells percentage augmented with increasing concentrations of saffron, and morphological changes enhanced by saffron lead to decrease in % of viable cells, encouraged apoptosis and activated caspase pathways. Long-term effect of saffron was seen as maximum anti-cancer activity against the cells of A549, at 72 h. Hence, The caspase-dependent pathways activation that the saffron aqueous extract uses to diminish the proliferation of cell and encourage the apoptosis in cancer cells may partly account for the extract's anti-cancer activity.[67]

Das et al., studied anti-cancer and chemo preventive effect of saffron in mice with skin carcinogenesis induced by DMBA. Study indicated that anti-cancer and chemo preventive effect of saffron occur due to crocin and crocetin present within. They found that crocin and crocetin stimulate anti-oxidant enzymes within the cells which surge the enzyme activity and downregulate the generation of LPO and ROS. With this mechanism saffron infusion inhibit papilloma growth, cell proliferation, dysplasia, and hyperplasia and also reduces the incidence of skin papilloma on the treated areas. Saffron also prevent tumor progression and angiogenesis by inhibiting micro vessels in papillomatosis and SCC.[65]

5.5. Hydroxytyrosol and luteolin from Olea europaea (Olive)

5.5.1. Hydroxytyrosol and oleuropein from olive oil

Olive oil, leaf and fruits are obtained from Olea europaea belonging to family Oleaceae. Virgin olive oil VOO contain high amount of phenolic compounds i.e. about 500 mg/L. Chemical constituents present in VOO include oleuropein, hydroxytyrosol, tyrosol, flavonoids, aglycon, ligstroside, and oleocanthal, among which hydroxytyrosol and oleuropein are major polyphenolic compounds which are powerful anti-oxidants responsible for anti-angiogenic, anti-inflammatory and anti-cancer properties. Olive oil possess anti-microbial, anti-viral, anti-oxidant, anti-inflammatory, anti-atherogenic, anti-angiogenic, anti-cancer and gustatory properties. Risk of several cancers like upper gastrointestinal, colorectal, respiratory tract and breast cancers can be reduced by consumption of virgin olive oil (VOO) rich diet. Topical application of VOO after UV-B exposure reduces oxidative damage of DNA in the epidermis leading to reduced risk of murine skin cancer/tumour. Biophenols of VOO have capacity to (i) inhibit initiation, propagation and metastasis stages of colon carcinogenesis, (ii) inhibit HER2 gene activity in HER2-overexpressing breast carcinoma cells by downregulating the expression of the fatty acid synthase enzyme FASN and by promoting the proteasomal degradation of the HER2 protein. Polyphenols present in olive oil induce apoptosis, reduce cell proliferation and viability, delay cell cycle, prevent metastasis, reduce angiogenesis, inhibit epithelial to mesenchymal transition, disassemble cytoskeleton, recover sensitivity to chemotherapeutics and scavenge free radicals and reactive oxygen species, which altogether lead to the anti-cancer effect.

Carvalho and his colleagues evaluated anti-cancer effect of hydroxytyrosol and secoiridoids (oleuropein aglycone) on human amelanotic melanoma cells (C32 cell line) in-vitro and found growth inhibiting activity in different concentrations.[68]

Rodriguez and his colleagues found in their investigation that hydroxytyrosol and oleuropein inhibited cell proliferation of E2-induced MCF-7 cells in a dose dependent manner. They induced generation of ROS and increased its production that in turn exert chemotherapeutic effect by suppressing the cancer cell growth.[69]

Rhouma et al investigated the anticancer potential of olive flower phenolic compounds on MCF-7 cells derived from the olive tree cultivar Chemlali. Immunoblotting was used to examine apoptosis-related biochemical markers. Flavonoids, secoiridoids, and simple phenols were the main phenolic compounds found in olive flower, according to investigation. MCF-7 cell viability was significantly reduced by the phenolic extract and EC50 values was approximately 223.56 g/ml. The cleaved forms of Parp-1 were found in Western blot analysis. The number of treated

cells decreased significantly, and their morphology changed significantly, according to the DAPI staining analysis. The Olea europaea flower contained numerous biophenols that could induce apoptosis and reduce the proliferation of breast cancer MCF-7 cells.[70]

5.5.2. Luteolin and apigenin from olive leaf

Olive tree leaves are widely used in anti-hypersensitive, anti-oxidant, anti-inflammatory, anti-atherogenic, hypocholesterolemic and hypoglycemic treatment in traditional medicine system. Polyphenols present in olive leaf are similar to that present in olive oil, in addition to these luteolin and apigenin are also present in leaf which are the major active polyphenolic constituents and responsible for the anti-cancer properties.[71]

Olive leaf contain high proportion of glycoside moiety hence, phenolic compounds of VOO and leaf differ in their structures. Presence of glucose moiety play pivotal role in improving bioactive potential and bioavailability of the polyphenols, thereby evidencing that olive leaf extract have excellent potential than VOO for to improve the health. In a variety of studies, it was discovered that in mouse cell lines, luteolin and apigenin act as aryl hydrocarbon receptor (AhR) antagonists. AhR is translocated to nucleus on ligand binding and activates the response elements in DNA sequence xenobiotic enzymes production. It Inhibits phosphorylated Akt levels via downregulating phosphatidylinosotide 3-kinase (P13K)/Akt pathway which leads to stimulation of apoptosis. Decreased the level of Phosphorylated Akt in all cell lines. It was found that both weight and volume of tumor was reduced by luteolin at dose of 10 mg/kg/day in a prostate xenograft mouse model in-vivo and, in-vitro it downregulated VEGF phosphorylation of VEGF2 receptor. Apigenin inhibit the phosphorylation of IkBα, NF-κB signaling pathway and nuclear translocation of p65 within the nucleus resulting in suppression of growth of MCF-7 cells and reduces STAT3 transcriptional activity in the cells, evidencing growth suppressive activity.

Seo et al showed that MCF-7 vec and MCF-7 HER2 cells were inhibited in their cell proliferation by apigenin, which was accompanied by an increase in sub-G0/G1 apoptotic fractions. By increasing the levels of cleaved caspase-8, apigenin induce apoptosis through the extrinsic apoptosis pathway, but do not induce via intrinsic mitochondrial apoptosis pathway as apigenin do not decrease mitochondrial membrane potential. B-cell lymphoma 2 (BCL2) and Bcl-2-associated X protein levels are unaffected by apigenin. It also reduces tyrosine phosphorylation of HER2 and up-regulate the levels of p21, p-53 and phospho-p53 in MCF-7 vec and MCF-7 HER2 cells. According to the study, apigenin activates apoptosis through a p53-dependent pathway. Apigenin reduces phosphor-JAK1 and phosphor-STAT3 expressions, decreases level of phosphorylation of IjBa in cytosol, decreases activity of STAT3-dependent luciferase reporter gene, abrogate the nuclear translocation f p65 within the nucleus which in turn blocks NFjB signaling pathway activation in MCF-7 vec and MCF-7 HER2 cells. Overall they conclude that apigenin is the phenolic compound that can be potentially effective in preventing and treating HER2-overexpressing breast cancer.[72]

Catalan and his colleagues showed anti-proliferative capacity of pure luteolin on breast cancer cells (JIMT-1). In cell cycle experiment they found luteolin induced cell death, apoptosis in JIMT-1. MAPK pathway on activation leads to cell differentiation, cell proliferation and migration and inhibition of apoptosis. Luteolin induce apoptosis by inhibiting MAPK pathway by inactivating ERK1/2 which is the major effector of MAPK pathway. This mechanism may produce anti-proliferative effects. By initiating early apoptosis which was caspase dependent and cell cycle arrest, luteolin also inhibited cancer cell proliferation and invasion. Caspase dependent apoptosis and cell cycle arrest are known to be mediated by inhibition of histone deacetylase, MAPK pathways like p38 MAPK or ERK induced by growth factor. The distribution of cell cycle phases for JIMT-1 treated with pure luteolin, and different concentration of complete olive leaf extract, and modulation of ERK1/2 activity in JIMT-1 treated with pure luteolin, and different concentration of complete olive leaf extract.[72]

5.6. Palmatine and tinocordiside Tinospora cordifolia (Giloy)

Tinospora cordifolia usually known as giloy which belongs to family Menispermaceae is extensively employed in traditional medicinal system for treat various diseases because of its possible health benefits, and lack or no side effects. It is recognized to have anti-spasmodic, anti-diabetic, anti-oxidant, anti-pyretic, anti-toxic, anti-neoplastic, anti-cancer hypolipidemic, hypoglycemic and immunomodulatory properties. Other than this it is commonly used in fever, loss of appetite, general weakness, dysentery, viral hepatitis, anemia, digestive disturbances and urinary diseases. Major chemical constituents present in it includes tinosporine, tinosporaside, tinosporide, cordifol, cordifolide, furano, diterpenoid furanolactone tinosporidine, β-sitosterol, bitter gilonin and non-gilonin.

Studies demonstrated anti-cancer activity of giloy in animal models. Different extracts play different roles in producing anti-cancer effects, such as (i) root extract shows radio protective role, in pre-irradiating mice this extract affected radiation and increased lipid peroxidation leading to decreased level of GSH in testes (ii) the giloy Dichloromethane extracts exhibits anticancer effects by inducing lipid peroxidation, LDH release and GST reduction.

Kamble S investigated effect of methanolic extract of giloy stem in MDA-MB-231. Researcher used cytotoxicity

assay based on MTT and wound healing migration assay to evaluate effect of extract against growth and migration ability of human breast cancer cell line respectively and observe that the giloy methanolic extract exhibited significant anti-tumor and anti-oxidant activity.

Bala and his colleagues isolated active compounds from T. cordifolia and characterized anti-cancer and immunomodulatory effects on four different cancer cell lines include CHOK-1, HT-29 (human colon cancer) and SiHa (human cervical cancer), KB (human oral squamous carcinoma). They isolated 8 compounds among which palmatine and tinocordiside were active against cancer cells. Palmatine was significantly cytotoxic against KB cells (87.271.8%, po0.001and IC50 of 46.1 μM) and HT-29 cells (82.774.3%, po0.001 and IC50 of 49.1 μg/ ml). Tinocordiside was found significantly cytotoxic against CHOK-1 cells (5771.6%, po0.001 and IC50 of 44.9 μM) and SiHa cells but mildly cytotoxic on HT-29 cells.[73]

6. Conclusion

The cancer is the second most chief reason of death and is increasingly taking the lead in older people. Polyphenols, a class of secondary plant metabolites that are mostly found in plants, have been the subject of a number of epidemiological and animal studies. These studies have suggested that polyphenols may protect against cancer and other chronic degenerative diseases. Consuming fruit and vegetables have a negative correlation with a reduction in cancer mortality and incidence. Polyphenol-rich fruits are thought to have antioxidant, chemo preventive, and chemotherapeutic potential. The cancer treatment requires therapies that are less harmful but still effective. HC is an allylbenzene that has acquired a lot of consideration because of its antitumor properties.

7. Source of Funding

None.

8. Conflict of Interest

None.

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