

REVIEW

Potential Phytochemicals for Cancer Treatment: A Review

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ABSTRACT

Today, cancer had been described as one of the deadliest diseases worldwide. It has been estimated that cancer causes about 9.9 million deaths in the year 2020. The conventional treatment for the disease involves single chemotherapy or a combination of mono-chemotherapy and or a combination of mono-chemotherapy and radiotherapy. However, there are negative sides to these approaches which have prompted the search for new therapeutic drugs. In view of this, scientific communities have started looking for innovative sources of anticancer compound of natural origin which include traditional plants. Nowadays, several studies have evaluated the anticancer properties of bioactive components (phytochemicals) derived from the plants both in vivo and in vitro. The phytochemicals are secondary metabolites or chemical compound produced during metabolic process in plants which are useful in the protection of plants. Most of these phytochemicals such as alkaloid, flavonoids, phenolic compounds, cyanidin, fisetin, genistein, gingerol kaempferol, quercetin, resveratrol possessed certain medicinal properties and found to have numerous applications in pharmaceutical industries for treatment of cancer. The paper was aimed to review some plants bioactive components (phytochemicals) used in cancer treatment.

1. Introduction

Today, cancer had been described as one of the deadliest diseases worldwide. It has been estimated that cancer causes about 9.9 million deaths in the year 2020^[1]. Cancer is a complex disease characterized by uncontrolled proliferation and development of cells in tissues forming

a tumour that may potentially expand to a whole organ or systematically to other tissues called metastasis^[2]. The severity of death due to cancer in the world every year indicated that the present standard of treatment with chemotherapeutic drugs is not enough. According to the World Health Organization (WHO), the global cancer rate could increase by half by 2020 in which majority

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of the affected population will be from medium and low income countries, with lack of chemotherapeutic drugs as well as other resources^[3]. As result, there is need for alternative anticancer therapeutic drugs. This has pushed researchers and scientist to search for innovative alternate source of anticancer drugs from natural source including plants^[4]. Initially, plants have been used in all cultures for healing wide ranges of diseases and as well to improve well-being^[5,6]. Further studies demonstrated that medicinal plants contain secondary metabolites called phytochemicals, which have a positive effect on health due to their medicinal properties. These effects of the phytochemicals are attributed to the biological properties such as anti-inflammatory, antioxidant, antimicrobial and anticancer they possessed. Today, the potential of plants as a source of anticancer agents is recorded well both in experimental findings and traditional medicine^[7]. In most cases, phytochemicals have been applied directly or modified chemically to develop chemical compounds used in modern medicine which include anticancer drugs. Food and Drug Administration (FDA) inform that over 60% of the drugs used in treatment of cancer are sourced from natural resources^[5].

Therefore, plant-anticancer compound has been considered as a possible option for the development of new chemotherapeutics and also to improve the affectivity of the conventional drugs^[8-10]. However, these plants derived compounds present many drawbacks, such as negative side effect (toxicity), low stability and difficulties in extraction from natural source^[11]. Hence, the application of phytochemicals still faces challenges and need for further research is vital. Phytochemicals are largely distributed in different parts of plants with the potential of reducing the risk of different types of diseases including cancer^[12].

2. Cancer

Today, cancer had been described as one of the deadliest diseases worldwide. It has been estimated that cancer causes about 9.9 million deaths in the year 2020^[1]. Cancer is a complex disease characterized by uncontrolled proliferation and development of cells in tissues forming a tumour that may potentially expand to a whole organ or systematically to other tissues called metastasis^[2]. The abnormal cell behavior due to cancer may be as a result of heredity genetics or alteration of oncogens related to cell cycle and regulation of cell death (apoptosis)^[13]. According to World Health Organization, the main causes behind the development of cancer include; ionization radiation, reactive oxidative species (ROS), random somatic mutation, chemical agents

such as alkylating agents, and biological agents^[14]. The ionization radiations such as x-rays are able to disrupt the hydrogen bond between nucleic acid thereby altering its chemical structure, which may lead to alteration in normal DNA expression regulation^[15]. Infectious caused by microorganisms such as bacteria, virus and fungi have also been significantly correlated with developing cancer^[16]. Virus that integrate their genetic materials into the host tissue or organ may alter normal genetic expression related to cell division or even induce oncogens that could derive into cancer development^[17-19]. Conversely, bacterial infection may evoke the release of toxins with cytotoxic effect and the disruption of the tissue cell matrix. Some common examples of bacterial toxins are enteric toxins from *Salmonella typhi* or CagA and vacuolating toxins of *Helicobacter pylori*, which may induce formation of new tissue (neoplasia), cell death, and alteration in the normal cell metabolism^[20,21]. Other infectious pathogens such as parasitic helminths and fungi that produce direct or toxin-mediated tisular damage are also considered as oncogenic agents^[22]. Apart from genetic alteration, the main recognized tumor-inducing mechanism of biological agents is tissue inflammation as a result of cell damage and subsequent neoplasia which, if unchecked, can result in potential chronic inflammation of the affected tissues (e.g., hepatic cirrhosis by Hepatitis virus)^[17,23].

Reactive oxygen species (ROS) such as hydroxyl radical or hydrogen peroxide are believed to provoke the alteration and damage of the cell membrane, DNA and lipids^[24]. They are also been identified to increase in tumor cells enhancing their survivability and proliferation^[25]. Nonetheless, the common factor besides possible genetic alterations by oxidative stress, infections and ultraviolet radiation is the associated inflammatory response^[22,24]. On this matter, chronic inflammation is considered both cause and symptom of other ailments, but particularly of cancer, as tumorous cells secrete several pro-inflammatory molecules^[26]. For example, it is well known that the pro-inflammatory mediator cyclooxygenase-2 (COX-2) is over-expressed in several types of cancer. As such, pro-inflammatory mediators are markers of cancer and could be also a possible target for anticancer therapies^[27,28]. Considering chemical carcinogens aside from potentially hazardous substances, the main carcinogens originate in diet. Major chemical carcinogens include polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds, heterocyclic amines (HCAs) and alcohol. PAHs like anthracene appear in combustion reactions, and are reported in grilled or smoked foods, as well as being part of urban air pollution. They are linked to lung and digestive tract cancer^[29,30]. Closely related in their

effects and occurrence, HCAs like 2-Amino-1-methyl-6-phenylimidazo [4,5-b] pyridine are the result of pyrolysis of proteins and amino acids in meat or fish foods [31,32]. It is worth mentioning that tobacco is reported to contain high levels of PAHs and HCAs, linking them to the pro-carcinogen effects of tobacco consumption [33]. N-nitroso compounds are additives in processed meats and include nitrites and nitrosamines like N-nitrosodimethylamine that have been correlated to gastric cancer development [34]. Ethanol as well as other alcohols present in beverages and spirits induce many metabolic and endocrine disorders along with being highly cytotoxic chemicals and attributed to cause many types of cancers [35]. Altogether, it should be considered that a variety of exogenous carcinogens from different sources can heavily prompt cancer development.

3. Phytochemicals

The phytochemicals are secondary metabolites or chemical compound produced during metabolic process in plants which are useful in the protection of plants [37]. Many of these secondary metabolites possess vital medicinal properties which have many applications in pharmaceutical industries. Phytochemicals such as alkaloids, tannin, quinones, flavonoids, vitamins and amines are free radical-scavenging molecules and possess antimicrobial, anti-inflammatory, antioxidant and anticancer activities [38]. In general, most plants bioactive components possess antioxidant property which protects human cells against oxidative damage. Phytochemical from such plants are used for reducing the intensity of inflammation related diseases and as well provide protective effect by countering reactive oxygen species (ROS) [39].

4. Some Phytochemicals Used as Anticancer Agents

4.1 Cyanidin

Cyanidin is an extract of pigment from red berries such as blackberry, apples, red onion, red cabbage, plums, raspberry, cranberry and grapes. The extract possesses radical scavenging and antioxidant effect which may reduce cancer risk. It is reported that cyanidin inhibits cell proliferation and gene expression in colon cancer cell [40]. Another research demonstrated that Cyanidin-3-glucoside (C3G) attenuated the benzo[a]pyrene-7,8-diol-9,10-epoxide-induced activation of AP-1 and NF- κ B and phosphorylation of MEK, MKK4, Akt, and MAPKs and blocked the activation of the Fyn kinase signaling pathway, which may contribute to its chemo-preventive

potential [41]. Cyanidin-3-glucoside inhibit ethanol-induced activation of ErbB2/cSrc/FAK pathway in breast cancer cells and may reduce ethanol-induced breast cancer metastasis [42], inhibition of growth and induction of apoptosis in tumorigenic rat esophagus cell line [43], and inhibition of UVB-induced COX-2 expression and PGE2 secretion in the epidermal skin cell line by suppressing NF- κ B and AP-1 which are regulated by MAPK [44-46].

4.2 Fisetin

Fisetin is the flavone found in several plants such as Eurasian smoke tree, apple, grape, onion, *Acacia*, cucumber, strawberries, and persimmon [47]. The compound has been found to reduce aging effect in fruit fly or yeast [48] and exert anti-inflammatory effect in LPS-induced acute pulmonary inflammation and anticarcinogenic effects in HCT-116 human colon cancer cells [49]. Fisetin is also a potent antioxidant and modulates lipid and protein kinase pathways. Along with other flavonoids such as luteolin, galangin, quercetin and EGCG, induced the expression of Nrf2 and the phase II gene product HO-1 in retinal pigment epithelial cells which could retinal pigment epithelial cells from death due to oxidative stress with high degree of potency and low toxicity and reduced hydrogen peroxide induced cell death. A study conducted by Khan et al. [50] found dual inhibition of PI3K/Akt and mTOR signaling in human non-small cell lung cancer cells by fisetin.

4.3 Genistein

Genistein is the isoflavane that originate from a number of plants such as fava beans, lupine, soy beans, coffee, *Flemingia vestita* and kudzu. Genistein functions as anthelmintic, antioxidant and as well found to have antiangiogenic effect i.e. blocking of blood vessels formation. It also found to block the uncontrolled cell growth associated with cancer most likely by inhibiting the enzyme that regulate cell survival (growth factor) and cell division. The genistein activity was actively functions as tyrosine inhibitor by inhibiting DNA topoisomerase II [51]. *In vivo* and *in vitro* studies show that genistein is important in treating leukemia [52].

4.4 Gingerol

Gingerol is an active component of fresh ginger with characteristics spiciness. It is known for its anticancer activity against cancer in the colon [53], ovary, breast [54], and pancreas [55]. A review recently conducted by Oyagbemi et al. [56] summed up the mechanisms in the medicinal effect of gingerol. In summary, gingerol has

demonstrated anti-inflammatory, antioxidant and antitumor promoting properties and decreases iNOS and TNF-alpha expression via suppression of I κ B α phosphorylation and NF- κ B nuclear translocation [56]. Treating MOLT4 and K562 with gingerol, the ROS level was significantly higher than the control, including apoptosis of leukemia cells by mitochondrial pathway.

4.5 Kaempferol

Kaempferol is a natural flavonol isolated from grape fruit, apples, tea, witch hazel, Brussels sprout broccoli etc. it has been studied for pancreatic cancer [57] and lung cancer [58]. Kaempferol has also been investigated for its radical scavenging effect, antiangiogenic and anticancer [59]. The compound displayed moderate cytostatic activity of 24.8 - 64.7 μ M in the cell line of PC3, HeLa, and K562 human cancer cell. Kaempferol has been studied as aryl hydrocarbon receptor antagonist showing inhibition of ABCG2 upregulation, thereby reversing the ABCG2-mediated multidrug resistance and this can be useful for treatment of esophageal cancer.

4.6 Lycopene

Lycopene as phytochemical is a bright red pigment from fruits such as watermelons, tomato, red papayas and red carrot. It shows antioxidant activity and chemopreventive effect in prostate cancer. The anticancer property of lycopene is largely attributed to activating cancer preventing enzymes such as phase II detoxification enzymes [60]. Lycopene was found inhibiting human cancer cell proliferation and suppressing insulin like growth factor-I-stimulated growth. This may open new avenue for its study on the role of the treatment and prevention of endometrial cancer and other forms of tumors. The Lycopene also possessed inhibitory effects on endometrial and breast cancer cell [61], prostate and colon cancer cells [60].

4.7 Quercetin

Quercetin is a flavonoid compound mostly found in leafy vegetables, berries and onions, to which the anticancer property is attributed [62]. In this sense, numerous studies *in vivo* and *in vitro* pre-clinical studies have shown positive results. Regarding its action mechanisms, quercetin has been demonstrated to induce cell cycle arrest by regulating cyclin D1 and p53-related pathways; apoptosis through the induction of pro-apoptotic factors and the decrease of anti-apoptotic ones; induces autophagy and inhibits proliferation, angiogenesis and metastasis [63]. These effects have been observed in

different *in vitro* cell lines, including breast, ovarian, lung and colon cancer cells, among many others [63], and also in different *in vivo* mice models [64]. Furthermore, quercetin has been reported to enhance the efficacy of chemotherapeutic drugs [65]. Regarding clinical trials, several have evaluated the suitability of quercetin as anticancer drug. For example, a study conducted on humans reported that a high intake of quercetin in the diet is inversely related to the risk of gastric adenocarcinoma [66]. Another study evaluated the use of quercetin to prevent and treat oral mucositis induced by chemotherapy. The results showed a significant reduction of oral mucositis incidence in the quercetin treated group, which may suggest that this compound could be used to palliate chemotherapy side-effects [67].

4.8 Resveratrol

Resveratrol is a phenolic compound present in some fruits, such as grapes, peanuts, blueberries and blackberries. Numerous studies have evaluated the anticancer properties of this compound. Several action mechanisms of resveratrol have been described: positive regulation of p53 and BAX proteins (related with proapoptotic pathways) and negative regulation of NF- κ B, AP-1, hypoxia-inducible factor 1-alpha (HIF-1 α), matrix metalloproteases, Bcl-2 protein, COX-2, cytokines and CDK [68]. Some pre-clinical studies performed *in vitro* demonstrated that resveratrol was able to suppress the cell proliferation through cell cycle arrest, induce apoptosis and modulate autophagy in different cancer cell lines, including ovarian cancer cell line, resistant human leukemia cells, non-small-cell lung cancer and human lung adenocarcinoma [69]. Regarding *in vivo* studies, the anticancer properties of these compounds were also significant. For example, in an *in vivo* study, resveratrol was administered to mice, leading to a 60% reduction in the appearance of sporadic colorectal cancer. Similarly, resveratrol inhibited cell proliferation, induced the apoptosis and suppressed the angiogenesis and metastasis in bladder cancer mice models [70]. Resveratrol has been also reported to enhance the efficacy of traditional chemotherapeutic drugs, including temozolomide, doxorubicin and paclitaxel in mice models [71].

5. Conclusions

Cancer is a complex disease that every year costs several millions of human lives. The uncontrolled proliferation of cells causes the incorrect functioning of the body, with a long list of symptoms and finally, death. So, given the health and social importance

of this disease, but also its economic impact on the health system, new therapeutic alternatives are being continuously investigated. Traditional plants have been historically considered as an endless source of new compounds for the development of new pharmaceuticals and drugs. Therefore, nowadays researchers have at their complete disposal, plenty of ethnomedicinal and ethnopharmacological information of very different plant species which is a tool for selecting candidates and lead the research to those plants more promising. In this context, a variety of phytochemicals obtained from plants have been discovered and are currently used in cancer therapies such as cyanidin, fisetin, genistein, gingerol kaempferol, quercetin, resveratrol.

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