PLANTS- DERIVED MATERIALS AND THEIR EFFECTS AS ANTICANCER AGENTS: A REVIEW

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ABSTRACT

Cancer is the main cause of death worldwide, in spite of improvement in early detection and treatments, and this request an active strategy for prevention and curing. Plants represent a huge source for bioactive materials that well known in folk medicines from thousands of years. The plants and plants derived compounds safe, low-cost, available and the toxic side effects are lower than the common used treatments, for this reason, considered as target for researches from decades. Several plants derived compounds have been identified as anticancer agents and considered as promising candidates for anticancer therapy. There, we focus on some these compounds and its mechanisms of action.

Keywords: Cancer, plants, plants derived materials


INTRODUCTION

Cancer one of the leading reasons of morbidity and mortality around the world. Nowadays, cancer accounts for about 1 per 7 deaths worldwide, and this more than other diseases like HIV/AIDS, tuberculosis, and malaria combined. There were an estimated 14.1 million cases of cancer in 2012, were diagnosed around the world and 8.2 million cancer deaths. More than 60% of cancer deaths occurred in low- and middle-income countries, many of which lack the medical resources and health systems to support the disease burden. By 2030, the global burden is expected to reach 21.6 million new cancer cases and 13.0 million cancer deaths only due to the growth and aging of the population¹. There are so many types of treatment for cancer some of them conventional like surgery of tumor, radiotherapy and some of new and novel treatments like immunotherapy, chemotherapy, cancer vaccinations, photodynamic therapy, stem cell transformation or combination between these treatments. Thereof these methods often accompanied by severe side effects including limited bioavailability, toxicity, nonspecificity, fast clearance and restriction in metastasis²³. Enormous efforts have been made to reduce the dangerous side effects of drugs during the process of cancer therapy like prohibiting the side effects on the neighbor cells and tissues, increasing drug accumulation and efficacy in the location, developing novel drug delivery and objective systems⁴. Plants and plants derived compounds are in medicinal practices since ancient times. It is estimated that 70–95% of the population in
developing countries continues to use traditional medicines. According to the World Health Organization, any plant that contains chemical compounds that can be utilized for therapeutic aims or which are precursors for chemo-pharmaceutical semi-synthesis can be termed as medicinal plant. These compounds can exist within one or more parts of the plant. Herbal products such as plant extracts, dry powders and parts of plants, fungi, and algae have been used as supportive treatments alongside conventional drugs. It has been researched that plant kingdom consisting of about 250,000 plant species and less than 10% have been studied for treatment of different kinds of diseases. Several plant products such as alkaloids, lignans, flavonoids, saponins, terpenes, taxanes, vitamins, minerals, glycosides, gums, oils, biomolecules and other primary and secondary metabolites play important roles in either inhibiting cancer cells or by activating DNA repair mechanisms. A new strategy, associated with isolation of plant active material, took place in the early 19th century. This strategy guided the discovery of the analgesic (painkilling) drugs morphine and codeine from *Papaver somniferum* L., cocaine from *Erythroxylum coca*, the cardiac glycoside, digitoxin that was isolated from *Digitalis purpurea* and *Digitalis lanata* that has been used for cardiac conditions and as an anti-cancer drug, and quinine from *Cinchonactisaya* Wedd. and *Cinchona succirubra* Pav. ExKlotzsch have antipyretic (fever reducing), antimalarial, analgesic, and anti-inflammatory properties. Some of these molecules, up to this time, employ in the medical field. Such natural compounds provide a large diversity, often with strong biological activity so that, they play a significant role in the development of therapeutics treatments. Since the expected increasing in the ratios of cancer due to population aging, there is a scientific and economic need for exploring new anticancer drugs or to make improvements on the existing ones. From this perspective, we will focus, in this review, on some plant-derived substances exhibiting anticancer activity and their mechanisms of action.

**Campothecin derivatives**

Campothecin (family of topoisomerase I poisons) is one of the plant-derived clinically-active chemotherapeutic agents possessing strong anticancer potential inhibiting topoisomerase I in a large number of cancers. It was first isolated from *Camptotheca acuminata*. The isolate of Camptotheca acuminata has been the only agent out of 1000 different plant extracts screened out for anticancer activity which has shown efficacy and the active constituents isolated has been identified as camptothecin. Extensive research is performed by several research organizations for effective camptothecin derivatives like topotecan (hycamtin) and irinotecan, where irinotecan is used to treat colorectal cancer, while topotecan is used in the first-line and second-line treatments as a chemotherapeutic agent for metastatic and small-cell lung cancers also used to treat ovarian cancer. The antitumour activity of this group of drugs resulting from formation of reversible DNA strand breaks in the normal cell cycle. The double-strand breaks introduced by the replication process thought to be the main cause of DNA damage in the tumour cells that are treated with camptothecin and its derivatives, that specifically take role on the S phase of the cell cycle.

**Paclitaxel (taxol)**

This compound found in extracts from the bark of the Pacific or American yew tree of *Taxus brevifolia* Nutt. (Western yew) or from the European yew (*Taxus baccata*), The cytotoxic activity of this taxane dipertene was
first announced by\textsuperscript{16}. Other Taxus species were found to produce paclitaxel. Later on, Taxol was also found to be produced at low levels by Taxus’ endophytic fungus \textit{Taxomyces andreanae}\textsuperscript{17} and also found to produce by other endophytic fungi\textsuperscript{18} allowing its possible production by future microorganism fermentation. Paclitaxel and its semisynthetic derivatives docetaxel (DTX) and cabazitaxel (CTX)\textsuperscript{19} are used to cure a wide range of cancers including ovarian, breast and lung cancer. Binding of paclitaxel with b-tubulin in the lumen of microtubules leads to decrease in microtubule dynamics and halt cell cycle at M phase and apoptotic cell death\textsuperscript{20}. In addition, in cancer clinical trials reported by National Cancer Institute by the 2004 there are 248 from 2069, are taxane-derived drugs, involved 134 with paclitaxel, 105 with docetaxel and 10 with miscellaneous taxanes which are used individual or combined together with other anticancer agents\textsuperscript{21}. A common problem observed in Taxol-treated patients is development of drug-resistance over time. However, a combined treatment of Taxol together with down-regulation of expression of Bcl-2 (B-cell lymphoma 2), a cell death regulator, or other apoptotic related genes inhibits invasion, angiogenesis tumor growth, and maintains Taxol sensitivity in different types of cancer cells\textsuperscript{22}.

\textbf{Curcumin}

Curcumin (diferuloylmethane) is the most prominent chemopreventive agent studied. This yellow–orange turmeric powder is a polyphenol that accumulates in the rhizome of Curcuma longa. Both the traditional Chinese medicine and the traditional Indian medicine have used curcumin as a medicine for treatments of diseases\textsuperscript{23}. Due to its capabilities to regulated important transcription factors, cytokines, protein kinases, adhesion molecules and redox status, curcumin can serve as an anti-inflammatory, anti-oxidant, anti-proliferative, anti-angiogenic, and antineoplastic agent. Thus it has been used to treat many different conditions such as neurodegenerative diseases, cardiovascular diseases, diabetes, allergy, asthma and bronchitis, inflammatory bowel diseases, rheumatoid arthritis, renal ischemia, psoriasis, scleroderma, acquired immune deficiency disease (AIDS), and cancer as well as an anti-aging and scar formation agent\textsuperscript{24}.

May be one of the most important features related to curcumin is the suppression of the transcription factor NF-k-B, a central protein in many types of cancer\textsuperscript{25}. This inhibition causes reduction in expression of NF-k-B target genes such as COX-2 and cyclinD1 resulting in apoptosis\textsuperscript{24}. Moreover, turmeric reduces the expression of various chemokines, cell surface adhesion molecules, cyclins and growth factor receptors, including epidermal growth factor receptor (EGFR)\textsuperscript{26}. In addition to its effects on gene expression, turmeric inhibits the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases\textsuperscript{27}. Turmeric has also been shown to inhibit tumor cell invasion and metastasis \textit{in vitro} by reducing MMP-2 activity and by inhibiting HEP2 (epidermoid carcinoma cell line) cell invasion\textsuperscript{28}. The cancer cells resist to the drugs that common used in treatment as they go through mutations. e.g., Drug resistant genes (ABCA4 and ABCA12) were over-expressed in human MCF-7 breast cancer cells respectively when docetaxel was applied. But, when phytochemical curcumin was applied in association with docetaxel down regulation of drug resistance genes was observed\textsuperscript{29}.

\textbf{Berberine}
Berberine is a strong anticancer compound in terms of its efficacy and clinical trials isolated from the root and rhizome of *Tinospora cordifolia*, *Berberis vulgaris*, *Berberis aquifolium* and *Rhizoma coptidis*\(^{30}\). Berberine has been used for the treat of variety of cancers by inducing apoptosis and cell cycle arrest at G2/M phase in breast, colorectal and liver cancer\(^{31}\). Also it was found that Berberine could resist oxidative stress induced apoptosis or cellular senescence by upregulation of sirtuin 1 (SIRT1) expression at a low dosage\(^{32}\). Berberine significantly reduced EGFR and AKT phosphorylation and may be a useful alternative to lapatinib, an EGFR inhibitor which can cause acquired drug resistance in breast cancer patients\(^{33}\).

**Cucurbitacin**

Cucurbitacins are a class of highly oxidized tetracyclic triterpenoids. Up to date, more than 40 new cucurbitacins and cucurbitacin-derived compounds have been isolated from the *cucurbitaceae* family and from other species of the plant Kingdom. Cucurbitacin B, a bitter toxin, has been one of the most explored for its role in biological systems\(^{34}\). Different cucurbitacin compounds exhibit antitumor proliferation inhibition and induce apoptosis alone or synergistically with other proven anticancer chemicals. In a structure-function related manner, cucurbitacins' inhibition of phosphorylation of STAT3 and/or JAK2 and their subsequent activation seemed as the major mechanism of their action\(^{35}\). Cucurbitacin B treatment caused strong anti-proliferative and apoptotic effects in BRCA1-defective breast cancer cells through downregulation of nucleophosmin/ B23 and disruption of microtubule polymerization\(^{36}\). Cucurbitacin B in lung cancer cells also caused DNA damage via ROS formation and let cells into G2/M cell cycle arrest\(^{37}\). However, other mechanisms may be implicated in their apoptotic effects, including the MAPK pathway, expression of active caspase-3, decreased pSTAT3 and JAK3 levels, as well as decreases in various downstream STAT3 targets such as Mcl-1, Bcl-2, BclxL, and cyclin D3, all of which are implicated in apoptosis and the cell cycle control\(^{38}\).

**Saffron (Crocetin)**

*Crocus sativus* L. commonly known as Saffron, that used as spice contain a several compound carotenoids, crocin, crocetin and safranal\(^{39}\). Crocetin, an important commercially available constituent of saffron, showed significant potential as an anti-tumor agent in animal models and cell culture systems\(^{40}\). Saffron is marked as a promising agent for a novel anticancer drug against different types of cancers. Crocetinexerts proapoptotic effect in MCF-7 breast cancer cells indicating caspase dependent pathway through increased expression of Bax protein\(^{41}\). The tumor growth-suppressing effect of crocetin could be due to the reduction in the synthesis of DNA, RNA and protein by crocetin in tumor cells. It has also been demonstrated that crocetin inhibited RNA polymerase II activity in neoplastic cells\(^{42}\). Crocetin also interferes with histone H1 structure and H1-DNA interaction suggesting that epigenetic mechanisms could be implicated in the anticarcinogenic action of this natural product\(^{43}\). In addition, crocetin thought to be promising anticancer agent by regulating different nuclear and cellular factors, inhibiting iNOS, COX-2 enzymes, reduced serum level IL-1b, TNF-a, cyclin B, cyclinA and cdk2, upregulate Bax/Bcl-2 ratio, regulate of caspase-3, 8 and 9 expression, down-regulate MMP-2, MMP-9 expression, induces apoptosis, targets microtubules and inhibit invasion and metastasis\(^{44}\).

**Gingerol**
Gingerol commonly as is also a group of bioactive compound isolated from the fresh rhizome of Zingiber officinale containing [6]-gingerol, [8]-gingerol, and [10]-gingerol with marked anticancer properties in colon\(^45\), ovarian\(^46\) and breast\(^47\) cancers. It's found that [6]-gingerol inhibited the cell growth through cell cycle arrest at G1 phase of human pancreatic cancer cell lines\(^48\). It down-regulates the expression of iNOS and TNF-alpha through suppressing NF-kB nuclear translocation and IkBa phosphorylation. In addition, the mechanisms of action of gingerol on K562 cells, MOLT4 cells with higher reactive oxygen species than the control, which lead to induced apoptosis in leukemia cells by mitochondrial pathway\(^49,50\). [10]-gingerol has strong anticancer potential than that of [6]-gingerol and [8]-gingerol and have shown promising results for the treatment of breast cancer cell line. The inhibitory effect of [10]-gingerol on breast cancer cells was associated with the minimize the number of cell divisions, cell cycle arrest, induces apoptosis and releases proapoptotic mitochondrial cytochrome c\(^51\).

**Vincristine**

Vincristine, also known as leurocristine and marketed under the brandname Oncovin among others. It is a vinca alkaloid, this group includes vincristine, vinblastine, anhydrovinblastine, and the semisynthetic derivatives vindesine, vinorelbine, and vinflunine, which can be obtained from the Madagascar periwinkle Catharanthus roseus\(^52\). Also is a chemotherapy medication used to treat a number of types of cancer namely, breast, liver, leukemia, testes lung cancer. It is given intravenously\(^53\). The mechanism of the cytotoxic action of Vincristine and others vinca alkaloids is associated with their effects on the tubulin protein, stopping the tubulin dimers from polymerizing to form microtubules, which form the mitotic spindle, that have an important role in the process of mitosis\(^54\), causing the cell to be unable to separate its chromosomes during the metaphase. The cell then undergoes apoptosis\(^55\). However, Vincristine does not only affect the division of cancer cells but it affects all rapidly dividing cell types, making it necessary for the very specific administration of the drug\(^56\).

**CONCLUSION**

In brief, cancer treatments by chemical drugs have been developed but they have a lot of limitations due to its toxic effects on non-cancerous tissues. So that, plants and plants derived materials provided important resources for discovery potential agents that can play significant roles in fighting cancers. The plants derived materials have cytotoxic properties with many different mechanisms of action, such as the inhibition of tumour cell growth, the induction of apoptosis, DNA damage, the inhibition of topoisomerases, the induction of apoptosis, and others, with relatively few side effects. In addition, the combination of plant derived materials with drugs showed high cytotoxic effects on cancer cells without any effect on normal cells. With consideration of the hugecost associated with discovery and development of chemical anticancer drugs, the natural plant materials can be inexpensive sources, readily available from the natural environment. Furthermore, future studies to explore these compounds and others plant derived materials to identified there potential effects and applications in anticancer fighting.
ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

CONFLICT OF INTEREST

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REFERENCES


