Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-019-00259-0

REVIEW ARTICLE

Novel Herbal Medicine-Based Approaches for Efficient Eradication of Cancer Cells

Manal Khalid Abdulridha[1] · Ali-H Al-Marzoqi[2] · Farha A. Ali Shafi[3] · Enas Abdul Kareem Jabbar[4] · Maryam Heydarifard[5] · Buthainah Alezzi[6] · Abdolmajid Ghasemian[7]

Abstract

Many agents cause disruption of the cell cycle and its signaling circuits leading to cancer progress. Cancer therapy is performed by surgery, radiation, and chemical drugs with some side effects. However, cancer mechanisms are multistage and complex; thus, successful therapy needs more experiments. Plants have a principal impact in the healing of numerous diseases with excellent biological activities. They have shown anticancer effects mostly through cancer cell apoptosis (via blocking the NFKB pathway by curcumin and terpenoides, CD95 signaling and enhancement of CD95L expression by resveratrol, inhibiting tyrosine kinas, angiogenesis and cell cycle arrest in the G2/M phase by β-lapachone-genistein, cytochrome-c release into the cytosol and caspase9 activation by biocalein and quercetin, impeding cell cycle in the G1 phase in ovarian cancer cells by 7-hydroxystaurosporine), immune cell enrichment (neutrophil and NK cell activation by *Viscum album L.*, T cell and NK cell activation, cytokine (e.g. tumor necrosis factor) release by *Ganoderma lucidum*, and microRNA regulation (by *Sinomenium acutum*, shikonin, Oleaeuropaea, curcumin, and ginseng), conferring implications for proper cancer cell therapies. It has been revealed that cytotoxic effects of herbal compounds (mostly those secondary metabolites) have eliminated a high percentage of several cancer cell lines such as lung cancer, breast cancer, ovarian cancer cell lines, etc., opening hopes for cancer therapeutic strategies. In addition, targeting microRNAs, nanoparticle-assisted herbal synergism, and novel drug delivery systems and combination chemotherapies have also emerged, exerting higher efficacies for specific cell targeting as novel cancer therapy approaches.

Keywords Cancer cells · Apoptosis · MicroRNAs · Nanoparticles · Anticancer herbal medicine

The Cell Cycle and Causes of Cancer

As a human tragedy, cancer is a multistage or multimechanism procedure leading to the uncontrolled proliferation of abnormal cells due to aberrations in numerous cell-signaling circuits [1]. It is able to invade other tissues as well. Given the growing understanding and developmental motivation of researchers about the molecular etiology of cancer, when the amount of DNA damage is restricted or possibly improved and repaired by prevention of abnormal growth of cancer cells, this process of cancer will be reduced. A wide variety of agents and factors has contributed to cancers such as genetics, radiation, obesity, sex, race, familial history, low physiological activity, smoking, fiber intake, epigenetics, nutrition, stressful conditions, antioxidant consumption, etc. [2, 3]. Cancers have been classified into carcinoma, leukemia, lymphoma and myeloma, and central nerve system cancer by the National Cancer Institute (NCI). The cases of cancer have been increasing in recent

✉ Abdolmajid Ghasemian
majidghasemian86@gmail.com

[1] Department of Clinical Pharmacy/College of Pharmacy, Mustansiriyah University, Baghdad, Iraq

[2] Department of Biology, College of Science for women, University of Babylon, Hillah, Iraq

[3] Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq

[4] Department of Biology, Thi Qar University, Sūq ash Shuyūkh, Iraq

[5] Biotechnology Department, Islamic Azad University of Tabriz Branch, Department of Chemical Engineering, Tabriz, Iran

[6] Clinical Laboratory Science, Al-Mustansiriya University, Baghdad, Iraq

[7] Department of Biology, Central Tehran Branch, Islamic Azad University, Tehran, Iran

years, possibly reaching 15 million cases by 2020 [4]. Each person has cancer cells in his body. These cancer cells do not show up in their standard tests until they increase to several billion cells. Each year, approximately seven million new human cancer cases are detected and five million people die from the disease. Published statistics show that about 14 million people in the world are currently infected with cancer. In recent years, efforts have been taken to combine anticancer drugs, followed by hundreds of chemical agents that have anticancer activity. It is noteworthy that an anticancer drug must firstly affect the cancer cells without causing much damage to the normal tissues. While chemical drugs have improved in relative terms, modifiable forms of chemical drugs have been investigated as critical aspects. Therefore, there is a need for a new precursor and a new pattern for designing the potential of treatment agents by chemical drugs. Plants are the most unique source of medicine for most people in the world, and plant products make up about 25% of pharmaceutical forms [5].

Lung cancer is the predominant cancer type and breast cancer is predominant in women, affecting one in every 31 women in the world [6]. Colon cancer is the second most common cancer in the world, and prostate cancer is often diagnosed in men. Also, skin cancer is diagnosed with a death toll of 180,000 people, of whom 37,000 are affected by this type of cancer. After cardiovascular disease, cancer is the second most common cause of death in humans in the world, and around 10 million people are diagnosed with cancer each year (10 million people are added to cancer patients every year). More than 22 million people suffer from cancer, with 6 million death cases. Although anticancer chemical agents have been used, there are some drawbacks following their consumption [7].

Medicinal Plants for Treatment of Cancers

It has been demonstrated that more than 60% of cancers are cured by vitamins and herbal compounds [8, 9]. Plants have a critical and insecure role for the healing of pain and treatment of many diseases from the ancient times for their excellent biological properties. Medicinal plants have exhibited incredible anticancer effects. Other effects of these anticancer agents are stimulating and repairing the DNA mechanism, apoptosis induction, regulation of miRNAs, increase of protective enzymes, antioxidant activity, and increase of immunity [1, 10–12]. According to the World Health Organization, 80% of people living in villages are dependent on medicinal herbs as the primary health care system. Nevertheless, the chemical anticancer therapeutic route is not usually affordable by most of the people due to the costs [13]. Herbal compounds are advantageous for the lack of the adverse, toxic, and dangerous side effects exerted by chemicals and radiation therapy. Scientists around the world have demonstrated the importance of herbal medicinal compounds to increase the immune cells' potential against cancer [10, 14, 15]. The treatment of cancer cells by chemicals and radiation therapy also affects normal cells in the body [16]. Some other strategies can be implemented as follows:

1. The proliferation of cancer cells can be prevented directly by stimulating phagocytic cells, increasing the activity of natural killer cells.
2. The progression of cancer cell appendages is preventable by increasing the production of interferons, interleukin-2, and antibodies in the serum.
3. Removing the tumor tissue from the body and preventing it from transmitting and spreading through the obstruction of the bloodstream of the tumor tissue.
4. Increasing the number of white blood cells (WBCs) and platelets.
5. Persuading the inverse transformation of tumor cells into normal cells.
6. Stimulating metabolism and prevention of normal cells' progress into cancer cells.
7. Promoting appetite, improvement of sleep quality, and relieving the pain being beneficial for the health [17–19].

Phytochemicals and Herbs with Anticancer Effect

It is noteworthy that over 60% of the commonly used anticancer agents have been derived from natural sources, such as plants, marine organisms, and microorganisms [8]. Phytochemicals have been proposed for protection and immunity against many chronic diseases, such as cardiovascular disease, obesity, diabetes, and various types of concessions, to protect cancer from implicit regimens. From phytochemicals, the risk of cancer is reduced by 20%. Natural plant products play an active role in generating a significant number of drug compounds in the drug discovery program [20]. Numerous cancer cell lines such as PC-3, A-549 and MCF-7, HCT 116, A549, PC-3, A-549, A549 (lung non–small cell carcinoma), SKOV3 (ovarian cancer cells), and HEp-2 cells have been incredibly affected by cytotoxicity of herbal compounds or metabolites [10, 21, 22]. On the other hand, natural products, including herbal drugs, microorganisms, and marine organisms, have a tremendous role in the improvement and development of traditional drugs for the treatment of most human diseases [8]. Bio-diverse plants have a principal role in this respect, and more than 50% of novel drugs used for cancer treatment come from natural products for control of cancer cells. Recent studies have revealed that over 60% of cancer therapies are performed by vitamins or plants [23] used against a variety of cancers, such as transplantation tumors, lymphatic tissues, and

Table 1 Most common herbal compounds and their effective substances [8, 10, 21, 22, 24]

Raw	Herbal name	Family	Effective compounds
1	*Allium sativum*	Liliaceae	Alin-allicin
2	*Aloe vera*	Liliaceae	Alevin-aloe emodin
3	*Ananas comosus*	Bromeliaceae	Bromlin
4	*Angelica sinensis*	Umbelliferae	Polysaccharide AR-4
5	*Annona* species	Annonaceae	Actogenis
6	*Arctium lappa*	Compositae	Potent
7	*Camellia sinensis*	Theaceae	Epigallocatechin gallate
8	*Catharanthus roseus*	Apocynaceae	Wayne Christine-Wayne
9	*Curcuma longa* Linn.	Zinziberaceae	Curcumin-thermotron
10	*Glycyrrhiza glabra*	Leguminosae	glycyrrhizin
11	*Gossypium barbadense*	Malvaceae	Gossypol
12	*Gyrophora esculenta*	Umbilicariaceae	Polysaccharide alpha/beta-glucanase
13	*Linum usitatissimum*	Linaceae	Glycoside-lignan
14	*Taxus brevifolia*	Taxaceae	Taxol
15	*Zingiber officinale*	Zingiberaceae	Curcumin
16	*Brassica nigra*	Brassicaceae	Phenergan glycosides
17	*Podophyllum hexandrum*	Berberidaceae	Pedophilin-astragalin
18	*Brassica oleracea*	Brassicaceae	Sulforane
19	*Crocus sativus*	Iridaceae	Lycopene-crocin
20	*Silybum marianum*		Slap bynyn

leukemia. Several most common herbal compounds and their effective substances have been briefly presented in Table 1.

Although tumors have been treated traditionally and by chemical agents, the advent of compounds that inhibit malignant tumors is suggested as a novel resort and emerging science [25]. Researchers have discovered almost 400 drugs, vitamins, hormones, and other factors that may help prevent cancer [26]. Despite the great development of the field of cancer awareness and treatment, there is still no reliable method to treat a number of them. Therefore, natural protective agents against cancer have recently been taken into consideration. It has been elucidated that acacia (through cytotoxicity against MCF-7 breast adenocarcinoma, A549 lung carcinoma, HepG2 hepatocellular carcinoma, and HCT-116 colorectal carcinoma) confers proper anticancer properties [21].

Chemotherapy has several side effects and can cause damage to organs such as the liver, kidneys, heart, and lungs. In addition, radiation therapy, even though it destroys cancer cells, can burn and destroy normal cells. Primary treatment by chemotherapy and dermal radiation often reduces tumor size, but there is the possibility of the spread of resistant cells [11, 27]. With this state of affairs, chemotherapy and long-term radiotherapy do not result in further tumor destruction. When the body is exposed to toxicity from chemotherapy and radiation, the immune system would be damaged. Therefore, a person may lose their resistance to various types of infections and complications. Chemotherapy and radiotherapy cause the genetic mutation of cancer cells to become more resistant and stable. Furthermore, surgery can cause metastasis of cancer cells to other parts of the body. Therefore, seeking alternative approaches or combination therapies can reduce these tragedies. The next critical step for herbal formulations is their standardization which provides consistent chemical profile, consistent biological activity, or simply a quality assurance program.

Induction of Cancer Cell Apoptosis by Herbal Compounds

Anticancer drugs should destroy cancerous cells with minimal side effects on normal cells which is probable through the induction of apoptosis, and mitochondria play a central role in the apoptosis. It occurs in two mechanisms including Apaf-1/caspase-9-caspases-3 and via Fas/TNF receptor-1-caspase-8-caspase-3. Resistance to apoptosis is a trait of cancer. As the programmed cell death, apoptosis can be induced by most cytotoxic antitumor agents. Several herbal compounds induce apoptosis of cancer cells, and are being proposed as proper anticancer alternative agents. Podo phyllotoxin, vinca alkaloids, texans, and camptothecins herbal compounds have been clinically consumed for this purpose [8]. Human nutrition has anticancer compounds such as phenols, curcumin (through blocking the NFKB pathway up to 8000 mg/day), ginger, resveratrol (through CD95 signaling and enhancement of CD95L expression), genistein and β-lapachone-genistein

(through inhibiting tyrosine kinas, angiogenesis, and cell cycle arrest in the G2/M phase), biocalein (through stimulated quercetin by release of cytochrome-c to the cytosol and caspase9 activation), quercetin (through release of cytochrome-c into the cytosol), alkaloids (7-hydroxystaurosporine, through impeding the cell cycle in the G1 phase in ovarian cancer cells), lectines (*Viscum album* L.), terpenoides (NFKB signaling pathway suppression and reduction in ornithine decarboxylase and cyclooxgenase-2 or cox-2 and matrix metallopeptidase 9 or MMP-9), and taxans (through terminating mitosis in metaphase and anaphase) [28–36]. In addition, IKB enzyme phosphorylation control and thus NFKB signaling pathway inhibition are major mechanisms employed by several herbal compounds [37]. *Scutellaria baicalensis* belonging to heat and toxin-clearing plant group induces apoptosis and stimulates the immune system. Zengshenping (zsp) also induces apoptosis by activation of the mitogen-activated protein kinase (MAPK) signaling pathway [36]. A Chinese herbal compound, known as matrine, exerted apoptotic effects on esophageal cancer KYSE-150 cells in a dose-dependent manner. It caused apoptosis through disruption of mitochondrial membrane potential (ROS production), downregulation of the Bcl-2 protein expression, and upregulation of the Bax protein expression and also caspase-3, 8, and 9 activation [38].

Nanoparticle-Enclosed Herbal Medicine for Cancer Therapy

The new approach in herbals as nanotechnology delivers new insights into scientific investigations for a desirable and accurate cancer treatment to avoid repeated administration and promote more compliance. Hence, many conditions like hepatotoxicity, chronic diseases like cancer, inflammation, bacterial infection, oxidation, and wound healing can be treated by nano herbals more effectively as compared to allopathic medicines [39]. In a review study by Muhammd, they suggested that in vitro and in vivo active-targeting nanoparticles enhance cellular uptake selectivity and/or cytotoxicity over the nontargeted nanoparticle platform and conventional chemotherapeutic drugs, especially increase of drug safety and efficacy. However, clinical surveys are needed to confirm these suggestions [40]. The Saratale study showed that the TOL-AgNPs had high cytotoxic effect against human liver cancer cells (HepG2). Thus, the synthesis and application of dandelion-mediated AgNPs represented a novel approach for the development of effective anticancer and antimicrobial drugs with an inexpensive and eco-friendly nature [41]. In addition, PEGylated resveratrol (RSV)-phospholipid complex bilayer coating casein-loaded micelles (PEGPC–CAS MCs) were developed as a passive-targeted nanosystem. Results exhibited that FA– and PEGPC–CAS MCs had a proper size with monomodal distribution, sustained drug delivery profiles, and appropriate hemocompatibility. The coloaded MCs demonstrated higher cytotoxicity to MCF-7 breast cancer cells compared to free drugs. Both nanosystems depicted desirable in vivo antitumor features in mice breast cancer with PEGylated MCs indicating comparable tumor suppression to folate-conjugated MCs. Therefore, evergreen nanoplatforms coloaded with monascus yellow pigments and RSV had a high efficiency for therapy against mouse breast cancer [42].

Yan demonstrated the inhibition of the colorectal cancer cell cycle by cationic nanomicelles led to an arrest at the G1 checkpoint, and the cell elimination induced by nanomicelles occurred through apoptosis. Moreover, western blot analysis demonstrated the mechanism was related to the activation of Fas/FasL and regulation of caspase-8 and caspase-3 enzymes. Hence, their cationic nanomicelles had the potential to increase the therapeutic effect of ursolic acid (UA) for colorectal cancer treatment [43]. In a study by Elgohary, a nano-in-nano approach was employed to facilitate the efficacy of the etoposide (ETP) as nanosuspension, in a synergistic manner to berberine (BER) into hydrophilic albumin nanoparticles (HSA NPs) against A549 lung cancer cells (IC_{50}, 12.4 μg/ml). Dual-targeted nano-in-nano albumin carriers exerted beneficial properties for the ETP/BER delivery to lung cancer [44].

In the Banu' study, the biogenic silver and gold nanoparticles were used against MCF-7 cancer cells. The elemental analysis highlighted the existence of nanoparticles with high purity and also the organic moieties from the plant compound functioning as capping and stabilizing agents. These agents also indicated a dose-dependent cytotoxicity against the MCF-7 cells and exhibited signs of apoptosis. In the immunoassay results, the pro-apoptotic protein p53 had been upregulated and the antiapoptotic protein Bcl-2 had been downregulated after the nanoparticle treatment [45]. The results of Lotfi-Attar showed that combinational chemotherapy using free drugs and nano-formulations exerted a dose-dependent cytotoxicity on Caco-2 cells and, particularly, Cur–Chr–PLGA/PEG NPs had a more synergistic inhibitory effect and significantly prevented the growth of cancer cells compared to other groups. Gene expression analysis showed that Cur, Chr, and their combination in free and encapsulated forms suppressed the hTERT gene expression. Furthermore, it was revealed that Cur–Chr–PLGA/PEG NPs than free combination forms led to a further decrease in the hTERT expression in all concentrations. Therefore, the results highlighted the efficacy of nano-combinational employment of the natural herbal materials with a one-step fabricated codelivery system to arrest the colorectal cancer [46]. Therefore, the application of herbal-based nanoparticles and novel delivery systems has demonstrated proper anticancer effects significantly higher than

either of single chemical drugs or herbal medicines, even against drug-resistant cancer cells.

Effects of Herbal Medicine on the Immune System

When the human immunity system is strong, cancer cells are destroyed and prevented from developing to a tumor. Moreover, nutritional deficiencies and genetic, environmental, food, and lifestyle factors take part in immune system strength. It has been demonstrated that *Viscum album* L. (VAL) stimulates the immune system, specifically by increasing the number and activities of neutrophils and NK cells [31]. In addition, immune-modulatory effects of *Ganoderma lucidum* (T cell and NK cell activation and cytokines such as tumor necrosis factor (TNF), interleukins, and interferon production), *Sophora flavescent* (increase in leukocytes), *Scutellaria baicalensis* (stimulatory effects on the immune system inhibiting platelet aggregation), *Isatistinctoria*, and matrine have been exhibited [28, 47, 48]. Jinfukang (JFK) increases immune system activity in patients with non–small cell lung cancer (NSCLC) [49]. It is noteworthy that health-strengthening herbs have exhibited enrichment in the immune-related pathways (e.g., cell-mediated cytotoxicity, natural killer cells, and antigen processing and presentation) significantly, while those pathogen-eliminating herbs have not shown these capabilities [50]. For instance, Fructus Ligustri lucidi (Nv Zhen Zi) could upregulate gene expressions in the T cell receptor signaling pathway leading to cancer immune microenvironment regulation and cancer prevention [50]. Traditional Chinese medicine (TCM) with several herbs has demonstrated a protective effect on immune functions via apoptosis (batatasin IV and dioscin), vascular endothelial growth factor (VEGF) signaling pathway (schisanhenol and gomisin J), cell cycle (ligustroflavone and specnuezhenide), T cell receptor signaling pathway (cinobufagin and telocinobufagin), toll-like receptor signaling pathway (pachymic acid and poricoic acid B), and nucleotide-binding oligomerization domain (NOD)-like receptor signaling pathway (ginsenoside Rh3, protopanaxadiol, bruceantin, and bruceine D) [50, 51]. The bioactive compound galloylpaeoniflorin also exhibited anticancer properties via immune-strengthening and antitumor and KEGG pathways. It was shown that ginsenoside Re can protect and activate NK cells [51, 52]. The presentation is suppressed in cancer cells; thus, several herbal compounds such as innamaldehyde upregulate genes associated with MHC biosynthesis and antigen processing. In addition, paeonol and galloylpaeoniflorin participate in the MAPK signaling pathway with inhibitory effects on proliferation of various cancer cell lines. Furthermore, Th17 cell differentiation, the B cell receptor signaling pathway, and the mTOR signaling pathway have been influenced by albiflorin, coumarin, and paeoniflorin, respectively [53]. As the immunity conditions are a critical factor for the prevention and hindering of the cancer, many herbal medicines increase and stimulate multiple immune compounds leading to cancer arrest.

It was demonstrated that CR and CLR herbal compounds had a potential of high cytotoxic effects on cancer cells, based on the IC_{50}. In addition, the application of these two medicines in combination with TRAIL revealed suitable synergistic cytotoxic effects on TRAIL-resistant A549 cells [54].

Regulation of MicroRNAs by Herbal Medicine

MicroRNAs (miRNAs) are small, noncoding RNAs conferring critical functions in development, regulation of cell cycle, stress response, inflammation, cell differentiation, and apoptosis through virtually all signaling circuits within a cell [55]. Regulation of miRNAs is conducted via epigenetic silencing, deletion, mutation, and amplification [56]. These small sequences have roles in physiological and pathological activities and can either initiate the cancer (oncomiRs) or inhibit it, associated with the progression, metastasis, and the stage of cancers. MiRNAs can inhibit target gene expression by binding to the 30′ UTR of target mRNA, leading to the cleavage of target mRNA or translational suppression. Therefore, targeting particular miRNAs has been examined by some novel therapeutic approaches for cancer treatment. A liposome-based miR-34 mimic was the first cancer-targeted microRNA drug to enter the phase I clinical trials in human patients [57]. Interestingly, some miRNAs have been recently regulated by herbal extracts (natural agents), providing implications for the suppression of cancer cell growth, EMT, metastasis, and drug resistance. It is our hope that the reports reviewed above clearly show that herbal extracts such as *Sinomenium acutum*, shikonin, Oleaeuropaea, curcumin, ginseng, and coptidis can change miRNA expression profiles, hence hindering the development of cancer [12, 24]. These novel achievements suggest that the use of herbal compounds could open new avenues for successful cancer treatment, particularly by combining conventional therapeutics with herbal extracts known to be nontoxic to humans [12]. In addition, food-derived compounds and diet for good health have been suggested as regulators of miRNAs preventing cancer progress [58]. Also, circular RNAs (cirRNAs) have shown inhibitory roles in cancer via miR-7 or miR-138 regulation; no herbal compound has been examined in exposure to them [59].

Conclusion

Plants have a principal impact on the healing of numerous diseases with excellent biological activities. They have shown anticancer effects mostly through cancer cell apoptosis (via

blocking the NFKB pathway by curcumin and terpenoides, CD95 signaling and enhancement of CD95L expression by resveratrol, inhibiting tyrosine kinase, angiogenesis and cell cycle arrest in the G2/M phase by β-lapachone-genistein, cytochrome-c release into the cytosol and caspase9 activation by biocalein and quercetin, impeding cell cycle in the G1 phase in ovarian cancer cells by 7-hydroxystaurosporine), immune cell enrichment (neutrophil and NK cell activation by *Viscum album* L., T cell and NK cell activation and cytokine (e.g., tumor necrosis factor) release by *Ganoderma lucidum*, and microRNA regulation (by *Sinomenium acutum*, shikonin, Oleaeuropaea, curcumin, and ginseng) conferring implications for proper cancer cell therapies. It has been revealed that cytotoxic effects of herbal compounds (mostly those secondary metabolites) have eliminated a high percentage of several cancer cell lines such as lung cancer, breast cancer, ovarian cancer cell lines, etc., opening hopes for cancer therapeutic strategies. In addition, targeting microRNAs, nanoparticle-assisted herbal synergism, and novel drug delivery systems and combination chemotherapies have also emerged, exerting higher efficacies for specific cell targeting as novel cancer therapy approaches. The wide variety of herbal compounds with anticancer properties provide a cornerstone in the field of herbal medicine considering their applications in cancer therapy approaches. The application of herbal-based novel methods opens a new avenue in cancer therapy. Health-strengthening medicine has become applicable for improvement of the tumor microenvironment, although large-scale experimentation is needed. Application of combination chemotherapy is another proper approach for cancer therapy. Herbal extracts such as *Sinomenium acutum*, shikonin, Oleaeuropaea, curcumin, ginseng, and coptidis can change miRNA expression profiles, hence hindering the development of cancer. Thus, regulation of miRNAs by herbal drugs is a helpful strategy in anticancer treatment. In addition, the reversal of drug resistance in cancer cells by herbal medicine combinations can be further investigated.

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