

FLOWERS FOR CANCER TREATMENT: FROM BEAUTY TO DUTY

Flores para el tratamiento del cáncer: de la belleza al deber

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ABSTRACT

Cancer is a worldwide disease that affects millions of people every year. Although there are several approved chemotherapeutic drugs for cancer treatment, there is constant search for new molecules. This search is supported by the need of new molecules that could target cancer cells specifically reducing side effects or that could act synergistically with approved anticancer drugs. In this review, research on flower extracts and flower-derived molecules is presented.

Keywords: Cancer, flower extracts, flower-derived molecules

RESUMEN

El cáncer es una enfermedad mundial que afecta a millones de personas cada año. Aunque existen varios fármacos quimioterapéuticos aprobados para el tratamiento del cáncer, existe una búsqueda constante de nuevas moléculas. Esta búsqueda está respaldada por la necesidad de nuevas moléculas que puedan apuntar a las células cancerosas reduciendo específicamente los efectos secundarios o que puedan actuar de manera sinérgica con los medicamentos contra el cáncer aprobados. En esta revisión, se presenta la investigación sobre extractos de flores y moléculas derivadas de flores.

Palabras clave: Cáncer, extractos de flores, moléculas derivadas de flores

INTRODUCTION

Cancer is a chronic disease that, in a simple idea, involves the uncontrolled proliferation of abnormal cells as a consequence of acquired somatic mutations. However, in addition to proliferation, cancer cells acquire other important features such as insensitivity to growth-inhibitory signals, evasion of programmed cell death, sustained angiogenesis and tissue invasion and metastasis (Hanahan and Weinberg, 2011). All of these features favor the growth of the tumor and the ability to reach other organs, thus, increasing its progression of malignancy.

Cancer is a major disease that has been responsible for 9.6 million cancer deaths around the world in 2018 (Bray et al., 2018). Among them, cancer of breast and lung are the most prevalent in female and males, respectively (Bray et al., 2018).

Since the high proliferative status of cancer cells is the most common characteristic of these malignant cells, many drugs have been developed to attack different aspects of cell division. In particular, a combination of anticancer drugs have been suggested to improve treatment efficacy (Blagosklonny, 2004).

In order to develop novel anticancer drugs, scientists began testing natural compounds present in plants. One of the most well-known plant-derived anticancer compounds is taxol, also known as paclitaxel. Taxol was isolated from the bark of *Taxus brevifolia* and demonstrated to have anticancer activity in 1966 (Wani et al., 1971) after eleven years of dedication of the U.S. National Cancer Institute for screening novel compounds against this disease (Goodman, Walsh, and Walsh, 2001). By the year 1992, the U.S. Food and Drug Administration office approved the use of taxol as an chemotherapeutic drug (Goodman et al., 2001). By 2010, more than 800 anticancer agents were under clinical development (Arrondeau et al., 2010) and from 1949 to 2014 the FDA has approved 150 compounds for cancer treatments (Sun et al., 2017).

Considering that there are many metabolites in the plant world that are not known for their anticancer activity, there is a constant interest in researching of plant's metabolites to identify novel chemotherapeutic molecules (Tan, Gyllenhaal, and Soejarto, 2006). In this review, we will focus on the investigations of flowers as a source of metabolites against cancer.

Traditional use of flowers for cancer treatment

Traditional plant utilization by indigenous cultures is a useful first step for drug discovery since information of herbal remedies by indigenous people include a vast period of time for selecting the optimal plant (and its parts) and defining the best method of preparation to achieve a cure.

In Palestine, there is a variety of plant species used as anticancer agents (Jaradat et al. 2016). Among them, flowers represent around 10% of the used part of medicinal plants (Table 1). In another study, hospitalized cancer patients in Morocco were interviewed to collect ethnopharmacological information where flowers used for cancer treatment reached around 2% of the total used parts of herbal remedies (Samouh et al., 2019)

Extracts from flowers with anticancer effect

The use of extracts is the first step towards finding a potential fraction with anticancer effect. Aqueous and organic chemicals are the most common solvents used to extract molecules from plants. A summary of in vitro and in vivo studies with FE is shown in Tables 2 and 3, respectively. The aqueous extract of the flower of *Butea monosperma* promoted the cell cycle arrest in G1 and apoptotic response of hepatoma cells with marginal effect on immortalized mouse hepatocytes in vitro (Choedon, Shukla, and Kumar 2010). Importantly, this extract increased the apoptosis of hepatocytes of the HBV-related X15-myc transgenic mice after 12-month treatment period. In another study, the aqueous flower extract (FE) of *Hibiscus rosa-sinensis* decreased cell viability of estrogen-receptor positive and triple-negative breast cancer cell

lines with doses equal or higher than 2000 µg/mL causing oxidative stress (Nguyen et al., 2019).

Using the MTT assay to evaluate cell viability, Al-Oqail et al. determined that the petroleum extract from the flower of *Aloe perryi* had a potent inhibitory effect of cancer cell proliferation assaying on a seven cell line panel (HepG2, HCT-116, MCF-7, A549, PC-3, HEp-2 and HeLa) (Al-Oqail et al., 2016). A methanolic extract of the flowers of *Iris pseudopumila* inhibited the proliferation of large lung cell carcinoma CORL-23 and amelanotic melanoma C32 cells in vitro (Conforti et al., 2009). Similarly, the methanolic extract of *Rhododendron arboretum* was reported to have a slightly effect on the growth proliferation of breast, cervical and lung epidermal cancer cells in vitro (Gautam et al. 2020). In this report, a concentration of 500 µg/mL was needed to inhibit cancer survival in a significant manner for all tested cell lines (Gautam et al., 2020).

The methanolic extract of the flowers of *Allium atroviolaceum* inhibited the proliferation of breast cancer cells but not in non-transformed mouse fibroblasts (Khazaei, Abdul Hamid, et al., 2017). This observation was accompanied with an *A. atroviolaceum*-induced arrest of cell cycle and increase of apoptosis. In addition, this group reported that the FE of *A. atroviolaceum* induced the apoptosis of cervical cancer cells by down-regulating Bcl-2 and activating both caspase-9 and -3 (Khazaei, Ramachandran, et al., 2017).

Another approach to present an anticancer activity is by contributing to the cancer toxicity effect of a chemotherapeutic drug. The combination of flower-derived novel compounds with well-established chemotherapeutic drugs may inhibit cancer cell proliferation with less amount of drug as possible to diminish then undesirable side effects. It has been reported that extract of flower of *Dimocarpus longan* acts synergistically with 5-fluorouracil to inhibit the in vitro proliferation of the colon cancer cells HT29 and Colo 320DM (Chen et al., 2020). In a similar manner, the combination of the FE of *A. atroviolaceum* with tamoxifen (Khazaei, Abdul Hamid, et al., 2017) or doxorubicin exerted a

significant synergistic anticancer effect in breast and cervical cancer cells in vitro, respectively (Khazaei, Ramachandran, et al., 2017). The FE of *Hibiscus rosa-sinensis* worked in synergy with taxol and cisplatin to decrease viability of triple-negative breast cancer cell line MDA-MB-231 (Nguyen et al., 2019).

It has been well documented that cancer cells have the ability to develop resistance to chemotherapeutic drugs by increasing ATP-dependent pumps in the plasma membrane. Therefore, using chemotherapeutic resistant cells for assaying the effect of slower extracts is a useful approach. It has been reported that the concomitant exposure of the methanolic FE of *Euryops pectinatus* with doxorubicin significantly decreases the IC50 of the later in in vitro models of drug resistance cells (M Elkady et al., 2020).

In some cancers, the use of agents to promote apoptosis via the activation of cell death receptors is an alternative way of treatment. It is well known that cancer cells prevent the activation of apoptosis despite the expression of the receptor. Thus, the ethanolic FE of *Thevetia peruviana* stimulated apoptosis of cervical cancer HeLa cells triggered by TNFα or TRAIL, two ligands of death receptors, by activating caspase-3 and PARP. Notably, FE of *T. peruviana* diminished the expression of the anti-apoptotic protein survivin (Managit, Sakurai, and Saiki, 2017)

A FE containing essential oils of *Pallines spinosa* decreased cell viability of breast cancer cells while a minor effect was detected in immortalized mammary epithelial cells (Saleh et al., 2017). This effect was accompanied by a decrease of the anti-apoptotic protein Bcl-2 and an increase of the pro-apoptotic protein Bax

Flowers from *Antirrhium majus* are among the most popular edible flowers, frequently used from preparing foods and drinks. It has been shown that FE from red and yellow flowers contain phytochemicals that induce cell cycle arrest in G2/M phases in both lung and colon cancer cells in vitro (Seo et al., 2020). Moreover, both FE could inhibit cell invasion. These anticancer effects

were observed with a minimal dose of 500 µg/mL (Seo et al., 2020).

A research group in India has developed silver nanoparticles containing aqueous FE of *Cassia fistula* that could reduce cell viability of breast cancer MCF-7 cells (Remya et al., 2015).

While in vitro studies offer a preliminary view of the direct effect of novel compounds on cancer cells, results from in vivo pre-clinical studies bring a closer idea of their effect on human subjects. A few studies have been performed using in vivo protocols to determine the effect of FE on tumor development. Thus, the FE of the Peruvian *Cordia lutea* at doses of 250 and 500 mg/kg for 5 months prevented the appearance of high-grade prostatic intraepithelial neoplasia in mice treated with cyproterone, testosterone, and N-methylurea to induce prostate cancer (Rojas-Armas et al., 2020). Another group in India explored the effect of FE of *Butea monosperma* on azoxymethane-induced colon cancer in rats where doses of 100 – 150 mg/Kg of the n-butanol FE reduced the aberrant crypt formation (Subramaniyan, Polachi, and Mathan, 2016).

Isolated compounds from flowers with anticancer effects

From the pharmaceutical point of view, the study of pure isolated compounds brings more opportunities to develop of chemical techniques for their isolation or in vitro synthesis. Some compounds with anticancer activities have been isolated from flowers (Table 4). Nymphayol (25,26-dinorcholest-5-en-3b-ol) extracted from the chloroform fraction of the edible petals of *Nymphaea stellata*, is a sterol terpenoid that has been shown to promote cell death of the MCF7 breast cancer cells in a dose and time-dependent manner while no effect was detected in normal cells (Al-Harbi et al., 2020). This effect of nymphayol was accompanied by significant changes in metabolic oxidative stress-related genes: up-regulation of gene expression of CYP1A, GSK3β, GPX and TNF-α; and down-regulation of NF-κB. In addition, it was observed that genes involved in cell cycle regulation were

up-regulated by nymphayol exposure, such as Cdkn2A, pRB1 and p53. Moreover, nymphayol increased the gene expression of the pro-apoptotic genes Bax, Caspase-3, Caspase-9 while decreasing the anti-apoptotic genes Bcl-2.

In a brief study, 14 compounds were isolated from the flowers of *Iris pseudopumila*. All of them showed an antiproliferative activity against two cancer cell lines. Two of these compounds scored over 95% of inhibition: irisolidone and kaempferol-3-O-β-D-glucopyranoside (Conforti et al., 2009).

Several lanceolein chalcones have been isolated from *Coreopsis lanceolata* and tested for its anticancer effect in human colon cancer cells (Kim et al., 2019). Among them, two lanceoleins decreased cell viability by activating pro-apoptotic signals. Importantly, these compounds have almost no effect on cell viability of murine macrophage cells.

Butea monosperma is another plant that offers several compounds from its flowers that have anticancer properties. The sodium salt butrin demonstrated a more potent inhibition of cell survival than curcumin on colorectal cancer cells (Subramaniyan, Kumar, and Mathan, 2017) by inducing cell-cycle arrest at G1-S phase and increasing expression of p53. The same scientific group isolated isocoreopsin, butrin and isobutrin that inhibited cell survival of colon and liver cancer cells in vitro (Subramaniyan et al., 2016).

CONCLUSION

This review offers a brief overview of the studies of FE that had an anticancer activity against several types of human cancers. Although many of them show a great potential in in vitro assays, in vivo studies are required to validate their effect. Therefore, flowers from these plants may not only be beautiful to our eyes, but also possess compounds to fight cancer.

Table 1
Ethnobotanical data of usage of flowers for cancer treatment

Species	Community	Preparation	Cancer	Ref.
<i>Cichorium endivia</i>	West Palestine	Bank, Infusion (oral)	Stomach and colon	(Jaradat et al. 2016)
<i>Inula viscosa</i>	West Palestine	Bank, Decoction (oral)	Kidney bladder	(Jaradat et al. 2016)
<i>Matricaria aurea</i>	West Palestine	Bank, Vapor inhalation or decoction (oral)	Lung, liver and prostate	(Jaradat et al. 2016)
<i>Onopordum cynarocephalum</i>	West Palestine	Bank, Infusion (oral)	Stomach and colon	(Jaradat et al. 2016)
<i>Trifolium philistaeum</i>	West Palestine	Bank, Decoction (oral)	Ovary, breast and non Hodgkin lymphoma	(Jaradat et al. 2016)
<i>Ziziphus spina-christi</i>	West Palestine	Bank, Decoction (oral)	Lung	(Jaradat et al. 2016)
<i>Lavandula vera</i>	Morocco	Infusion (oral)	Breast and uterus	(Samouh et al. 2019)
<i>Eugenia aromatica</i>	Morocco	(No information)	Colon	(Samouh et al. 2019)

Table 2
Summary of the in vitro anticancer effects of FEs on cancer cells. Effective dose refers to the tested concentration that reached at least 50% of activity inhibition

Species	Type of extract	Cell line	Effective doses (µg/mL)	Period of treatment	Effect	Reference
<i>Allium atroviolaceum</i>	Methanolic	Human breast cancer MCF7, MDA-MB-231	40 – 67	48 h	Decrease cell viability	(Khazaei, Abdul Hamid, et al. 2017)
<i>Allium atroviolaceum</i>	Methanolic	Human cervical HeLa	50	48 h	Decrease cell viability	(Khazaei, Ramachandran, et al. 2017)
<i>Antirrhinum majus</i>	Ethanolic	H1299 human lung cancer cells and HCT116 human colon cancer cells	100, 500, 1000	72 h	Decrease cell viability and invasion	(Seo et al. 2020)
<i>Butea monosperma</i>	Aqueous	Human hepatoma Huh7 Human hepatocarcinoma HepG2 Immortalized mouse hepatocyte CRL 2254	100, 300 and 1000	48 h	Decrease cell viability Normal cells not significantly affected	(Choedon et al. 2010)
<i>Echinacea purpurea</i>	Ethanolic	Human colorectal cancer HCT-116 and Caco-2	50, 100, 200, 1000	48 h	Decrease cell viability	(Tsai et al. 2012)
<i>Euryops pectinatus</i>	Defatted methanolic	Human breast MCF7/Dox Human leukemia CEM/ADR5000	5	72 h	Decreased the IC50 of doxorubicin	(M Elkady et al. 2020)
<i>Hibiscus rosa-sinensis</i>	Aqueous	Human breast cancer MCF-7, MDA-MB-231	2000 – 5000	48-96 h	Reduce cell viability Synergize with taxol and cisplatin in MDA-231 cells	(Nguyen et al. 2019)
<i>Iris pseudopumila</i>	Methanolic	Human lung carcinoma CORL-23 Human amelanotic melanoma C32	100	48 h	~ 40% inhibition of proliferation	(Conforti et al. 2009)
<i>Pallenis spinosa</i>	Essential oils	Human breast cancer MCF-7, MDA-MB-231	0.1 – 5	48 h	Induce caspase-dependent apoptosis	(Saleh et al. 2017)
<i>Rhododendron arboreum</i>	Methanolic	Human cervical HeLa Human breast MCF7 Human lung A549	500	24 h	45 – 84% inhibition of proliferation	(Gautam et al. 2020)
<i>Thevetia peruviana</i>	Ethanolic	Human cervical HeLa	30 – 300	24 h	Increase sensitivity to TNF-α or TRAIL-induced cell death.	(Managit et al. 2017)

Table 3
Summary of anticancer effects of FEs tested in animals developing experimental tumors

Species	Administration/dosis	Period of time	Model	Disease	Effect	Reference
<i>Butea monosperma</i>	Oral (daily, 5 days a week)/100 - 400 mg/Kg	12 months	HBV-related transgenic mouse model (X15- myc)	Hepatocellular carcinoma	Reduced serum VEGF and alanine aminotransferase Increase apoptotic cells	(Choedon et al. 2010)
<i>Butea monosperma</i>	Intraperitoneal injection (daily, 150 mg/Kg)	1 week	Chemically induced cancer in rat	Colon cancer	Reduced the appearance of aberrant crypt foci	(Subramaniyan et al. 2016)
<i>Cordia lutea</i>	Intraperitoneal injection (daily)/250 – 500 mg/Kg	5 months	Chemically induced cancer	Prostate cancer	Reduced PSA in blood	(Rojas-Armas et al. 2020)

Table 4
Summary of isolated compounds from flowers with anticancer effects

Species	Compounds	Cell line	Doses	Exposure time	Effect	Reference
<i>Butea monosperma</i>	Sodium salt of butrin	Colorectal cancer SW480	10-120 μ M/mL	48 h	Reduced cell viability, increased apoptosis	(Subramaniyan et al. 2017)
<i>Butea monosperma</i>	Isobutrin Butrin Isoreopsin	Human colon cancer HT29 Hepatocarcinoma HepG2	100 – 750 μ M/mL	48 h	Reduced cell viability	(Subramaniyan et al. 2016)
<i>Coreopsis lanceolata</i>	Lanceoleins	Human colon cancer HCT15	~40 μ M	24 h	Trigger apoptosis, no effect on macrophage cell line RAW264.7	(Kim et al. 2019)
<i>Iris pseudopumila</i>	Irisolidone, kaempferol-3-O- β -D-glucopyranoside	Human lung carcinoma CORL-23 Human melanoma C32	100 μ M	48 h	~90% inhibition of proliferation <i>in vitro</i>	(Conforti et al. 2009)
<i>Lonicera japonica</i>	Pectin	Human pancreatic cancer BxPC-3 and PANC-1, and normal pancreatic cells LO2	16 – 125 μ g/mL	72 h	Reduced cell viability but not in normal cells	(Lin et al. 2016)

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