

Anticancer properties of polyphenolic compounds in two plants, *Ruellia simplex* C. Wright and *Oenothera speciosa* Nutt

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Abstract

Plant polyphenols have attracted increasing attention due to their strong antioxidant properties and their obvious effects in the prevention of various diseases related to oxidative stress, such as cancer. Polyphenols have many anticancer properties, including inhibitory effects on proliferation. Cancer cells show tumor growth, angiogenesis, metastasis, inflammation, and induction of apoptosis. In addition, they can modulate the immune system response and protect normal cells from free radical damage. Naturally, phenolics range in structure from a very simple phenolic molecule to a complex polymer.

This article aims to investigate the phenolic compounds found in plants, especially two plants, *Ruellia (simplex* C. Wright) and evening primrose (*Oenothera speciosa* Nutt), and their role in cancer prevention. In the last few years, identifying and developing of phenolic compounds or extracts from various plants has become a significant area of research related to health and medicine.

Keywords: Anticancer, Antioxidants, Natural compounds, Polyphenols

1- Introduction

Cancer is a complex disease associated with multiple risk factors, such as bacterial and viral infections, oxidative stress, genetic mutation, poor nutrition, and epigenetic

disorders [1]. Cancer is one of the primary causes of death worldwide, and the discovery of new anticancer drugs is the most critical need in the world. Natural products have been effective in fighting various diseases, including cancer, for over 50 years. The high toxicity of some cancer chemotherapy drugs, as well as their adverse side effects and drug resistance, increase the demand for natural compounds as new anticancer drugs [2]. Polyphenols constitute a diverse group of abundant secondary metabolites in plants, which play a crucial role in regulating growth, metabolism, and protection against UV rays and various pathogens, and so far, more than 8000 polyphenolic compounds in different species a plant has been identified [3].

Extensive studies have been conducted on polyphenols and their potential health benefits, including protection against oxidative stress, cardiovascular diseases, diabetes, asthma, neurological diseases, and aging. This group of substances has also been studied for anticancer properties, such as modulating cell proliferation, tumor growth, angiogenesis, metastasis, inflammation, and apoptosis [4].

The chemical structure of polyphenols consists of aromatic rings with one or more hydroxyl groups attached to them, and based on the number of phenol rings and the structural elements that connect these rings, they are classified as flavonoids, xanthenes, and catechins, hesperetin, quercetin [5].

Ruellia simplex C. Wright, commonly known as Mexican petunia, is a perennial plant with significant biological uses, especially in traditional medicine. This plant has been studied for its cardiovascular, anti-hyperglycemic, antioxidant, antimicrobial, anti-bacterial, anti-cancer, anti-pain, and anti-inflammatory medicinal properties. This plant contains a variety of phytochemicals such as flavonoids, tannins, steroids, triterpenoids, and phenolic compounds [6]. These compounds are known for their antioxidant and anticancer properties, which help fight oxidative stress and cell damage associated with cancer progression [7].

Oenothera speciosa Nutt, commonly known as evening primrose, has many medicinal properties. *Oenothera speciosa* Nutt, which contains a high percentage of γ -linoleic acid, is used in traditional medicine to treat various diseases, as well as the methanol extract of various species. *Oenothera* is used as an antioxidant and antitumor agent due to its high content of flavonoids and tannins. Plants are very important in cancer prevention strategies

Considering the adverse effects and high cost of cancer treatment methods such as chemotherapy, the use of natural compounds as an alternative for cancer treatment and prevention is very important [8].

2- Methodology

Articles related to the the anticancer effects of polyphenolic compounds in two plants, *Ruellia simplex* C. Wright and *Oenothera speciosa* Nutt were studied and reviewed from 2009 to 2024 by searching various databases such as Scopus, PubMed, BioRxiv, and Google Scholar.

3- Results

3-1- Types of polyphenols

Flavonoids are the most abundant polyphenols in the diet. They are classified into flavones, flavonols, flavanols, flavanones, isoflavones, and anthocyanins. These compounds have the basic skeleton of phenylbenzopyrone, which consists of 2 aromatic rings. In nature, flavonoids can exist both free and conjugated. Among the dominant flavonols, quercetin is mentioned. The main food sources include onions, cherries, apples, broccoli, cabbage, tomatoes, berries, tea, cumin and buckwheat [9]. Flavonoids can target cascades that activate cell death pathways [10].

Quercetin is one of the most abundant natural polyphenols. Quercetin is found in several plant parts (leaves, grains, and fruits), foods, and beverages, including tea. Quercetin has many biological activities, including antioxidant, antimicrobial, anticancer, antidiabetic, and anti-inflammatory activities [11].

Resveratrol is a polyphenolic compound that occurs naturally in berries, grapes, peanuts, and other plant sources [12]. Resveratrol has antioxidant, cardioprotective, anti-inflammatory, and anti-tumor properties. Also, several laboratory studies have shown that resveratrol prevents a wide range of diseases, including cardiovascular disorders, diabetes, obesity, cancers, liver diseases, Parkinson's disease, and Alzheimer's disease, and has protective effects on a variety of Cancers such as breast, prostate, colorectal, lung, ovary, cervix, liver and stomach are indicated [13].

Curcumin is a hydrophobic polyphenol that consists of two phenyl rings that are replaced by hydroxyl and methoxyl groups and connected through a seven-carbon ketonol linker [14]. Curcumin's therapeutic benefits have been observed in several chronic diseases, including arthritis, neurological diseases, metabolic syndrome, liver disease, obesity, inflammation, and several types of cancer. Curcumin also targets a variety of apoptotic mechanisms, including transcription factors, and has the ability to modulate several cell signaling pathways related to carcinogenesis and inhibiting cancer growth, such as suppressing angiogenesis and inducing apoptosis in several cancers, including liver, lymphoma, brain, breast, ovary, bone, leukemia [15].

3-2- Antioxidant properties of phenolic compounds

Antioxidants are defined as compounds that can delay the oxidation of oxidizable substances by eliminating free radicals and reducing oxidative stress. Oxidative stress is important in the development of chronic diseases, including coronary heart disease, cancer, and aging.

Recently, phenols have been considered potent antioxidants in vitro and have been shown to be more potent than vitamins C and E and carotenoids [16]. The inverse relationship between fruit and vegetable consumption and the risk of oxidative stress-related diseases such as cardiovascular disease, cancer, or osteoporosis has been partially attributed to phenols.

The metabolic activity of polyphenols depends on intrinsic activity, relative absorption from the intestine, rate of metabolism, and excretion. In addition, gastrointestinal or

hepatic metabolic activity may cause metabolites that reach the blood and target organs to differ in biological activity from their original form [17]. Cancer development is a multistage process that includes initiation, promotion, and progression. Dietary polyphenols can influence and modulate various biochemical processes and pathways involved in carcinogenesis. In addition, they can act as biological response modifiers that support immune system function and protect living cells from free radical damage [18].

Phenols can modulate cell signaling pathways that play a role in cancer progression. They affect pathways such as NF- κ B and MAPK. Phenols can activate NF- κ B, a transcription factor, and potentiate residual cellularity, thus potentially reducing cancer cell growth. These compounds can also affect the mitogen-activated protein kinase (MAPK) pathway, which is involved in cell proliferation and survival [19]. Recent studies indicate that polyphenols inhibit senescence-associated secretory phenotype (SASP) and form an anti-cancer microenvironment to prevent cancer [20]. Studies conducted on the human breast cancer cell line (MDA-MB-231) showed that flavonoids such as kaempferol, fisetin, quercetin, catechin, genistein, naringenin, and cyanidin inhibit DNA damage checkpoints and repair pathways. The tested polyphenols inhibited etoposide-induced Chk1 Ser345 phosphorylation, which led to disruption of the ATR-Chk1 pathway. Therefore, polyphenols can enhance the therapeutic effect of chemotherapy by making cancer cells more sensitive to drugs [21].

3-3-Anticancer properties of *Ruellia simplex* C. Wright

Ruellia simplex C. Wright, or Mexican petunia, is a flowering plant in the *Acanthaceae* family. In the *Ruellia* genus, many species are named Mexican Atlas, whose flowers are almost similar, and most are medium to tall plants. Recent research has also discovered the presence of polyphenols in the plant and potential anticancer properties. Research shows that *Ruellia simplex* exhibits significant anticancer potential. The extract of this plant has been studied due to its ability to inhibit the proliferation of cancer cells and induce apoptosis in different types of cancer [22]. The anticancer activity mechanism of *Ruellia simplex* is believed to be due to its antioxidant properties which help neutralize free radicals and reduce oxidative stress in cells. This mechanism is fundamental because oxidative stress is a well-known factor in cancer development. In addition, the anti-inflammatory properties of *Ruellia simplex* may contribute to its anticancer effects by reducing inflammation, which is often associated with tumor progression [23].

3-4- Anticancer property of *Oenothera speciosa* Nutt.

Pink evening primrose with the scientific name *Oenothera speciosa* Nutt. is a biennial plant of the *Onagraceae* family. This family includes about 150 species worldwide, ranging from small to large plants and mostly weeds. Simple toothed leaves appear in late spring and are about 3 to 8 cm long and about 2 cm wide [24]. This plant contains several bioactive compounds, including flavonoids, phenolic acids, and essential fatty acids, which are believed to be involved in its anticancer effects. These compounds have antioxidant properties that can help neutralize free radicals and reduce oxidative stress, a

factor that promotes cancer development. Research shows that this plant extract may induce apoptosis in cancer cells and thus inhibit tumor growth.

In one study, the methanolic extract of *O. speciosa* was investigated for its anticancer potential. The extracts showed dose-dependent antiproliferative effects against human melanoma cells and impaired the migratory potential of these cells in a concentration-dependent manner [25]. At higher concentrations, the extracts altered mitochondrial function and reduced angiogenesis, essential to tumor growth and metastasis. In addition, *O. speciosa* extract has been found to induce anti-inflammatory effects in laboratory animal models of otitis media. Chronic inflammation is a known risk factor for cancer development, and the anti-inflammatory properties of *O. speciosa* may contribute to its anticancer activity. For example, *O. speciosa* extract showed significant anti-proliferative and pro-apoptotic activity against human melanoma cell line A375. The extract also impaired the migration potential of A375 cells in a cell-dependent manner [26].

3-5- Increasing the anticancer effects of polyphenols using a drug delivery system

Polyphenols have great potential for cancer prevention and treatment. However, their poor solubility and stability limit their potential use as therapeutics. Therefore, the development of delivery systems capable of overcoming critical drawbacks to prevent precipitation, rapid degradation, and purification of bioactive compounds and improve their bioavailability is emphasized. By exploiting the differences between cancer cells and normal cells in the tissue, nanoformulation enables high loading efficiency, drug protection, and specific delivery.

Lipid-based system Lipid-based formulations are mainly used to entrap polyphenols with low water solubility. Lipid nanoparticles can improve biocompatibility, cellular penetration, and drug stability for effective drug delivery. Commonly used formulations include liposomes, phytosomes, emulsions, and nanoparticles [27].

3-6- Limitations of polyphenols as anticancer agents

Polyphenolic compounds, abundant in food sources, are very promising in cancer prevention and treatment. However, one of the main concerns of using polyphenols as anticancer agents individually is their poor bioavailability in the human body. Additionally, their interactions with other natural ingredients in a diet may disrupt or complicate the consistency of their effectiveness. Therefore, specially designed combinations of several polyphenols or combinations of polyphenols with other natural agents aimed at defined biological targets extend the metabolic effects of the constituents of such mixtures in controlled and reproducible ways [28].

4- Conclusions

Natural bioactive compounds based on medicinal plants have played an important role in human health. Polyphenols in plant extracts naturally have antioxidant activity against cancer cells. These bioactive compounds, in addition to acting as absorbers of reactive oxygen species, can modulate the inflammatory response. One of the main concerns of

using polyphenols as anticancer agents individually is their poor bioavailability in the human body. In addition, their interaction with other natural compounds in a diet may disrupt or complicate the consistency of their effectiveness, so encapsulation can protect them from degradation and improve their solubility and absorption in the body.

Ruellia simplex C. Wright and *Oenothera speciosa* Nutt. are rich sources of various polyphenolic compounds, including flavonoids, phenolic acids, and tannins. Preliminary studies show that the polyphenols in these two plants have anti-cancer properties, and several studies have been done to prove it, but more research is still needed to confirm and expand these findings.

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