Review article

A review on anticancer potential of *Quercus infectoria* and its bioactive compounds

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ABSTRACT

Cancer is a life-threatening disease if not diagnosed and treated early. Available cancer treatments with undesirable side effects have led to the search for safer and more effective treatments. Therapeutic intervention using plant-derived natural products have been of great interest these days. Many plant-derived phytochemicals have been implicated with anticancer activities. *Quercus infectoria* is one of the prominent candidates for its chemopreventive mechanisms of action in cancer. Worldwide, this plant has been used in various medicinal purposes. Based on the available data from previous scientific researches, this review focuses on the anticancer potentials of *Q. infectoria*, as well as its bioactive compounds such as tannic acid, gallic acid and ellagic acid. This review will trigger of generating new insights into possible application of this plant in cancer therapy.

Keywords: *Quercus infectoria*; anticancer; tannic acid; gallic acid; ellagic acid.

INTRODUCTION

Cancer is a complex disease that progresses locally and has the ability to metastasize into multiple organs in the body. Worldwide, the number of new cancer cases and deaths was estimated at 14.1 million and 8.2 million, respectively (1). Chemotherapy is one of the techniques to treat cancer and the improvements in anticancer drugs have strengthened the patient care. However, the conventional remedies also have harmful side effects on normal cells/tissue. Thus, many studies have been focusing on the development of agent for cancer therapies (2-4). Therefore, the use of medicinal plants in cancer treatment is seen as a promising strategy to reduce these adverse side effects (5). Medicinal plants are highly treasured throughout the history for their value in medicine and drug development (6). The World Health Organization (WHO) reported that 70-95% of the populations in developing countries depends on medicinal plants as primary source of treatment. Due to their non-toxic nature on the normal cells while exerting cytotoxic effects on cancerous cells, medicinal plants are in great demand these days (7).

There have been on-going efforts to discover effective phytochemical compounds in plants to cure, prevent or delay the progression of cervical cancer (5,8). Therefore, several criteria such as regulation of cell cycle and apoptosis, anti-oxidative stress and anti-inflammatory activities, drug resistance of cancer cells and specific molecular targets in targeting carcinogenesis and metastasis have been addressed for the evaluation of anticancer phytochemicals (9). Thus, this review covers the current knowledge from the scientific studies on the selected medicinal plant, *Q. infectoria* and its bioactive compound as a potential candidate for anticancer therapy.

Quercus infectoria: A potential candidate for cancer chemoprevention

Quercus infectoria Olivier (Family: Fagaceae) is a small oak native to Iran, Asia Minor and Greece. This small tree is about 4 to 6 feet tall with crooked stem, and its leaves are smooth and bright, acorn long and narrow, scaly and downy (10). The galls or nut-galls formed on the young branches are as a result of the deposition of eggs by an insect such as *Adleria gallae tinctoriae* (11). Extracts from the galls of *Q. infectoria* contains large amount of tannins: gallic acid, syringic acid, ellagic acid, β-sitosterol, amentoflavone, hexamethyl ether, isocryptomerin, methyl betulate, methyl oleanate, hexagalloyl glucose. *Q.infectoria* is a reputed plant in ayurvedic medicine with great medicinal values for its astringent, anti-diabetic, anti-tremor, local anaesthetic, antipyretic and anti-Parkinson actions (12). In Malay traditional medicine practice, *Q.infectoria* is useful to boost the health of female sexual organ and for post-natal care (13).

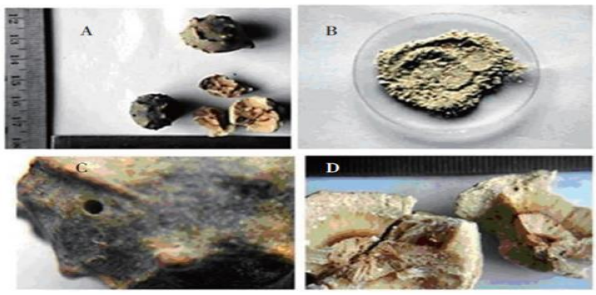

Fig. 1: Macroscopic observation of gall extract of *Q. infectoria*. A: Crude drug: B: Powder form: C: External surface showing pore of insect exit: D: Internal surface is broken drugs (10).

In view of its diverse medicinal applications, Q. infectoria gall extracts has been tested for its cytotoxic potential on cervical (HeLa) and ovarian (Caov-3) cancer cell lines which, have shown positive results (14). The result demonstrated that *Q. infectoria* galls ethanol and aqueous extracts at its lower doses exhibited a significant cytotoxicity on HeLa and Caov-3 cells in a concentration dependent manner, with the inhibitory concentrations at 50% cell population (IC_{50}) values of 2.82 ± 0.21 µg/ml and 6.50 ± 0.24 µg/ml, respectively. Moreover, the morphological changes associated with apoptosis in the cells treated with the ethanolic extract therefore confirms the presence of active compound in the galls extract which has the potential as anti-cancer agent, especially for the treatment of cervical cancer (14). Besides, the cytotoxicity effect of other Quercus sp. against HeLa cervical cancer cell line are also reported in other studies (15,16).

A number of studies have documented the chemopreventive potential of *Q. infectoria* in cancer (12,17). Previous study tested the effects of *Q. infectoria* against renal carcinogenesis in terms of xenobiotic metabolizing enzyme activities, lipid peroxidation (LPO), redox status, serum toxicity markers, inflammatory and proinflammatory markers and cell proliferation in the kidney tissue. Analysis of results showed that oral administration of *Q. infectoria* at a dose of 75 and 150 mg/kg significantly inhibited renal oxidative stress, inflammation and tumour incidence. In addition, this treatment resulted in downregulation of serum toxicity markers and upregulation of xenobiotic metabolizing enzyme activities. Therefore, these findings suggested that *Q.infectoria* can be one of the useful means to prevent cancer (17).

Bioactive compounds

Tannic acid

Tannins are polyphenolic biomolecules with a backbone of carbohydrates. Tannins can be classified into two main groups which are hydrolysable and non-hydrolysable or condensed tannins. Hydrolysable tannins are composed of a central core polyhydric alcohol such as hydroxyl groups which are esterified partially or wholly by gallic acid (gallotannins) or hexahydroxydephenic acid (ellagitannins). One of the gallotannins that available is Turkish tannin which is extracted from the *Quercus infectoria* (18). The hydrolysis of the gallotannins yields both glucose and gallic acid. Tannic acid is a specific tannin that comprising 10 units of galloyl (3, 4, 5-trihydroxyphenyl) surrounding a glucose centre. However, natural tannic acid is made of molecules of 2–12 galloyl moieties (19).

Tannic acid does not contain carboxyl groups, but due to the phenolic hydroxyl multiplicity, it is weakly acidic. The hydroxyls make it highly water-soluble. Tannic acid, a mixture of glucose's digallic acid esters, is a popular component in many foods (20). Tannic acid, one of the plant's furthermost available reserve contents, is a gallotannin composed of esters of gallic acid and glucose, comprising galloyl groups esterified directly to the glucose molecule. Tannic acid is advantageous to health due to its chemopreventive characteristics against carcinogenesis and mutagenesis (21).

Tannic acid was found to suppress tumours caused by chemical carcinogens in skin, forestomach and lung. Tannic acid activity was linked to decrease activation of carcinogens arising from the inhibition of different cytochrome P450 types, electrophilic trapping, arachidonic acid metabolism modulation. Besides acting as a potential chemo-preventive candidate, tannic acid has been revealed previously to directly inhibit the cancer cell development (20).

Traditional Chinese Medicine regularly uses tannic acid and has long been a part of this tradition. Tannic acid is also considered to improve the effectiveness of herbal medicines. Tannic acid has been found to inhibit proliferation in different types of cancer cells *in vitro* and caused cancer cell death through apoptosis. In an animal model study, tannic acid has been shown to have chemopreventive function against cancer, including hairless mice, and has been able to suppress about 70 percent of the promotion of ultraviolet-induced skin tumour (22). Tannic acid indicates anticancer activity and cancer defence against a variety of cancer types, including the disease caused by chemical insulated (23). Tannic acid was also found to be a potent chemosensitizer to combat multidrug resistance (20).

Moreover, the mechanism that exerted by tannic acid which is important for cancer chemoprevention and therapy are inhibition of cancer promotion and progression, induction of cell cycle arrest and apoptosis of cancer cells, inhibition of cancer cell proliferation, angiogenesis, migration, invasion and colony formation. Besides, tannic acid act as a carrier element of anticancer drug delivery system plays a role in chemosensitization and impact on multidrug resistance and inhibition of epithelial-to mesenchymal transition (20). Numerous studies are available where tannic acid has been revealed to suppress proliferation in multiple types of cancer cells in vitro and apoptosis induces cancer cell death (22). In other research, tannic acid blocked tumours of the skin, lung, and forestomach caused by polycyclic aromatic carcinogens and N-methyl-N-nitrosourea in mice (24).

According to Naus *et al.*, (25), polyphenol plant-derived, tannic acid affects cholangiocarcinoma. This effect includes the inhibition of the growth by blocking the cell cycle progression *in vitro* and the declined growth of xenografts in nude athymic mice. This provides the rationale for the usage of tannic

acid in cancer treatment (25). Based on the previous research, tannic acid potentially inhibits the activity of definite proteasomes resulting in the accumulation of proteasome substrates, namely cyclin-dependent kinase inhibitor 1B and the X apoptosis regulator associated with B-cell lymphoma 2 (BCL2). The arrest of the cell growth cycle in the G1 phase and the induction of apoptosis occurred due to the accumulation of substrates (22). According to Zielińska-Przyjemska *et al.*, (26), tannic acid had no effect on the distribution of cell cycles in C6 cells but showed a significant rise in the amount of dead cells in the both the rat C6 and human T98G glioma cell line (26).

The activation of apoptosis was induced by the loss of mitochondrial membrane potential and elevated caspase-3 levels. Moreover, tannic acid also mediated cell death by apoptosis and cell cycle arrest, reducing the development and size of the colonies, cell migration and adhesion. Tannic acid also possesses the anti-glioma effect *in vivo*, as the reduction of tumour volume accompanied by elevation in the intra-tumoural necrosis and lymphocyte infiltration area without causing systemic damage (27).

Gallic acid

Gallic acid (3,4,5-trihydroxicbenzoic acid), naturally occurring polyphenols found largely in plant-based foods such as tea, grapes, berries, nuts and wine is infamous for its anticarcinogenic effects against multiple types of cancerous cells including cervical cancer thus making this compound as an important biomolecule for therapeutic purposes (28). You and co-workers (29) assessed the ability of gallic acid to induce cell growth inhibition and death on HeLa cells. It was demonstrated by the results that gallic acid possess inhibitory activity against the tested cell in a dose-dependent manner, with an IC_{50} of 80 µM using MTT assay and induced apoptosis as evidenced by the increase in annexin-positive cells and caspase inhibitor-tested results. They also found that gallic acid induced the loss of mitochondrial membrane potential (MMP) level in HeLa cells following 24 and 72-hours treatment. The percentage of MMP reduction was estimated at 75% after exposure to 100 µM of gallic acid for 24 hours as compared to control (29).

Further analysis demonstrated that gallic acid induced cell death was accompanied by increase in reactive oxygen species (ROS) level and glutathione (GSH) depleted cells in HeLa cells (29). Subsequent study by Zhao and Hu (30) further confirmed its anti-cancer potential by significantly reduced the viability of cervical cancer cells (HeLa and HTB-35) in a dose dependent manner at 5, 10 and 15 µg/ml concentration with 92%, 84% and 66% of growth inhibition, respectively. In addition to that, they also found that gallic acid at a dose of 10, 15 and 20 µg/ml remarkably inhibit cell migration to 73%, 40% and 34% in the HeLa cells and to 45%, 22% and 17% in the HTB-35 cells, respectively, as compared with the control. Moreover, treatment with gallic acid at similar concentrations also reduced the invasiveness of the HeLa cells ($P < 0.05$) to 92%, 68% and 29%, suggesting that gallic acid is a promising agent for the treatment of cervical cancer (30).

Gallic acid manifests its anticancer activity by targeting various pathways involved in oncogenesis (28). Regulation of apoptosis by gallic acid involves two major pathways known as the death receptor-mediated (extrinsic) pathway and the mitochondrial-mediated (intrinsic) pathway. Caspases belongs to the family of protease enzymes that plays a crucial role in the execution of both apoptosis pathways. When activated, caspases induce cell death through inactivation of anti-apoptotic proteins, prevention of DNA replication and cytoskeletal reorganization. Caspase-3, most important caspases executioner interacts with caspase-8 and caspase-9 in the regulation of extrinsic and intrinsic apoptosis pathways, respectively (31).

Ellagic acid

Ellagic acid (2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde]chromene-5,10-dione) has been suggested as a cancer chemopreventive agent in the cancer of colon, breast, prostate, skin, oesophageal and osteogenic sarcoma (32). Other characteristics such as radical scavenging activities and antiviral activities also have been described to ellagic acid (33). Early study concerning the cytotoxic and anti-proliferative potentials of ellagic acid in cancer was conducted by Losso and co-workers using HUVEC, HEL 299, Caco-2 colon, MCF-7 and Hs 578T breast and DU 145 human prostate cancer cells. They observed that ellagic acid exerted selective cytotoxicity effects against the cell lines in a dose-dependent manner. It was found that normal fibroblast cells were not affected by treatment with ellagic acid at concentration range between 10-100 µmol/L following 24 hours incubation. Instead, an increase in adenosine triphosphate (ATP) bioluminescence between 18-21% was observed, indicative of increased mitochondrial activity (33).

Conversely, ellagic acid at 1-100 µmol/L concentration exhibited anti-proliferative effect against Caco-2, MCF-7, Hs 578T and DU 145 cancer cells with the IC50 values of 37 µmol/L, 72 µmol/L, 59 µmol/L and 42 µmol/L, respectively. At this concentration, almost 50% reduction in ATP levels had been reported which was associated with a decrease in the cell viability as indicated by the morphological changes in the cells exposed to the elevated concentration of ellagic acid. In addition, ellagic acid induced inhibition of angiogenesis was demonstrated via suppressing the angiogenic factors MMP-2, MMP-9 and VEGF165 levels (33).

Based on the reports, ellagic acid at concentration of 50 µmol/L effectively reduced MMP-2 and MMP-9 activities in all cells to less than 50% as compared to the control. As the concentration was increased at 100 µmol/L, their activities were inhibited to less than 40% of the control. Similarly, low VEGF165 levels were detected in all cells treated with 100 µmol/L concentration of ellagic acid. Findings clearly demonstrated the chemopreventive properties of ellagic acid and therefore could be used natural anticancer ingredients in the treatment of cancer (33). Additionally, regulation of apoptosis by ellagic acid was demonstrated via caspase-3 activation and a shift in Bax/Bcl-2 balance where increased in Bax pro-apoptotic protein level resulting in the decrease of Bcl-2 anti-apoptotic protein, a key event in mitochondrial-mediated (intrinsic) apoptosis pathway (34).

Current study by Guo *et al.,* (35) reported a dose-dependent anti-invasive and anti-proliferative effect of ellagic acid on human cervical cancer (HeLa) cells. Their study revealed that ellagic acid treated groups at 2.5, 5.0 and 10.0 µM concentrations lowered the invasion rate of HeLa cells to 76.43%, 65.54% and 56.44%, respectively. In addition to increase in the rate of apoptotic cells, IGFB7 gene expression level and AKT/mammalian target of rapamycin (mTOR) signalling pathway were both increased and decreased by ellagic acid treatment. These results suggest that ellagic acid has anti-cervical cancer activity and is therefore a potential candidate for cervical cancer treatment (35).

CONCLUSION

Cancer chemoprevention by phytochemicals derived from plants of dietary and non-dietary origin have attracted a great research interest for their highly accessible, cost effective and lower side-effects in the control and management of cancer. Technological advances in medicine have brought a multitude of phytochemicals into preclinical or clinical trials for their anticancer effects. Studies demonstrated that *Q. infectoria*, as well as its related phytochemicals including gallic acid and ellagic acid elicited anticancer effects via several signalling cascades. Therefore, it is evident that *Q. infectoria* could be regarded as a promising candidate plant for the prevention and treatment of cervical cancer. Several issues concerning the time, effective dosage, and routes of administration for *Q. infectoria* derived compounds should be taken into accounts and warrants further in-depth studies before acknowledging its anticancer potential in the treatment of this disease.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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