

Natural Medicine as a Therapy for Renal Carcinoma: A Review

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ABSTRACT

Renal Cell Carcinoma (**RCC**) is the most common solid lesion found within the kidney and accounts for approximately 90% of renal malignancies. RCC is commonly found the tubules of the kidney and is characterized by lack of clinical signs until metastatic stages. Hence, most of the modern cancer treatment methods are ineffective against renal cell carcinoma. Lack of proper treatment and prominent side effects of modern therapeutic agents are the main reason for an increasing number of people seeking alternative therapies that may have less severe or no side effects. Several medicinal plants have been used to control RCC in the traditional medicinal systems of many cultures worldwide. The present review profile-gives information on extracts from different parts from different species that is effective against RCC.

INTRODUCTION

Incidences of renal carcinoma are increasing globally. According to the American Cancer Society, 36,160 cases of renal carcinoma incidences were reported in 2005. In fact more than 80% of kidney cancers are renal cell carcinomas. Renal carcinoma is commonly found in the lining of the tubules of the kidney. The characteristic feature of renal carcinoma is lack of early warning

clinical signs resulting in patients diagnosed with metastatic stage [1]. Metastasis, a common feature of RCC, is a multistep process leading to the development of secondary tumors [2]. During the metastatic cascade, primary tumor cells digest their surrounding extracellular matrix, migrate through interstitial spaces, and enter the blood or lymphatic vessels and will be migrated to distant organs [3]. The adhesion of circulating tumor cells to the micro vascular endothelium of organs at distant sites is an important step in metastasis. Once lodged in the target organs, these cells migrate into the interstitial spaces and continue to grow and develop a secondary tumor, or they metastasize [4]. Thus, the adhesion, migration, and invasion of cancer cells provide many potential targets for therapeutic intervention. Yet, typical therapeutic approaches such as radiotherapy, chemotherapy or hormone-therapy show no or little effect. Hence mortality incidences among renal carcinoma patients are comparatively high [5].

Current treatment of renal carcinoma includes metastesctomy, radiotherapy and modalities. Nevertheless, treatment for renal carcinoma is a challenge. It was suggested that patients treated with complete metastesctomy have a better survival rate and symptom control than those who did not undergo metastesctomy. However, complete metastesctomy treatment is still remains a debate [6]. Moreover, potential role of immune modulation, cytokines, or differentiating agents in the inhibition of tumor growth had been considered [7-9]. However, currently available methods do not address metastases and can promote tumor progression by impairing the immune system [10]. Therefore, it is vital to continue study of novel treatment strategies and the identification of new agents with better antitumor activity remain the highest priorities for clinical trials in patients with this refractory tumor [11].

Over the past 30 years, the treatment of renal carcinoma cells has made little progress and no chemotherapeutic agents currently available are completely effective against it [12,13]. There is a need for novel and more selective drugs that are able to interfere with targets directly involved in the process of renal cancer development and progression. On the other hand, the biological heterogeneity of renal cell carcinoma, its resistance to anti-cancer drugs, and the side effects of chemotherapeutics are the major obstacles in controlling of renal carcinoma. Radical nephrectomy of localized renal carcinoma cells is effective only in a few cases because the rate of systemic metastasis is high with nearly 50% of the patients developing metastasis after surgery [14,15]. Currently, median survival rate of patients with metastatic renal carcinoma is 10 months and only <2% of patients survive beyond 5 years [13] thus indicating ineffectiveness of the available interventions. Therefore, the search for effective therapeutic agents for this malignancy is urgently needed.

Over the last decade, use of natural remedies for diverse ailments has increased. Natural remedies are effective against diabetes [16,17], infertility [18] and diseases. Recently, a greater emphasis has been given towards the research on complementary and alternative medicine that deals with cancer management. Currently available treatments for renal carcinoma besides being

expensive produce serious side effect including acceleration of tumor progression. Apart from modern clinical therapy, herbal plant and other medicine with minimum or no side effects have been recommended in traditional medicinal systems. Plant medicines have been used throughout the world for generations for the treatment of various cancers including renal carcinoma. Herbal medicine has shown to possess antioxidant activities and other beneficial properties [19]. Several studies have been conducted on herbs under a multitude of ethno botanical grounds. It had been shown that many herbal plants possess anticancer properties and subsequently been used as potent anticancer drugs [20]. Folk medicine of plant drugs has been successful from very early times in using these natural drugs and preventing or suppressing various tumours using various lines of treatment.

MEDICINAL PLANT TO TREAT RENAL CELL CARCINOMA

Over 50 year's development of new chemotherapeutic agents have been developed in the treatment and management of cancer [21]. All over the world thousands of plants species are known to have medicinal values. Different parts of these plant species are still widely used in traditional Ayurveda and Siddha-Ayurveda medicine practices to cure various diseases. More than 60–70% of the rural population still relies on traditional medicine for their primary health care needs [22]. Recently scientific interest in medicinal plants has burgeoned due to increased efficiency of plant derived drugs and raising concern about the side effects of modern medicine.

Therefore in recent years natural products have been identified as sources of anticancer drugs. For instance, taxanes extracted from the bark of the *Taxaceae*, *Taxus brevifolia*, *T. canadensis*, or *T. baccata* [23] and the camptothecins, extracted from bark and wood of the *Nyssaceae* *Camptotheca acuminata* [24] was pioneering natural medicine in cancer research for their anti-solid tumor efficacy. Certain drugs were approved in many countries for the treatment of ovarian and breast small cell lung cancers [25]. Semi-synthetics from the lead compound camptothecin have been approved for the treatment of advanced colorectal cancer [26] and ovarian cancer [27]. Since surgery remains as the main therapy for patients whose carcinoma is confined to the kidney, it is important to examine the natural medicine used in treatment of renal carcinoma directing towards developing an effective therapeutic agent.

Englerin

Englerin, an extract from *Pyllanthus. engleri* (eupobiasease) selectively inhibited renal cell cancer growth in 5 different renal cancer cell lines [28].

Coumarin

Coumarin isolated from *Dipteryx odorata* Wild belonging to family fabaceae, is classified as a member of the benzopyrone family of compounds of which the flavonoids are foremost members. Coumarins comprise a very large class of compounds found in many plants [29-31]. They are found at high levels in some essential oils, particularly cinnamon bark oil (7,000 ppm), cassia leaf

oil (up to 87,300 ppm) and lavender oil. Coumarin is also found in fruits (e.g. bilberry, cloudberry), green tea and other foods such as chicory [32]. Among higher plants, rich sources of coumarin were found in families Rutaceae and Umbelliferae. Although distributed throughout all parts of the plant, the coumarins occur at the highest levels in the fruits, followed by the roots, stems and leaves. Six coumarins have been isolated from the fruits and the stem bark of *Calophyllum dispar* (Clusiaceae). The genus *Calophyllum*, which comprises 200 species, is used in folk medicine to manage renal cancer [33]. According to Thrans et al. [34], when coumarins were given orally at a dose of 100mg / day for 15 days reduced metastatic development among patients with renal cell carcinoma with no side effects. Similar results were obtained from both *in vitro* studies [31] and *in vivo* studies where patients were treated with 600 mg – 5000 mgs of coumarins [35].

Lapachol

Compound isolated from fruits of *Kigella. Pinnata* L. using dichloromethane exhibited growth inhibitory effects in renal cell carcinoma cell line (Caki-2). The activity was dose-dependent [36].

Bullatacin and Bullatacinon

Both bullatacin and bullatacinon are highly potent bioactive compounds isolated from stem bark of *Annona bullata* Rich. Was studied against different human carcinoma cell including renal cell carcinoma. Bullatacin showed high cytotoxic activity at concentrations as low as 1ppm indicating to be a promising candidate for treatment of renal cancer [37].

Annonaceous Acetogenins

Annonaceous acetogenins isolated from the EtOH extract of the bark of *Annona bullata* Rich. by bioactivity-directed fractionation found to be lethal to brine shrimp. These acetogenins include bullatencin, a new single tetrahydrofuran acetogenin having a double bond in the hydrocarbon chain; 4-deoxyasimicin, a new adjacent bis-tetrahydrofuran acetogenin; and the uvariamicins, an isomeric mixture of four single tetrahydrofuran acetogenins. These acetogenins showed selective cytotoxicities for human kidney solid tumor cell lines comparable to or better than Adriamycin [38].

Honey

Significant decrease in cell viability and increase of cell apoptosis were shown at concentrations of 2.5%, 5%, 10% and 20% in ACHN cell lines. Apoptosis was evident at both early and later stages [10].

In addition to above mentioned different plant species from which bioactive compounds were isolated, some added plant species have shown to possess anticancer activities against renal carcinoma. *Aeginetia indica* Linn. (Guan-Jen-Huang) has a synergistic effect on with 5-fluorouracil-mediated apoptosis and inhibits cell adhesion and motility. Hence authors indicate valuable chemotherapeutic agent for the treatment of renal cancer [39].

This review elaborates use of plant extract such as englerin, coumarin, and lapachol isolated from different plant species. Moreover, honey can also be used as a potent cell apoptotic agent. The methods of isolation are mainly methanol or ethanol extractions. From the literature, it is evident that extractions from herbal plants have a major role to play in managing renal cell carcinoma. Hence it is significant to explore further on plant constituents that can be isolated from different species in lieu of development of new drugs. In conclusion there are bioactive compounds in different plant species that can be used in the treatment of renal cell carcinoma, which are sometimes more effective than modern day therapeutic agents against renal cell carcinoma. However, many other active compounds in the plants are yet to be characterized. Further it is essential to elucidate mechanisms of action and possible side effects of these active bio-compounds.

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