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Commentary

2′-Hydroxyflavanone: A promising molecule for kidney cancer prevention

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ABSTRACT

Kidney cancer, also known as renal cell carcinoma (RCC), is one of the top 10 diagnosed cancers in the USA, and the incidence is rising. Despite major improvements in drug therapy strategies, RCC remains a deadly malignancy if not found and removed in its early stages. RCC is so highly drug-resistant that no effective life-prolonging regimen of cytotoxic chemotherapy has been demonstrated for RCC, despite several decades of effort. It is also highly radiation-resistant, thus circumventing therapies to prevent local recurrence or to control metastatic disease. In the last few years, extensive research has been conducted to elucidate the functional significance of the plant-derived compounds, and their derivatives, as anticancer agents. This review is focussed on a chemo-dietary prevention strategy against RCC using a citrus-derived compound called 2′-hydroxyflavanone. RCC is frequently caused by *VHL* gene mutations, which contribute to 75% of all RCCs. These mutations are positively linked to cigarette smoking, and exposure to the tobacco carcinogen, *N*-nitrosodimethylamine and benzopyrene, can disrupt *VHL*. According to *in vitro* and preclinical mouse studies, 2′-hydroxyflavanone can both protect the *VHL* locus and prevent the progression of *VHL*-mutant cancer. Human clinical trials examining the effect of supplementation of 2′-hydroxyflavanone, either alone or in combination with chemotherapeutic drugs, on RCC prevention have not been conducted, although there is considerable potential for 2′-hydroxyflavanone and its derivatives to be developed as RCC chemoprevention agents. Therefore, the discovery of plant-derived cancer therapies, such as 2′-hydroxyflavanone, offers a new strategy for combating this highly resistant cancer.

1. Introduction

Kidney cancer, known as renal cell carcinoma (RCC), is an increasingly frequent and often lethal malignancy for which there is no effective preventative and therapeutic strategy. RCC accounts for 3% of all adult cancers and 90–95% of neoplasms of the kidney. It arises from the epithelial cells of the renal nephron and manifests as many different cytological and histological variants [1]. Approximately 75% of RCC cases are caused by heritable and somatic mutation or deletion of the von Hippel–Lindau (*VHL*) tumor suppressor gene [2,3]. Patients with *VHL* are at risk of developing up to 600 tumors in each kidney. RCC is a primary cause of death in patients with *VHL* disease, along with hemangioblastoma [4,5]. Drug treatment for advanced RCC has been unsatisfactory, with a low chance of temporary remission, small improvement in average survival, and substantial toxicity. Advanced RCC is resistant to many types of drug therapy, and new approaches are needed. Targeted agents inhibit known molecular pathways involved in cellular proliferation and angiogenesis. Angiogenesis is of special interest in the clear cell histological subtype of RCC because this disease variant is highly vascularized and shows

Abbreviations: 2HF, 2′-hydroxyflavanone; AKR1C1, aldo-keto-reductase family 1 member C1; BP, benzopyrene; CDKs, cyclin-dependent kinases; EGF, epidermal growth factor; GST, glutathione-*S*-transferase; HIF, hypoxia-inducible factor; NDMA, N-nitrosodimethylamine; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol 3-kinase; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor; *VHL*, von Hippel–Lindau.

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constitutively activated hypoxia-inducible signaling pathways. RCC occurs most often in people between the ages of 50 and 70, with a male: female ratio of 1.6:1. According to the National Cancer Institute, 1 in 67 men and women will develop RCC. Loss of *VHL* is associated with increased angiogenic and metastatic capacity in renal tumors. Chemical carcinogens such as *N*-nitrosodimethylamine (NDMA) and benzopyrene (BP) in tobacco smoke are associated with loss of *VHL* [6–8].

RCC therapy has historically been limited by lack of early detection and lack of effective cures for late-stage disease. Early detection has improved, partially due to incidental discovery of RCC during abdominal scans conducted for other symptoms such as hematuria and flank pain [9]. However, effective surgical and drug-based therapies are necessary to cure RCC. Surgical therapy frequently fails in advanced-stage RCC that involves the renal vein and lymph nodes or invasion through the renal cortex [10]. Metastatic RCC is notoriously, inherently, chemotherapy-resistant; cytotoxic chemotherapy drugs are ineffective and do not prolong survival. The highly drug- and radiation-resistant nature of RCC, when compared with other neoplasms such as lung or breast cancer, is a major reason why there is still no effective and life-prolonging traditional cytotoxic chemotherapy for RCC. Multidrug resistance can be mediated by membrane proteins, such as P-glycoprotein, multidrug resistance-associated proteins [11,12], and non-ATP binding cassette multidrug transporters, such as RLIP76, which transport not only chemotherapeutic agents but also glutathione–electrophile conjugates out of the tumor cell in an ATP-dependent manner [13–15]. The expression of RLIP76 was found in a high percentage of surgically removed specimens and RCC cell lines [15–25]. However, RLIP76-targeted therapeutic strategy for RCC in humans has not been conducted.

Multiple chemotherapeutic strategies for RCC have been attempted. RCC can be treated with immunotherapy such as interferon or IL2, but response rates are low and the survival benefit is confined to selected subpopulations. Improved knowledge of cellular signaling mechanisms affected by immunotherapy, and the development of capacity for targeted therapeutics, has led to new and effective targeted therapies for RCC that have substantially altered its natural history [10,26–29]. The introduction of multispecific kinase inhibitors, sorafenib (BAY 43-9006; Nexavar, Bayer) and sunitinib (SU011248; Sutent, Pfizer), into the clinical arena has strengthened the therapy of advanced kidney cancer [30–32]. As soon as optimal drug dosages and combination regimens are developed, these agents are likely to have an even more substantial impact on RCC survival. The recent approval of the drug temsirolimus (CCI-779; Torisel, Wyeth), the first mammalian target of rapamycin inhibitor approved for RCC, offers an alternative for patients who do not respond to the kinase inhibitors, although the toxicity is greater. Torisel provides significantly higher median overall survival and progression-free survival compared with interferon-alpha [33,34]. Clinical trials of receptor tyrosine kinase inhibitors such as the vascular endothelial growth factor (VEGF) receptor-2 and platelet-derived growth factor (PDGF) receptor-β inhibitors such as sorafenib and sunitinib, respectively, have shown positive results in prolonging progression-free survival in ~70% of patients with clear cell RCC, the most common RCC subtype. However, neither of those newer drugs had significant effects on overall tumor clearance and patient survival [35,36]. Although prolonged remissions are occasionally seen, the benefit offered by these agents is most often short-lived [37], and there is still a need for more effective therapies. Therefore, RCC remains a highly lethal disease that is incurable when metastatic, and novel chemoprevention strategies and molecular mechanisms are still greatly needed. Recently, compounds from natural sources have received ample attention as anticancer agents. Many epidemiological studies published over the past few decades show strong correlation between consumption of vegetables, fruits, or plant-derived products and reduced incidence of cancer. The present review focusses on the potential antitumor effects of flavonoids in RCC.

2. Flavonoids in RCC

In the USA, there are approximately 64,000 new cases of RCC each year and about 14,000 deaths from RCC [38]. Although some patients are surgically cured, the stage-specific survival rate at 5 years is only 80.9%, 73.7%, and 53.5% for patients with stage I, II, and III disease, respectively [39,40]. The toxicity of currently available active treatments, such as sunitinib, sorafenib, and pazotinib, renders them non-suitable for long-term administration [41]. This calls for the development of novel agents that prevent and treat RCC with minimal toxicity. In contrast to currently available chemotherapeutics and anti-angiogenic compounds [42], many natural products, such as the flavonoids, have highly tolerable toxicity profile, even at high doses [43–45], and are not likely to be associated with surgical complications when used as neoadjuvant therapies. Flavonoids can modulate the drug action by multiple mechanisms, including the following: influencing intestinal absorption, altering the rate and nature of metabolism, altering the biodistribution of the drug, and most importantly impacting multiple signaling networks in the tumor. When co-administered with chemotherapy drugs, the flavonoids can produce additive, antagonistic, or synergistic effects. These factors make flavonoids excellent candidates for translational research in RCC.

The flavonoids are polyphenolic compounds that are ubiquitously expressed in dietary sources such as red and yellow citrus fruits and vegetables. Flavonoids exhibit anticarcinogenic, anti-inflammatory, and antioxidant properties [46–48]. Structure–activity studies have demonstrated that flavonoids with more hydroxyl groups exhibit greater antioxidant and anti-inflammatory activities. Moreover, polyhydroxyflavonoids such as genistein (5,7,4-trihydroxyisoflavone), apigenin (5,7,4-trihydroxyflavone), and quercetin (3,3,4,5,7-pentahydroxyflavone) are effective inducers of apoptosis in diverse cancer cells. However, flavanones containing zero or one hydroxyl group are even more potent inhibitors of lung and colon cancer cell proliferation than the polyhydroxyflavanones. Studies from the Chen laboratory [49] have indicated that flavonoids with single hydroxyl group show greater antiproliferation potential in colorectal carcinoma cells (HT29, COLO205, and COLO320HSR) and mouse fibroblast NIH3T3 cells in dose (0–200 μM)- and time (up to 48 h)-dependent manners than flavonoids with more hydroxyl substitutions.

Although intake of flavonoids has been inversely related to the risk of various neoplasms, limited literature exists on RCC. For instance, oranges present a rich dietary source of many antioxidant compounds with anticancer properties [50–52]. Multicenter international RCC trials conducted in Australia, Denmark, Sweden, Germany, and the USA have established that the intake of oranges is associated with decreased risk of RCC. A total of 1185 incident histopathologically confirmed RCC cases (698 men and 487 women) and 1526 controls (915 men and 611 women) frequency-matched to cases by sex and age were included in these studies, and food choices were evaluated. The researchers found that fried dishes were associated with increased RCC risk, whereas vegetables and fruits were protective, with the strongest benefit observed for the highest quartile of orange and green vegetable consumers. Significant negative associations with RCC were more pronounced in non-smokers and frequent consumers of cruciferous vegetables or oranges. Overall, this clinical trial indicates an important role of nutrition, and potentially nutrition-derived protective compounds, in the development of RCC [53].

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