In Renal Cell Carcinoma, the Role of Natural Supplement Compounds as Anticancer Agents

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Abstract

Renal Cell Carcinoma (RCC) is the most common kidney cancer that arises from the renal tubules, accounting for around 85% of all malignant kidney cancers. Every year, about 60,000 new instances of RCC are reported, with approximately 14,000 people dying from the disease. In the United States and other countries, the frequency of this has been steadily growing. A better understanding of RCC's molecular biology and genetics has revealed multiple signalling pathways implicated in cancer growth. Agents licenced by the Food and Drug Administration (FDA) that target these pathways have been reported to make significant advancements in the treatment of RCC. Because of their therapeutic value and enhanced survival in patients with metastatic disease, these medications have become the treatments of choice. Patients, on the other hand, eventually relapse and acquire resistance to these medications. The search for more effective medicines and preventative methods is necessary to enhance outcomes and find approaches for establishing long-term sustainable remission. One of these techniques to lessen the incidence of RCC is to treat it with natural products. Recent research has focused on these chemoprevention medicines as anti-cancer therapeutics due to their ability to limit tumour cell growth while avoiding the significant side effects associated with synthetic chemicals. The present state of knowledge on natural products and their mechanisms of action as anti-cancer medicines is discussed in this study. The information included in this study will be useful in determining whether these products can be used alone or in combination with chemotherapy to prevent and cure RCC.

Keywords: Carcinoma • Cancer cell • Immunosenesce • Natural supplement • Immunotherapy

Introduction

Renal Cell Carcinoma (RCC) is cancer that develops in the tubule lining of the kidney [1]. It is the most common type of kidney cancer in adults, accounting for nearly 85% of all malignant kidney cancers [2,3]. It can cause weight loss, fever, hypertension, hypercalcemia, night sweats, and malaise, among other symptoms. Despite its rarity, RCC is still one of the top 10 malignancies, affecting mostly those over the age of 45 [4]. Men are more likely than women to develop this malignancy, with the typical age of diagnosis being about 60 years [5,6]. Over the last two decades, its incidence rates have been steadily increasing by 2%-4% per year [7]. According to the most recent cancer data, almost 64,000 new instances of kidney cancer will be diagnosed in the United States in 2017, with around 14,400 persons dying from renal cancer-related complications [8]. Patients with this condition have a five-year survival rate of about 85 percent if they are diagnosed and treated early, but just 10% if they are diagnosed later [9]. With a better understanding of RCC's molecular biology and genetics, multiple signalling pathways linked to the disease's progression have been identified [10]. Agents approved by the FDA that target multiple pathways have resulted in significant breakthroughs in the treatment of RCC. Inhibitors of the mammalian target of rapamycin (mTOR) and tyrosine kinase inhibitors are two examples (TKIs). In patients with advanced RCC, these medications provided therapeutic benefits without lowering the overall quality of life and had a good influence on particular symptoms such as cough, fevers, shortness of breath, ability to enjoy life, and fear that the condition might worsen. Patients, on the other hand, eventually relapse and acquire resistance to these medications. Improved identification, prevention, and treatment strategies are needed to minimise the fatality rate linked with RCC. Natural items typically investigated in chemoprevention, i.e. the use of chemicals, bioactive plant compounds, or dietary components to block, inhibit, or reverse the formation of cancer in normal or preneoplastic tissue as therapeutics for the treatment of RCC, will be evaluated in this study. Many chemicals derived from natural products have been discovered to be effective as both preventative and therapeutic agents in previous investigations. They have been proven to improve the efficacy and tolerance of chemotherapeutic drugs in various tumours when used in combination with chemotherapy or alone. The present state of knowledge about the usefulness of naturally occurring anti-cancer drugs in the treatment of RCC will be discussed in this review paper. Epigallocatechin-3-gallate (EGCG), Englerin A, Quercetin, coumarins, curcumin, and other natural compounds have been studied for their impact on RCC.

Renal cell carcinoma and natural products

Natural products have been utilised for medical purposes for thousands of years, but researchers have only just begun to look into the function they play at the molecular level. These natural products are significant because their use in ancient history has been established and can be used in modern therapy with proven results. Indeed, natural goods have been employed as traditional medicines, cures, potions, and oils by nearly every major ancient civilisation, with many of these bioactive natural ingredients remaining unknown. Natural products have been utilised for therapeutic purposes since 2600 B.C. when oils from Cupressus sempervirens (cypress) and Commiphora species (myrrh) were documented as being used to heal ailments. Natural products have been pushed to the sidelines in recent medical history, with human-made medications generated from molecular biology and combinatorial chemistry practically always taking precedence. However, these medications are frequently prohibitively expensive. Furthermore, they frequently have terrible side effects that render them unsuitable for treating human ailments, such as having the opposite impact as planned. Herbal or natural remedies, in general, offer little to no adverse effects while generating excellent tumour therapy results. The therapeutic actions of the chemicals contained in these products, however, have not been well investigated in RCC. As a result, it's a good idea to look into the pathways that are influenced by the molecules found in these natural products. The fact that tumour cells frequently bypass the apoptotic process, allowing uncontrolled multiplication, is a key contrast between normal healthy cells and tumour cells. As a result, triggering apoptosis would be a viable therapy option. Tissue factor pathway inhibitor-2 (TFPI-2) expression is inversely associated with the aggressiveness of RCC cells. As a result, larger TFPI-2 concentrations would reduce the malignancy of these cells and, most likely, cause apoptosis. Green tea (Camellia sinensis) contains epigallocatechin-3-gallate (EGCG), which has anti-tumour activities in numerous malignancies, including RCC. It suppresses tumour development and invasiveness in RCC by upregulating TFPI-2 expression and inhibiting DNA methyltransferase (DNMT) activity. Multiple independent investigations have demonstrated that EGCG is a highly effective therapy in vitro. The data previously presented suggests a few ways to use EGCG. A large epidemiological investigation, for example, found an inverse relationship between green tea consumption and overall RCC tumour burden. Another option would be to combine EGCG with TKI or mTOR inhibitors to investigate if the combo sensitises tumour cells more effectively than either TKI or mTOR inhibitor alone. Sato et al. claim that EGCG administration increased the chemical sensitivity of vinblastine by inactivating Src and activating the c-Jun NH2-terminal kinase (JNK) de RCC cells via restoring the connexin 32 (Cx32) gene, a tumour suppressor.

Englerin A: Englerin A is a natural substance obtained from the root and stem bark of the African plant *Phyllanthus engleri*. Through a pharmacological screen of the NCI 60 (National Cancer Institute 60) cell line panel, it was discovered to preferentially inhibit the growth and viability of RCC cells. This natural substance is a guaiane sesquiterpene with a tricyclic structure that may be synthesised in a lab using a systematic technique. Multiple suggested mechanisms for Englerin A's suppression of RCC growth have been discussed in detail by Beutler and associates in a comprehensive review. Ramos' group has proposed that Englerin A can stop RCC cell lines from growing by causing necrotic cell death rather than apoptosis. In vivo studies have been few, and those that have been done on mice models suggest that the amounts of Englerin A required for anti-tumor efficacy are potentially deadly. If the results of this in vivo model properly reflect the effects of the natural chemical, it would be a significant barrier to its application in cancer treatment. The complex, on the other hand, is well worth examining. If a non-lethal derivative of Englerin A could be discovered and applied, it would be tremendously successful in treatment. Furthermore, the mechanisms by which Englerin A elicits anti-tumor properties are currently being debated. If it is discovered that Englerin A suppresses tumours through many mechanisms, it could be used to treat various cancers.

Quercetin: Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonoid pigment that can be found in a variety of foods, including tea, onions, grapes, and apples. Quercetin has been proven to have a chemopreventive effect in a variety of malignancies, including liver, lung, prostate, breast, and kidney cancers. When combined with other substances, this natural product has proven to be quite beneficial. When combined with hyperoside, quercetin exerts a therapeutic impact in 786-0 renal carcinoma cells. Downregulation of miRNA-27a is the mechanism behind this activity, which we haven't looked into yet in this article. Most natural compounds we've looked at use alternative mechanisms to cause apoptosis or necrosis. Meanwhile, a drop in specificity protein (SP) transcription factors is triggered by a decrease in miRNA-27a paired with an increase in ZBTB10 (the zinc finger and BTB domain-containing protein 10). These transcription factors are highly expressed in cancer cells, and quercetin's ability to reduce its expression demonstrates quercetin's therapeutic promise.

The chemopreventive action of EGCG was considerably reduced when it was methylated by the catechol-O-methyltransferase (COMT) enzyme in different malignancies. By reducing COMT activity, quercetin has been shown to boost the activity of EGCG in terms of bioavailability in animal models. Snail is a zinc-finger transcription factor that regulates EMT, migration, and metastasis in cells. In Caki-2 cell lines, silencing it with short hairpin RNA (shRNA) inhibited cell proliferation, cell cycle progression, cancer cell migration, and accelerated apoptosis. Quercetin, when combined with snail silencing, has much more potent suppressive effects on these cells. Quercetin has a lot of therapeutic potentials, which can be polished with more research and analysis. Sunitinib and isoquercetin, which is hydrolyzed in vivo to quercetin, are now being studied in conjunction. The researchers in this ongoing clinical trial believe that isoquercetin can minimise sunitinib-induced weariness, which is reported in 51-63 percent of advanced RCC patients.

Conclusion

Many agents, such as anti-angiogenesis and immunotherapy medicines, are currently available for the treatment of RCC (interleukin and interferon). Renal cell carcinoma is one of the deadliest malignancies, and late stages, despite the numerous therapy choices, are incurable. There is a definite need for drugs that are efficient against tumours while also avoiding undesirable drug reactions in the patient. Nature products have been presented as an alternative, however, few of these chemicals have been used on a broad scale in the treatment of cancer patients yet. Many natural chemicals have been demonstrated to be extremely successful *in vitro* and *in vivo* cancer models in recent studies, and history has shown that this class of drug has few to no negative side effects. EGCG, Englerin A, curcumin, resveratrol, quercetin, and honokiol are just a few of the natural substances that have shown promise in RCC preclinical trials. The anticancer mechanism of these drugs has been summarised. It's a good idea to keep looking into natural compounds as anti-tumour agents that don't have a lot of side effects, either alone or in a well-designed combination. Alpinumisoflavone is a plant isoflavon isolated from Erythrina lysistemon, and nothing is known about its anti-cancer properties in RCC. Wang et al. have discovered the mechanism of this natural compound's anti-cancer action, claiming that it inhibits tumour growth and metastasis through altering miR-101/RLIP76 signalling. A clerodane diterpene (CD) isolated from Polyalthia longifolia var. pendula leaves, 16-hydroxycleroda-3,13-dien-15,16-olide, has been found to suppress the proliferation of numerous human cancer cell lines. However, the mechanism of CD's anti-RCC activity is unknown. In RCC cells, a recent study revealed the mechanism of action of CD, suggesting that it inhibits cell growth and promotes mitochondrial-dependent apoptosis via the AKT, mTOR, and MEK/ERK pathways. According to a recent study, Korean red ginseng extract can boost sorafenib's anticancer efficacy by decreasing cyclic adenosine monophosphate response element-binding protein and c-Jun activation, inducing p53 phosphorylation, and improving sorafenib's chemosensitivity in RCC.

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