

Review

An Overview of Renal Cell Carcinoma Hallmarks, Drug Resistance, and Adjuvant Therapies

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Abstract. Renal neoplasms are highlighted as one of the 10 most common types of cancer. Renal cell carcinoma (RCC) is the most common type of renal cancer, considered the seventh most common type of cancer in the Western world. The most frequently altered genes described as altered are VHL, PBRM1, SETD2, KDM5C, PTEN, BAP1, mTOR, TP53, TCEB1 (ELOC), SMARCA4, ARID1A, and PIK3CA. RCC therapies can be classified in three groups: monoclonal antibodies, tyrosine kinase inhibitors, and mTOR inhibitors. Besides, there are targeted agents to treat RCC. However, frequently patients present side effects and resistance. Even though many multidrug resistance mechanisms already have been reported to RCC, studies focused on revealing new biomarkers as well as more effective antitumor therapies with no or low side effects are very important. Some studies

reported that natural products, such as honey, epigallocatechin-3-gallate (EGCG), curcumin, resveratrol, and englerin A showed antitumor activity against RCC. Moreover, nanoscience is another strategy to improve RCC treatment and reduce the side effects due to the improvement in pharmacokinetics and reduction of toxicities of chemotherapies. Taking this into account, we conducted a systemic review of recent research findings on RCC hallmarks, drug resistance, and adjuvant therapies. In conclusion, a range of studies reported that RCC is characterized by high incidence and increased mortality rates because of the development of resistance to standard therapies. Given the importance of improving RCC treatment and reducing adverse effects, nanoscience and natural products can be included in therapeutic strategies.

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Cancer is a complex multifactorial disease considered the greatest problem of public health in recent decades and the second leading cause of death in the world, with an average of 9.8 million deaths per year (1).

Renal neoplasms are highlighted as one of the 10 most common types of cancer, mainly in the West. These cancers are classified into four main types: renal cell carcinoma (RCC), Wilms tumor, renal urothelial carcinoma, and renal sarcoma (2).

RCC is the most common type of renal neoplasm, considered the seventh most common type of cancer in the Western world, with an increase in incidence of 80%-90% of kidney cancers in adults, prevalence of 2%-3% of all malignancies in adults, and mortality of approximately 40% (3-5).

RCC is the third most prevalent type of genitourinary cancer and the most common malignancy in the kidneys, with 403,000 new diagnoses per year (2.2% of all tumors), and more than 175,000 deaths in the same period (1.8% of mortality from cancer) (6, 7). The USA incidence is estimated at 76,080 new cases and 13,780 deaths in 2021 (3). The survival of patients with locally advanced and metastatic disease at 5 years is 69.6% and 12%, respectively (8, 9). The GLOBOCAN study estimated an incidence of 2.2%-3.3% and mortality of 1.8%-2.6% in developed countries (7, 10).

Moreover, several risk factors can be associated with this group of neoplasms, such as predisposition to chronic kidney disease, estrogen therapy, exposure to asbestos, petroleum and heavy metal products, diabetes, sedentary lifestyle, family history, poorly controlled hypertension, smoking, obesity, alcohol intake, and diet (8, 11-21).

RCC can trigger local symptoms such as hematuria, pain in the lower back, palpable abdominal mass, and systemic symptoms, for example, weight loss, fever, and abdominal pain (22, 23). Hematuria, low back pain, and palpable abdominal mass are considered the classic triad in diagnostic approaches to RCC. Furthermore, between 50%-80% of cases are diagnosed incidentally through abdominal ultrasound, contributing to the early detection of asymptomatic tumors (24-26).

Although more cases have been diagnosed early due to the increase in imaging exam applications, RCC still constitutes a great challenge to public health considering that it is characterized as a tumor frequently asymptomatic and with reduced clinical manifestation, when compared to the other types of cancers (9).

Renal Cell Carcinoma Staging and Subtypes

RCC is considered a complex disease characterized as a heterogeneous group of tumors with different genomic, histological, and clinical characteristics. In addition, other factors such as the extent of the disease, the presentation of different clinical phenotypes, and different responses to treatment make it even more complex (23, 27-29).

RCC staging is determined considering the anatomical site of the primary tumor (T) (Figure 1), regional lymph node (N), and metastasis distance (M) according to American Joint Committee on Cancer (AJCC), known as TNM (30, 31). Regarding the primary tumor (T): in the absence of evidence of a primary tumor is classified as T0, a tumor 7 cm or less and limited to the kidney as T1, if >7 cm and limited to the kidney as T2, if it reaches larger vessels or the perirenal tissue without going beyond Gerota's fascia as T3, if it invades Gerota's fascia as T4, and if it cannot be evaluated as TX. Regarding regional lymph nodes (N): if there are no metastases in lymph nodes is classified as N0, if there is lymph node metastasis as N1, if lymph nodes could not be evaluated

as NX. Regarding distant metastasis (M): in the absence of distant metastases is classified as M0, if there are distant metastases as M1, if the metastasis cannot be evaluated as MX. Thus, these parameters can receive numerical graduations (T0 to T4; N0 to N1 and M0 to M1), alphabetical (a, b, c), and "X" when the category cannot be evaluated, giving more details on each of these analyzed aspects (30, 32) (Table I).

There are three main subtypes based on the appearance of RCC, such as clear cell (ccRCC), papillary (pRCC), and chromophobic (crRCC). These subtypes represent approximately 90% of all RCCs. The remaining 10% comprise rare and benign subtypes (Table II) (5).

Genetic and Metabolic Hallmarks of RCC

Although the histological classification of renal tumors is an important tool in the diagnosis and evaluation of the prognosis of patients (33), molecular characteristics that differentiate the subtypes of this disease have been increasingly used. It is important to more precisely characterize the subtypes, as well as to improve the prognosis and treatment (34).

Taking this into account, studies have focused on the molecular mechanisms of RCC. Thus, The Cancer Genome Atlas (TCGA) includes several genomic studies, focusing on individual tumor subtypes, using data generated from multiple platforms (35).

Regarding the molecular profile of RCCs, recurrent alterations are described into specific subtypes. For example, the most prevalent RCC subtype, ccRCC, is associated with some mutations. The most frequent genes described as altered are *VHL*, *PBRM1*, *SETD2*, *KDM5C*, *PTEN*, *BAP1*, *mTOR*, *TP53*, *TCEB1* (*ELOC*), *SMARCA4*, *ARID1A*, and *PIK3CA*. In addition to punctual alterations, alterations in chromosomes 3, 5, 10, and 14 are also frequently described in this subtype (34, 36-40).

Approximately 80% of ccRCCs present inactivation of the Von Hippel Lindau (*VHL*) gene by mutation or methylation (34, 41). The *VHL* gene is a tumor suppressor and, in many cases, one of its alleles is inactivated by some kind of mutation, and the second is affected by a deletion in the 3p25-26 region in approximately 90% of cases of ccRCC (42-44), thereby playing an important role in both hereditary and sporadic disease (41). This mutation causes elevated levels of factors that induce hypoxia and increases the levels of vascular endothelial growth factor (VEGF), thereby facilitating tumor-associated angiogenesis. VEGF mediates neoangiogenesis that allows tumor nutrition and growth (45).

ccRCC is the subtype frequently present in hereditary von Hippel-Lindau syndrome, an autosomal dominant condition with germline mutations in the *VHL* gene. In this syndrome, approximately 40% of those affected will develop RCC, which is usually characterized by the presence of small tumors that develop in the kidneys (46, 47).

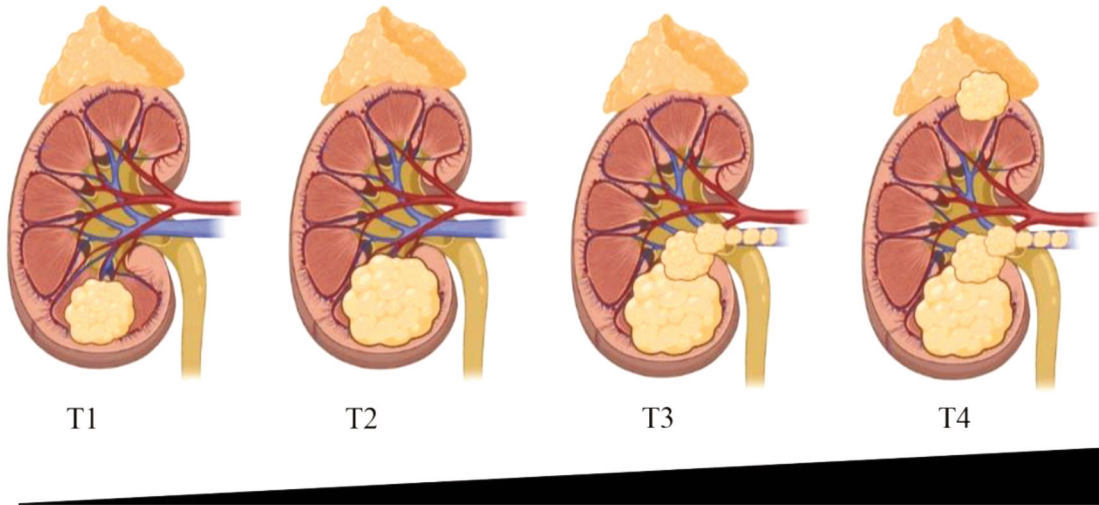


Figure 1. Renal cell carcinoma staging by primary tumor classification (T).

Table I. Most used staging system in renal tumors. System TNM (American Cancer Society, 2020).

Stage	Stage grouping	Description
I	T1 N0 M0	The tumor is 7 cm across or smaller and is only in the kidney (T1). There is no spread to lymph nodes (N0) or distant organs (M0).
II	T2 N0 M0	The tumor is larger than 7 cm across but is still only in the kidney (T2). There is no spread to lymph nodes (N0) or distant organs (M0).
III	T3 N0 M0	The tumor is growing into a major vein (like the renal vein or the vena cava) or into tissue around the kidney, but it is not growing into the adrenal gland or beyond Gerota's fascia (T3). There is no spread to lymph nodes (N0) or distant organs (M0).
	T1-T3 N1 M0	The main tumor can be any size and may be outside the kidney, but it has not spread beyond Gerota's fascia. The cancer has spread to nearby lymph nodes (N1) but has not spread to distant lymph nodes or other organs (M0).
IV	T4, any N e M0	The main tumor is growing beyond Gerota's fascia and may be growing into the adrenal gland on top of the kidney (T4). It may or may not have spread to nearby lymph nodes (any N). It has not spread to distant lymph nodes or other organs (M0).
	Any T, N e M1	The main tumor can be any size and may have grown outside the kidney (any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant lymph nodes and/or other organs (M1).

Table II. Renal cell carcinoma subtypes.

Common	Rare	Benign
Clear cells Papillary I and II Chromophobe	Bellini's duct (collector) Renal medullary Neoplasia renal cystic multilocular Translocation renal cell carcinoma Mucinous tubular and spindle cell carcinoma Succinate dehydrogenase-deficient renal cell carcinoma Tubulocystic carcinoma Renal cell carcinoma associated with acquired cystic disease	Papillary adenoma Oncocytoma

The pRCC type, subdivided into types 1 and 2, also has specific genetic characteristics. Type 1 tumors are characterized by variants in *MET* gene, a proto-oncogene, which encodes a cell surface protein for hepatocyte growth factor, while type 2 tumors are characterized by alterations in the *CDKN2A*, *SETD2*, and *FH* genes (48). Changes in *PBRM1*, *BAP1*, and *SETD2* are also found in the pRCC type 2 subtype, however, in lower frequencies than those observed in the ccRCC (35, 37, 48). In addition, methylation patterns have also been associated with subtype 2, characterizing a more aggressive disease with a lower survival rate (48).

The molecular characteristics of RCC of the chromophobe subtype have also been analyzed. Since it is a rare subtype, the identified alterations presented a lower frequency (approximately 10%) than those found in other subtypes. The genes found mutated in these cases were *PTEN* and *TP53*. However, it was also possible to identify alterations in *mTOR*, *NRAS*, and *FLCN* (variants germline related to hereditary syndrome). Furthermore, gene fusions with the gene *TERT* have been reported frequently in this subtype, and methylation profiles have been related to a more aggressive disease (49). Moreover, chromosomal changes are frequent in this subtype, such as loss of chromosomes Y, 1, 2, 6, 10, 13, 17, and 21 (23). In addition, a previous study reported that *FH*, *FLNN*, *SDHB*, and *SDHD* are also linked to hereditary RCC recurrence (50).

Renal Cell Carcinoma Treatments

RCC tumors have a rounded shape and variable size from few centimeters to complete occupancy of the abdomen. Small renal masses that increase over time and show increased contrast in computed tomography (CT) scans, should be considered extremely suspicious for renal neoplasms, although there are many inherent uncertainties (23). Therefore, the most suitable therapy for cases of localized disease is total or partial surgical resection of the tumor. Total resection is performed when the most conservative surgery is impossible, in cases of locally advanced disease, which occasionally will require resection of adjacent organs (8). Although it is an established and well-recognized therapy approach, studies show a certain heterogeneity between detected renal masses, where approximately 20% have a benign profile, 60% are considered indolent tumors, and 20% potentially aggressive tumors (51, 52). These findings suggest that a more detailed characterization of these tumors may contribute to the choice of a less aggressive strategy in certain cases and intervention surgery in others.

Patients with metastatic disease present a heterogeneous group. Hence, different initial therapies can be used, and the most recurrent metastases are found in the lymph nodes, lungs, bones, and liver (8, 53). Approximately 25% of

patients diagnosed with RCC present with metastasis at diagnosis and 20-40% will develop metastasis after treatment of the primary tumor. Patients with metastatic disease have a survival average of 6 months to 1 year, and less than 20% of these patients survive more than 2 years (54, 55).

Regarding the prognosis of patients with RCC, therapeutic strategies such as targeted therapy, inhibitors of tyrosine kinase and monoclonal antibodies, as well as the age of the patient and early diagnosis are essential factors for a good prognosis (56). RCC therapies can be categorized into three groups: monoclonal antibodies [such as bevacizumab (anti-VEGF) and nivolumab (anti-PD-1)], tyrosine kinase inhibitor (TKIs) (sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib), and mTOR inhibitors (mTORi; temsirolimus and everolimus). Moreover, further investigations are being carried out to reveal additional target agents, for example, TKIs regorafenib, cediranib, tivozanib, dovitinib, and lenvatinib (57).

RCC is a vascular tumor that is highly resistant to chemotherapy and radiotherapy. Some randomized studies have shown no benefits in using adjunctive systemic therapies such as interleukin-2 and interferon immunotherapies alpha (58), radiotherapies, and hormone treatments in patients with this neoplasm (23). Therefore, further advances in the understanding of biology of RCC are required to enable the use of new drugs (targeted therapy) in patients with RCC, such as therapies that inhibit the VEGF pathway, mTOR protein inhibitors, and PDGFR. Although these new therapies have increased overall survival and are specific to these patients, metastatic disease, in most cases, is still incurable and requires constant patient follow-up (59). In this scenario, numerous clinical and preclinical studies exploring the potential of therapies for the inhibition of immunological checkpoints have shown that these therapies can substantially contribute to the survival of patients with advanced renal neoplasms. These new therapeutic strategies work by blocking immune checkpoints, which normally prevent the development of an immune response against normal cells. This happens because some neoplasms can acquire these checkpoints, preventing tumor cells from being recognized by the immune system, and consequently inactivating the immune cells that can destroy them (60). Thus, the mechanisms of action of these immune checkpoint inhibitor therapies involve the removal of inhibitory signal activation of T cells, which enable tumor cells to overcome the mechanisms of immune system regulators (61-63). As a result, immunotherapies with checkpoint inhibitors (anti PD-1 and anti CTLA-4) are emerging in urologic cancer as promising treatment options. Clinical studies are ongoing, and thus far the results show that certain patients have a good response to treatment; however, more personalized strategies need to be used to better stratify the patients, taking into account their clinical and mainly molecular characteristics (64-67) (Figure 2).

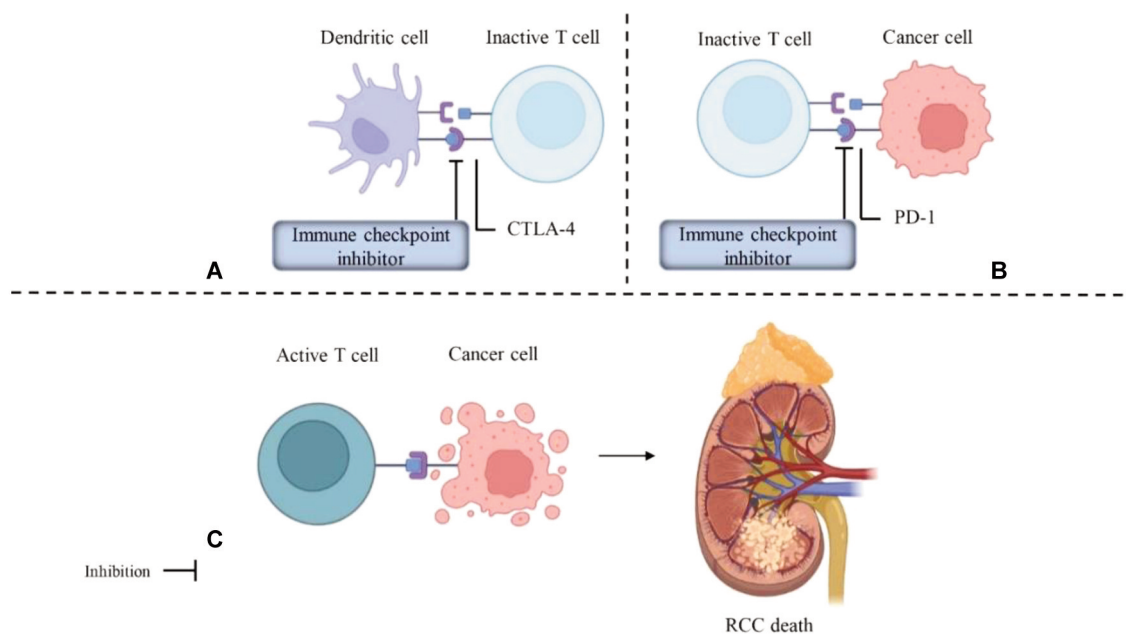


Figure 2. Potential therapies for the inhibition of immunological checkpoints against renal cell carcinoma.

The most used drugs for the treatment of advanced RCC are sorafenib, sunitinib, and temsirolimus. Sorafenib, a new oral small-molecule multikinase inhibitor, inhibits tumor growth and angiogenesis by targeting the RAF/MEK/ERK pathway and receptor tyrosine kinases with a response rate of 10%. Sunitinib acts as an antiangiogenic agent, inhibiting angiogenesis in tumors. This activity is achieved by inhibiting the receptor of vascular endothelial growth factor (VEGFR), which in turn inhibits angiogenic growth factors. Temsirolimus has an anticancer activity acting directly on the mTOR, a key mediator of tissue growth, proliferation, and angiogenesis, and its inhibition may also lead to growth reduction and stabilization, making it an immunosuppressant (58).

RCC tumors are highly infiltrated by immune cells, especially T cells. Taking advantage of these characteristics of the microenvironment, immunotherapy has advanced in the last decade, with VEGF TKIs, and immune checkpoint blockade. However, they also have other targets, which explains toxicity and possible additive antitumor effects (59).

Side Effects of Renal Cell Carcinoma Therapies

Antiangiogenic agents are considered standard therapy for RCC. Although these therapies are considered inhibitors of angiogenesis, they also present other mechanisms. This aspect is important to determine the efficacy and side effects of the therapy. These therapeutic agents can be divided into three groups: VEGF, Tyrosine kinases, and mTOR inhibitors (68).

Bevacizumab, also known as avastin, is a recombinant human IgG1 monoclonal antibody (MAb) that recognizes all isoforms of human VEGF and binds to it and prevents VEGF from binding to VEGF receptors on endothelial cells. This treatment has demonstrated a range of side effects (68, 69).

Some adverse effects have been associated with these agents, such as hypertension caused by the decrease in the production of vasodilator substances, stimulated by VEGF and VEGFR-2, increasing peripheral vascular resistance. Proteinuria is another side effect since inhibition of VEGFR affects the glomerular filtration barrier due to its cytoprotective function of endothelial cells. Regarding wound healing and bleeding, agents inhibiting VEGF can affect endothelial turnover in response to trauma and trigger high clotting, leading to thromboembolic events (68, 69).

Tyrosine kinases participate in the process of growth and development of cancer through signaling pathways, such as VEGF. TKIs inhibit the activity of receptor tyrosine kinases 1, 2, and 3; however, it is non-specific, which leads to enhancement of other receptor tyrosine kinases. Thus, this treatment affects transmission of multiple signaling pathways, which leads to a wide range of side effects (70).

The side effects caused by TKIs are manifested according to the signaling pathway that the TKIs will act on; when the TKIs affect the VEGF pathway, the side effects are identical to those of VEGF inhibitors. When they affect other signaling pathways, the effects can be those observed in Table III (69).

The inhibition of mTOR activity is very important in RCC therapies because, together with tyrosine kinase receptors,

Table III. *Non-vascular endothelial growth factor (VEGF)-related side effects of VEGF receptor tyrosine kinase inhibitors.*

Side effects not related to VEGF	Pathways	Physiopathology
Dermatological effects: rash and HFSR	VEGFR, PDGFR	It may interfere with pericyte-mediated endothelial cell survival mechanisms and lead to capillary endothelial damage in the hands and feet.
Depigmentation of skin and hair	SCF, c-KIT	These are important pathways for melanocyte proliferation and differentiation for pigment production, so inhibitions can lead to depigmentation.
Cardiac dysfunction	VEGFR, PDGFR, RAF-1, c-KIT	It may inhibit several intracellular pathways involved in cardiac repair, leading to cardiomyocyte apoptosis and toxicity.
Myelosuppression	VEGF	Intracellular inhibition affects the VEGF-dependent internal autocrine cycle which controls hematopoietic stem cell survival.
Hypothyroidism and fatigue	VEGFR-1 e -2	Through inhibition, the interruption of the synthesis of thyroid hormones may result.

HFSR: Hand-foot skin reaction; VEGFR: VEGF receptor; PDGFR: receptor platelet-derived growth factor; SCF: stromal cell factor.

mTOR regulates protein biosynthetic pathways that promote cell growth and angiogenesis. The most used mTOR therapies are temsirolimus and everolimus (70).

The most observed side effects of mTOR inhibition are related to metabolic abnormalities such as hyperglycemia, hypertriglyceridemia, hypercholesterolemia, and hypophosphatemia. As reported for TKIs, these inhibitors present no selective profile, they also affect other signaling pathways, which can lead to side effects similar to those of TKIs. Due to the great complexity of mTOR-related signaling pathways, the pathophysiology of side effects caused by these inhibitors is still not completely clear. However, some side effects can be explained.

Resistance to Systemic Therapies in Renal Cell Carcinoma

Response Evaluation Criteria in Solid Tumors (RECIST) are criteria used to measure the response to anticancer therapy. Cancer resistance is determined if RECIST achieves a result of 20% or more in the sum of some parameters, such as measurable lesions, the development of new tumors, or an unequivocal progression of non-measurable disease, for example, small lung nodules or bone lesions (71).

Two types of cancer resistance to targeted therapeutics can be found, intrinsic (primary) and acquired (secondary) resistance. When the therapies immediately fail, the tumor is classified as intrinsic resistant due to the presence of resistant cells before the treatment *via* inherited resistance or evolutionary clonal selection. However, when cancer cells resume proliferation after the first regression, during the treatment, resistance is classified as acquired. Some resistance pathways have already been revealed (72). However, more studies should be performed to further explain these cancer cell strategies to resist therapies.

A previous study reported some processes associated with primary resistance in RCCs, such as apoptosis inhibition, epigenetic modifications of histone proteins, and ATP-binding cassette (ABC) drug transporters. Primary resistance is also associated with apoptosis blockage *via* a rise in B-cell lymphoma-2 (Bcl-2) and/or Bcl-XL proteins and a decrease in CD95 expression (73, 74). Moreover, another dysfunctional pathway that has been associated with primary resistance is the VEGF pro-angiogenic signaling pathway (75).

Regarding acquired resistance, activation of alternative pro-angiogenic pathways, resistance mediated by the tumor microenvironment, increased invasiveness and metastasis, lysosomal sequestering, single-nucleotide polymorphisms, and microRNAs play important roles (76).

Studies have reported that 26% of patients treated with sorafenib and sunitinib exhibit primary resistance to the treatment. Most of these patients present poor results, independently of subsequent therapy (77). Besides, some patients that are susceptible to therapies targeting the VEGF pathway, frequently develop secondary or acquired resistance after chronic treatment (Figure 3).

Primary and Acquired Resistance to Systemic Therapeutic Agents: Acquired Mechanisms

Lysosomal sequestration via TKIs. Reduced influx of TKIs by RCC is one of the mechanisms of multidrug resistance (78). Lysosomal sequestration of TKIs has been shown to play an important role in cellular adaptation to the treatment (79). Moreover, TKIs resistance and increased metastasis can be related to epithelial-to-mesenchymal transition (80).

Studies reported that lysosomes have 50 different acid hydrolases activated by the acidic pH around 4.6 to 5.0,

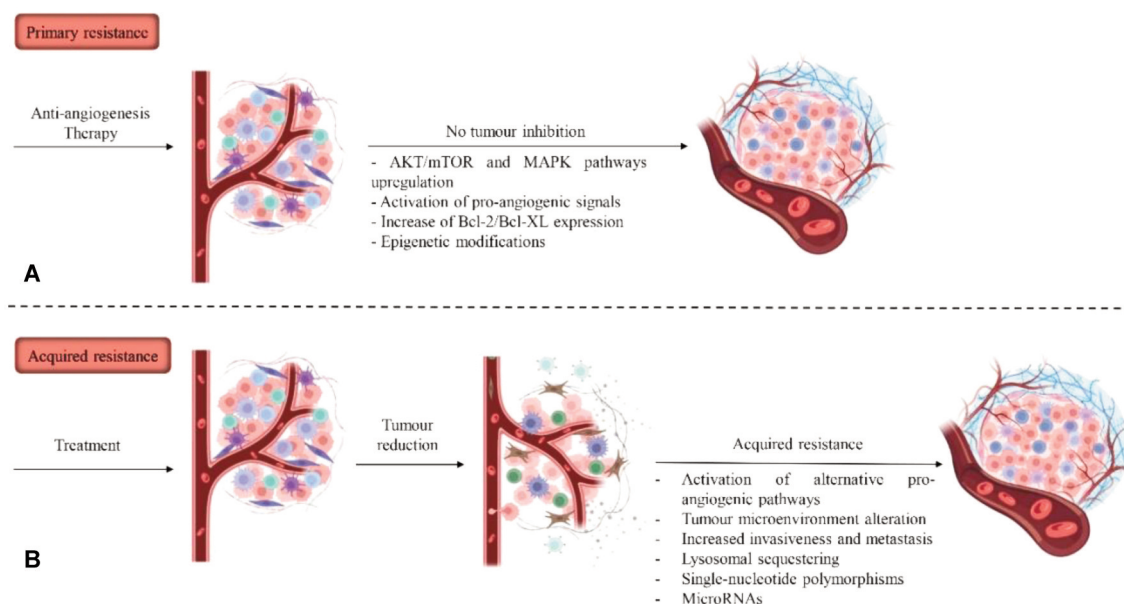


Figure 3. Renal cell carcinoma primary (A) and acquired (B) resistance.

which is maintained through the use of vacuolar ATPases. Since sunitinib is a hydrophobic weak base, it might favorably accumulate in acidic lysosomes. TKIs are weak bases, which are sequestered by being trapped in their protonated form and they do not reach their local target. Resistance to sunitinib, erlotinib, and pazopanib can be associated with this mechanism (81).

Inactivation of Von Hippel Lindau protein. The inactivation of VHL proteins triggers over-expression and activation of receptor tyrosine kinases MET and AXL. Both MET and AXL signaling pathways have been associated with clinical resistance to VEGF-targeted therapeutics agents (72). High levels of MET or AXL oncoproteins are associated with poor clinical prognosis. Given the fact that MET and AXL up-regulation present an important role in association with VEGF for RCC development and progression, agents that are able to inhibit these molecules can be an excellent strategy to selective RCC therapy (82).

In addition, the increase in VEGF action is related to the connection of receptor tyrosine with the angiopoietin 1 and 2 (Ang 1 and Ang 2) pathway (83). HIFs are responsible for increasing VEGF, interleukins 6 and 8 (IL-6 and IL-8), hepatocyte growth factor (HGFR/C-MET), fibroblast growth factor (FGF2) and some other growth factors (72, 83). IL-6 and IL-8 also have an important role in tumor angiogenesis, and their levels are increased during treatment with sunitinib and pazopanib. The activation of chemokine receptor 2 contributes to the transcription and translation of VEGF

mRNA leading to increased levels of VEGF protein, which activates VEGFR-2 in an autocrine manner (84).

Increased invasiveness and metastasis via angiogenic switch. Some studies have reported that alterations in genes associated with angiogenesis and the rise in pericyte coverage of tumor vessels result in the recruitment of pro-angiogenic inflammatory cells from the bone marrow and metastatic activity in RCC (75).

Moreover, studies have shown that the use of sunitinib facilitates the formation of tubules and the proliferation of endothelial cells through FGF. This growth factor also activates alternative pathways such as MAPK, ERK, PI3K, and AKT (84).

Antiangiogenic mechanisms are up-regulated by hypoxia-inducible factors and correlate with poor prognosis and resistance to VEGF receptor inhibitors in preclinical models of RCC and other cancers (82, 85). Besides, RCC cells express HLA-G and HLA-E on their surface that decrease the immune response and promote early tolerance (86).

Growth increase via alternative pathways activation. A study reported some molecular patterns associated with primary resistance in ccRCCs, such as the absence of HIF- α protein and wild-type VHL alleles; VHL-deficient tumors, expressing detectable HIF-1 α and HIF-2 α ; and VHL-deficient tumors expressing HIF-2 α exclusively (87). Wild-type tumors and those that expressed both HIF-1 α and HIF-2 α showed an increase in AKT/mTOR and MAPK pathways and were more

sensitive to TKI. In contrast, tumors that expressed only HIF-2 α showed increased c-Myc activity, triggering proliferation and increased resistance. These results suggest that HIF-1 α and HIF-2 α activate distinct oncogenes in ccRCC (87).

Studies reported that loss of PTEN is correlated with sunitinib resistance in renal cells. However, the up-regulation of PTEN or the inhibition of AKT/mTOR pathway increases the response of PTEN-deficient ccRCC cells to sunitinib *via* apoptosis activation (88). Moreover, PTEN down-regulation is associated with poor sensitivity to bevacizumab (89).

ATP-binding cassette (ABC) efflux transporters. Membrane structures were associated with multidrug resistance, for example, ATP-binding cassette (ABC) drug transporters [P-glycoprotein (Pgp, ABCB1), and multidrug resistance associated protein (MRP) 1 (ABCC1)] (90).

Alterations in gene expression levels. The action of histone deacetylases and methyltransferases, enzymes that control epigenetic modifications, have been reported to be modified in RCC (37). Histone methyltransferase EZH2 over-expression is associated with tumor angiogenesis *via* blocking anti-angiogenic factors by promoter gene methylation, causing low response to sunitinib (91).

Tumoral heterogeneity. Heterogeneity can be found even among cells in the same tumor, including variations in gene, microRNA, and protein expression (89). For example, post-sunitinib metastatic lesions show FLT4, KMT2D, and BMP5 mutations, which were not found in the primary tumor (92).

Previous studies reported that after treatment with sorafenib, RCC cancer cells developed mutations and morphologic heterogeneity compared to untreated subjects (93). Moreover, studies suggest that VEGF-targeted therapy can induce polyclonal outgrowth of tumor cell subclones that can result in poor treatment response (93).

Tumor microenvironment. The tumor microenvironment is composed of tumor cells, extracellular matrix (ECM), signaling molecules, and stromal cells, such fibroblasts, vascular endothelial cells, pericytes, and immune cells. Myeloid-derived suppressor cells (MDSCs) are significantly found in the tumor microenvironment since they are potent immunosuppressors. Due to this fact, MDSCs are highly recruited by tumors to trigger low response to anti-angiogenic drugs *via* increasing pro-angiogenic factors that can activate VEGF-independent angiogenesis (94).

It has been shown that patients that received sunitinib treatment presented a reduction in MDSCs in peripheral blood; on the other hand, the tumor tissue did not show a decrease in MDSCs (95). Moreover, pericytes, which are considered stromal cells, are also involved in aberrant tumor angiogenesis and drug resistance.

Resistance mediated by the action of microRNAs. RCC can exhibit different patterns of miRNA expression that can result in therapy resistance. Sunitinib-resistant RCC tumors present an increase in the expression of miRNA-942, miRNA-133a, miRNA-628-5p, and miRNA-484 when compared to sunitinib-sensitive tumors.

The up-regulation of miRNA-942 in an mRCC cell line can increase the production of MMP-9 and VEGF that result in the migration of endothelial cells and sunitinib resistance (96).

Adjuvant Therapies to Improve RCC Treatment Focus on Natural Products

Even though many multidrug resistance mechanisms already have been reported in RCC, studies focusing on new biomarkers as well as selected antitumor therapies with no or low side effects and more effective are very important.

Currently, the standard therapy for RCC is partial nephrectomy (97). Alternative treatment options are available, such as stereotactic body radiotherapy, microwave ablation, cryoablation, radiofrequency ablation, and active surveillance (98). Unfortunately, there is no adjuvant treatment for RCC. However, investigations in this field are very important, due to the fact that the 5-year relapse rate for intermediate- and high-risk early-stage RCC is 30% to 40% (99). Metastatic RCC can be treated successfully with immune therapy and targeted therapy (100). Pazopanib and sunitinib are currently the standard first-line treatment for metastatic RCC, both with similar efficacy, although the safety profile favors the use of pazopanib (101). Various adjuvant trials with immune therapy have been conducted. However, they reported no benefit in disease-free survival, and clinical trials with targeted agents have not reported results yet (102). Taking this into account, new treatments against RCC that present a selective profile and are more effective should be developed. Thus, some natural products that exhibit several bioactivities have been investigated in this area.

Honey

Previous studies have indicated that honey may have antitumor activity in human renal carcinoma cell lines (ACHN), mainly by activating apoptosis (103). Samarghandian *et al.* (104) reported that treatment of ACHN cells with different concentrations of honey for three days decreased cell viability in a concentration and time-dependent manner. The IC₅₀ values of honey against the ACHN cell lines were 1.7 \pm 0.04% and 2.1 \pm 0.03% μ g/ml after two and three days post treatment, respectively. However, further studies are necessary to understand the exact molecular mechanism behind the antitumor activity of honey in this context.

Table IV. Overview of the main natural products with anticancer effects in renal cell carcinoma.

Natural product	Source	Anti-tumor effect
Honey	Bees	Induction of apoptosis
Epigallocatechin-3-gallate (EGCG)	Green Tea (<i>Camellia sinensis</i>)	Inhibition of tumor growth and invasiveness <i>via</i> TFPI-2 \uparrow . Induction of apoptosis <i>via</i> c-FLIP \downarrow , Mcl-1 \downarrow and Bcl-2 \downarrow .
Curcumin	Turmeric (<i>Curcuma longa</i>)	Inhibition of cancer cells proliferation <i>via</i> STAT3 \downarrow , Akt/mTOR \downarrow and beclin-1 \uparrow . Induction of apoptosis <i>via</i> PI3K/Akt \downarrow .
Resveratrol	Grapes	Induction of apoptosis, cell cycle arrest and inhibition of cancer cells proliferation <i>via</i> JAK-1 \downarrow , C-Src \downarrow , STAT3/5 \downarrow , PTP ϵ \uparrow and SHP-2 \uparrow .
Englerin A	<i>Phyllanthus engleri</i>	Induction of apoptosis, inhibition of cell migration, activation of autophagy and cell cycle arrest <i>via</i> PI3/Akt/ERK \downarrow and PKC θ \uparrow .

Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate (EGCG), a component derived from *Camellia sinensis* (green tea) that is also found in apple, shows cytotoxic effects in RCC; it inhibited tumor growth and invasiveness in RCC by up-regulating expression of TFPI-2 through inhibition of DNA methyltransferase (DNMT) activity (105). Additional studies indicated that EGCG sensitized human 786-0 renal cell carcinoma cell lines to apoptosis by down-regulating c-FLIP, Mcl-1, and Bcl-2 proteins in a caspase-dependent pathway, while inhibited proliferation and migration of these cells by down-regulating matrix metalloproteinase-2 and matrix metalloproteinase-9 (106, 107).

Curcumin

Curcumin, (1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione, is the primary bioactive substance found in turmeric (*Curcuma longa*). This molecule presents anti-cancer effects in melanoma cell lines and RCC by inhibition of Signal transducer and activator of transcription 3 (STAT3) phosphorylation with specificity for the Jak-2-STAT3 pathway (108). Several studies also showed that curcumin promoted apoptosis *in vitro* in various human cancer cell lines, including RCC (26, 109, 110), by decreasing activation of the PI3K/AKT signaling pathway. Besides apoptosis, curcumin can also inhibit the proliferation of RCC and activate autophagy *via* Akt/mTOR suppression and beclin-1 activation (111).

Resveratrol

Resveratrol, (trans-3,5,4'-trihydroxystilbene), a polyphenolic compound found in grapes, can induce apoptosis and cell cycle arrest, and inhibit proliferation of RCC *via* JAK-1, c-Src, and STAT3/5 over-expression and PTP ϵ and SHP-2 tyrosine phosphatase activation (112). Other findings suggest

that resveratrol induces differential expression of genes that are related to the inhibition of RCC cell growth and induction of RCC cell death, and these effects depend directly on resveratrol concentration (113). Resveratrol also seems to have inhibitory effects on the expression of *VEGF* gene and the proliferation of RCC cells (786-0) (83).

Englerin A

Englerin A is a compound derived from the *Phyllanthus engleri*, a Southern Africa native tree known to have medicinal properties (114). It has been shown that Englerin A induces cell death in RCC *via* induction of apoptosis, inhibition of cell migration, activation of autophagy, and cell cycle arrest by PI3/AKT/ERK inhibition and PKC θ activation (115, 116). The main mechanism of action of this compound is through activation of canonical transient receptor potential channels (TRPCs, especially TRPC4 and TRPC5), which are found in the membranes of renal cells (117). Englerin A acts on these channels, elevates the intracellular concentration of calcium, and induces cell death (118). Englerin A can also prevent the migration and invasion of RCC cells by TGF- β 1 transformation (119). Studies investigating the *in vivo* effects of Englerin A have not been conducted yet, however, trials on mouse models suggest that the levels of this compound needed for anti-tumor effects may be fatal (120).

Despite of the many treatment options currently available, RCC is still one of the deadliest forms of cancer, which demonstrates a great need for new drugs that are effective against this disease. After reviewing the scientific literature on the subject, it is understood that there are bioactive natural products with anti-tumor effects in RCC, acting through mechanisms such as induction of apoptosis, inhibition of tumor growth, and activation of autophagy (Table IV). Therefore, it is evident that natural products may have a broad range of potential applications in the future; however, more clinical studies regarding these molecules are necessary.

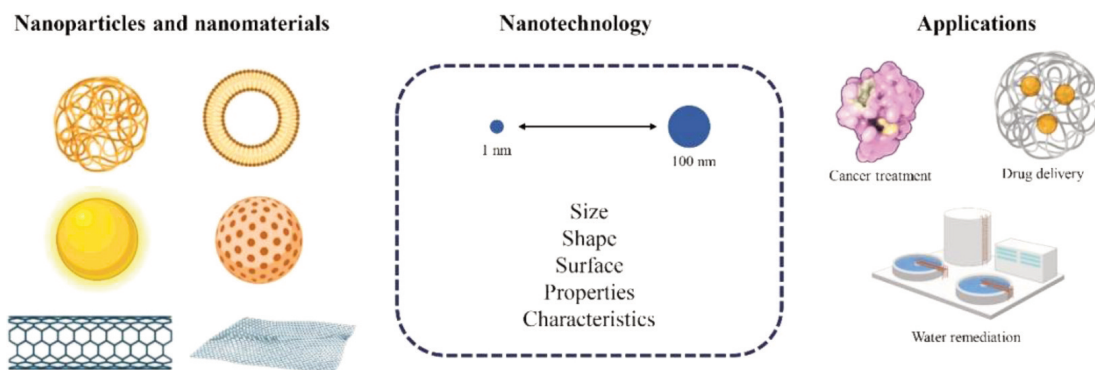


Figure 4. Nanoparticles and nanomaterials.

Nanoparticles Can Enhance Renal Cell Carcinoma Treatment

Nanotechnology and nanoscience are fundamentally related regarding to develop new materials and devices with improved properties in a nanometric scale between 1 and 100 nm (121, 122). At this size, their proprieties and characteristics are distinct from their bulk form mostly due to the surface and quantum confinement effects (123). The effects related to the surface properties are associated with the increase in the area/volume ratio, which can enhance the specific area and porosity (124). Besides, quantum confinement is involved in the optical and electronic characteristics (125).

Diverse nanomaterials have been developed and improved to increase the performance in different applications. The unique properties and characteristics of nanomaterials (NMs) and nanoparticles (NPs) make them excellent agents for application in different areas, such as water remediation (126, 127), medicine (128, 129), development of sensors (130), drug delivery (131), and cancer treatment (132). Figure 4 shows some characteristics of nanoparticles.

Nanoparticles, due to their extraordinary ability to co-encapsulate different therapeutic agents, can also be employed to overcome drug resistance in cancer. Nanoparticles have excellent properties, such as reactive and surface area, that can be used to improve the interactions between drugs and cells as well as overcome cancer resistance. In support, NPs showed benefits in cancer therapy: greater pharmacokinetics, precise targeting, and reduced side effects (133). For instance, polymeric nanoparticles (NPs) have been extensively studied due their physico-chemical properties allowing encapsulation of known drugs. Biocompatible polymers are used mostly for their ability to transport drugs directly to the targeted tissue through surface modifications (134). Also, micelles are suitable as a template to incorporate gold NPs, regulating their sizes with a pH-sensitive triblock copolymer micelle, *i.e.*,

bringing relevant applications to circumvent drug resistance by acting in biological processes such as ion transport and targeted drug delivery (135). It is well-known that conventional therapies have several drawbacks relating to their efficacy and side effects, such as damage in healthy cells and tissues. In this manner, the size and shape furnished by the nanotechnology, allows a decrease in the oxidative stress and delivery of the drug to the target organ/tissue (136).

RCC is fundamentally originated from the renal cortex and presents a high metastatic rate (137). Nevertheless, due to the side effects of cancer treatment, such as nausea and blood clots, new research develops alternatives to improve the treatment efficiency and appease the effects (138). NPs are an excellent alternative for cancer cell treatment due to the improvement in the pharmacokinetics and reduction of toxicities of chemotherapies (133) (Figure 5).

Magnetic nanoparticles (MNPs), such as magnetite (Fe_3O_4) and hematite (Fe_2O_3), are widely used in different areas due to their excellent properties: biocompatibility, reactivity, and high surface area (139). To evaluate the anticarcinogenic activity of nanoparticles, Abbas and co-workers (140) synthesized an $\alpha\text{-Fe}_2\text{O}_3$ (NPLAA@IONP-PEG) employing polyethylene glycol (PEG) and ascorbic acid (LAA), and tested it against the HEK-293 human embryonic kidney cell line. LAA@IONP-PEG decreased cell viability in a dose-dependent manner. The high cytotoxicity against cancer cells of the nanocomposite was attributed to the small size and the presence of PEG and LAA (141). It was shown that LAA@IONP-PEG presents an antioxidant capability.

Furthermore, Nagajyothi *et al.* (142) synthesized iron oxide NPs ($\alpha\text{-Fe}_2\text{O}_3$) and analyzed their catalytic and anticancer behavior. The *in vitro* experiments indicated that $\alpha\text{-Fe}_2\text{O}_3$ inhibited the growth of the RCC line Caki-2in a dose-dependent manner. However, only the highest concentration (0.8 mg ml^{-1}) (Figure 6) showed a cytotoxic effect on normal cells.

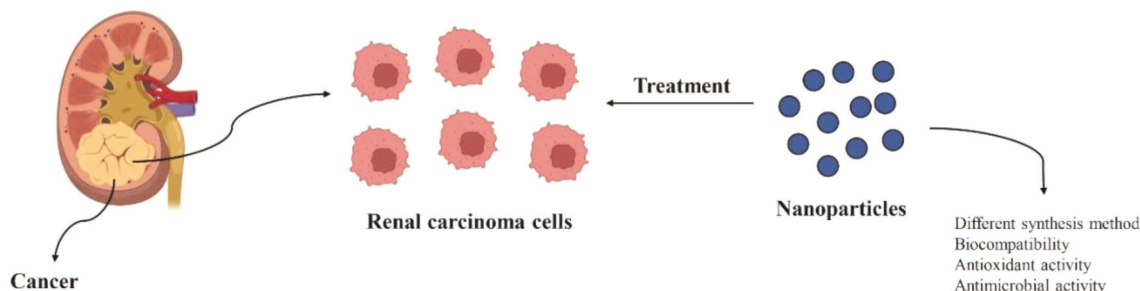
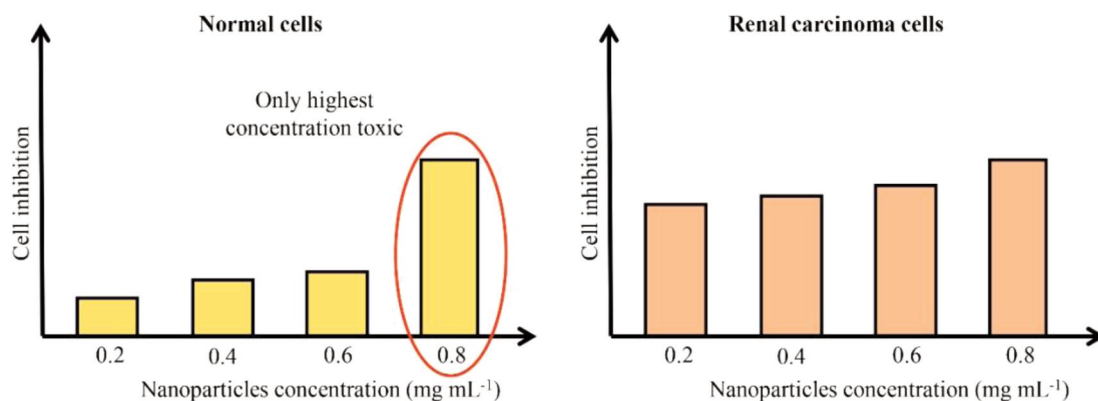


Figure 5. Nanoparticles for cancer cell treatment.

Figure 6. Toxicity of $\alpha\text{-Fe}_2\text{O}_3$ against normal and renal carcinoma cells.

Inorganic nanoparticles, such silver (AgNPs) and gold (AuNPs) nanoparticles, are an important alternative employed in cell treatments due to their excellent properties, such as antibacterial and antimicrobial activities (143, 144). Chen and coauthors (135) reported the mechanisms and toxicity effects of AgNPs against HEK293T and A498 cell lines. The results showed that low concentrations (1–8 $\mu\text{g mL}^{-1}$) had no significant effect on cell viability and ROS production compared to the untreated control. However, AgNPs increased autophagy even at low concentrations; increasing the LC3II level and autophagy-associated genes.

Inorganic nanoparticles are also a viable alternative for gene delivery. Shi *et al.* (2020) developed a polyethylene glycol modified with manganese dioxide (PEG-MnO₂), which they loaded with osteopontin siRNA, as the gene drug (siRNA OPN) (PEG-MnO₂-OPN siRNA), and used for magnetic resonance imaging (MRI) for guided gene delivery (145). *In vitro* assays demonstrated that the PEG-MnO₂ was cytotoxic against the RCC line 786-O and umbilical vein EA hy926 cell line. Furthermore, contrast of MRI showed that the nanocomposite resulted in a significant improvement,

even at low concentrations, due to the presence of Mn²⁺ ions and the anti-tumor effect of nanoparticles. Nonetheless, Chai and co-authors (146) synthesized folate grafted PEI600-CyD (H1) nanoparticles for the delivery of AIM2 gene (H1/pAIM2) for renal carcinoma cell treatment (786-O and OSRC-2). The nanocomposite significantly decreased tumor volume and weight. The *in vitro* results showed that the NPs enhanced the effect of AIM2 against cancer cell lines, decreasing cell migration and invasion.

Soliman and co-workers (147) synthesized NPs with succinyl chloride (SC) and loaded them with gemcitabine (GT) and 5-Fluoracil (5FU), called GT-SC-5FU. *In vitro* experiments showed that GT-SC-5FU significantly decreased the viability of the RCC line SNU-349 in a dose-dependent manner. Nonetheless, GT-SC-5FU presented higher cytotoxicity when compared to individual drugs (GT and 5FU), suggesting a drug synergistic effect in the SNU-349 cell line.

Green synthesis can be used to produce high quality inorganic nanoparticles with good yields (148). Along with this, biological synthesis (green approaches) of metal NPs are an excellent alternative to produce ecological and

environmentally friendly nanomaterials with diverse benefits (149). Liu *et al.* (150) used an easy and green technique for development of gold nanoparticles, *Curcuma wenyujin* extraction, which was called CWAuNP. Treatment of the RCC lines A498 and Sw-156 increasing concentrations of gold nanoparticles (5-50 µg/ml) significantly decreased cell viability. In addition, the production of reactive oxygen species (ROS) increased and the mitochondrial membrane potential decreased.

Furthermore, Li and co-workers (151) synthesized copper nanoparticles (Cu-NPs) using the medicinal plant *Ziziphus zizyphus* (Cu-ZZ NPs) and evaluated the anti-cancer activity against A498 cells. Cu-ZZ NPs significantly decreased viability and increased mitochondrial membrane potential (MMP) in a concentration dependent manner (10-50 µg ml⁻¹). These results suggest that Cu-ZZ NPs has a dose-dependent anti-tumor activity due to the DNA damage.

Considering their excellent characteristic, zinc oxide nanoparticles (ZnO-NPs) produced through a green synthesis approach can be used in different applications (152). Lokapur and co-workers (153) evaluated the toxicity of ZnO-NPs produced using *Hologarna grahamii* (HG) against the A498 cell line. The results showed that by increasing the concentration of nanoparticles the cytotoxicity effect increased and cell viability decreased to approximately 50%. Nevertheless, no significant toxicity was observed against health cells.

Zhou and Chen (154) developed supramolecular nanoparticles with cisplatin (CIS-PT-NPs) and evaluated their anticancer properties, such as antiproliferative activity and toxicity, against the RCC lines Caki-1 and A498 and compared them to those of CIS-PT (no nanometric material). MTT assay showed a higher cytotoxic activity of CIS-PT-NPs in comparison to CIS-PT; treatment resulted in a significant and dose-dependent decrease in cell viability. However, none of the materials (CIS-PT and CIS-PT-NPs) presented toxicity against non-cancerous cells (NIH-3T3). The drug release profile showed that CIS-PT liberate the drug faster than the nanoparticles (90% after 25 h). However, the kinetic baum profile of CIS-PT-NPs demonstrated a continuous drug release, enhancing cancer treatment.

Conclusion

In conclusion, RCC present increased incidence and mortality rates. This can be because this type of cancer frequently exhibits resistance to treatment. Furthermore, most anticancer agents used to treat RCC have side effects, since they present a non-selective profile. In this scenario, studies have been performed to reveal new therapies with low or null side effects. Nanoscience and natural products can be highlighted in this area. However, further clinical studies regarding these new RCC anticancer agents are necessary.

Conflicts of Interest

The Authors have no conflicts of interest to report in relation to this study.

Authors' Contributions

Wrote the manuscript: Josiéle da Silva Prade, Ruan Soares de Souza, Camila Medianeira da Silva D'Ávila, Thayline Correia da Silva, Isadora Cassel Livinalli, Ana Clara Zanini Bertoncelli, Fernanda Krapf Saccol, Tallys de Oliveira Mendes, Larissa Gindri Wenning, Theodoro da Rosa Sallesa, Cristiano Rodrigo Bohn Rhodena, Francine Carla Cadoná. Provided figures and tables: Theodoro da Rosa Sallesa, Cristiano Rodrigo Bohn Rhodena, Francine Carla Cadoná, Ruan Soares de Souza, Camila Medianeira da Silva D'Ávila, Thayline Correia da Silva, Isadora Cassel Livinalli. Conception and design of the study: Francine Carla Cadoná, Cristiano Rodrigo Bohn Rhodena, Josiéle da Silva Prade.

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