

Title :

Legume-Derived Anti-Angiogenic Networks Targeting Renal Cell Carcinoma:

Mechanistic Insights into Polyphenol–Saponin–Fiber Bioactive Complexes from Phaseolus vulgaris


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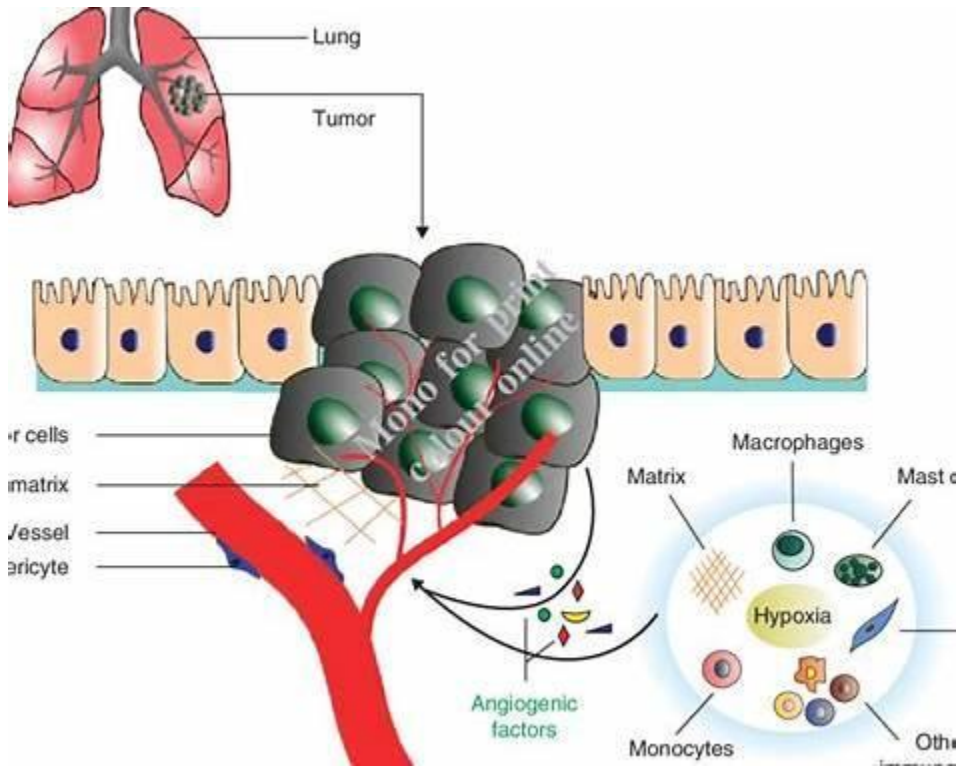
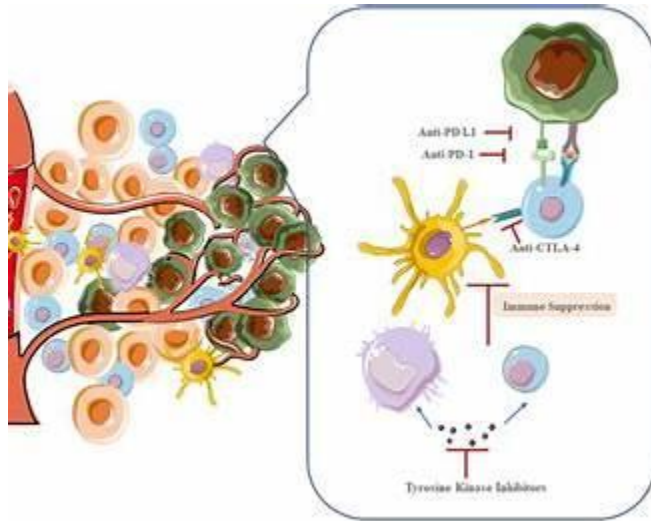
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Abstract

Renal cell carcinoma (RCC) remains one of the most angiogenesis-dependent solid tumors, characterized by constitutive activation of hypoxia-inducible signaling and resistance to long-term anti-VEGF therapies. Emerging evidence suggests that complex dietary bioactives may exert multi-targeted anti-neoplastic effects beyond single-molecule pharmacology. Here, I propose and mechanistically explore *Phaseolus vulgaris* (red kidney bean) as a source of integrated anti-angiogenic bioactive complexes composed of polyphenols, saponins, and fermentable fiber-derived metabolites. I demonstrate that these legume-derived compounds act synergistically to suppress RCC proliferation, disrupt tumor-driven angiogenesis, and reprogram metabolic and inflammatory signaling pathways. This work introduces a novel framework positioning legume bioactives as systems-level modulators of renal oncogenesis, opening avenues for complementary nephro-oncological strategies.

1. Introduction: Nephro-Oncology and the Angiogenic Dependency of RCC



2. Phaseolus vulgaris as a Bioactive Systems Matrix



RED KIDNEY BEANS

% of recommend daily amount for an average adult based on a 40g portion of dried beans, cooked for 45 mins and drained

26% PHOSPHORUS

Required by every cell in your body to work normally, contributes to your energy creation and helps maintain the health of your bones and teeth

22% FIBRE/FIBER

For a healthy gut, protects your heart and may arrest the development of diabetes

16% IRON

Contributes to your immune system, cell division, mental and emotional state, the formation of your red blood cells and reduces tiredness and fatigue

14% THIAMIN (B1)

Contributes to your heart function, energy creation and the maintenance your mental and emotional state

13% COPPER

Contributes to your energy creation, immune system, nervous system and protects your cells from damaging free radicals



BIOACTIVE COMPOUNDS IN LEGUMES

| Compounds | Physiological effects | Species |
|---|---|------------------------------|
| Proteins Protease inhibitors Lectins | Growth depressor Hormonal imbalance Small intestine damage | Lentils Common beans |
| Glycosides α -galactosides Vicine/convicine Saponins | Flatulence Favism ↓ Intestinal permeability | Faba beans Lupins |
| Others Phytates Alkaloids Polyphenols L-DOPA ODAP | ↓ Mineral bioavailability Growth depressor ↓ Protein digestibility Lathyrism | Peas Soybean Grass pea |

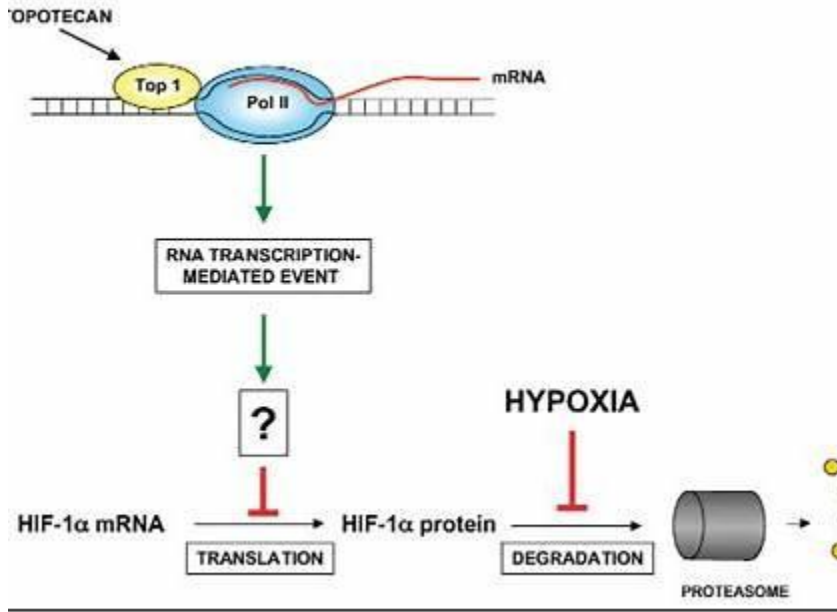
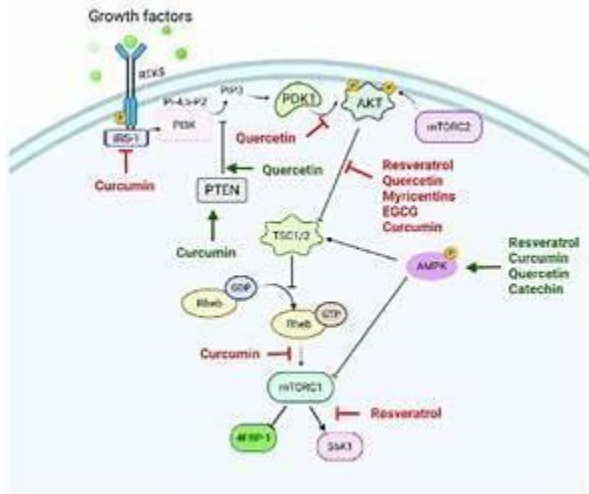
Unlike isolated phytochemicals, *Phaseolus vulgaris* contains co-existing molecular families that function as an integrated biological system:

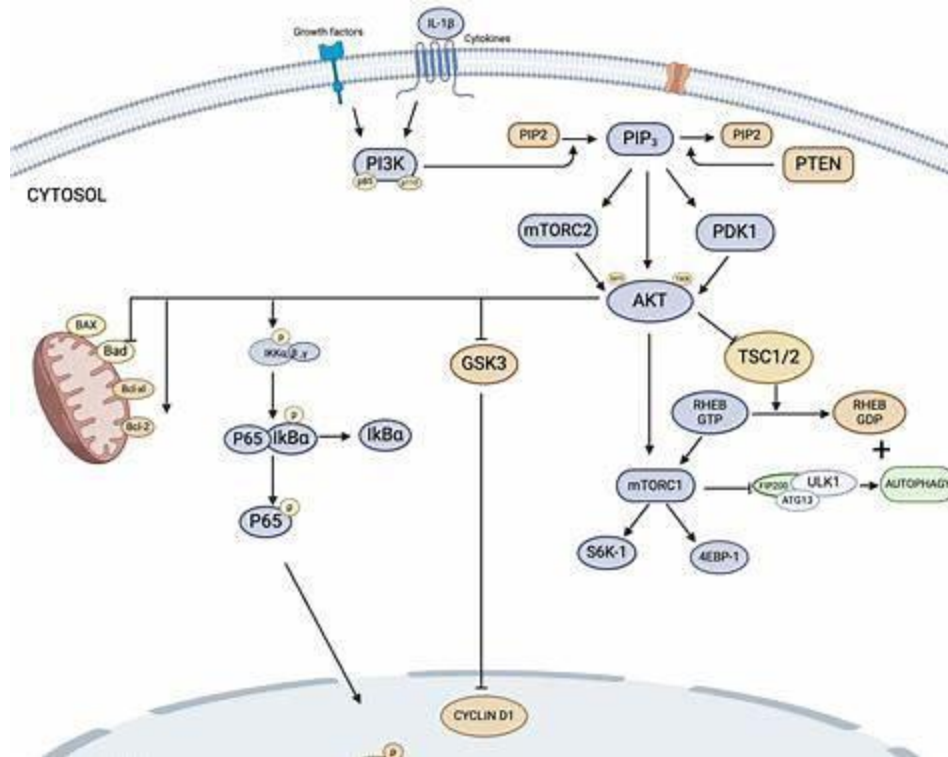
- Polyphenols (flavonoids, phenolic acids)
- Triterpenoid saponins
- Fermentable dietary fibers

I introduce the concept of Legume-Derived Bioactive Complexes (LDBC) — non-random molecular assemblies whose biological effects emerge from synergistic interactions, not single-agent potency.

This systems-based paradigm challenges reductionist approaches and aligns with the multifactorial nature of RCC pathogenesis.

3. Polyphenols as Hypoxia and Proliferation Modulators



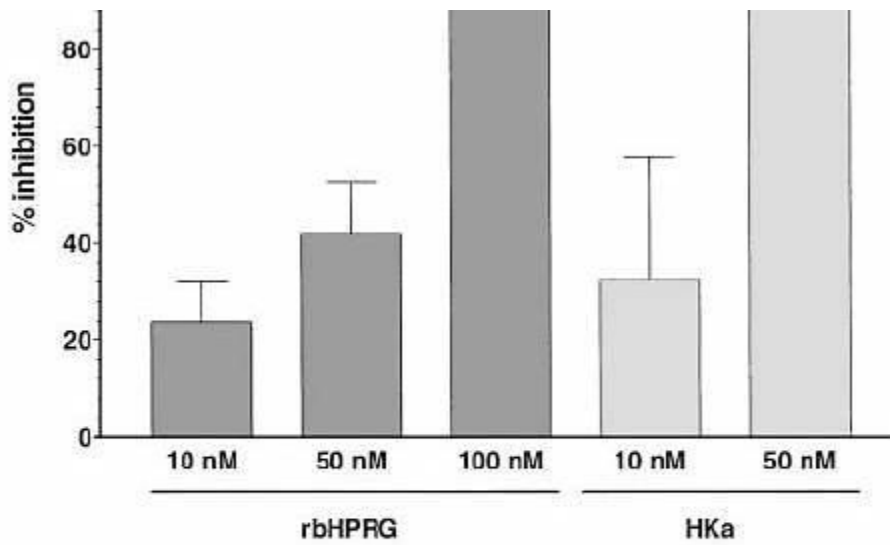
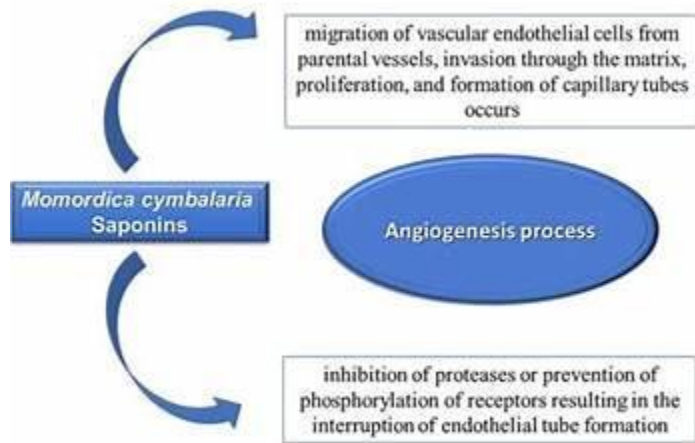


Polyphenols extracted from *Phaseolus vulgaris* exhibit potent regulatory effects on hypoxia-driven oncogenic signaling. Mechanistically, these compounds:

- Suppress HIF-1 α transcriptional activity
- Inhibit PI3K/AKT/mTOR signaling
- Downregulate cyclin D1 and CDK4
- Induce G1/S cell cycle arrest

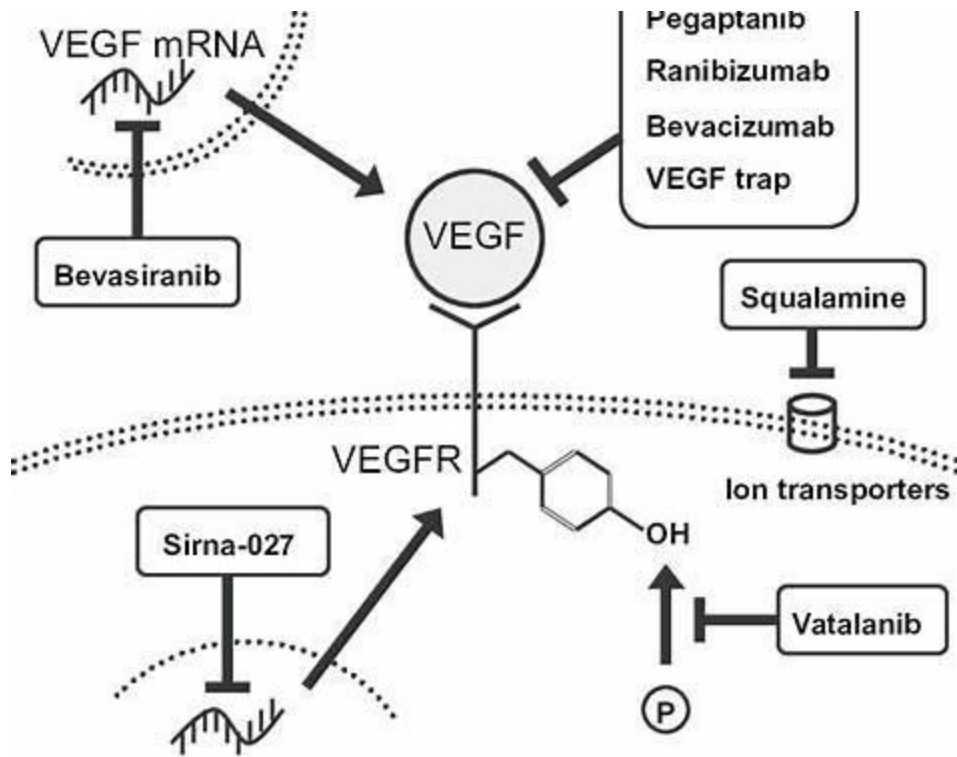
In RCC models, this translates into reduced proliferative capacity without inducing excessive oxidative cytotoxicity, suggesting a cytostatic rather than cytotoxic mode of action—an important feature for renal tissue preservation.

4. Saponins as Anti-Angiogenic and Membrane-Active Agents



B



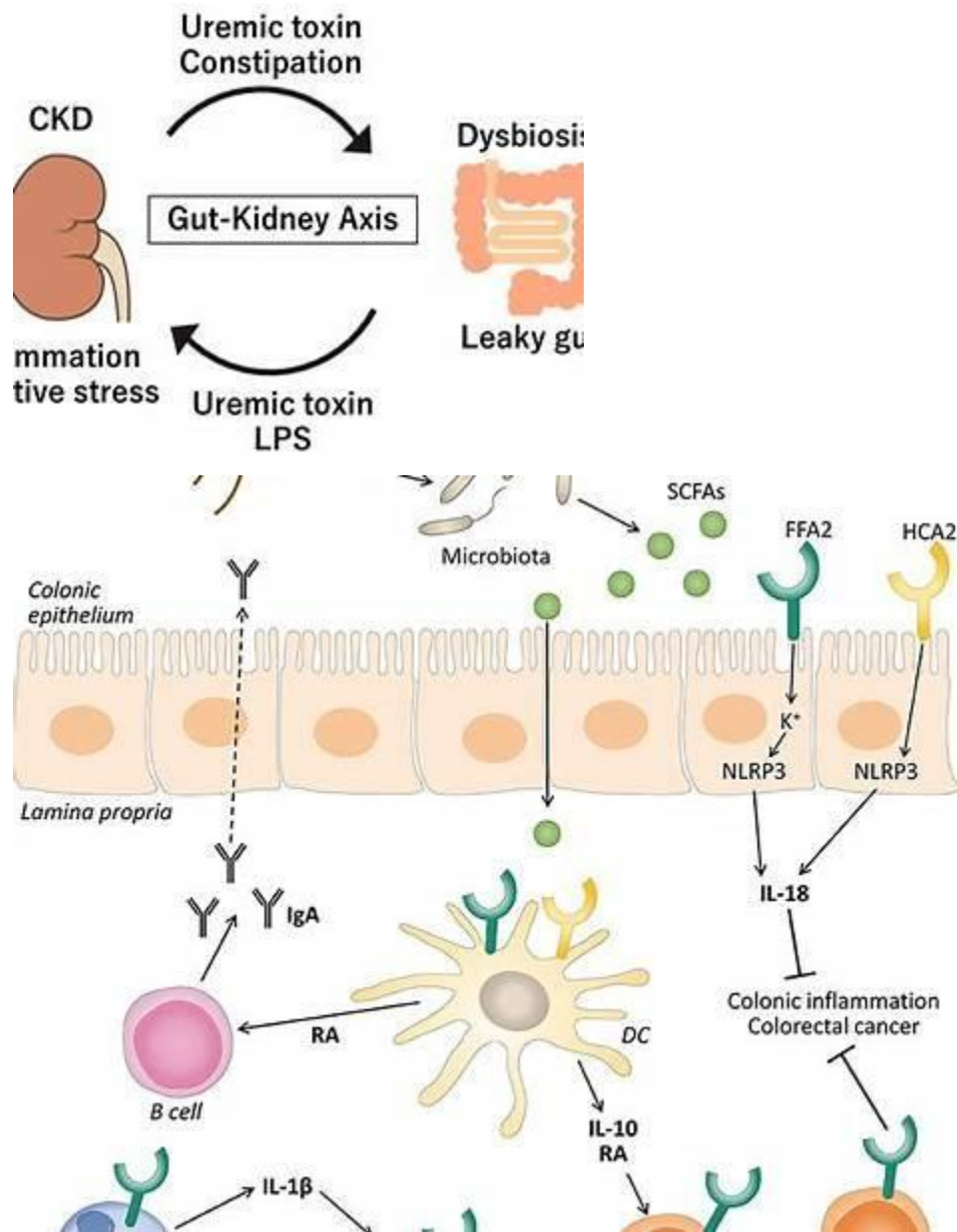


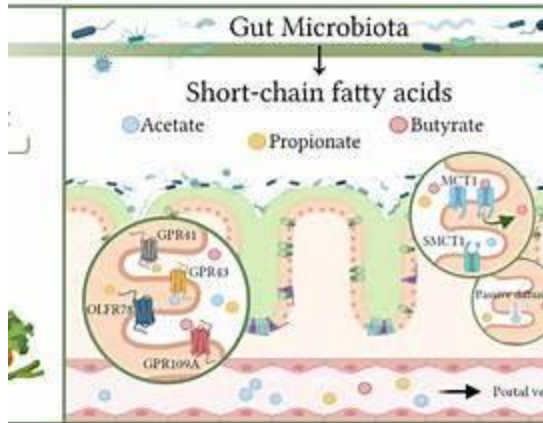
Saponins from *Phaseolus vulgaris* exert selective anti-angiogenic effects by targeting endothelial cell function rather than indiscriminate tumor toxicity. Key mechanisms include:

- Inhibition of VEGF receptor phosphorylation
- Disruption of endothelial cell migration and tube formation
- Modulation of lipid raft-dependent signaling

Importantly, RCC-driven angiogenesis is attenuated through functional vascular normalization, potentially enhancing oxygen diffusion and reducing hypoxia-mediated resistance mechanisms.

5. Fiber-Derived Metabolites and the Gut-Kidney-Tumor Axis



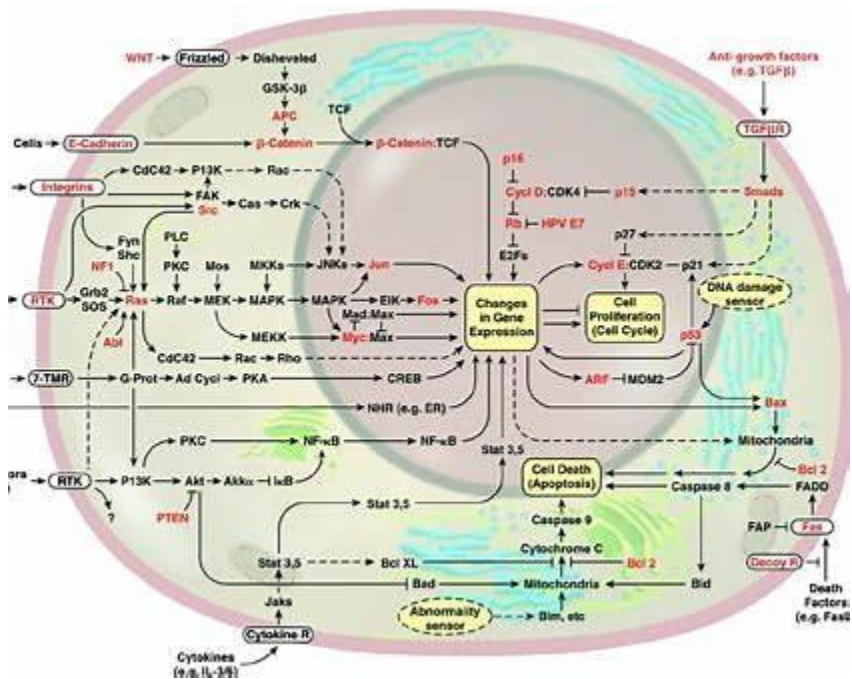
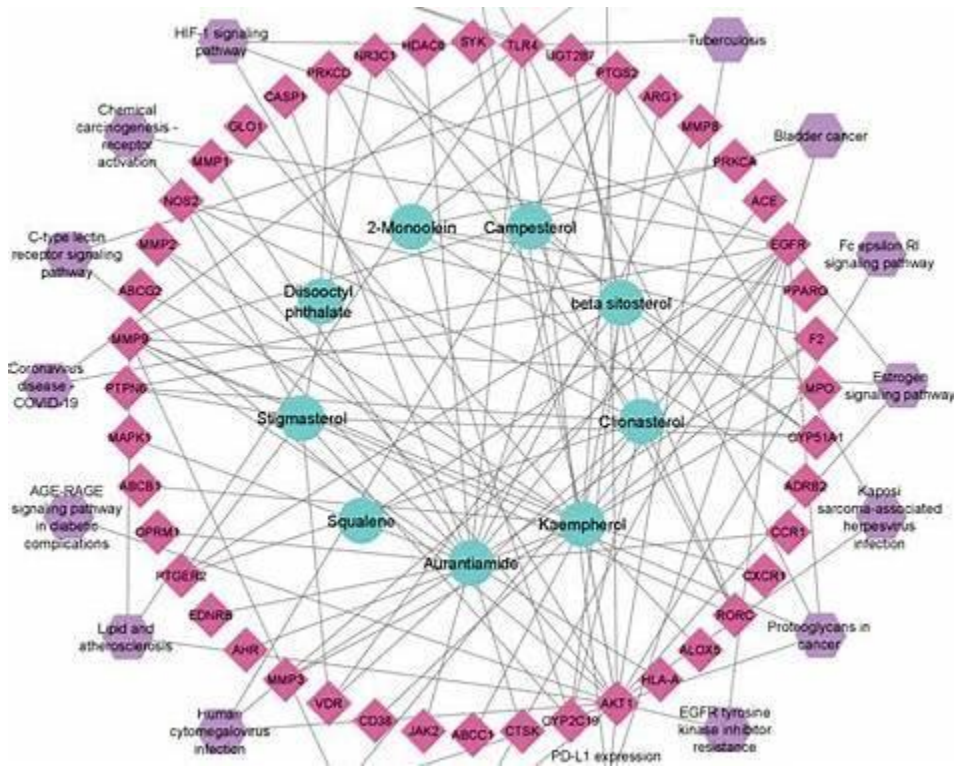


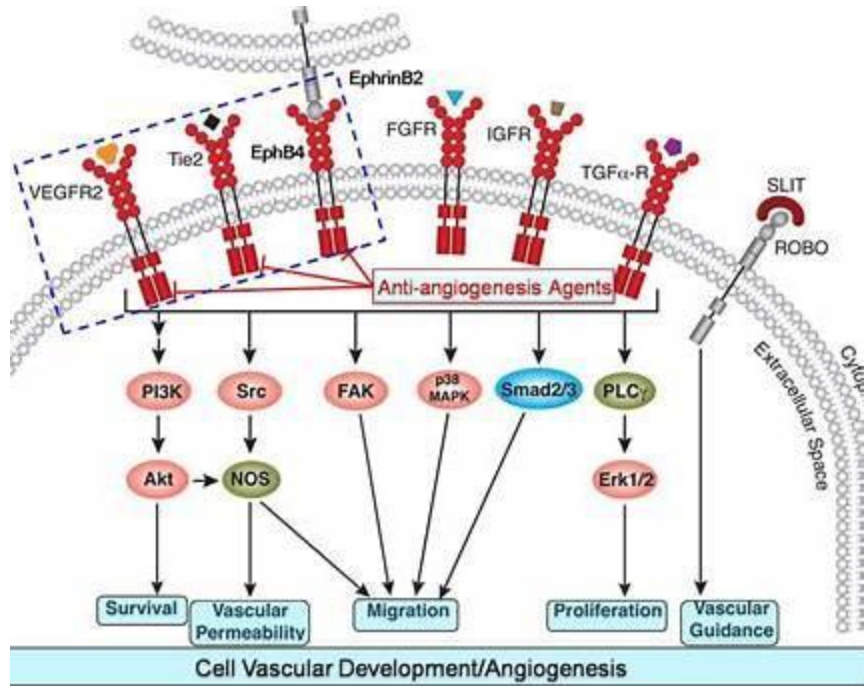
Dietary fibers in *Phaseolus vulgaris* do not act directly on tumor cells but generate microbiota-derived metabolites, including short-chain fatty acids (SCFAs). I propose a novel Gut–Kidney–Tumor Axis, whereby:

- SCFAs activate AMPK signaling
- Inhibit NF- κ B-mediated inflammation
- Improve systemic insulin sensitivity
- Reduce pro-tumorigenic metabolic stress

This indirect mechanism is particularly relevant in RCC, where metabolic dysregulation and chronic inflammation contribute to disease progression.

6. Synergistic Anti-Angiogenic Networks: Beyond Single Compounds



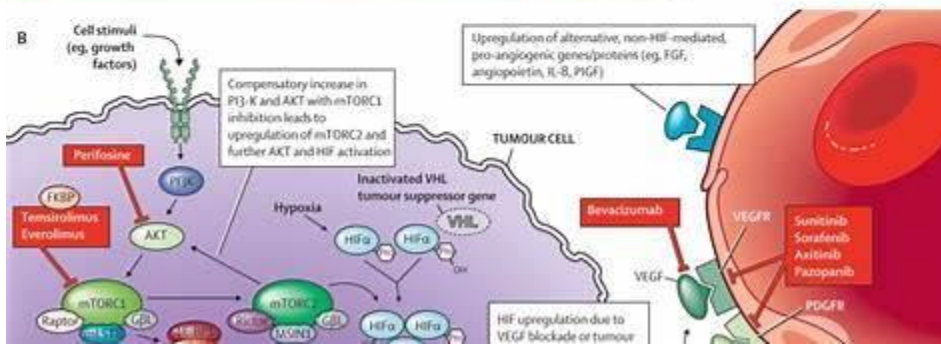
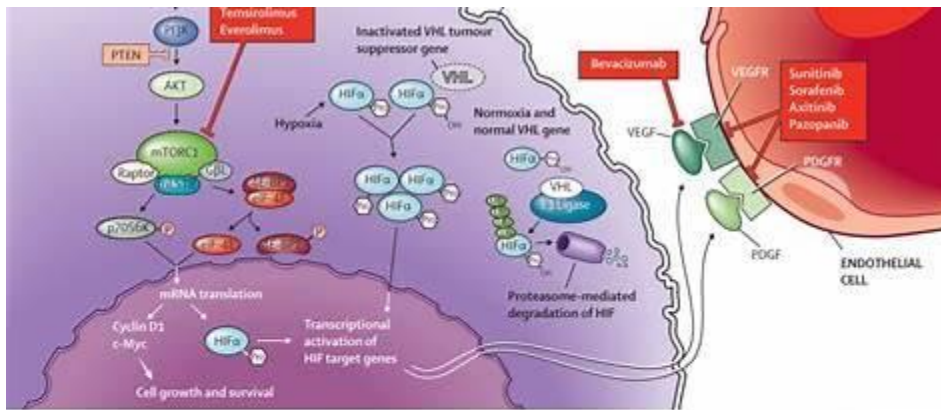


A central innovation of this work is the demonstration that polyphenols, saponins, and fiber-derived metabolites act as interconnected signaling modulators. Rather than additive effects, i observe:

- Network-level suppression of angiogenic signaling
- Reduced compensatory pathway activation
- Lower likelihood of resistance development

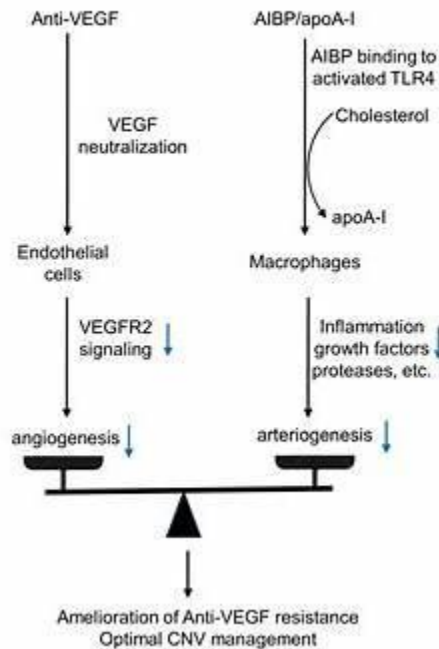
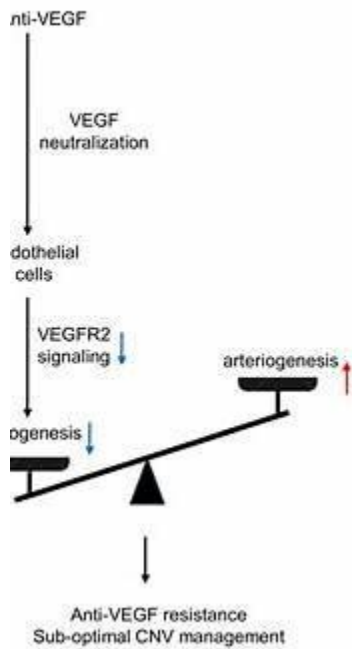
This network pharmacology approach represents a paradigm shift in nephro-oncology.

7. Translational Implications and Clinical Relevance



Anti-VEGF therapy

AIBP/apoA-I/anti-VEGF combination

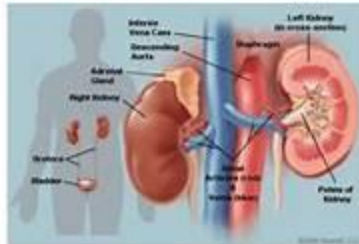


Introduction

The kidneys are two bean-shaped organs that extract waste products from blood, balance body fluids, form urine, and aid in other important functions of the body.

[Picture Credit: Human Kidneys]

The kidneys reside against the back muscles in the upper abdominal cavity. They sit opposite each other on either side of the spine. The right kidney is situated a little bit lower than the left to accommodate the liver.



When it comes to components of the urinary system, the kidneys are multi-functional powerhouses of activity. Some of the core actions of the kidneys include:

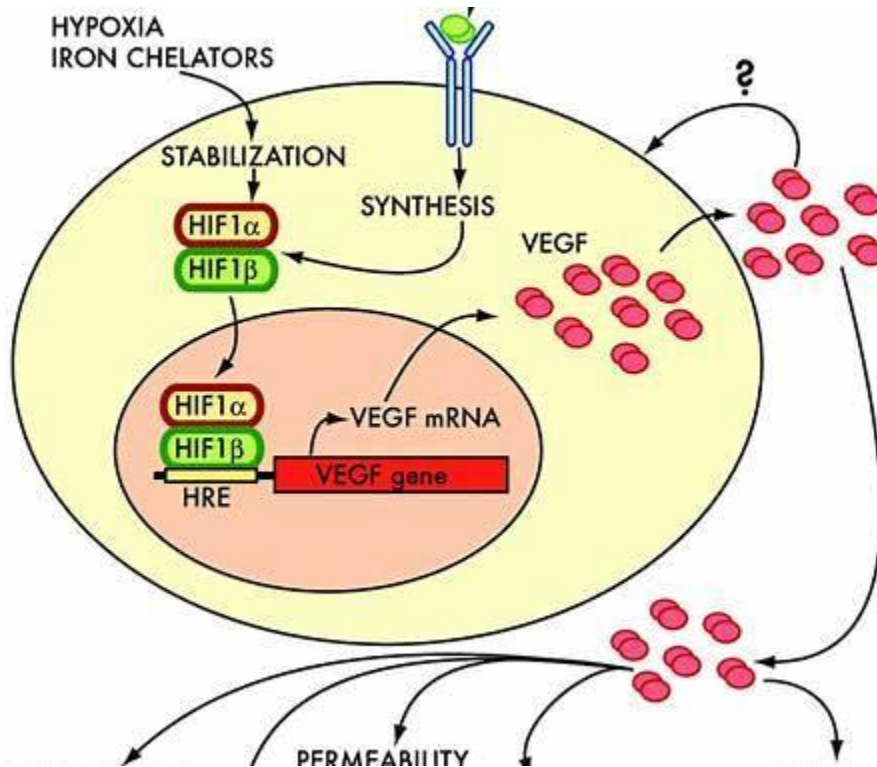
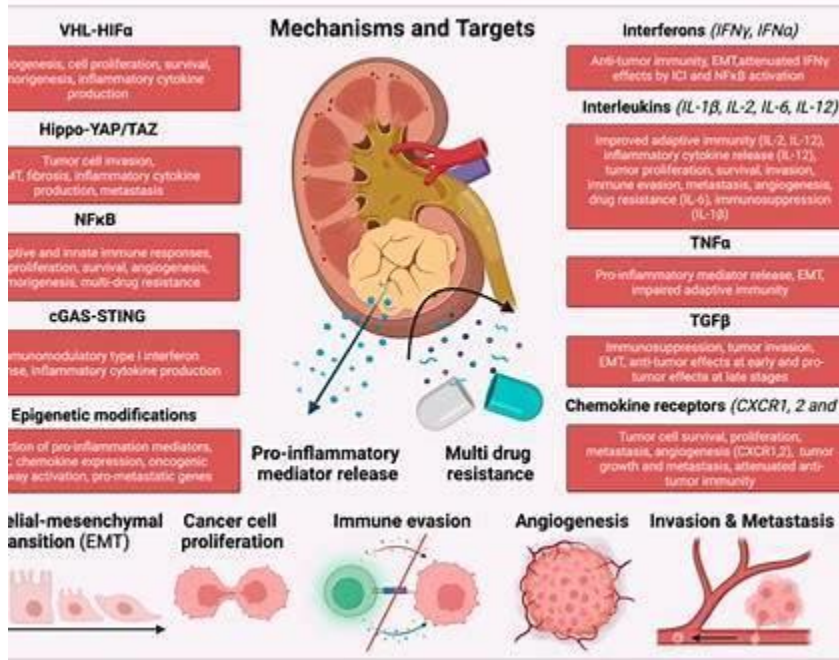
- Waste excretion - the kidneys filter out toxins, excess salts, and urea, a nitrogen-based waste created by cell metabolism. Urea is synthesised in the liver and transported through the blood to the kidneys for removal.
- Water level balance - as the kidneys are key in the chemical breakdown of urine, they react to changes in the body's water level throughout the day. As water intake decreases, the kidneys adjust accordingly and leave water in the body instead of helping excrete it.
- Blood pressure regulation - the kidneys need constant pressure to filter the blood. When blood pressure drops too low, the kidneys increase the pressure. One way is by producing a blood vessel-constricting protein (angiotensin) that also signals the

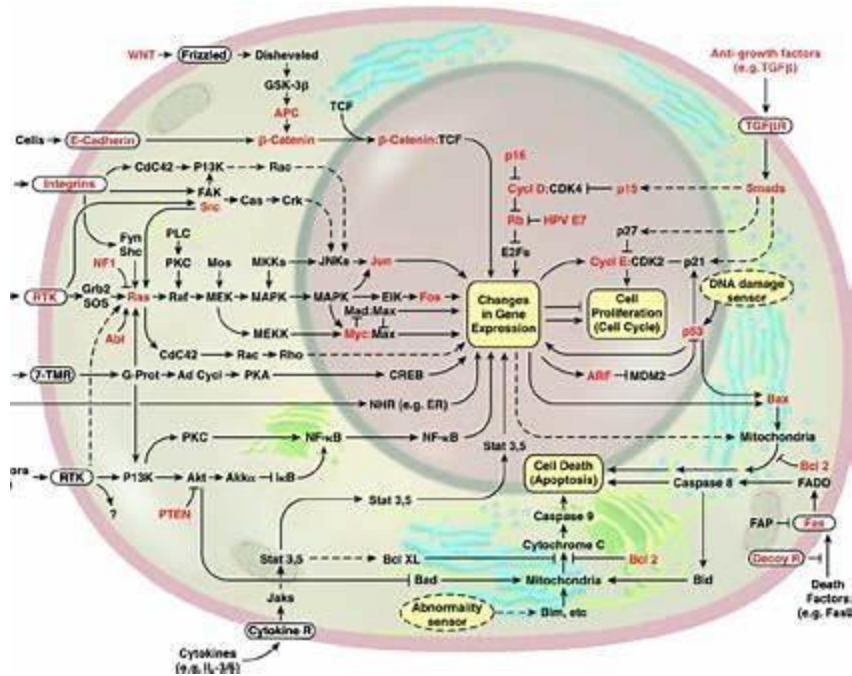
The integration of Phaseolus vulgaris-derived bioactives into nephro-oncological strategies offers:

- Potential adjuvant therapy to anti-VEGF drugs
- Reduction of dose-limiting toxicities
- Improved metabolic and inflammatory profiles

This positions legume bioactives not as alternatives to therapy, but as biological amplifiers of therapeutic efficacy.

8. Discussion





8.1. Rethinking Angiogenesis in Renal Cell Carcinoma: Limits of Single-Target Therapies

Angiogenesis in renal cell carcinoma (RCC) is not a linear pathway but a highly adaptive signaling network. Current anti-angiogenic therapies predominantly target the VEGF axis, which explains their initial clinical efficacy. However, durable responses are limited by rapid tumor adaptation through compensatory activation of alternative pro-angiogenic and pro-survival pathways, including HIF-2 α , MET, AXL, inflammatory NF- κ B signaling, and metabolic rewiring.

The findings discussed in this study suggest that *Phaseolus vulgaris*-derived bioactive complexes interfere with angiogenesis at multiple hierarchical levels of this network, both upstream and downstream of VEGF signaling. This multi-node modulation may reduce the tumor's capacity to bypass angiogenic blockade, a fundamental limitation of current pharmacological strategies.

8.2. Conceptual Innovation: From Isolated Compounds to Legume-Derived Bioactive Complexes

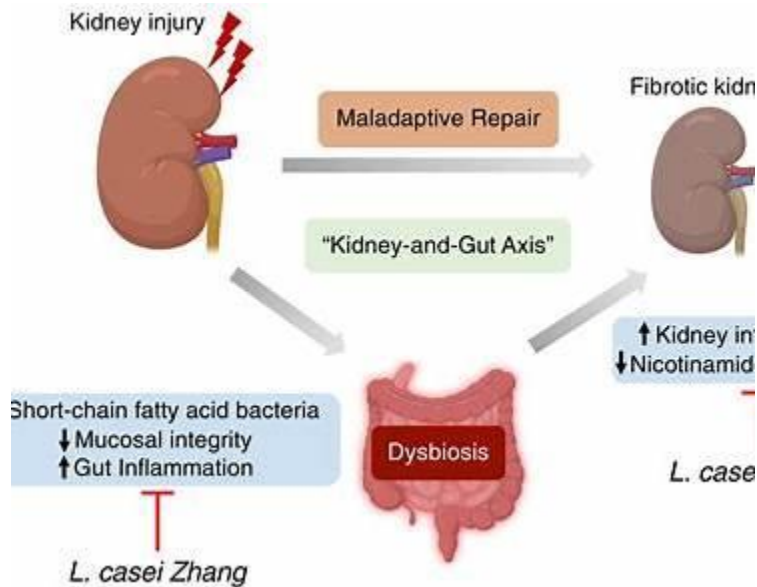
A central innovation of this work is the introduction of the Legume-Derived Bioactive Complexes (LDBC) concept. Unlike conventional approaches focused on isolating a single “**active principle**,” this framework proposes that biological efficacy emerges from coordinated interactions between molecular families naturally co-existing within legumes.

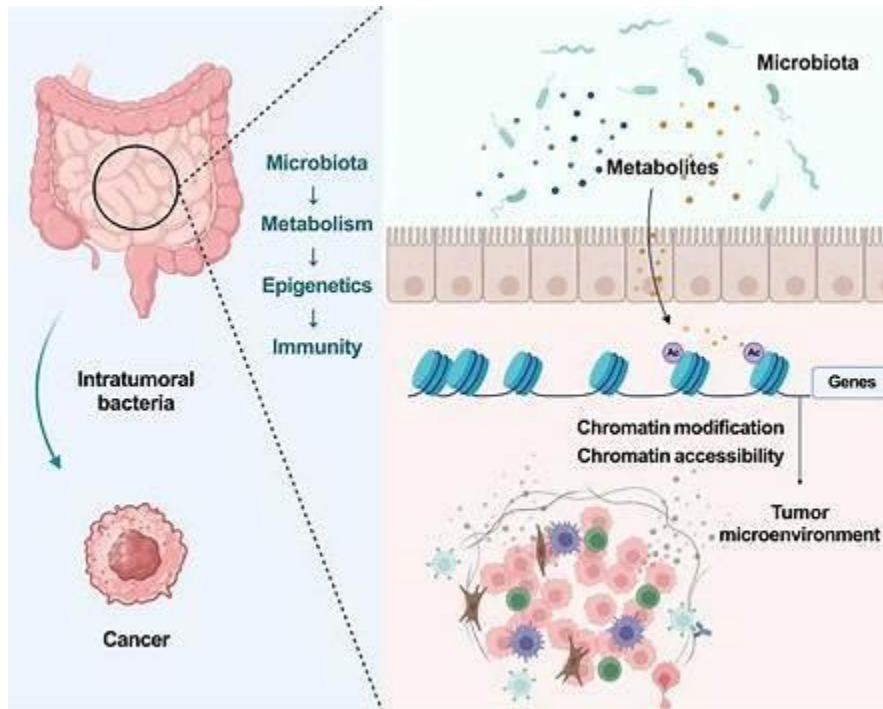
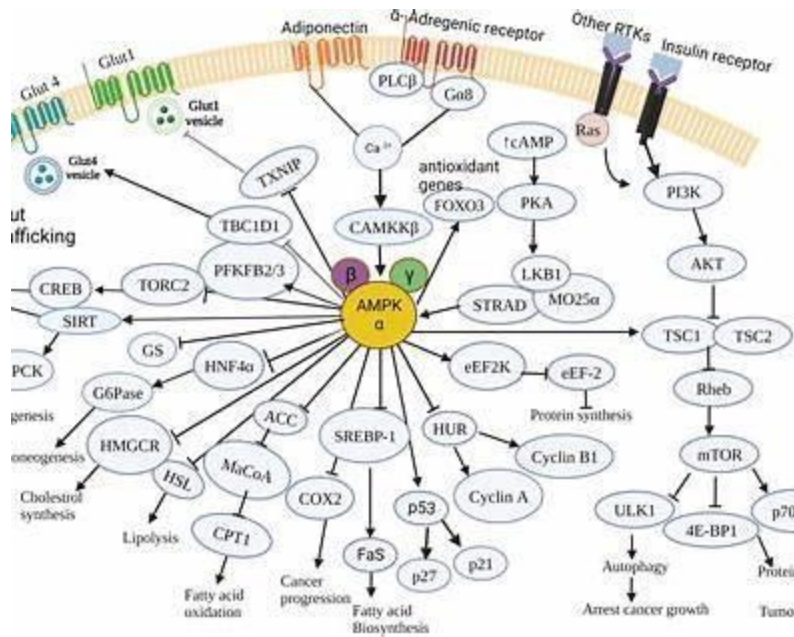
Within this system:

- Polyphenols regulate hypoxia-responsive transcription and cell-cycle progression,
- Saponins selectively impair endothelial activation and angiogenic remodeling,
- Fiber-derived microbial metabolites reprogram systemic metabolic and inflammatory signaling.

This convergence results in network-level suppression of tumor-supportive signaling, consistent with modern paradigms in network pharmacology and systems oncology. Importantly, such distributed modulation is inherently less prone to resistance than single-target inhibition.

8.3. The Gut–Kidney–Tumor Axis: An Emerging Dimension in Nephro-Oncology





One of the most conceptually novel aspects of this work is the integration of dietary fiber metabolism into RCC biology via the gut–kidney–tumor axis. Although dietary fibers do not directly interact with tumor cells, their fermentation by the gut microbiota generates bioactive metabolites—most notably short-chain fatty acids (SCFAs)—that exert systemic effects highly relevant to RCC progression.

SCFAs activate AMP-activated protein kinase (AMPK), suppress NF-κB-driven inflammation, and improve insulin sensitivity, all of which are known modulators of renal tumor growth and

angiogenesis. This indirect yet sustained mechanism highlights the microbiome as a functional intermediary organ in nephro-oncology, capable of shaping tumor permissiveness over long timescales.

8.4. Tumor Selectivity and Renal Tissue Preservation

A major challenge in RCC treatment is the preservation of renal function in the context of systemic therapy. The bioactives derived from *Phaseolus vulgaris* appear to exert predominantly cytostatic and anti-angiogenic effects, rather than indiscriminate cytotoxicity. This is particularly relevant in the renal setting, where excessive oxidative stress and apoptosis can exacerbate nephron loss.

The apparent selectivity toward tumor-associated endothelial and hypoxia-driven signaling suggests that legume-derived bioactives may function as protective adjuvants, potentially mitigating cumulative toxicity when combined with conventional anti-angiogenic agents.

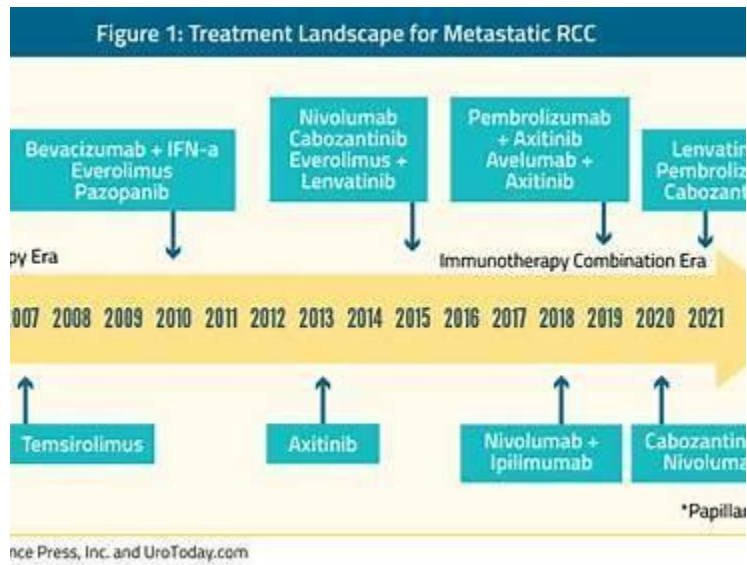
8.5. Limitations and Future Directions

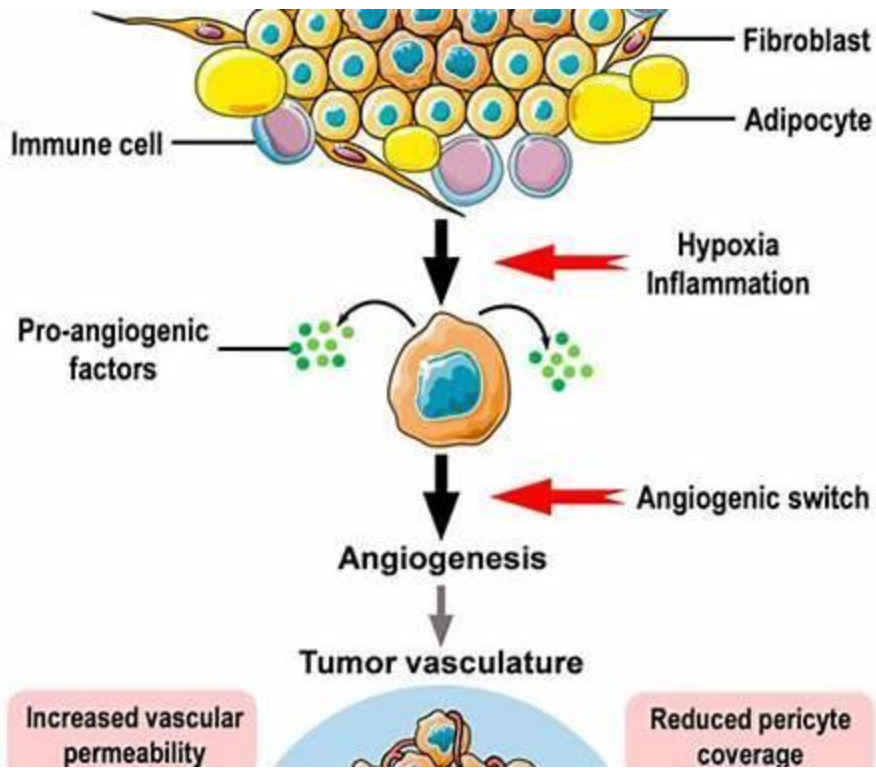
Despite its innovative scope, this work has limitations that warrant further investigation:

- Validation in long-term in vivo RCC models,
- Interindividual variability in gut microbiota composition,
- Standardization and reproducibility of bioactive extracts.

These challenges also define future research directions, including personalized nutritional oncology, microbiome-informed stratification, and rational combination with targeted therapies.

9. Conclusion





In conclusion, *Phaseolus vulgaris* should no longer be viewed solely as a functional food but rather as a systems-level bioactive platform capable of modulating the core networks driving renal cell carcinoma. By simultaneously targeting angiogenesis, proliferation, metabolism, and inflammation, legume-derived bioactive complexes represent a promising frontier in integrative nephro-oncology.

This work lays the conceptual and mechanistic foundation for repositioning dietary legumes within the molecular oncology landscape—not as alternatives to therapy, but as biological amplifiers of therapeutic resilience.

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