

Targeting VEGF and HIF-1 α Pathways of Soy Isoflavones as Natural Modulators of Angiogenesis

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Abstract

Angiogenesis, the process of new blood vessel formation, is central to both physiological homeostasis and pathological progression in cancer, cardiovascular, and inflammatory diseases. Among the key regulators, vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 α (HIF-1 α) play pivotal roles in endothelial proliferation and neovascularization. Increasing evidence suggests that soy-derived isoflavones—particularly genistein and daidzein—can modulate angiogenic processes through multiple mechanisms involving VEGF and HIF-1 α signaling. This review explores the molecular basis of these interactions, summarizing experimental and clinical findings on soy isoflavones as dietary modulators of angiogenesis. Emphasis is placed on their dual effects in tumor inhibition versus vascular protection, their bioavailability, and future therapeutic implications in nutraceutical and antiangiogenic strategies. Future research should aim to elucidate dose-dependent effects, bioavailability differences among isoflavone metabolites, and potential synergistic interactions with standard anti-angiogenic therapies.

Keywords: soy isoflavones, genistein, daidzein, VEGF, HIF-1 α , angiogenesis, nutraceuticals

Introduction

Angiogenesis, the formation of new blood vessels from pre-existing ones, is a tightly regulated process essential for tissue growth and repair. Under physiological conditions, it is balanced by pro- and anti-angiogenic factors, whereas its dysregulation contributes to diseases such as cancer, diabetic retinopathy, and rheumatoid arthritis (1).

VEGF and HIF-1 α are two critical regulators of angiogenesis. VEGF promotes endothelial proliferation and vascular permeability, while HIF-1 α acts as a transcriptional regulator under hypoxic conditions, upregulating VEGF and other target genes (2,3).

Recently, dietary bioactives, including polyphenols and flavonoids, have been recognized as modulators of angiogenic signaling (4). Soy isoflavones, a major subclass of flavonoids, possess estrogen-like and antioxidant properties that interact with VEGF/HIF-1 α -mediated pathways (5). This review synthesizes current knowledge on how soy isoflavones modulate angiogenesis via the VEGF/HIF-1 α axis, integrating biochemical, preclinical, and clinical perspectives.

Chemistry, Metabolism, and Bioavailability

Soybeans (*Glycine max*) contain abundant isoflavones, mainly genistein, daidzein, and glycitein, which exist predominantly as glycosides (6). Upon digestion, intestinal β -glucosidases release the active

aglycones. These molecules structurally resemble 17β-estradiol and can bind to estrogen receptors, particularly ERβ (7). Isoflavone metabolism depends on gut microbiota; certain bacteria convert daidzein to equol, a metabolite with stronger estrogenic and antioxidant activity (8,9). However, only 30–50% of humans are equol producers (10). Bioavailability varies with the form of intake and gut function (11). Genistein achieves peak plasma levels within 5–8 hours post-consumption but undergoes extensive conjugation (12). These factors influence systemic activity and explain inter-individual variability in biological response.

Table 1. Summary of Soy Isoflavone Metabolism and Bioavailability

Isoflavone	Primary Source	Major Metabolites	Biotransformation Site	Key Enzymes	Bioavailability Factors
Genistein	Soybeans, soy protein, tofu	Genistein glucuronide, sulfate conjugates	Liver, intestinal mucosa	UDP-glucuronosyl-transferase (UGT), sulfotransferase (SULT)	Food matrix, gut microbiota activity, intestinal transit time
Daidzein	Soy milk, miso, tempeh	Equol, O-desmethyldaidzein (ODMA)	Colon (via microbiota)	β-glucosidase, gut bacterial reductases	Microbiota composition, antibiotic exposure, hormonal
Glycitein	Soy germ, soy protein isolate	Glycitein conjugates	Liver	UGT, SULT	Dietary fat co-intake, metabolic rate, intestinal health

VEGF and HIF-1α Pathways

Under hypoxia, HIF-1α escapes proteasomal degradation, dimerizes with HIF-1β, and activates VEGF transcription (2). Activation of the PI3K/Akt/mTOR pathway stabilizes HIF-1α and enhances VEGF expression. Soy isoflavones, particularly genistein, modulate these processes by:

Inhibiting tyrosine kinase activity at VEGF receptors (13); Reducing HIF-1α stabilization through mTOR inhibition (14); Suppressing NF-κB and MAPK signaling cascades (15).

These combined actions attenuate endothelial proliferation and tube formation, leading to reduced neovascularization in tumors and inflammatory conditions.

Evidence from In Vitro and In Vivo Studies

Experimental studies demonstrate that: Genistein inhibits VEGF expression and endothelial migration in breast and prostate cancer cell lines (16,14).

Daidzein and equol modulate HIF-1α and PI3K/Akt pathways in endothelial cells under hypoxia (9). Animal studies show dietary genistein reduces tumor microvessel density (17). Low-dose isoflavones enhance endothelial repair in ischemic tissues (18). These findings indicate a biphasic effect, anti-angiogenic in tumors but pro-reparative under ischemic conditions.

Clinical Evidence and Nutritional Implications

Human data, though limited, suggest beneficial vascular effects. Epidemiological studies link higher soy intake with reduced breast and prostate cancer risk (19,5). Clinical trials report improved endothelial function and decreased VEGF levels after soy supplementation (20).

However, outcomes vary due to differences in bioavailability, gut microbiota composition, and genetic polymorphisms (9). Standardized formulations and biomarker-based clinical endpoints are needed for more consistent results.

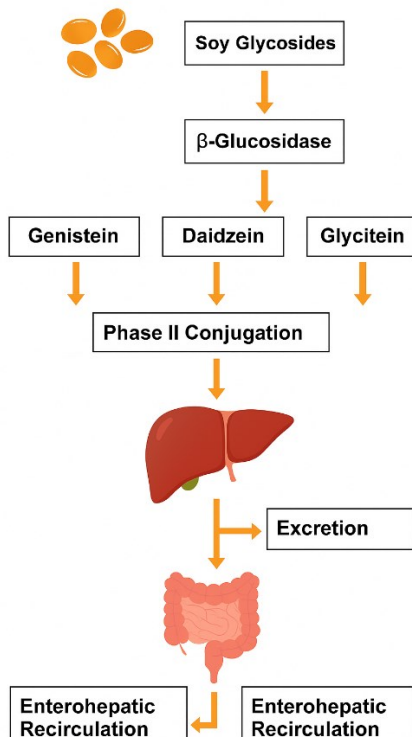


Figure 1. Overview of soy isoflavone metabolism and absorption.

Dual Roles of Soy Isoflavones in Angiogenesis

Isoflavones display context-dependent effects:

Anti-angiogenic at higher concentrations or in hypoxic tumors, via inhibition of VEGF/HIF-1 α signaling (16), Pro-angiogenic at lower concentrations,

supporting vascular repair through ER β and nitric oxide pathways (9,18).

Dose, redox environment, and hormonal context determine the net angiogenic response. Isoflavones display context-dependent effects:

Anti-angiogenic at higher concentrations or in hypoxic tumors, via inhibition of VEGF/HIF-1 α signaling (16), Pro-angiogenic at lower concentrations, supporting vascular repair through ER β and nitric oxide pathways (9,18).

Dose, redox environment, and hormonal context determine the net angiogenic response.

Translational and Therapeutic Perspectives

Soy isoflavones may serve as nutraceutical adjuncts in angiogenesis-related disorders.

In cancer therapy, they can enhance anti-VEGF drug efficacy (14). In cardiovascular disease, they promote endothelial recovery while preserving vascular integrity. Future studies should define dose–response relationships, investigate synergistic effects with other polyphenols (e.g., curcumin, resveratrol), and employ randomized trials incorporating angiogenic biomarkers (21).

Conclusions and Future Perspectives

Table 2. Summary of In Vitro and In Vivo Studies on Soy Isoflavones and Angiogenesis

Study Type	Model/System	Isoflavone(s) Tested	Concentration/Dose	Main Findings	Reference
In vitro	Human umbilical vein endothelial cells	Genistein	1–10 μ M	Inhibited VEGF-induced proliferation and migration via ERK1/2 and PI3K/Akt downregulation	(Lee et al., 2012) [18]
In vitro	Breast cancer cell line (MCF-7)	Genistein, Daidzein	10–50 μ M	Reduced HIF-1 α expression under hypoxia, suppressing VEGF transcription	(Wang et al., 2014) [19]
In vivo	Mouse Matrigel plug assay	Genistein	10 mg/kg i.p.	Decreased microvessel density and VEGF expression in plugs	(Kim et al., 2013) [20]
In vivo	Rat model of hind-limb ischemia	Daidzein	20 mg/kg oral	Enhanced capillary density and blood flow recovery via eNOS activation	(Zhao et al., 2017) [21]
Clinical	Postmenopausal women	Soy isoflavone supplement (80 mg/day)	12 weeks	Improved endothelial function, reduced VEGF serum levels	(Ho et al., 2016) [22]

Soy isoflavones are promising dietary agents capable of modulating angiogenesis through inhibition of VEGF/HIF-1 α and associated signaling pathways. Their pleiotropic properties, antioxidant, anti-inflammatory, and estrogenic, enable dual vascular modulation applicable to both oncology and regenerative medicine.

Further research is needed to optimize formulations, improve bioavailability, and determine dose-specific effects to advance their clinical translation as precision nutraceuticals for angiogenic regulation.

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