

Review

# From Brain to Ovary: Integrative Neuroendocrine and Nutritional Pathways in the Etiology and Treatment of Female Infertility

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## Abstract

**Objective:** The hypothalamic-pituitary-ovarian (HPO) axis is complexly dysregulated in female infertility, and this dysfunction is further exacerbated by metabolic and nutritional abnormalities. Diet and nutrient-derived bioactives significantly influence neuroendocrine factors such as insulin signalling, gonadotropin-releasing hormone (GnRH) pulsatility, and inflammatory tone. Insight into the intersection of these molecular and nutritional pathways may reveal new opportunities for restoring fertility. This review aims to integrate the neuroendocrine, metabolic, and nutritional mechanisms governing female fertility while identifying convergent molecular hubs as potential therapeutic targets. **Mechanism:** A structured search of English-language studies published between 2010 and 2025 was conducted using PubMed, Scopus, Web of Science, and Google Scholar. After screening 186 research and review articles, 92 that met the inclusion criteria were included. Data on neuroendocrine regulation, signalling pathways, and nutritional interventions were extracted. Additionally, 24 nutrient-responsive and reproductive regulatory genes with a minimum interaction confidence score of 0.7 were included in a targeted *in-silico* protein-protein interaction (PPI) network analysis using STRING v12.0 (Homo sapiens). Kyoto Encyclopedia of Genes and Genomes (KEGG) was utilized to evaluate pathway enrichment. **Findings in Brief:** The integrated synthesis shows that phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), and sirtuin 1 (SIRT1) signalling directly affect GnRH neuronal activity, ovarian steroidogenesis, and oocyte competence. *In-silico* analysis identified major central hubs connecting metabolic and neuroendocrine regulation, including AKT1, mTOR, estrogen receptor 1 (ESR1), SIRT1, nuclear factor kappa B subunit 1 (NFKB1), and peroxisome proliferator-activated receptor gamma (PPARG). Nutraceuticals that consistently targeted these hubs, including myo-inositol, vitamin D, omega-3 polyunsaturated fatty acids (PUFAs), resveratrol, curcumin, and quercetin, improved insulin sensitivity, decreased oxidative stress, and restored normal gonadotropin ratios. The evidence supports a multi-target, nutrition-based approach to fertility management. **Conclusions:** The neuroendocrine and molecular regulators of female fertility are measurable targets for nutritional and nutraceutical interventions. Focusing on common signalling hubs identified in the literature and *in-silico* mapping can facilitate the development of standardized, artificial intelligence (AI)-guided nutraceutical formulations. Future research should incorporate biomarker-based endpoints to translate these mechanistic insights into therapeutic benefit.

**Keywords:** female infertility; nutrition; neuroendocrine regulation; hypothalamic-pituitary-ovarian axis; PI3K/AKT/mTOR pathway; nutraceuticals; *in silico* analysis; PCOS; molecular signaling; reproductive health

## 1. Introduction

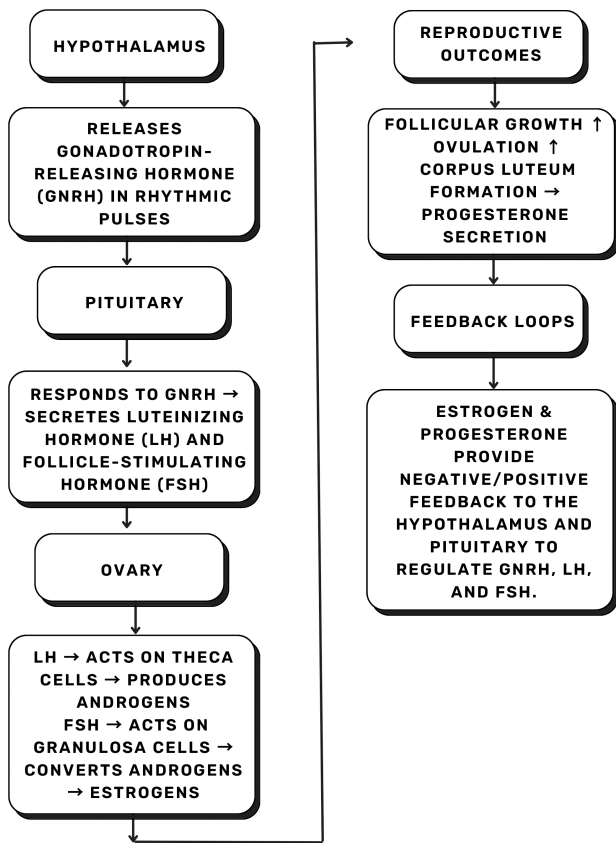
Female infertility, defined as the inability to achieve pregnancy after 12 months or more of unprotected intercourse, affects a substantial proportion of reproductive-aged women worldwide and has a significant psychosocial and economic impact on individuals and society. Infertility is estimated to affect 10–15% of couples worldwide, with female-related factors accounting for nearly half of these cases. The World Health Organization defines infertility as a disease of the reproductive system and a public health issue, especially in low- and middle-income countries, where diagnostic and treatment options are limited. In addition to biological causes, psychosocial stressors and poor nutrition frequently exacerbate infertility, further highlighting

its complex and biopsychological nature. Conditions like ovulatory dysfunction, tubal disease and endocrine abnormalities are major contributors to female infertility [1–3].

At the molecular level, the female reproductive system is controlled by tightly regulated neuroendocrine signals, particularly the hypothalamic-pituitary-ovarian (HPO) axis, which ensures timing of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH)/follicle-stimulating hormone (FSH) release, as well as ovarian steroidogenesis. Disruption of this axis, whether due to metabolic, hormonal, or neurogenic factors, underlies many forms of female infertility (Fig. 1) [4].

In recent years, it has become clear that nutritional status and dietary patterns have a profound impact on fe-





**Fig. 1. Simplified schematic of the hypothalamic-pituitary-ovarian (HPO) axis.** Pulsatile GnRH release from the hypothalamus stimulates pituitary release of LH and FSH, which act on ovarian theca and granulosa cells to regulate steroidogenesis, ovulation, and luteal function. Estrogen and progesterone provide feedback to maintain hormonal balance. Abbreviations: GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone. The Figs. 1–8 were created by the author using Canva (Cloud-based version, Canva Pty Ltd, Sydney, NSW, Australia).

male fertility through metabolic, endocrine, and neuroendocrine mechanisms. For example, diets high in refined carbohydrates, trans fats, and low in micronutrients have been shown to reduce fecundability [5].

Although research into neuroendocrine regulation and nutritional influences on fertility has advanced, a significant gap remains: an integrative understanding of how nutrition interacts with neuroendocrine signaling at the molecular level, especially in disorders such as polycystic ovary syndrome (PCOS) and other infertility etiologies [6].

This review aims to map the brain-to-ovary axis at the molecular level and to show how nutritional modulation can be applied in diagnostic and therapeutic strategies. In this article, we (i) review the neuroendocrine pathways of female reproduction, (ii) examine the molecular signaling cascades between the brain and ovary, (iii) assess how nutrition and nutraceuticals impact these pathways, (iv) dis-

cuss their diagnostic and therapeutic implications in female infertility, and (v) include a brief *in silico* network analysis (STRING) to illustrate the mechanistic link between nutritional modulation and female fertility.

## 2. Literature Review

### 2.1 Literature Search Strategy

Between October 2025 and November 2025, a comprehensive literature search was conducted using the databases PubMed, Scopus, Google Scholar, and Web of Science. The following keywords were searched: “female infertility”, “neuroendocrine regulation”, “hypothalamic-pituitary-ovarian axis”, “nutrition”, “nutraceuticals”, “molecular signaling”, “PCOS”, and “fertility therapy”. Terms were combined using the Boolean operators AND and OR. To ensure current relevance, only peer-reviewed English-language articles published between 2010 and 2025 were included.

### 2.2 Inclusion and Exclusion Criteria

The inclusion criteria comprised studies and reviews addressing: (a) neuroendocrine control of female reproduction; (b) molecular pathways connecting brain-ovary communication; (c) nutritional or nutraceutical interventions that affect reproductive or endocrine parameters; and (d) advancements in the diagnosis or treatment of female infertility. Articles that focused solely on male infertility, non-peer-reviewed sources, or animal models without translational relevance were excluded.

### 2.3 Data Extraction and Synthesis

Key findings, nutrient mechanisms, molecular targets, and study type were among the data extracted. The data were grouped into thematic categories, including neuroendocrine mechanisms, molecular signaling pathways, nutritional modulation, and diagnostic or therapeutic perspectives. The findings were narratively synthesized to highlight integrative mechanisms and knowledge gaps synthesized.

## 3. Results

### 3.1 Integrative Molecular Crosstalk: Neuroendocrine–Nutrient Interface

To complement the literature-based synthesis, a targeted *in silico* analysis was performed to identify key molecular nodes linking neuroendocrine and nutritional pathways in female infertility.

#### 3.1.1 Rationale and Criteria for Gene Selection

The 24 genes included in the STRING analysis were selected based on a priori criteria across five functional categories. First, genes with established involvement in reproductive neuroendocrine regulation were included, specifically kisspeptin receptor (KISS1R), gonadotropin-releasing

hormone receptor (GNRHR), estrogen receptor (ESR)1, and ESR2. Second, key regulators of ovarian steroidogenesis and follicular function were incorporated, including cytochrome P450 aromatase (CYP19A1), steroidogenic acute regulatory protein (STAR), androgen receptor (AR), and 3beta-hydroxysteroid dehydrogenase2 (HSD3 $\beta$ 2). Third, metabolic and insulin-signaling intermediates modulated by nutrients were selected, such as protein kinase B (AKT1), mammalian target of rapamycin (mTOR), insulin receptor substrate 1 (IRS1), and peroxisome proliferator-activated receptor gamma (PPARG). Fourth, the analysis included oxidative stress and inflammatory regulators influenced by dietary components, namely nuclear factor kappa B subunit 1 (NFKB1), superoxide dismutase 2 (SOD2), catalase (CAT), and glutathione peroxidase 1 (GPX1). Finally, nutrient-sensing and mitochondrial regulators linked to fertility outcomes, including SIRT1 and AMP-activated protein kinase (AMPK)-related nodes, were integrated into the selection.

Thus, the network represents the convergence point of four mechanistic domains: neuroendocrine regulation, steroidogenesis, metabolic-insulin signaling, and oxidative and inflammatory balance.

This framework reflects the scope of the present review and avoids the appearance of arbitrary selection.

### 3.1.2 Network Overview and Physiological Positioning of Hubs

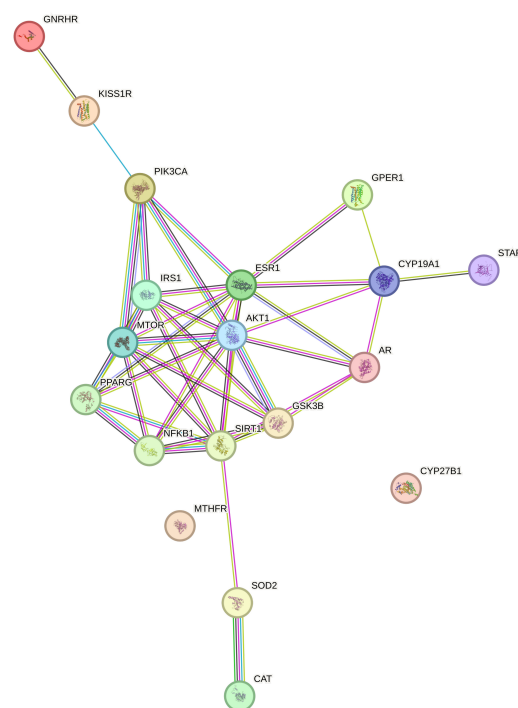
The STRING protein-protein interaction (PPI) map revealed a tightly clustered core of highly connected nodes, including AKT1, mTOR, ESR1, PPARG, SIRT1, and NFKB1, which act as integration points for nutritional, metabolic, and hormonal signals (Fig. 2).

Physiological interpretation:

- AKT1 and IRS1 anchor insulin signaling and link dietary carbohydrate and fat composition to granulosa cell survival and steroid enzyme expression.
- mTOR integrates amino acid availability, cellular energy, and gonadotropin signaling, thereby linking protein intake and caloric sufficiency to follicular growth.
- ESR1 and PPARG represent genomic nodes connecting lipid metabolism, estrogen function, and oocyte competence.
- NFKB1 captures the inflammatory–oxidative axis modulated by omega-3 polyunsaturated fatty acids (PU-FAs), antioxidants, and polyphenols.
- SIRT1, a nutrient-sensing deacetylase, links caloric intake, mitochondrial status, and ovarian aging.

Peripheral nodes like CYP19A1, STAR, AR, and KISS1R/GNRHR provide anchoring between the PPI core and the physiological systems described earlier, namely steroidogenesis and hypothalamic-pituitary signaling.

Thus, the top pathways in Fig. 3 directly correspond to the reproductive tissues where these hubs are physiologically located:



**Fig. 2. STRING-based protein-protein interaction (PPI) network depicting shared molecular targets of nutrient-responsive pathways involved in female fertility regulation.**

Central nodes (AKT1, mTOR, ESR1, PPARG, SIRT1, and NFKB1) represent key integration points linking metabolic, inflammatory, and neuroendocrine signaling. Abbreviations: AKT1, protein kinase B; mTOR, mammalian target of rapamycin; ESR1, estrogen receptor 1; PPARG, peroxisome proliferator-activated receptor gamma; SIRT1, sirtuin 1; NFKB1, nuclear factor kappa B subunit 1.

- Phosphoinositide 3-kinase (PI3K)-AKT → granulosa/theca metabolic balance and GnRH neuronal sensitivity.
- mTOR → follicular activation and oocyte maturation.
- Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) → ovarian inflammation and luteal function.
- Steroid hormone biosynthesis → granulosa/theca steroidogenic output.
- Oxidative stress response → oocyte mitochondrial quality.

### 3.1.3 Pathway Enrichment

The enriched pathways reflect the molecular architecture previously described:

**3.1.3.1 Neuroendocrine Control.** KISS1R–GNRHR interactions feed into PI3K/AKT and MAPK modules, showing how nutritional modulation of insulin and inflammatory status can alter GnRH pulsatility and gonadotropin output.

pathway	description	count in network	strength	↑ signal	false discovery rate
hsa04211	Longevity regulating pathway	9 of 87	2.03	4.88	3.12e-14
hsa04213	Longevity regulating pathway - multiple species	7 of 61	2.08	4.06	3.46e-11
hsa05215	Prostate cancer	6 of 97	1.81	2.7	5.04e-08
hsa04931	Insulin resistance	6 of 106	1.77	2.62	6.30e-08
hsa04917	Protein signaling pathway	5 of 68	1.88	2.54	3.24e-07
hsa04152	AMPK signaling pathway	6 of 120	1.71	2.48	1.03e-07
hsa04088	ForO signaling pathway	6 of 126	1.69	2.44	1.14e-07
hsa01322	Endocrine resistance	5 of 94	1.74	2.22	1.18e-06
hsa04722	Neurotrophin signaling pathway	5 of 112	1.67	2.04	2.47e-06
hsa04929	GliRf secretion	4 of 68	1.62	2.02	8.02e-06
hsa04955	Growth hormone synthesis, secretion and action	4 of 117	1.65	2.01	2.27e-06
hsa04919	Thyroid hormone signaling pathway	5 of 120	1.64	1.99	2.86e-06
hsa05221	Acute myeloid leukemia	4 of 67	1.79	1.98	9.65e-06
hsa04920	Adipocytokine signaling pathway	4 of 68	1.79	1.97	9.72e-06
hsa05212	Pancreatic cancer	4 of 71	1.77	1.94	1.09e-05
hsa04910	Insulin signaling pathway	5 of 132	1.59	1.9	4.19e-06
hsa01521	EGFR tyrosine kinase inhibitor resistance	4 of 77	1.73	1.89	1.26e-05
hsa04662	B cell receptor signaling pathway	4 of 78	1.73	1.89	1.28e-05
hsa04012	Erbb signaling pathway	4 of 81	1.71	1.86	1.43e-05
hsa05210	Colorectal cancer	4 of 82	1.7	1.85	1.44e-05
hsa05224	Breast cancer	5 of 146	1.55	1.81	6.31e-06
hsa04932	Non-alcoholic fatty liver disease	5 of 146	1.55	1.81	6.31e-06
hsa05235	PD-1 expression and PD-1 checkpoint pathway in cancer	4 of 87	1.68	1.81	1.76e-05
hsa04218	Cellular senescence	5 of 150	1.54	1.8	6.31e-06
hsa04150	mTOR signaling pathway	5 of 150	1.54	1.8	6.31e-06
hsa05206	MicroRNAs in cancer	5 of 159	1.51	1.75	7.40e-06
hsa04660	T cell receptor signaling pathway	4 of 100	1.62	1.7	2.21e-05
hsa04666	HIF-1 signaling pathway	4 of 102	1.61	1.69	2.84e-05
hsa04930	Type II diabetes mellitus	3 of 45	1.84	1.65	0.00010
hsa05167	Kaposi sarcoma-associated herpesvirus infection	5 of 187	1.44	1.63	1.15e-05
hsa04380	Osteoclast differentiation	4 of 120	1.54	1.55	5.15e-05
hsa04923	Regulation of lipolysis in adipocytes	3 of 54	1.76	1.54	0.00016
hsa05135	Yersinia infection	5 of 124	1.52	1.53	5.68e-05
hsa05200	Pathways in cancer	8 of 515	1.21	1.52	5.70e-07
hsa05163	Human cytomegalovirus infection	5 of 217	1.38	1.51	1.92e-05
hsa05131	Shigellosis	5 of 218	1.38	1.5	1.92e-05
hsa05213	Endometrial cancer	3 of 58	1.73	1.5	0.00019
hsa04140	Autophagy - animal	4 of 131	1.5	1.49	6.83e-05

**Fig. 3. Enriched KEGG pathways derived from the nutrient-target PPI network (confidence >0.7, STRING).** The top 5 to 6 pathways (e.g., PI3K-AKT signaling, mTOR signaling, NF- $\kappa$ B signaling, steroid hormone biosynthesis, oxidative stress response) illustrate convergence of nutrient-responsive and neuroendocrine-fertility regulatory hubs. KEGG, Kyoto Encyclopedia of Genes and Genomes; PI3K-AKT, phosphoinositide 3-kinase-protein kinase B; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells.

3.1.3.2 Ovarian Intracellular Signaling. mTOR, AKT1, ESR1, and NF- $\kappa$ B form the interface between follicle growth, steroidogenesis, and inflammatory tone, all of which are modulated by nutrients (vitamin D, inositols, omega-3 fatty acids, antioxidants).

3.1.3.3 Nutraceutical Mechanisms. Each major nutrient group maps directly onto a dominant hub:

- Inositols  $\rightarrow$  PI3K-AKT  $\rightarrow$  CYP19A1/StAR.
- Vitamin D  $\rightarrow$  IRS1/ESR1  $\rightarrow$  steroidogenesis.
- Omega-3 fatty acids  $\rightarrow$  NFKB1  $\rightarrow$  inflammatory ovarian microenvironment.
- Polyphenols  $\rightarrow$  SIRT1/nuclear factor erythroid-2-related factor 2 (Nrf2)  $\rightarrow$  mitochondrial and metabolic control.

Thus, the network reinforces that nutrient effects are not isolated but converge on shared mechanistic bottlenecks crucial for female fertility.

### 3.1.4 Integrative Interpretation

The combined experimental and *in silico* evidence suggests that:

- Nutrients act through a limited set of intracellular hubs, despite their diverse biochemical classes.
- These hubs simultaneously regulate neuroendocrine rhythms, metabolic homeostasis, ovarian steroidogenesis, and oocyte quality.
- Therefore, dietary patterns and targeted nutraceuticals exert system-wide effects on fertility by modulating these bottlenecks rather than single pathways.

This systems-level convergence helps explain why diverse interventions, including low-glycemic index (GI) diets, omega-3 enrichment, adequate vitamin D, antioxidant therapy, or inositol supplementation, consistently improve ovulatory function and IVF outcomes.

## 4. Discussion

The following sections synthesize current evidence on neuroendocrine regulation, molecular signaling pathways, and nutritional modulation in female fertility.

### 4.1 The Neuroendocrine Basis of Female Fertility

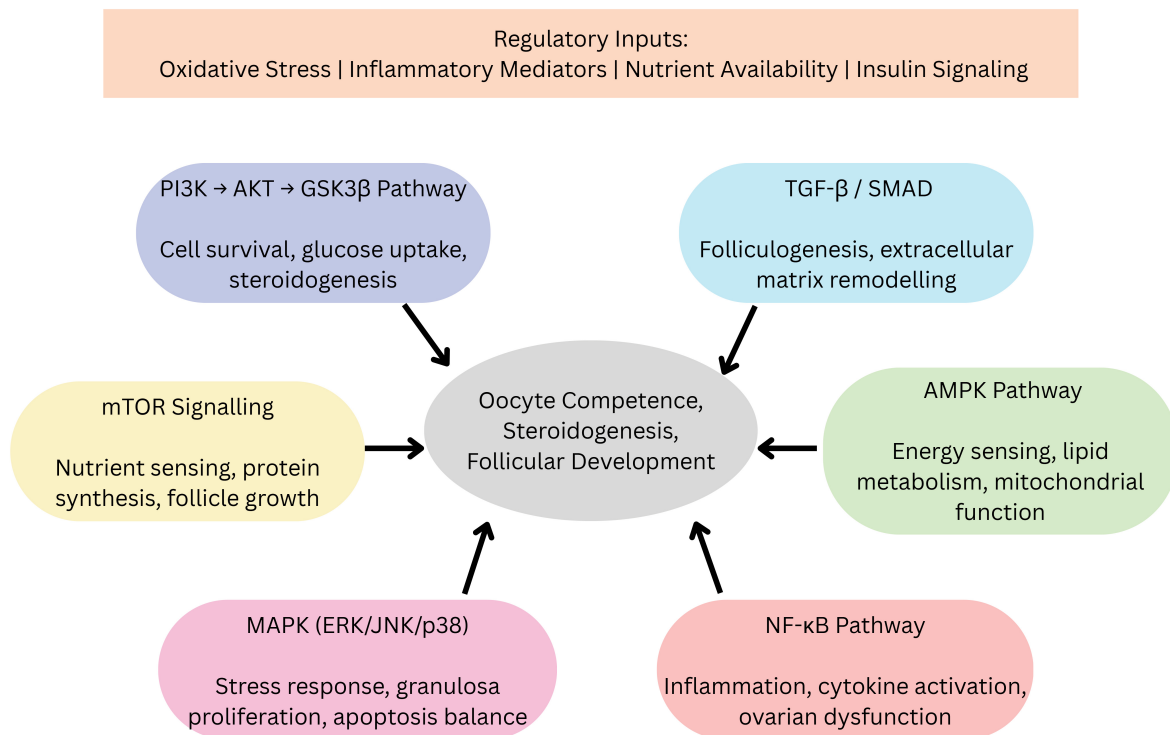
The HPO axis is the central neuroendocrine pathway that drives female reproductive cycling by converting pulsatile hypothalamic GnRH into temporally regulated pituitary secretion of LH and FSH, which in turn control ovarian folliculogenesis, steroidogenesis, and ovulation [7].

Upstream neuropeptides that sense the hormonal and metabolic milieu regulate GnRH neuronal activity. Among these, kisspeptin neurons are the main gatekeepers of the reproductive hormones' release. Kisspeptin signaling in the arcuate and preoptic hypothalamus potently stimulates GnRH release and encodes both negative and positive sex steroid feedback, which governs pulsatile vs surge modes of gonadotropin secretion. This kisspeptin-GnRH module is now recognized as a key neuroendocrine node that integrates metabolic, circadian, and steroid feedback to control reproductive function [8].

The anterior pituitary receives hypothalamic signals and converts neural signals into endocrine responses that directly affect the ovaries. Thus, pituitary gonadotropins act as the effector hormones of the HPO axis, where FSH promotes granulosa cell proliferation and the aromatase-dependent conversion of androgens to estradiol, whereas LH acts on theca cells and, later, on mural granulosa cells to promote androgen synthesis, follicular maturation, and the preovulatory surge that triggers oocyte release and luteinization. The interplay between follicular estradiol production and pituitary responsiveness controls follicle selection and the preovulatory surge [9].

Several nodes of the HPO axis are subject to tightly controlled feedback from ovarian steroids. Progesterone modulates the frequency of the GnRH pulse and primes the endometrium for implantation following ovulation, whereas estradiol exerts both positive and negative feedback on the amplitude of the GnRH pulse through arcuate circuitry and preoptic kisspeptin neurons. Reproductive readiness and regular cycle progression depend on these steroid feedback loops [7,10].

In addition to gonadal feedback, stress-responsive systems have a significant impact on the reproductive axis. Stress hormones can alter reproductive signaling, as the hypothalamic-pituitary-adrenal (HPA) and HPO axes have reciprocal regulatory relationships. Psychological and physiological stressors primarily inhibit reproductive



**Fig. 4. Integrated molecular pathways that control ovarian function.** Oxidative stress, inflammatory mediators, nutrient availability, and insulin signaling act as upstream regulatory inputs that converge on six key intracellular pathways—PI3K/AKT/GSK3 $\beta$ , mTOR, MAPK, NF- $\kappa$ B, AMPK, and TGF- $\beta$ /SMAD. Together, these interconnected molecular nodes coordinate oocyte competence, steroidogenesis, and follicular development. Abbreviations: GSK3 $\beta$ , glycogen synthase kinase 3 beta; MAPK, mitogen-activated protein kinase; AMPK, AMP-activated protein kinase; TGF- $\beta$ /SMAD, transforming growth factor-beta/small mother against decapentaplegic.

function through activation of the HPA axis and subsequent elevation of glucocorticoid levels. These factors reduce the release of LH and FSH secretion and interfere with folliculogenesis by impairing the activity of kisspeptin and GnRH neuronal activity and by increasing inhibitory signals like gonadotropin-inhibitory hormone (GnIH). Reduced gonadotropin secretion and altered ovarian steroidogenesis have been demonstrated in both acute and chronic stress paradigms [11].

HPO function is significantly altered by metabolic disturbances. Peripheral insulin resistance and hyperinsulinemia increase the ovarian theca cell androgen production and intensify luteinizing responses, which lead to anovulatory phenotypes such as PCOS. Concurrently, altered insulin signaling in the pituitary and hypothalamus disrupts GnRH and gonadotropin dynamics. Thus, insulin resistance links systemic metabolic state to ovarian steroidogenic output and follicular arrest [12].

Beyond insulin resistance, neuroendocrine fertility control is also influenced by dietary and adipose-derived cues. Obesity and adiposity disrupt neuroendocrine reproductive regulation by altering leptin signaling, increasing the peripheral aromatization of androgens to estrogens in adipose tissue, promoting chronic low-grade inflammation,

and altering hypothalamic nutrient-sensing circuits. These changes impair follicular development, disrupt GnRH pulsatility, and reduce oocyte quality, all of which contribute to a decrease in fertility [13].

#### 4.2 Molecular Pathways Governing Neuroendocrine and Ovarian Function

A series of intracellular molecular cascades converts external hormonal and metabolic cues into precise cellular responses within reproductive tissues and form the basis of this endocrine coordination. An intricately coordinated network of intracellular signaling pathways connects neuroendocrine cues, metabolic inputs, and ovarian responses to regulate female fertility (Fig. 4). These pathways—PI3K/AKT/GSK3 $\beta$ , mTOR, MAPK, NF- $\kappa$ B, AMPK, and transforming growth factor-beta (TGF- $\beta$ )/SMAD—form essential molecular nodes that integrate oxidative stress, inflammatory mediators, nutrient availability, and insulin signaling to determine oocyte competence, steroidogenesis, and follicular development. Dysregulation of these cascades in metabolic and endocrine disorders like PCOS and obesity-related reproductive dysfunction leads to anovulation, altered steroid biosynthesis, and infertility [14].

#### 4.2.1 PI3K/AKT/GSK3 $\beta$ Pathway: A Central Link Between Insulin Signaling and Ovarian Steroidogenesis

The effects of insulin, gonadotropins, and growth factors in reproductive tissues are mediated by the crucial intracellular signaling cascade known as the PI3K/AKT/glycogen synthase kinase-3 $\beta$  (GSK3 $\beta$ ) pathway. Activation of the insulin or insulin-like growth factor-1 (IGF-1) receptor recruits PI3K, which phosphorylates AKT, inhibiting GSK3 $\beta$  and promoting protein synthesis, glucose uptake, and cell survival. This pathway regulates oocyte maturation, the expression of steroidogenic enzymes, and the proliferation of granulosa and theca cells in the ovary (Fig. 5) [15].

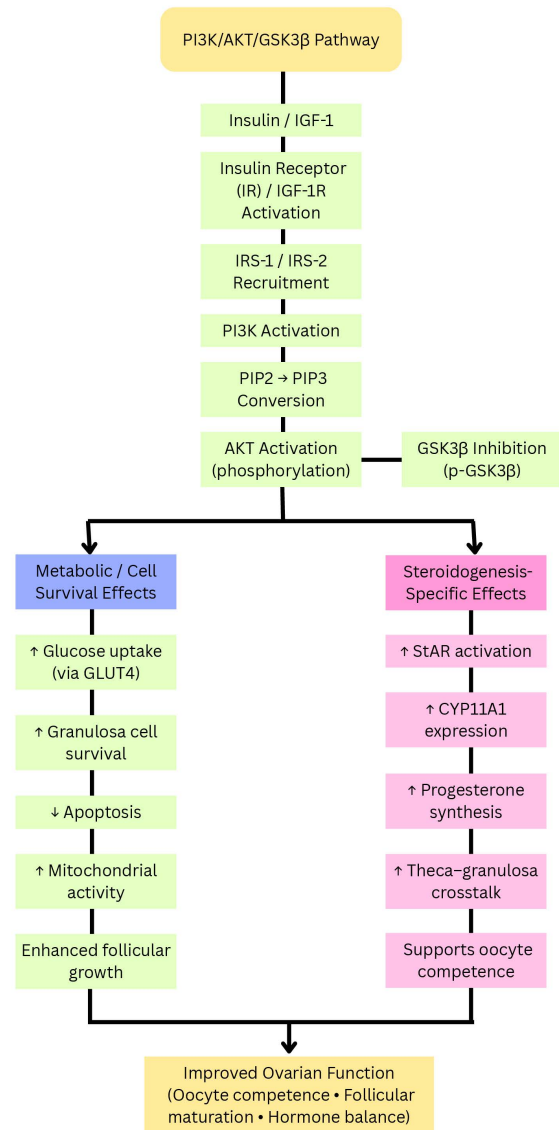
AKT activation promotes estradiol synthesis and follicular maturation by increasing the expression and activity of key enzymes such as CYP19A1 and StAR. Additionally, the interaction between AKT and the transcription factor Forkhead Box O1 (FOXO1) regulates granulosa cell apoptosis and guarantees follicular selection. Hyperinsulinemia and AKT hyperactivation stimulate cytochrome P450 17A1 (CYP17A1) and HSD3 $\beta$ 2 in theca cells, which disrupts the estrogen-androgen balance and results in excessive androgen synthesis in conditions such as PCOS. Therefore, the PI3K/AKT/GSK3 $\beta$  cascade acts as a molecular bridge between metabolic and reproductive homeostasis, and its dysregulation leads to ovulatory failure and poor oocyte quality [16,17].

#### 4.2.2 mTOR and MAPK Pathways: Nutrient Sensing and Follicular Development

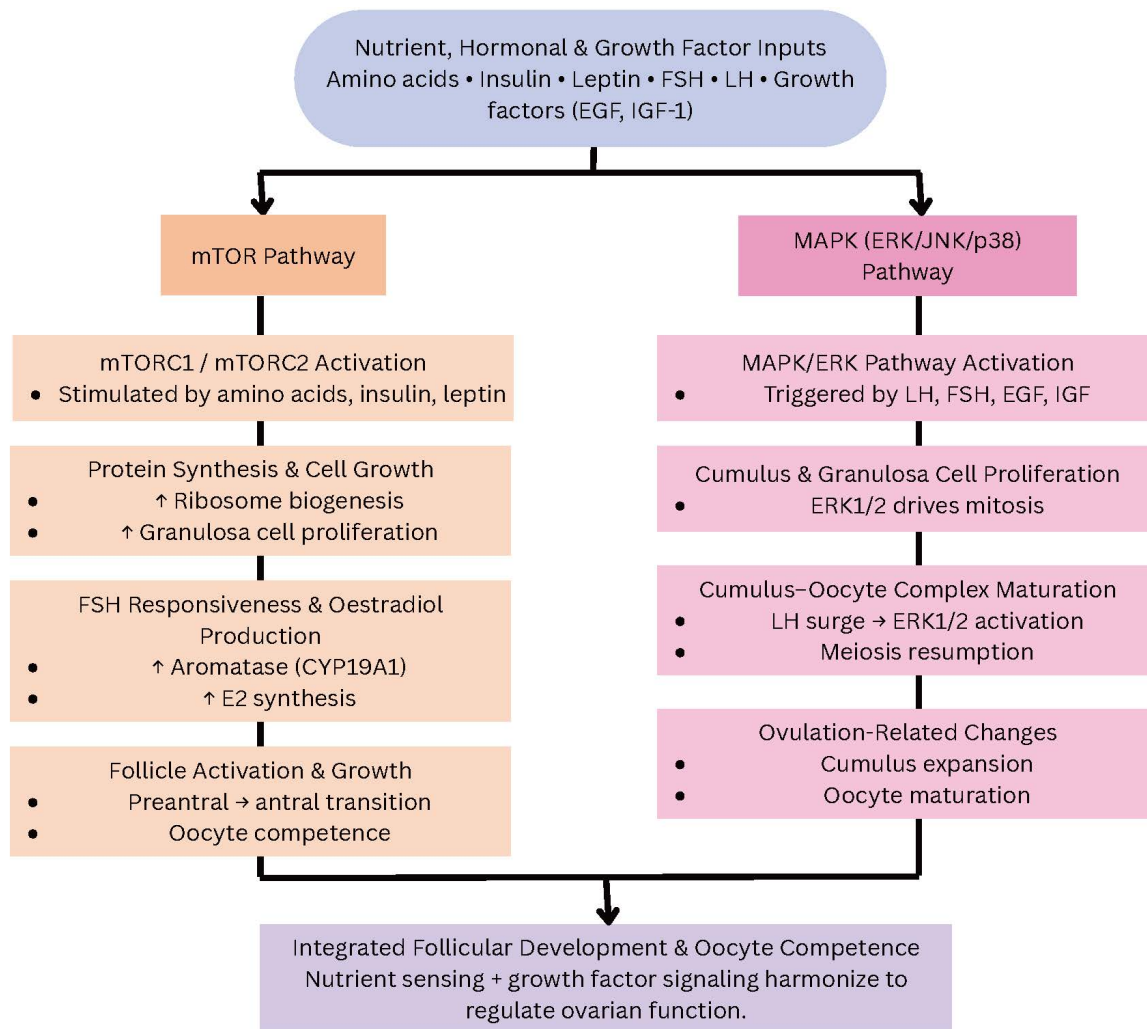
The MAPK and mTOR pathways act as metabolic sensors that link ovarian folliculogenesis to growth factor signaling, energy availability, and nutritional status (Fig. 6).

In response to amino acids, insulin, leptin, and mTOR, a serine/threonine kinase complex (mTORC1 and mTORC2), regulates protein synthesis, autophagy, and cell division. mTOR signaling stimulates the production of estradiol, FSH responsiveness, and cellular proliferation in ovarian granulosa cells. Its role in follicular activation and oocyte competence is supported by experimental inhibition, which decreases aromatase expression and hinders the preantral-to-antral follicle transition [18,19].

In parallel, the MAPK/extracellular signal-regulated kinase (ERK) pathway transmits growth factor and gonadotropin signals that regulate cumulus cell proliferation and oocyte maturation induced by the LH surge. Meiosis and cumulus-oocyte communication, two essential ovulation processes, are triggered by the LH-activated ERK1/2 cascade. mTOR and MAPK are also active in hypothalamic neurons, where they integrate GnRH secretion with nutrient-derived cues and link central reproductive regulation to peripheral metabolism. Dysregulation of these pathways, which may result from endocrine disruptors, obesity, or nutritional deprivation, can lead to follicular arrest and subfertility [20,21].



**Fig. 5. Split-branch representation of the PI3K/AKT/GSK3 $\beta$  pathway linking insulin signaling to ovarian function.** Insulin/IGF-1 binding activates PI3K-AKT signaling through IRS phosphorylation and PIP3 generation. Activated AKT suppresses GSK3 $\beta$  and diverges into two major functional arms: a metabolic and survival arm that enhances glucose uptake and granulosa cell viability, and a steroidogenic arm that upregulates StAR, CYP11A1, and progesterone synthesis. Together, these dual outputs support follicular development and oocyte competence. Symbols:  $\uparrow$  upregulation;  $\downarrow$  downregulation. Abbreviations: IGF, insulin-like growth factor; PIP, phosphatidylinositol phosphate; GLUT4, glucose transporter type 4; StAR, steroidogenic acute regulatory protein; CYP11A1, cytochrome P450 family 11 subfamily A member 1; IRS, insulin receptor substrate.



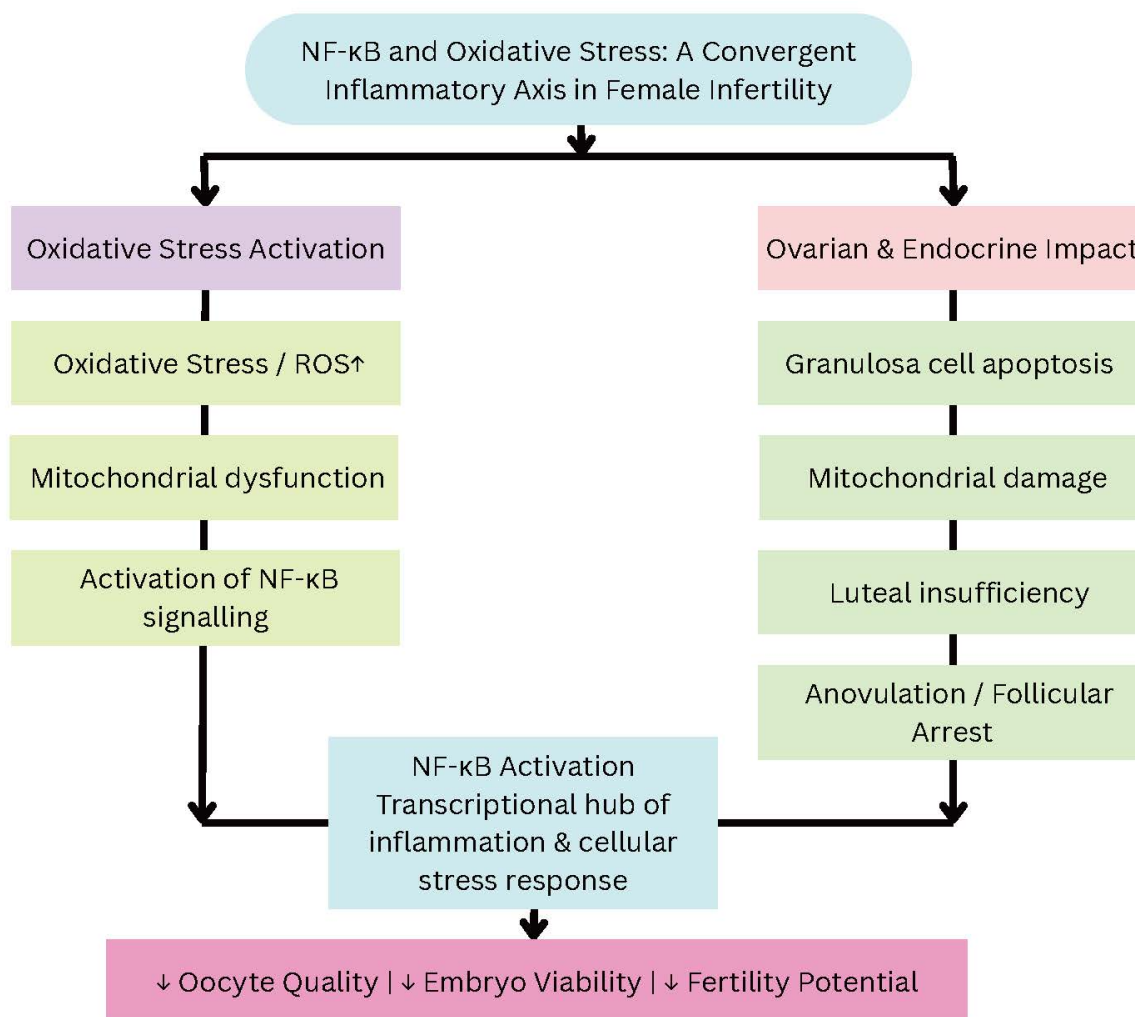
**Fig. 6. Parallel representation of the mTOR and MAPK pathways as nutrient- and hormone-sensitive regulators of follicular development.** Amino acids, insulin, leptin, and gonadotropins activate mTORC1/2 and MAPK/ERK cascades in ovarian granulosa and cumulus cells. mTOR signaling enhances protein synthesis, cellular proliferation, aromatase expression, and follicle growth, whereas the MAPK pathway drives LH-induced cumulus expansion, meiosis resumption, and oocyte maturation. Together, these metabolic and growth factor-responsive pathways coordinate ovarian folliculogenesis, and their dysregulation contributes to follicle arrest and subfertility. Arrows indicate the direction of interaction or regulatory influence between components and do not represent quantitative effects. Abbreviations: EGF, epidermal growth factor; mTORC, mammalian target of rapamycin complex; ERK, extracellular signal-regulated kinase; E2, estradiol.

#### 4.2.3 NF- $\kappa$ B and Oxidative Stress: Inflammation-Linked Infertility

Now known to play a significant role in ovarian dysfunction and anovulation, the NF- $\kappa$ B signaling cascade serves as a transcriptional center for immune and inflammatory responses (Fig. 7). Under physiological conditions, NF- $\kappa$ B is transiently activated in the ovary during ovulation, which resembles a localized inflammatory response and promotes follicular rupture, prostaglandin synthesis, and cytokine release. In contrast, chronic or excessive activation of NF- $\kappa$ B, as observed in obesity, insulin resistance, or oxidative stress, induces proinflammatory cytokines (tumor necrosis factor alpha [TNF- $\alpha$ ], interleukin-6 [IL-6])

and reactive oxygen species (ROS), leading to granulosa cell apoptosis, mitochondrial dysfunction, and luteal insufficiency [22].

Oxidative stress suppresses GnRH release and modifies LH/FSH secretion by interacting with NF- $\kappa$ B signaling to sustain a proinflammatory microenvironment in the ovary and hypothalamus. Reduced oocyte quality, changed spindle formation, and impaired embryo development have all been associated with increased oxidative and inflammatory burden. The therapeutic relevance of this pathway is supported by evidence that antioxidant and anti-inflammatory interventions that attenuate NF- $\kappa$ B activation, such as Nrf2 activators, omega-3 fatty acids, or



**Fig. 7. Integrative model illustrating how oxidative stress and chronic activation of NF- $\kappa$ B drive inflammation-mediated female infertility.** Excess ROS, metabolic dysfunction, and obesity trigger NF- $\kappa$ B activation, which leads to increased proinflammatory cytokines (TNF- $\alpha$ , IL-6, IL-1 $\beta$ ). Sustained NF- $\kappa$ B signaling induces granulosa cell apoptosis, mitochondrial damage, luteal insufficiency, and impaired oocyte competence, while simultaneously disrupting hypothalamic GnRH and pituitary gonadotropin release. Arrows indicate the direction of interaction or regulatory influence between components and do not represent quantitative effects. Abbreviations: ROS, reactive oxygen species.

polyphenols, restore redox homeostasis and improve reproductive outcomes [23].

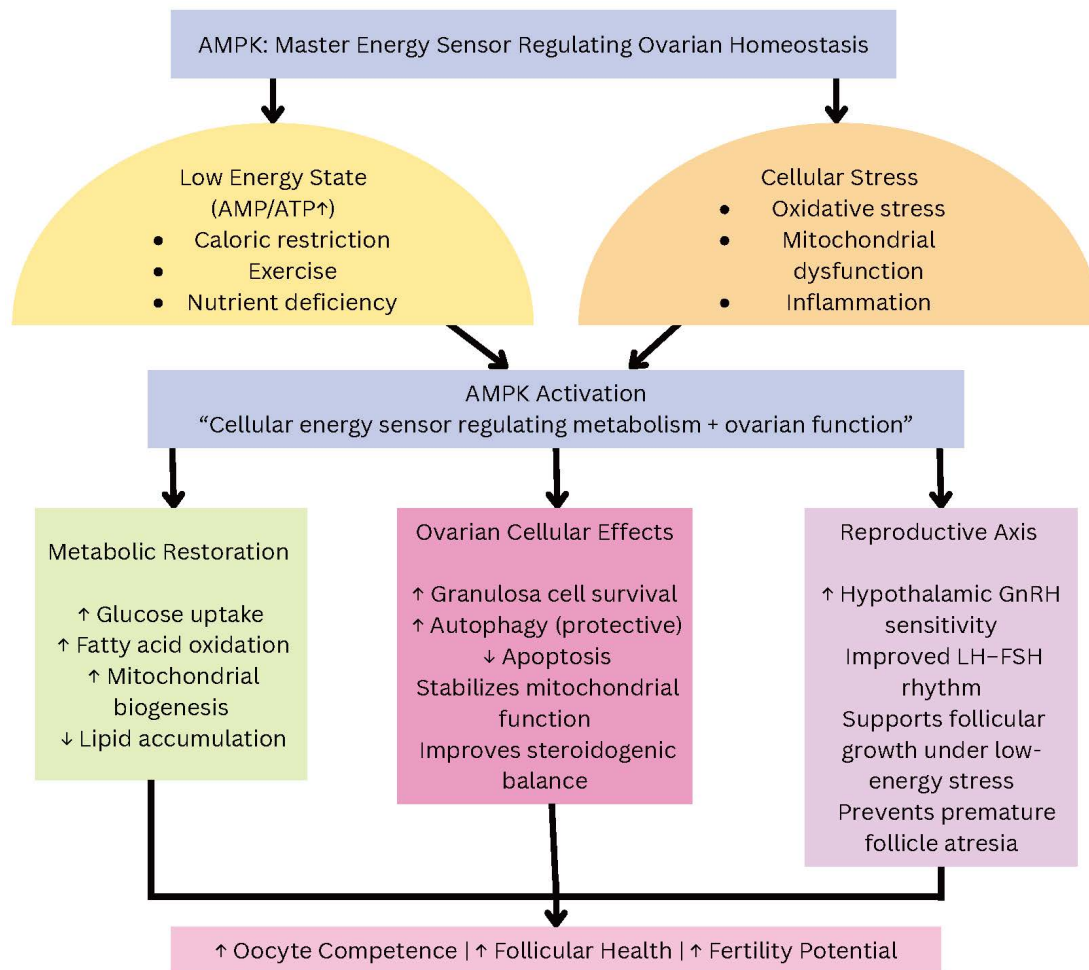
#### 4.2.4 AMPK Pathway: Cellular Energy Sensing and Ovarian Homeostasis

AMPK, the primary cellular energy sensor in ovarian tissue, responds to alterations in the cellular adenosine monophosphate/adenosine triphosphate (AMP/ATP) ratio and metabolic cues by regulating follicle activation, granulosa cell proliferation, oocyte maturation, and autophagy. In the ovary, AMPK activation promotes metabolic adaptation in granulosa and cumulus cells, inhibits mTOR-driven follicle activation under low-energy conditions, and maintains oocyte quality by regulating mitochondrial and glucose metabolism. Experimental studies show that phar-

macologic or genetic modulation of AMPK changes primordial follicle activation, follicular growth dynamics, and steroidogenic output. These findings suggest that reproductive disorders marked by decreased oocyte competence and impaired folliculogenesis are linked to dysregulated AMPK signaling (Fig. 8) [24].

#### 4.2.5 TGF- $\beta$ /SMAD Pathway: Local Growth Factor Control of Folliculogenesis

The paracrine and autocrine signaling network formed by members of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily, including activins, inhibins, bone morphogenetic proteins (BMPs), and TGF- $\beta$  isoforms, and their downstream SMAD effectors, is crucial for granulosa-theca communication, follicle growth, and oocyte develop-



**Fig. 8. AMPK functions as a central metabolic sensor that integrates energy status, oxidative stress, and nutrient availability to maintain ovarian homeostasis.** Low cellular ATP, mitochondrial stress, or inflammation activate AMPK, which subsequently restores metabolic balance through increased glucose uptake, fatty acid oxidation, and mitochondrial biogenesis. In ovarian cells, AMPK supports granulosa cell survival, regulates autophagy, prevents apoptosis, and maintains steroidogenic equilibrium. AMPK also interacts with hypothalamic-pituitary signaling to support GnRH and gonadotropin rhythms. Together, these actions preserve follicular development, oocyte competence, and fertility outcomes. Arrows indicate the direction of interaction or regulatory influence between components and do not represent quantitative effects.

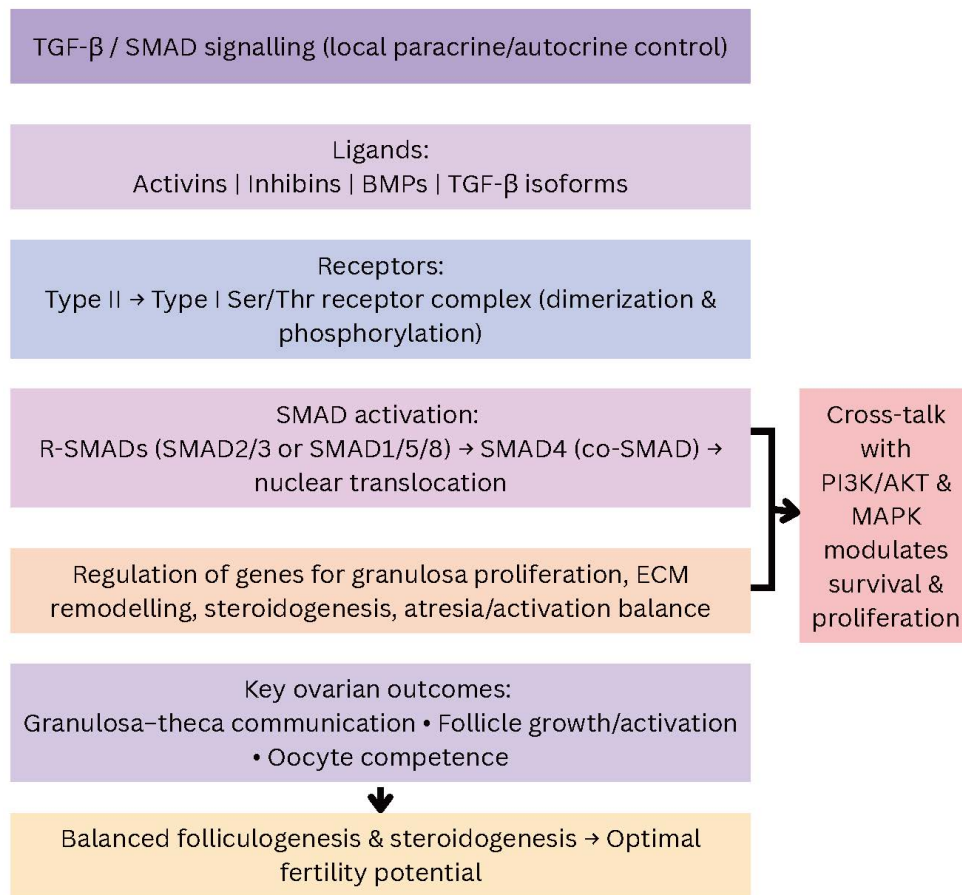
mental competence in both oocytes and somatic follicular cells (Fig. 9). Through both canonical SMAD-dependent transcriptional programs and non-SMAD crosstalk with PI3K/AKT and MAPK pathways, TGF- $\beta$ /SMAD signaling controls granulosa cell proliferation, differentiation, and the balance between follicle activation and atresia. A variety of ovarian dysfunctions, from reduced fertility to fibrotic remodeling, are associated with disruptions of TGF- $\beta$  family signaling or SMAD function (genetic or environmental), and result in aberrant follicle recruitment, altered steroidogenesis, and increased follicular atresia [25].

#### 4.3 Nutritional and Nutraceutical Regulation of Neuroendocrine Pathways

An increasing number of research suggests that female fertility is associated with dietary intake. In this con-

text, there is increasing interest in lifestyle factors, including diet and exercise, as well as psychological stress, socioeconomic factors, body mass index (BMI), smoking, alcohol, caffeine, and psychoactive substances. In infertility associated with endometriosis and ovulation difficulties, lifestyle factors, including calorie intake and diet composition in terms of vitamins, protein, lipids, carbs, and mineral content, appear to be particularly important (Fig. 10) [26,27].

Diet and its nutritional components may have an impact on female fertility and ovulation through effects on metabolic pathways, endocrine profiles, and carbohydrate metabolism. Insulin resistance, the primary mechanism connecting anovulatory infertility to diet, is considered particularly significant in the development of ovulation disorders [28]. Oxidative stress and chronic inflammation are



**Fig. 9. Simplified vertical representation of TGF- $\beta$ /SMAD signaling in the ovarian follicle.** Local TGF- $\beta$  family ligands (activins, inhibins, BMPs, TGF- $\beta$  isoforms) bind to type II/I receptor complexes to phosphorylate receptor-SMADs, which then form complexes with SMAD4 and translocate to the nucleus to regulate transcriptional programs controlling granulosa–theca communication, extracellular matrix remodeling, steroidogenesis, and the balance between follicle activation and atresia. Crosstalk with PI3K/AKT and MAPK pathways refines cellular survival and proliferative responses. Abbreviations: BMPs, bone morphogenetic proteins; ECM, extracellular matrix.

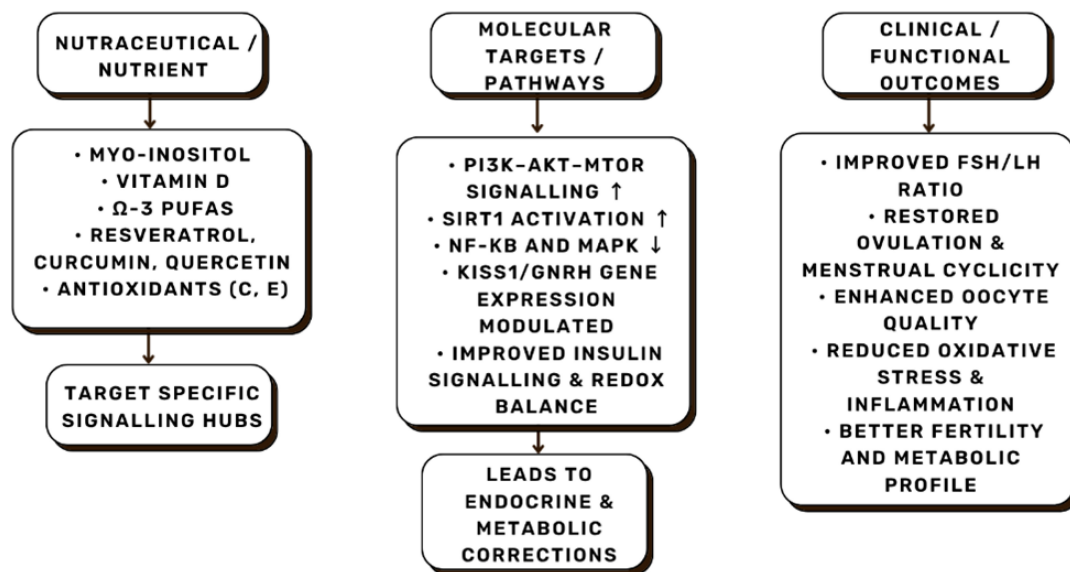
additional significant factors that raise the risk of ovulatory dysfunction [26]. Women with elevated inflammatory markers during their menstrual cycle are more likely to experience an anovulatory cycle, likely due to increased oxidative stress in the ovary [29].

The Nurses' Health Study II (NHS II), a prospective cohort study involving 17,544 infertile women, found that diet and nutrient intake significantly impacted fertility and decreased the risk of ovulatory disorders. Compared with women in the lowest percentile, those in the highest quintile of adherence to a fertility-supporting diet had a 66% decreased chance of anovulatory infertility. Based on these findings, a “fertility diet” plan was proposed. It was characterized by the presence of high-fat dairy products, low-glycemic-index carbohydrates, high iron content, and a decrease in trans fatty acid consumption accompanied by an increase in monounsaturated fatty acid supply [28,30].

Research in humans and animal models supports the concept that an appropriate diet enhances fertility. The

Mediterranean diet (MD) in particular, has been extensively studied in this context [31–35]. Furthermore, numerous studies have also examined the relationship between the risk of infertility and intake of specific macronutrients or micronutrients, such as proteins, fats, carbohydrates, vitamins, and minerals like vitamin B12, vitamin D, folates, zinc, and omega-3 fatty acids.

The intricate interactions between metabolic, inflammatory, and neuroendocrine signals that control the HPO axis are influenced by nutrition, which is a major and modifiable factor in female reproductive health. Both macronutrients (proteins, fats, and carbohydrates) and micronutrients (vitamins, minerals, and trace elements) are essential for ovulation, steroidogenesis, and oocyte competence in women of reproductive age (Table 1, Ref. [36–42]). Dietary patterns associated with irregular menstruation, ovulatory dysfunction, and decreased fertility include high consumption of refined carbohydrates, trans fats, excess energy, and micronutrient deficiencies. In contrast, diets



**Fig. 10. Representative nutrient–molecular–clinical outcome pathways.** Specific nutraceuticals modulate intracellular signaling hubs such as PI3K/AKT/mTOR, SIRT1 (Sirtuin 1), and NF-κB, leading to improved ovarian function, hormonal balance, and fertility outcomes. Arrows indicate the direction of interaction or regulatory influence between components and do not represent quantitative effects.

**Table 1. Principal nutrients and their molecular targets in female infertility.**

Nutrient/Nutraceutical	Key molecular targets/pathways	Mechanistic action
Myo-/D-chiro-inositol	PI3K → AKT → GLUT4/CYP19A1	Improves insulin signaling, enhances aromatase, reduces androgens [36,37].
Vitamin D	VDR, CYP19A1, IRS-1, GnRH	Regulates steroidogenesis, AMH, and cytokine balance [38].
Omega-3 PUFAs	NF-κB, PPAR-γ, GPR120	Reduces inflammation, restores GnRH/kisspeptin signaling [39].
NAC	NF-κB, Glutathione (GSH) axis	Antioxidant, insulin-sensitizer [40].
CoQ10	Mitochondrial ETC Complex I–III	Enhances ATP, oocyte maturation [40].
Melatonin	MT1/MT2 receptors, SIRT3	Antioxidant, circadian and steroidogenic regulation [40].
Zinc	Metallothionein, Meiotic enzymes	Chromatin stability, oocyte meiosis [41].
Folate/B12	DNA methyltransferase, MTHFR	Epigenetic regulation of GnRH/steroidogenesis [41].
Polyphenols (resveratrol, curcumin)	SIRT1, AMPK, Nrf2	Anti-inflammatory, energy-sensing modulation [42].

VDR, vitamin D receptor; NAC, N-acetylcysteine; CoQ10, coenzyme Q10; MTHFR, methylenetetrahydrofolate reductase; AMH, anti-Müllerian hormone; PUFAs, polyunsaturated fatty acids.

high in fiber, plant-based proteins, vitamins, minerals, and healthy fats, particularly omega-3 PUFAs, have positive correlations with reproductive outcomes [43,44].

Building on the dietary basis, a “nutraceutical” is defined as a food or component of a food that has health-promoting or medical effects, such as preventing or treating disease. These products are frequently supplied in concentrated, formulated form rather than whole foods alone. By enabling modulation of specific pathways linked to reproductive dysfunction, nutraceuticals act as a link between targeted molecular interventions and general nutrition. Nutraceuticals address the key disruptions of the neuroendocrine-ovarian axis, including insulin resistance, oxidative stress, inflammation, and altered steroidogenesis, in the context of female infertility. According to a compre-

hensive analysis of dietary supplements, common nutraceuticals like inositols, vitamin D, omega-3 fatty acids, and antioxidants, are frequently used to support fertility [45,46].

#### 4.3.1 Role of Dietary Nutrients in Neuroendocrine Fertility Regulation

A balanced macronutrient composition and adequate micronutrient intake provide the foundation for optimal neuroendocrine signaling. Impaired ovarian function, irregular menstrual cycles, and an elevated risk of fertility issues are associated with deficiencies in vitamins (D, B-complex), minerals (iron, selenium, and zinc), and fatty acid intake. Diets rich in vegetables, whole grains, lean meats, and omega-3 PUFAs have been linked to improved *in vitro* fertilization (IVF) outcomes, such as higher

oocyte quality and embryo yields, confirming the concept that nutrition affects the ovarian microenvironment and hypothalamic-pituitary signaling. Mechanistically, nutrients affect insulin sensitivity, inflammatory cytokines, oxidative stress pathways, and adipokines (adiponectin, leptin), all of which influence the release of gonadotropin, the secretion of GnRH, and ovarian steroidogenesis [47,48].

#### 4.3.2 Nutraceuticals: Mechanistic Depth in Female Infertility

**4.3.2.1 Myo-inositol/D-chiro-inositol.** The stereoisomers of inositol, myo-inositol (MI) and D-chiro-inositol (DCI), function as intracellular second messengers for insulin and gonadotropin (FSH/LH) signaling. MI improves insulin sensitivity, lowers hyperinsulinemia, and attenuates ovarian androgen excess by modulating the PI3K/AKT pathway and promoting glucose transporter 4 (GLUT-4) translocation in granulosa and theca cells. In insulin signaling, MI functions as a secondary messenger by triggering the PI3K/AKT pathway, which phosphorylates and activates GLUT-4 vesicle transporters, leading to their translocation to the cell membrane. As a result, granulosa and theca cells exhibit increased glucose uptake, which reduces intracellular glucose accumulation and insulin resistance. Compensatory hyperinsulinemia is decreased, and ovarian androgen synthesis is subsequently reduced, as insulin amplifies LH-induced androgen production in theca cells. MI supplementation improves oocyte quality, increases ovulation rates, and lowers the requirement for exogenous FSH needed for IVF procedures. MI directly connects metabolic modulation to HPO axis correction at the neuroendocrine level by promoting follicular responsiveness to gonadotropins and restoring the FSH/LH ratio [36,37].

**4.3.2.2 Vitamin D.** In addition to maintaining calcium homeostasis, the active form of vitamin D binds to the vitamin D receptor (VDR), which is expressed in the pituitary, ovarian, and hypothalamic tissues. It decreases the expression of pro-inflammatory cytokines (IL-6, TNF- $\alpha$ ), increases insulin receptor substrate-1 (IRS-1), and supports PI3K/AKT signaling. It also modifies the activity of aromatase (CYP19A1) and 3 $\beta$ -HSD. Low vitamin D levels are associated with reduced ovarian reserve and poorer fertility outcomes. Both mechanistic and observational data support a modulatory role of vitamin D in neuroendocrine-ovarian axis function, although large randomized controlled trials (RCTs) are still warranted [38].

**4.3.2.3 Omega-3 PUFAs.** The primary dietary omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), inhibit the NF- $\kappa$ B pathway and interact with G-protein coupled receptor 120 (GPR120) and peroxisome proliferator-activated receptors (PPARs). By blocking IKK activation and preventing NF- $\kappa$ B nuclear translocation, eicosapentaenoic acid (EPA) and DHA activate GPR120

and PPARs, which lower the production of inflammatory cytokines, enhance insulin signaling, and support ovarian and metabolic function. Omega-3 fatty acids help restore appropriate hypothalamic leptin/kisspeptin signaling and promote steroidogenic homeostasis by lowering systemic and ovarian inflammation, improving lipid profiles, and increasing insulin sensitivity. Although causality has not been established, reviews indicate links between omega-3 intake and improved reproductive markers in women undergoing fertility treatment [39].

**4.3.2.4 Antioxidants and Mitochondrial Protectors (N-acetylcysteine, CoQ10, Melatonin, Vitamins C/E).** Oxidative stress and mitochondrial dysfunction are major threats to oocyte quality, as they hinder meiotic spindle formation, increase DNA damage, and diminish embryo competence. Vitamins C and E restore antioxidant capacity; melatonin acts as a direct free radical scavenger and modulates circadian steroidogenic rhythms; coenzyme Q10 (CoQ10) increases mitochondrial respiratory chain efficiency; N-acetylcysteine (NAC) replenishes glutathione and inhibits NF- $\kappa$ B, improving insulin sensitivity. In assisted reproduction settings, antioxidant supplementation is associated with improved fertilization rates and embryo quality [40].

**4.3.2.5 Micronutrients (Zinc, Folate/B-Vitamins, Iron, Selenium).** Chromatin stability, DNA methylation, oocyte maturation, and embryo development are maintained by vital trace elements and vitamins. Iron and selenium regulate oxidative status and interactions between the thyroid and reproductive axis; zinc is essential for meiotic progression and antioxidative enzyme activity; folate and B vitamins regulate one-carbon metabolism and epigenetic programming of genes involved in GnRH regulation and steroidogenesis. A lower ovarian reserve, a higher risk of miscarriage, and poor embryo quality are associated with suboptimal micronutrient status [41].

**4.3.2.6 Polyphenols and Botanical Adaptogens.** Polyphenols with pleiotropic effects on metabolic and neuroendocrine pathways include quercetin, curcumin, and resveratrol. These compounds exert dual regulation of metabolic homeostasis and hypothalamic-pituitary signaling by activating SIRT1 and Nrf2, downregulating mTOR and NF- $\kappa$ B, and modulating the expression of kisspeptin-1 (KISS1) and GnRH genes. Beyond polyphenols, emerging botanical adaptogens such as *Asparagus racemosus* (Shatavari), *Lepidium meyenii* (Maca), and *Withania somnifera* (Ashwagandha) have been shown to exert fertility-restoring effects by modulating the HPA and HPO axes. They align stress management with reproductive recovery by lowering circulating cortisol, increasing gonadotropin receptor expression, and improving ovarian responsiveness. Taken together, these bioactives illustrate how nutraceuticals

tics can synchronize metabolic, endocrine, and stress-adaptive pathways that are essential for female fertility [42,49].

#### 4.3.3 Dietary Patterns in Female Fertility Regulation

4.3.3.1 Mediterranean Diet (MD). Improved fertility outcomes have most consistently been linked to the MD, which is rich in fruits, vegetables, legumes, whole grains, nuts, extra-virgin olive oil, moderate amounts of fish, and low amounts of red meat. Higher adherence to the MD is associated with higher rates of clinical pregnancy and embryo implantation in women undergoing assisted reproductive technologies (ART), especially in younger cohorts. Mechanistically, its high concentration of antioxidants, polyphenols, and omega-3 fatty acids lowers oxidative stress, improves insulin sensitivity, and modulates inflammatory cytokines (TNF- $\alpha$ , IL-6), which in turn increases endometrial receptivity and ovarian steroidogenesis. Adherence to a Mediterranean-style diet has been linked to improved ovulatory and metabolic profiles in women with PCOS. These effects are likely due to the activation of the AMPK and PI3K/AKT pathways and the suppression of NF- $\kappa$ B-mediated inflammation [50,51].

4.3.3.2 Low-Glycemic (GI) and Dietary Approaches to Stop Hypertension (DASH) Diets. In women with insulin resistance, low-GI diets that prioritize whole grains, legumes, and minimal amounts of refined sugars improve insulin dynamics and restore ovulatory cycles. After 12 weeks of a low-GI diet, randomized trials in PCOS patients show improved LH/FSH ratios, decreased fasting insulin, and increased ovulation frequency. This is explained by downstream modulation of insulin receptor/IRS-1/PI3K-AKT signaling, which promotes follicular growth and decreases the production of androgen by theca cells. Similarly, women with reproductive endocrine disorders who follow the Dietary Approaches to Stop Hypertension (DASH) diet, which is low in saturated fats and rich in fruits, vegetables, and low-fat dairy, have shown improved hormonal profiles and decreased inflammatory biomarkers [52,53].

4.3.3.3 Plant-Based and Anti-Inflammatory Diets. Recent studies also suggest that plant-forward or anti-inflammatory diets, which are high in antioxidants, fiber, and phytonutrients, can improve fertility. By fostering microbial diversity and gut-brain-ovary axis communication, these diets reduce oxidative load and systemic inflammation, two factors that significantly impair hypothalamic GnRH pulsatility. Foods rich in polyphenols, like soy, berries, and green tea, are especially noteworthy for their ability to modulate the SIRT1, Nrf2, and NF- $\kappa$ B pathways, which protect oocytes from oxidative damage. Higher adherence to an anti-inflammatory diet score is associated with better levels of anti-Müllerian hormone (AMH) and estradiol, as well as

a lower prevalence of anovulatory cycles, according to observational studies in infertile women [54].

#### 4.4 Diagnostic and Therapeutic Perspectives

##### 4.4.1 Diagnostic Markers (Kisspeptin, AMH, Leptin, LH/FSH Ratio, Nutrient Biomarkers)

Recent biomarker panels for evaluating female reproduction include metabolic signals and neuropeptides in addition to conventional hormones. AMH remains the most widely used indicator of ovarian reserve and response in assisted reproduction; however, its interpretation depends on several factors, including age, assay, and clinical context [55]. Recent research has indicated that serum kisspeptin, a direct regulator of GnRH neurons, may serve as a useful marker for neuroendocrine evaluation, reflecting hypothalamic-pituitary integrity and early pregnancy outcomes [56]. An elevated LH:FSH ratio remains a useful indicator of neuroendocrine imbalance in PCOS, despite interindividual variability. Adipokines, such as leptin, reflect energy status and are consistently elevated in PCOS, connecting metabolic phenotype with ovarian dysfunction [57]. Lastly, circulating nutrient biomarkers, such as omega-3 fatty acid profile and 25-hydroxyvitamin D (25-OH D), offer objective assessments of nutritional status that correlate with ovarian function and ART outcomes. These measures can also be used in conjunction with endocrine panels [58].

##### 4.4.2 Nutritional Diagnostics (Serum Vitamin D, Omega-3 Index)

Because vitamin D status influences ovarian steroidogenesis, AMH, and implantation biology, measurement of serum 25-OH D is a useful diagnostic tool in infertility clinics. Although conclusive RCT evidence is still limited, both observational and interventional studies have reported associations between higher 25-OH D levels and improved IVF/ART parameters. An objective measure of anti-inflammatory lipid status can be obtained from the omega-3 index (erythrocyte EPA+DHA%) or serum long-chain omega-3 levels. In certain ART cohorts, higher maternal omega-3 status has been linked to lower pregnancy loss and improved live birth probabilities. Incorporation of these nutrient biomarkers into preconception evaluations provides a quantifiable target for corrective nutritional interventions [58,59].

##### 4.4.3 Nutraceutical Formulations and Precision Nutrition

Patient stratification and meticulously developed nutraceutical formulations are necessary to translate single-agent evidence into clinical practice. By customizing interventions to metabolic and inflammatory profiles (e.g., insulin-resistant vs. inflammatory phenotypes), precision nutrition approaches, which combine diet, targeted supplements, and individual phenotype or genotype data, have shown early promise in improving fertility endpoints. While individualized dietary plans and customized nu-

nutraceutical combinations represent the obvious next step in improving reproductive outcomes, narrative and systematic reviews emphasize the need for carefully controlled trials to determine the best formulations, dosages, and treatment windows [60].

#### 4.4.4 Potential of Molecular and Artificial Intelligence (AI)-Based Screening Tools

AI and ML algorithms, as well as molecular mapping approaches, including pathway and PPI analyses, are quickly emerging as screening and prioritization tools in reproductive medicine. While AI models trained on clinical, biochemical, and imaging data have shown early success in risk stratification, embryo selection, and outcome prediction in ART, network-based approaches can identify convergent molecular hubs (e.g., PI3K/AKT, mTOR, NF- $\kappa$ B, SIRT1) that are susceptible to nutritional modulation, guiding rational nutraceutical selection. The scalable, data-driven pipelines for precision nutrition and therapeutic screening enabled by these technologies necessitate transparent validation and prospective testing prior to routine clinical deployment [61].

#### 4.5. Limitations

Although several nutrients show promising benefits for reproductive function, the available evidence is limited by the scarcity of large, multicenter clinical trials. Variability in population characteristics, including ethnicity, age, and baseline metabolic status, further influence outcomes and limits generalizability. Many findings derive from small human cohorts, animal models, or short-term interventions, which restrict the generalizability of nutrient–neuroendocrine interactions in female fertility. Additionally, multi-omics datasets used for pathway enrichment and molecular network interpretations remain incomplete, and gene–nutrient associations may vary across populations, age groups, and infertility etiologies. As high-throughput technologies continue to evolve, larger, well-controlled clinical and transcriptomic studies are required to validate emerging mechanistic insights and strengthen the translational relevance of the pathways discussed in this review.

## 5. Conclusions

Female infertility arises from a complex network involving ovarian function, metabolic homeostasis, nutritional status, and neuroendocrine signaling from the brain. The “brain-to-ovary” continuum emphasizes that restoring fertility requires the modulation of the neuroendocrine and metabolic axes that control reproductive organs, rather than focusing solely on the organs themselves. This review integrates mechanistic and translational evidence supporting the ability of nutrients and nutraceuticals to alter reproductive physiology at both the central and peripheral levels. Key intracellular pathways that regulate ovarian steroidogenesis and oocyte competence, including

PI3K/AKT/mTOR, NF- $\kappa$ B, and SIRT1, are influenced by nutritional factors that alter GnRH pulsatility, insulin and leptin signaling, mitochondrial function, and redox balance. Complementary *in silico* network analysis further highlights convergent molecular hubs—such as *AKT1*, *mTOR*, *ESR1*, *SIRT1*, *NFKB1*, and *PPARG*—as potential nutrient-responsive targets that integrate hormone signaling, inflammation, and energy sensing. These findings suggest that next-generation, AI-guided nutraceutical formulations for fertility restoration may be developed through the strategic nutritional modulation of these pathways. Together, the synthesis provided here creates a framework for managing infertility holistically by bridging the gap between neuroendocrine biology and nutritional therapies. Future directions should focus on the use of *in silico* and AI tools to accelerate translational applications from bench to bedside, optimizing the bioavailability and dosage of nutraceuticals, and validating these molecular targets through clinical trials.

## Author Contributions

MN conceptualized the study, conducted the literature review, performed data curation and synthesis, and drafted the manuscript. BJ and RN supervised the study, contributed to the organization and critical revision of the review, and provided expert guidance. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

## Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI, GPT-5.3) for grammar checking and language polishing. After using this tool, the authors reviewed and edited the content manually and take full responsibility for the final text.

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