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Curcumin and Silymarin in Modern Medicine: A Comprehensive Review of Efficacy, Research Progress, and Clinical Challenges

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Abstract This medical review summarizes the efficacy and research progress of curcumin and silymarin. Both natural compounds demonstrate broad therapeutic potential across liver diseases, neurological disorders, cancer, and metabolic syndrome, supported by preclinical and clinical evidence. Curcumin and silymarin exhibit anti-inflammatory, antioxidant, and multi-pathway modulatory effects. Key challenges include poor bioavailability, which is being addressed through advanced formulations like nanoparticles and liposomes. Clinical trials show promise, particularly for liver conditions and metabolic syndrome, with evidence of synergistic effects when combined. However, further standardized, large-scale clinical trials are needed to fully establish their therapeutic protocols and long-term efficacy.

Silymarin is a complex mixture of flavonolignans extracted from the seeds of milk thistle (Silybum marianum), with its primary bioactive component being silybin (also known as silibinin)[9]. Curcumin, a polyphenol derived from the rhizome of turmeric (Curcuma longa), exhibits a broad spectrum of pharmacological activities including anti-inflammatory, antioxidant, antimicrobial, antidiabetic, and neuroprotective effects[10].

Keywords Curcumin; Silymarin; Hepatoprotection; Neuroprotection; Anticancer; Metabolic syndrome

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1. Introduction and Pharmacological Properties of Curcumin and Silymarin

1.1 Chemical Structures, Sources, and Basic Properties

Curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione) is a naturally occurring polyphenol molecule extracted from the rhizomes of turmeric (Curcuma longa L.), a member of the Zingiberaceae family. With a molecular formula of $C_{21}H_{20}O_6$ and molecular weight of 368.38 g/mol, curcumin exists as a crystalline yellow-orange compound with a melting point of 183°C[1]. Its chemical structure features two aromatic ring systems connected by a seven-carbon linker with an α,β-unsaturated β-diketone moiety, which exhibits keto-enol tautomerism. In turmeric, curcumin constitutes approximately 94% of curcuminoids, with demethoxycurcumin (6%) and bisdemethoxycurcumin (0.3%) as minor components[1].

Silymarin is a complex mixture of flavonolignans extracted from the seeds of milk thistle (Silybum marianum). The primary bioactive component is silybin (also known as silibinin), which has a molecular weight of 482.441 g/mol and is composed of taxifolin (a flavononol) linked to a phenylpropanoid unit[2]. Silymarin's chemical structure gives it highly hydrophobic and non-ionizable properties, with poor water solubility of less than 50 μg/mL[2].

1.2 Pharmacological Properties and Mechanisms of Action

Curcumin exhibits a broad spectrum of pharmacological activities including anti-inflammatory, antioxidant, antimicrobial, antidiabetic, neuroprotective, and anticancer properties[1]. Its mechanisms involve modulation of multiple cellular signaling pathways, binding to key molecules such as transcription factors, inflammatory mediators, and enzymes including protein kinase, reductase, and histone acetyltransferase. Curcumin selectively inhibits phosphorylase kinase, reduces glycogen metabolism, and alters proteasomal pathways[3].

Silymarin demonstrates potent antioxidant, anti-inflammatory, anti-fibrotic, anti-carcinogenic, neuroregenerative, and immunomodulatory effects[4]. Its antioxidant mechanisms include direct scavenging of reactive oxygen species (ROS) and activation of the transcription factor Nrf2, leading to increased expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1)[4]. Its anti-inflammatory action involves suppressing the expression of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 by inhibiting NF-κB and TLR4/NF-κB signaling pathways[4].**Pharmacokinetic Limitations and Bioavailability Challenges**

Both compounds face significant bioavailability challenges that limit their clinical efficacy. Their pharmacokinetic profiles are summarized below(1–5):

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Table 1

Parameter	Curcumin	Silymarin
Water Solubility	Poor (lipophilic, water-insoluble in acidic/neutral solutions)	Poor (<50 μg/mL)
Oral Bioavailability	0.16-1%	23–47%
Absorption	Poor intestinal absorption	20–50% absorption by GI tract
Metabolism	Rapid metabolism and systemic elimination	Extensive first-pass metabolism (55% by UGT isoforms, 28% by sulfation)
Plasma Concentrations	Low even at high doses	50–300 ng/mL active plasma concentrations
Tmax	Rapid absorption	6–8 hours
Elimination	Rapid systemic clearance	Mainly biliary route (<3% in urine)

Curcumin's limitations include poor water solubility, rapid degradation by autoxidation in aqueous solutions (half-life of 2.5 hours at pH 8), instability under alkaline conditions, and susceptibility to photodegradation[1]. Silymarin's challenges stem from its highly hydrophobic nature, low aqueous solubility (classified as a Biopharmaceutical Classification System (BCS) Class IV compound), and insufficient intestinal absorption[2] [5].

1.3 Formulation Advancements to Improve Bioavailability

To overcome these limitations, extensive research has focused on advanced drug delivery systems.Nanoparticle-Based Delivery Systems for Curcumin:

- Biodegradable nanoparticles using polysaccharides (e.g., chitosan, alginate), proteins (e.g., zein), and polymers enhance solubility and bioavailability[6].
- Nanoemulsions (20–500 nm droplet size) improve permeability and modify release profiles[6].
- Nanocrystals stabilized with surfactants like Tween 80 or Poloxamer 188 show low toxicity and high structural stability[6].
- Nano-micelles, such as cocrystal micelles for nose-to-brain delivery, are being explored to enhance brain distribution for neurodegenerative diseases[6].
- Solid lipid nanoparticles and nanostructured lipid carriers improve drug loading and enable sustained release[6].Liposomes (phospholipid bilayer carriers) enhance dissolution, bioavailability, and stability. For instance, milk fat globule membrane (MFGM) liposomes show superior encapsulation and stability compared to those made from soy phospholipids[6].
- Advanced Formulations for Silymarin:
- Self-emulsifying drug delivery systems (SMEDDS) have demonstrated a 3.6–4.1-fold increase in the

area under the curve (AUC) and a 4-fold increase in maximum plasma concentration (Cmax) in clinical studies[7].

- Nanocrystals increase surface area and dissolution rate, leading to a 1.5-fold increase in AUC in human studies[7].
- Solid dispersions with hydrophilic carriers like polyvinylpyrrolidone (PVP) or hydroxypropyl methylcellulose (HPMC) enhance wettability and dissolution, increasing oral bioavailability by 2.1–2.7-fold in animal models[7].
- Phytosomes/phospholipid complexes (e.g., Siliphos®) enhance lipophilicity and membrane permeability, showing a 4-fold increase in oral bioavailability[7].
- Cyclodextrin inclusion complexes increase solubility approximately 20-fold for hydroxypropyl-β-cyclodextrin (HP-β-CD) and improve oral bioavailability 2.0–2.1-fold in rats[7].
- Lipid nanoparticles, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), provide an 8-fold enhancement in oral bioavailability with a longer half-life for NLCs[7].
- Liposomes demonstrate a 34-fold higher oral bioavailability and increased hepatoprotective activ-ity[7].
- Metal–organic frameworks (MOFs) show promise, with a 4.2-fold increase in plasma levels and substantial prevention of chemically induced hepatic injury in preclinical models[8].

These formulation strategies are critical for translating the promising pharmacological properties of curcumin and silymarin into effective clinical therapies[1][8].

2. Hepatoprotective Efficacy in Liver Diseases

The hepatoprotective properties of curcumin and silymarin have been extensively studied across various liver conditions, including non-alcoholic fatty liver disease (NAFLD/metabolic dysfunction-associated steatotic liver disease, MASLD), alcoholic liver disease, drug-induced hepatotoxicity, and viral hepatitis. Clinical evidence demonstrates their therapeutic potential, with emerging data suggesting synergistic benefits when used in combination.Clinical Evidence for Curcumin in Liver Diseases

Clinical trials support curcumin's efficacy in improving liver health markers. A 4-week study involving patients with NAFLD found that curcuminoids significantly improved liver enzyme indicators and serum lipid levels[11]. More robust, long-term evidence comes from a 180-day randomized, double-blind, placebo-controlled trial of a multi-ingredient nutraceutical containing curcumin, dandelion, milk thistle, and ginger in healthy participants. The group receiving the active supplement showed significant improvements in key liver function tests compared to the placebo group, which experienced numerical increases in liver enzyme levels[12].

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Table 2

Parameter	Test Product (Mean Change)	Placebo (Mean Change)	p-value
ALT	-6.0 ± 5.2 IU/L	+10.6 ± 15.0 IU/L	< 0.001
AST	-6.5 ± 11.0 IU/L	+4.2 ± 11.7 IU/L	< 0.001
ALP	+2.3 ± 28.5 U/L	+15.6 ± 30.5 U/L	0.01
GGT	-4.0 ± 19.8 IU/mL	+9.8 ± 19.6 IU/mL	< 0.001

The study's discussion attributes these improvements to curcumin's hepatoprotective activity, suggesting it may improve hepatic steatosis and block disease progression by inhibiting fatty acid synthesis and the biosynthesis of unsaturated fatty acids[12].

2.1 Clinical Evidence for Silymarin in Liver Diseases

Silymarin's clinical efficacy varies significantly depending on the liver condition. For alcoholic liver disease, a controlled, double-blind, randomized multicenter trial found that silymarin showed no significant benefit on survival or disease progression in patients with alcoholic cirrhosis[13]. In viral hepatitis, systematic reviews indicate limited efficacy; while it may reduce serum transaminase levels, it does not impact viral load or liver histology[14]. However, one study in patients with advanced hepatitis C-related liver disease suggested silymarin use was associated with reduced histological progression from fibrosis to cirrhosis, though no effect was observed on clinical outcomes[15].

For NAFLD, the ongoing SILIVER trial (NCT03749070) is a 12-week randomized, double-blind study investigating the efficacy of 700mg silymarin combined with vitamin E and phosphatidylcholine, with the primary outcome being a change in NAFLD degree assessed by computed tomography[8].

2.2 Synergistic Potential of Combination Therapy

Emerging evidence highlights the promise of combining curcumin and silymarin. The aforementioned 4-week NAFLD trial found that both compounds, particularly in combination, demonstrated significant therapeutic effects, including antioxidant, antimicrobial, and anticancer potential[11]. Preclinical studies strongly support this synergy. In a mouse model of NAFLD, a combination of antarctic krill oil, curcumin, and silymarin significantly inhibited high-fat diet-induced disease by regulating genes involved in triglyceride synthesis and fatty acid metabolism, reducing inflammation, and enhancing antioxidant capacity[17]. Another study noted that a dietary supplement containing curcumin and silymarin, among other ingredients, prevented both NAFLD and atherosclerosis in mice fed a high-fat diet[18].

2.3 Mechanisms of Action Specific to Liver Protection

The hepatoprotective effects of these compounds are mediated through distinct pathways relevant to liver pathology:

- Curcumin counteracts the oxidative stress and lipid peroxidation fundamental to liver injury by neutralizing free radicals like reactive oxygen species (ROS). It also regulates cellular responses to

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prevent damage from protein misfolding and DNA damage, and influences molecular pathways related to inflammation and apoptosis[19].

- Silymarin exerts its effects primarily through free radical scavenging and membrane stabilization of hepatocytes. It also promotes liver regeneration and inhibits fibrosis progression[9].

A significant challenge for both compounds is poor bioavailability. Curcumin has low water solubility and rapid metabolism[10], while silymarin's clinical efficacy is limited by poor water solubility, prompting research into enhanced formulations[20]. The evidence suggests that curcumin and silymarin are most promising for metabolic liver conditions like NAFLD, where their complementary mechanisms targeting oxidative stress, inflammation, and lipid metabolism exert additive therapeutic effects.

3. Neuroprotective Effects in Neurological Disorders

3.1 Overview

Both curcumin and silymarin have demonstrated neuroprotective potential in preclinical and clinical studies, with particular relevance to neurodegenerative diseases, mood disorders, and other central nervous system (CNS) pathologies. Their effects are primarily mediated through anti-inflammatory, antioxidant, and protein aggregation-modulating activities.

3.2 Molecular Mechanisms of Neuroprotection

Curcumin's Multifaceted Neuroprotective Pathways

Curcumin exerts neuroprotective effects through a multi-targeted approach. A key mechanism involves the inhibition of the HDAC6–NLRP3 inflammasome pathway, which alleviates neuronal degeneration in Parkinson's disease (PD) models by reducing neuroinflammation[21]. Its broad anti-inflammatory action extends to suppressing spinal neuroinflammation by modulating astroglial activity[22]. Furthermore, curcumin influences neurotrophic factors; clinical evidence indicates it can restore brain-derived neurotrophic factor (BDNF) levels in conditions like Alzheimer's disease (AD) and depression[23]. These combined actions on inflammation, epigenetic regulation, and neurotrophic support underpin its therapeutic potential in neurological disorders.

Silymarin's Neuroprotective Mechanisms

Silymarin is recognized as a potential neuroprotective agent for neurodegenerative conditions including AD and PD[[24],[25]]. Its primary mechanisms involve potent antioxidant activity, inhibition of pathological protein aggregation (such as amyloid-β and α-synuclein), and anti-inflammatory effects[[26],[27]]. By reducing oxidative stress and modulating inflammatory pathways, silymarin helps protect neuronal cells from damage and death, which are hallmarks of diseases like AD[[26]].

3.3 Clinical Evidence in Specific Neurological Conditions

Alzheimer's Disease (AD)

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Clinical surveys support the potential usefulness of curcumin in AD and dementia, attributed to its anti-inflammatory and anti-aggregation properties[28]. For silymarin, while numerous preclinical studies demonstrate efficacy, clinical research in AD is still emerging, though its pharmacological activity in the nervous system is promising[19].

Parkinson's Disease (PD)

In PD, curcumin's efficacy is linked to its specific inhibition of NLRP3-mediated neuroinflammation, as shown in preclinical models[21]. Silymarin's role in neuroprotection and symptom management in PD is an active area of investigation, with clinical trials underway to evaluate its effects[29].

Depression and Mood Disorders

Curcumin shows therapeutic promise in depression, with clinical studies reporting its ability to modulate BDNF levels and other neurochemical pathways[23]. Silymarin's mechanisms also suggest protective effects against depression, likely through its modulation of oxidative stress and inflammatory pathways[24].

3.4 Comparative Analysis of Neuroprotective Properties

Table 3

Parameter	Curcumin	Silymarin
BBB Penetration	Demonstrated ability to cross the blood-brain barrier (BBB)	Evidence of neuroprotective effects suggests CNS activity, though direct BBB penetration data is less extensive
Primary Mechanisms	HDAC6–NLRP3 inflammasome inhibition, BDNF modulation, broad anti-inflammatory action	Antioxidant activity, inhibition of pathologic protein aggregation, anti-neuroinflammatory effects

4. Anticancer Properties and Clinical Applications

4.1 Molecular Mechanisms of Anticancer Activity

Curcumin and silymarin exhibit multifaceted anticancer mechanisms targeting multiple hallmarks of cancer, including uncontrolled proliferation, apoptosis evasion, and metastasis. Their primary activities are rooted in potent antioxidant and anti-inflammatory effects, which disrupt the tumor-promoting microenvironment.

Curcumin's Anticancer Mechanisms

Curcumin demonstrates a broad spectrum of anticancer activity by modulating numerous signaling pathways. It acts as an antioxidant and anti-inflammatory agent, and induces apoptosis in cancer cells[30]. Its molecular targets include immune mediators and key oncogenic pathways such as NF-κB[31]. Specific growth-inhibitory effects in breast cancer cells involve arresting the MAPK and NF-κB pathways[32]. These multi-targeted actions underpin its chemopreventive and therapeutic potential.

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Silymarin's Antitumor Pathways

Silymarin, and its active constituent silibinin, exhibits cancer chemopreventive properties by targeting fundamental cellular processes. Its mechanisms include regulating the cell cycle, modulating apoptosis, and inhibiting inflammatory and metastatic processes[33]. These effects are mediated through key signaling pathways involving p53, Akt, and caspases[34].

4.2 Clinical Trial Evidence Across Cancer Types

Clinical investigations into these compounds span several cancer types, with varying levels of evidence

Breast Cancer

Clinical trials indicate that curcumin can halt disease progression and lower tumor markers when used alongside chemotherapy agents like docetaxel[35]. Preclinical studies have consistently shown curcumin's efficacy against breast cancer models[36].

Prostate Cancer

Curcumin shows promise for improving prostate cancer treatment by targeting critical pathways and potentially enhancing conventional therapies[37]. A systematic review identified 22 studies on curcumin in prostate cancer, and ongoing clinical trials, such as NCT03769766, are prospectively evaluating whether curcumin can reduce cancer progression in patients with low-risk disease[38]. Another trial, NCT01740323, is a Phase II study investigating whether curcumin reduces NF-κB DNA binding and its downstream mediator IL-6 in patients[39].

Colorectal and Liver Cancers

Preclinical evidence supports curcumin's efficacy in colorectal cancer, with studies showing it impedes the growth of xenograft tumors in mice[40]. Synergistic effects have been observed when colon cancer cells are treated with a combination of curcumin and silymarin[41]. For liver cancer, while specific clinical trial data is limited, the established hepatoprotective and anticancer potential of both compounds against liver and colorectal cancers suggests a relevant clinical application[11].

4.3 Combination Therapy and Chemoprotection

A significant area of interest is the use of these compounds alongside conventional cancer treatments.

Enhancing Chemotherapy and Reducing Toxicity

Silymarin shows clinical promise as an adjunct to mitigate toxicity induced by chemotherapy and radiotherapy[33]. Both curcumin and silymarin exhibit potential to enhance chemotherapy efficacy, overcome drug resistance, and provide organ-protective benefits[42].

Synergistic Interactions

Research indicates that curcumin and silymarin may act synergistically. They share molecular targets, such as the NF-κB pathway, to alleviate inflammation, which is a common mechanism in their anticancer action[43]. This shared pathway suggests potential for combined therapeutic strategies in oncology.

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4.4 Clinical Translation: Challenges and Advances

The transition from promising preclinical data to clinical utility faces significant hurdles, primarily concerning bioavailability.

Bioavailability Limitations

The clinical application of curcumin is restricted by its poor solubility, rapid metabolism, and consequent low bioavailability, necessitating advanced delivery systems for therapeutic efficacy[30]. Similarly, silymarin's clinical use is hindered by poor water solubility and low bioavailability[20].

Advanced Formulation Strategies

To overcome these barriers, nanoformulations are being actively developed. For silymarin, nanoformulations enhance drug delivery and tumor targeting potential[44]. For curcumin, formulations like Lipocur™ (liposomal curcumin) and Sinacurcumin® (nanomicellar) have demonstrated improved bioavailability and antitumor activity in clinical trials[45].

Safety Profiles

Both compounds are generally well-tolerated with minimal toxicity, contributing to their reliable therapeutic profile[9]. However, further studies are needed to fully elucidate long-term safety in diverse cancer patient populations.

4.5 Comparative Analysis of Anticancer Properties

Table 4

Aspect	Curcumin	Silymarin
Primary Mechanisms	Antioxidant, anti-inflammatory, apoptosis induction, multi-pathway inhibition (e.g., NF-κB, MAPK)	Cell cycle regulation, apoptosis modulation, anti-inflammatory, anti-metastatic activity
Clinical Evidence Level	Moderate (clinical trials in breast, prostate, and other cancers)	More limited; stronger preclinical evidence, with clinical promise as a chemoprotectant
Major Limitation	Poor bioavailability	Poor water solubility and bioavailability

Therapeutic Potential in Metabolic Syndrome

Metabolic syndrome (MetS) is a cluster of interconnected cardiometabolic risk factors, including insulin resistance, dyslipidemia, hypertension, and central obesity. Both curcumin and silymarin have demonstrated therapeutic potential across these components through distinct yet complementary mechanisms, supported by a growing body of clinical evidence.

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4.6 Effects on Insulin Resistance and Glucose Metabolism

Clinical trials and meta-analyses confirm that both compounds significantly improve insulin sensitivity and glycemic control in patients with MetS or type 2 diabetes. Curcumin supplementation has been shown to reduce fasting blood glucose, hemoglobin A1c (HbA1c), and insulin resistance as measured by the homeostatic model assessment (HOMA-IR)[46]. These improvements appear more pronounced with bioavailability-enhanced curcumin formulations, which overcome the compound's inherent poor absorption[47].

Similarly, silymarin exhibits robust glucose-lowering effects. A meta-analysis of clinical trials found that silymarin significantly reduced fasting blood glucose and HbA1c levels in patients with glucose/lipid metabolic disorders[48]. The underlying mechanisms involve modulation of insulin signaling pathways, enhancement of peripheral glucose uptake, and protection of pancreatic β-cells from oxidative stress[49].

4.7 Lipid Profile Improvement

Both agents positively influence dyslipidemia, a core component of MetS, though their efficacy profiles differ slightly.

Table 5

Parameter	Curcumin Effects	Silymarin Effects
Total Cholesterol	Significant reduction demonstrated in meta-analyses	Significant reduction in systematic reviews
Triglycerides	Marked reduction in multiple trials	Significant improvement, particularly in MASLD patients
LDL Cholesterol	Variable effects across studies	Significant reduction in meta-analyses
HDL Cholesterol	Moderate improvement in some studies	Significant increase demonstrated in clinical research

Silymarin shows a particularly consistent effect across all lipid parameters[48], while curcumin's most robust and consistent effect is on triglyceride reduction[46].

4.8 Impact on Obesity-Related Parameters and Adipokine Regulation

Curcumin demonstrates more substantial effects on body composition and adipokine profiles compared to silymarin. Meta-analyses indicate that curcumin intake leads to significant reductions in body mass index (BMI), body weight, and waist circumference[50]. It also favorably modulates adipokines, increasing serum adiponectin (an insulin-sensitizing hormone) and decreasing leptin levels[51]. The increase in adiponectin is notable even with unformulated curcumin, suggesting biological activity despite bioavailability challenges[51].

In contrast, silymarin's effects on anthropometric measures like BMI are generally non-significant in

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systematic reviews, despite its metabolic benefits[52]. However, it shows specific efficacy in reducing hepatic fat accumulation, a common comorbidity in obese patients with MetS[53].

Blood Pressure Regulation and Anti-Inflammatory Effects

Both compounds exhibit modest effects on blood pressure, with more consistent evidence for curcumin. Curcumin supplementation has been associated with significant reductions in diastolic blood pressure, though effects on systolic pressure are more variable[46]. These antihypertensive effects are linked to improved endothelial function and reduced vascular inflammation.

A key shared mechanism is the reduction of systemic inflammation, a driver of MetS progression. Both curcumin and silymarin significantly lower levels of inflammatory markers such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α)[[46],[49]]. This anti-inflammatory action contributes to their overall cardioprotective potential.

4.9 Synergistic Potential in Combination Therapy

Emerging evidence suggests that combining curcumin and silymarin may yield synergistic benefits, especially for hepatic manifestations of MetS like MASLD. A 4-week clinical trial in patients with NAFLD found that the combination of curcuminoids and silymarin produced greater improvements in liver enzyme levels and serum lipids than either agent alone[11]. Preclinical studies also support this synergy; a mixture of krill oil, curcumin, and silymarin significantly inhibited diet-induced NAFLD in mice by regulating genes involved in lipid metabolism and enhancing antioxidant capacity[17].

The differential strengths of each compound suggest a rational basis for combination:

- Curcumin appears more effective for improving systemic insulin sensitivity, reducing body weight, and modulating adipokines.
- Silymarin shows greater potency for hepatoprotection, transaminase reduction, and consistent lipid profile improvement.

For clinical use, recommended daily doses range from 500–2000 mg/day for standardized curcumin extracts, and 140–420 mg/day for standardized silymarin extracts[52]. Treatment durations of at least 8–12 weeks are needed for measurable metabolic benefits, with longer durations (24+ weeks) potentially yielding more substantial effects, particularly on hepatic parameters.

Both compounds have excellent safety profiles with minimal adverse effects at recommended doses. Gastrointestinal discomfort is occasionally reported with curcumin supplementation.

Current evidence is constrained by heterogeneity in study designs, variability in formulations and dosages, and often short trial durations. The critical influence of formulation on curcumin's bioavailability makes cross-study comparisons challenging[54]. Future high-quality, long-term randomized controlled trials with standardized, high-bioavailability formulations are needed to definitively establish their roles in MetS management and to explore optimal combination protocols.

In summary, curcumin and silymarin offer a multi-targeted, natural approach to mitigating MetS. Their

actions span improving glycemic control, correcting dyslipidemia, reducing inflammation, and—in combination—potentially addressing associated hepatic steatosis, thereby contributing to comprehensive cardiovascular risk reduction.

5. Evidence-Based Recommendations for Clinical Practice

Given the current evidence, the following cautious, evidence-informed recommendations can be made:

Liver Diseases (NAFLD/MASLD): Curcumin and silymarin, individually or in combination, can be considered as supportive adjuncts to lifestyle intervention. Treatment initiation earlier in the disease course may be more beneficial, and liver function tests should be monitored regularly[[11],[12]].

- **Neurological Disorders**: Curcumin's multi-target neuroprotective mechanisms support its exploration in neurodegenerative conditions. Silymarin shows preclinical promise for Alzheimer's and Parkinson's diseases, but its clinical application in neurology awaits further validation from large-scale randomized controlled trials[[24],[26]].
- **Cancer**: Both agents are primarily positioned as supportive therapies. They may help mitigate chemotherapy-induced toxicity and, based on preclinical evidence, could potentially enhance the efficacy of conventional treatments or overcome drug resistance[[33],[42]]. Their use alongside standard oncology care should be managed with awareness of possible drug-drug interactions.
- **Metabolic Syndrome**: Curcumin supplementation may offer benefits for improving insulin sensitivity and dyslipidemia, though clinical results vary by formulation[[46],[47]]. Silymarin also shows potential for improving glycemic parameters in metabolic conditions[48].

A critical general consideration is the selection of formulations with proven enhanced bioavailability. Dosing should align with the protocols used in positive clinical studies, and patients should be monitored appropriately, especially during long-term use or when taking other medications.

6. Conclusion

Curcumin and silymarin are promising natural compounds with pleiotropic pharmacological effects relevant to liver disease, neurological disorders, cancer, and metabolic syndrome. Their excellent safety profiles make them attractive candidates for integrative therapeutic approaches. However, their widespread clinical adoption is currently hampered by bioavailability challenges, a lack of product and protocol standardization, and sometimes inconsistent clinical trial data.

The path forward lies in the convergence of pharmaceutical science—developing reliable, advanced-delivery formulations—and rigorous clinical research through well-designed, large-scale, standardized trials. As these efforts progress, curcumin and silymarin are poised to transition from traditional herbal remedies to valuable components of evidence-based, complementary medicine, offering multi-target therapeutic strategies with favorable safety margins.

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Feline Myelodysplastic Syndrome: A Case Report

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Abstract: Myelodysplastic syndrome (MDS) is a rare heterogeneous myeloid clonal disorder originating from hematopoietic stem cells, with weakness and anemia as the most common clinical signs. Owing to the dysplasia of myeloid precursor cells, MDS is frequently characterized by pancytopenia and a history of chronic non-regenerative anemia, which can be fatal in severe cases.Due to the insufficient understanding of myelodysplastic syndrome (MDS) and the high difficulty in its definitive diagnosis, affected animals often require frequent blood transfusions for supportive maintenance during treatment. Early definitive diagnosis and treatment of MDS can significantly reduce the frequency of blood transfusions, alleviate the pressure on pet owners, and prolong the survival time of affected animals.We herein report a case of feline myelodysplastic syndrome (MDS), with the aim of providing clinical diagnostic and therapeutic insights for veterinarians.

Key words：myelodysplastic syndrome（MDS）；non-regenerative anemia；bone marrow cytology；azacitidine

Myelodysplastic syndrome (MDS), also known as primary myelodysplasia, is a heterogeneous group of rare diseases affecting young to middle-aged animals, and is considered as a pre-leukemic condition. Affected animals present with clinical signs including fever, weakness, severe non-regenerative anemia, and/or thrombocytopenia, and/or leukopenia, and may progress to acute leukemia[1]. The pathogenesis of this disease remains poorly understood; potential underlying causes include monoclonal proliferation of hematopoietic stem cells, as well as impaired differentiation and maturation of bone marrow progenitor cells. Currently, there is no standard treatment protocol for this disease, which carries a poor prognosis, with most affected animals having a short survival time.

Azacitidine is a demethylation inhibitor, which exerts its pharmacological effects by interfering with the activity of RNA transcription enzymes and DNA methyltransferase 1 (DNMT1). It is currently used in human clinical practice to prolong the survival time of patients with myelodysplastic syndrome (MDS). In this study, a case of feline MDS was treated with a combination regimen of azacitidine and prednisolone, and the treatment process was analyzed, with the aim of investigating the clinical efficacy of azacitidine in feline MDS.

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1. Case Presentation

1.1 Signalment

A 4-year-old spayed female Domestic Shorthair (DSH) cat, weighing 3.27 kg, with up-to-date vaccinations and regular parasite prevention.

1.2 History

The cat had a history of severe non-regenerative anemia. It was previously treated at an external hospital for suspected feline leukemia virus (FeLV) infection and cytauxzoonosis, with medications including prednisolone [2 mg/(kg·*d*)], cyclosporine [8 mg/(kg·*d*)], atovaquone [52 mg/(kg·*d*)], azithromycin [10 mg/(kg·*d*)], doxycycline, erythropoietin (EPO), a commercial pet hematopoietic supplement (Buxue Gan Jing), vitamin B12, and zidovudine [11 mg/(kg·*d*)], but no satisfactory therapeutic response was achieved. The cat received 3 blood transfusions within the past month, and was subsequently referred to our hospital for further treatment.

2. Physical Examination

The cat presented in good mental condition with a body temperature of 39.4℃, heart rate of 150 beats/min, respiratory rate of 34 breaths/min, body condition score (BCS) of 2/5, and 6% dehydration. Mucous membranes were pale, and capillary refill time (CRT) was less than 2 seconds. The cat showed normal appetite and water intake, with unremarkable urination and defecation.

3. Diagnosis

3.1 Complete Blood Count

The packed cell volume (HCT) was 11.3% (reference range: 30.3%–52.3%), reticulocyte count was 1.8×10^9/L (reference range: 3–50×10^9/L), and total platelet count was 99×10^9/L (reference range: 151–600×10^9/L), indicating severe non-regenerative anemia. The corrected total white blood cell count was 8.85×10^9/L (reference range: 2.87–17.02×10^9/L). Manual differential counting of blood smears revealed segmented neutrophils accounting for 81%, band neutrophils 2%, and lymphocytes 17%. All leukocyte subsets except band neutrophils fell within normal reference ranges. Eight nucleated red blood cells were observed per 100 white blood cells counted.

3.2 Serum Biochemistry

No significant abnormalities were detected via IDEXX 10-item serum biochemistry panel.

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3.3 Bone Marrow Cytology

Bone marrow aspiration was performed at the femoral trochanteric fossa, and multiple cytological smears were prepared for differential counting of 500 bone marrow nucleated cells. All bone marrow smears demonstrated consistent findings with high cellularity and significant hemodilution. Scant bone marrow particles were visible with myeloid hyperplasia (hematopoietic cells >75%, adipocytes <25%); bone marrow particles are shown in Figure 1. The differential count of 500 nucleated cells yielded the following results:

- Erythroid series (45.5%): orthochromatophilic normoblasts 14%, polychromatophilic normoblasts 17.5%, basophilic normoblasts 11%, rubriblasts 3%. Rubriblasts in the cat's bone marrow are presented in Figure 2.
- Myeloid series (31.5%): segmented neutrophils 18%, band neutrophils 3%, metamyelocytes 2%, myelocytes 0%, promyelocytes 1%, myeloblasts 7.5% (13.6% of non-erythroid nucleated cells).
- Lymphocytes: 21%
- Monocytes: 2%
- The myeloid-to-erythroid (M:E) ratio was decreased at approximately 1:1.43 (feline normal reference range: 1.21–2.16), accompanied by erythroid hyperplasia. Myeloid precursor cells were diminished with incomplete maturation stages. Erythroid precursors were markedly increased (Figure 3); although maturation stages were complete, disordered erythropoiesis was evident. Binucleation (Figure 4), megaloblastoid change, and asynchronous nuclear-cytoplasmic maturation were identified in polychromatophilic and orthochromatophilic normoblasts. Megakaryocytic lineage was adequate (1–5 megakaryocytes per 10 high-power fields) with normal platelet production, and no hemoparasites were observed. Lymphoid cells consisted of small mature lymphocytes within normal quantitative limits. No evidence of immune-mediated destruction, such as erythrophagocytosis by macrophages or erythroblastic islands, was identified on any bone marrow cytology slide.

3.4 Imaging Examination

Abdominal ultrasonography revealed hepatomegaly with rounded hepatic margins and increased parenchymal echogenicity. The pancreas exhibited coarse parenchymal echotexture with mild hyperechogenicity of peripancreatic fat. The splenic tail was rounded, splenic body thickness measured 1.33 cm, perisplenic fat was hyperechoic, and a small volume of peritoneal effusion was present. Ultrasonographic images of the spleen are shown in Figure 6.

3.5 Additional Diagnostic Tests

Fecal examination yielded no parasite ova. Polymerase chain reaction (PCR) testing for feline leukemia virus (FeLV) and Mycoplasma haemofelis returned negative results.

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3.6 Diagnosis results

The cat presented with a chronic, severe non-regenerative anemia, and PCR assays for pathogenic microorganisms capable of inducing feline non-regenerative anemia were negative. Systemic illness and inflammatory causes of anemia were ruled out based on complete blood count, serum biochemistry, and abdominal ultrasound findings. Bone marrow cytology demonstrated blast cell proportion <20%, myeloblast proportion >6%, M:E ratio <1, and characteristic erythroid dysplasia (binucleation and megaloblastoid change). The definitive diagnosis was myelodysplastic syndrome (MDS-RAEB or MDS-EB).

4. Treatment and Outcome

A combination regimen of azacitidine and prednisolone was administered, with adjunctive medications including S-adenosylmethionine, vitamin B12, folic acid, and doxycycline.

- Azacitidine protocol: Subcutaneous injection at 35-70 mg/ ($m^2 \cdot d$) for 4 consecutive days per treatment cycle, for a total of 3 cycles, with a 30-day interval between cycles.
- Prednisolone dosage: 1.5 mg/(kg·d).

For the first cycle, azacitidine was dosed at 70 mg/($m^2 \cdot d$). On the day of initial administration, the cat developed worsening anemia, vomiting, diarrhea, and lethargy. Supportive care included transfusion of 50 mL fresh whole blood, lactated Ringer's solution (LRS) for fluid resuscitation, maropitant, bismuth subcarbonate, omeprazole, and metronidazole to control gastrointestinal adverse effects. For the second and third cycles, azacitidine was reduced to 35 mg/($m^2 \cdot d$) administered subcutaneously for 4 days; only soft stool was noted during treatment without other notable adverse reactions.HCT and platelet counts steadily increased throughout chemotherapy, with serial changes documented in Figure 7. Prednisolone tapering was initiated on day 24 after completion of the third cycle. When the dose was reduced to 0.25 mg/($kg \cdot d$), HCT declined, prompting an upward adjustment to 0.5 mg/($kg \cdot d$). On day 190 following the third cycle, HCT rose to 40.9%, and prednisolone was tapered to 0.25 mg/($kg \cdot d$) for long-term maintenance. At the time of manuscript writing, the cat's HCT remained stable at approximately 41% with excellent overall clinical condition. The survival time from initial diagnosis to date totals 792 days.

5. Discussion

This report represents the first publicly documented case in China describing azacitidine therapy for feline myelodysplastic syndrome (MDS). This case progressed to classic multilineage cytopenia dominated with severe non-regenerative anemia. Systemic disease, infectious etiologies, drug reactions, toxicosis, and nutritional deficiencies as underlying causes of non-regenerative anemia were excluded via signalment, medical history, clinicopathology, and imaging. Bone marrow hypercellularity confirmed myeloproliferation. Nucleated cells predominantly composed of erythroid precursors. The M:E ratio was depressed accompanied by erythroid hyperplasia, Characterized by rubriblasts and basophilic normoblasts

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accounting for 14% of erythroid cells. Concurrent cytopenia, erythroid dysplastic features (asynchronous nuclear-cytoplasmic maturation, binucleation, megaloblastoid change), rubriblasts comprising <50% of erythroid cells, and myeloblasts <20% of non-erythroid nucleated cells excluded acute leukemia, establishing a diagnosis of MDS-RAEB[2-4].

MDS is a heterogeneous clonal myeloid disorder originating from hematopoietic stem cells with incompletely elucidated pathogenesis, likely driven by somatic mutations or dysfunction of hematopoietic stem cells. It is a rare hematologic disease, with only approximately 80 cases reported globally to date[4-7]. MDS is characterized by myeloid dysplasia including left shift, hypersegmentation, and asynchronous nuclear-cytoplasmic maturation. Key laboratory findings include severe non-regenerative anemia or multilineage cytopenia (predominantly erythroid and thrombocytic reduction, with occasional leukopenia).

No standardized diagnostic criteria for MDS in dogs and cats exist in veterinary medicine,diagnosis is adapted from the minimal diagnostic criteria for human MDS. Criteria include: (1) cytopenia affecting one or more lineages, with all alternative causes of cytopenia ruled out; (2) dysplastic cells in erythroid, myeloid, or megakaryocytic lineages accounting for ≥10% , or myeloblast proportion <20%[2]. Small animal MDS is commonly classified via a modified French-American-British (FAB) system overseas[8], consisting of three subtypes: MDS-erythroid predominance (MDS-Er), MDS-refractory cytopenia (MDS-RC), and MDS-excess blasts (MDS-EB), with MDS-EB carrying the poorest prognosis. A retrospective analysis of 34 cats with myelodysplasia， 13 cats were diagnosed with MDS-EB patients with a median survival of only 0.7 months, among which 9 cats died or were euthanized within 30 days due to critical disease. Eight cats diagnosed with MDS-RC had a median survival of 11.7 months[8].

No standardized therapeutic protocols of MDS for veterinary are currently established[9-11]. A case report by Masaharu Hisasue et al. successfully managed one MDS-EB cat with azacitidine combined with prednisolone and vitamin K2[7]. Based on the above chemotherapy regimen, this case was treated with the combined protocol of azacitidine and prednisolone. Common adverse effects of azacitidine include nausea, anorexia, gastrointestinal upset, constipation, injection site reactions (erythema, pruritus, inflammation), myelosuppression, and fever[12]. In this case, the 70 mg/($m^2 \cdot d$) azacitidine dose induced severe vomiting, diarrhea, and lethargy, which resolved with supportive care. Dose reduction to 35 mg/($m^2 \cdot d$) eliminated severe adverse events, with only one blood transfusion required throughout chemotherapy.

Several limitations of this study should be noted. Human MDS protocols typically administer six azacitidine cycles, with treatment discontinuation criteria based on normalized bone marrow cytology and peripheral blood parameters. This case ceased chemotherapy after only three cycles without post-treatment bone marrow cytology re-evaluation, relying solely on clinical remission and blood parameters returned to normal, compromising diagnostic rigor. Furthermore, human MDS diagnostic guidelines mandate comprehensive testing including Bone marrow cytology， bone marrow core biopsy (to assess cellularity, CD34 immunohistochemistry, fibrosis grading, and megakaryocyte cytochemistry) and karyotype analysis.

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Due to restricted diagnostic resources in china veterinary practice compared to human medicine, only a bone marrow cytology examination was conducted in this case; although slide interpretation followed standards set by international veterinary cytopathologists, diagnostic certainty remains limited. Previous research findings indicate that FeLV infection is associated with the development of tumors such as MDS and AML, and may lead to tumor recurrence in affected animals[7]. This case lacked FeLV ELISA testing, precluding definitive exclusion of FeLV-associated disease and limiting accurate prognostic assessment.

By summarizing the clinical management of this feline MDS case, this manuscript systematically reviews the clinical manifestations and diagnostic principles of MDS, and discusses the dose of azacitidine and treatment cycle for feline MDS, aiming to provide clinical reference for veterinary practitioners.

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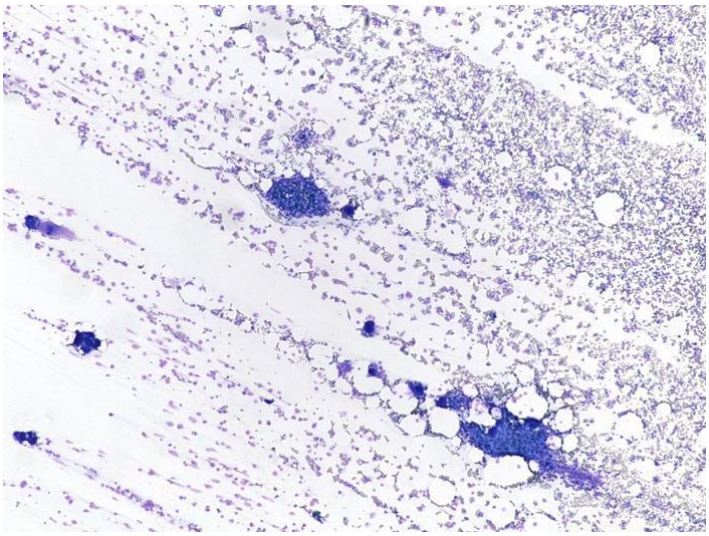

Fig.1 A few unit particles fromlowpower（Wright-Giemsa staining，40×）

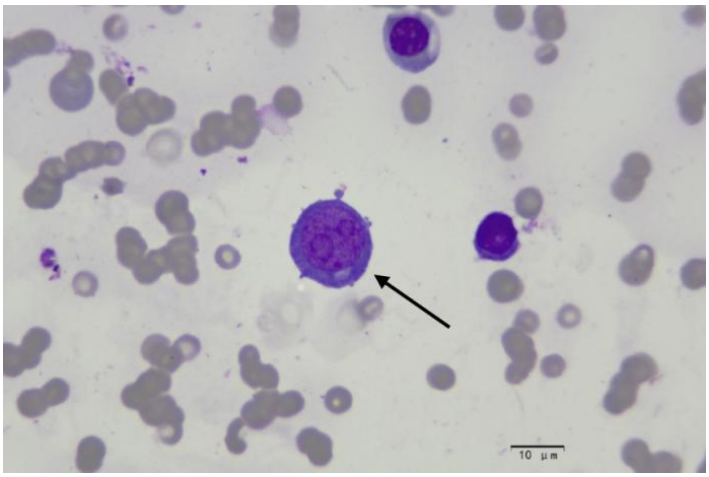

Fig.2 Bone marrow cytology smear of the cat（Wright-Giemsa staining，1 000×）

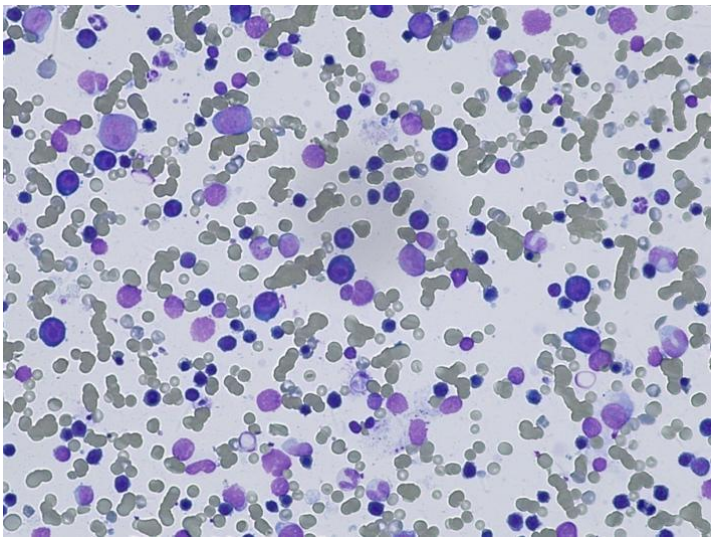

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Fig.3 A closer view of the erythroid precursors（Wright-Giemsa staining，200×）

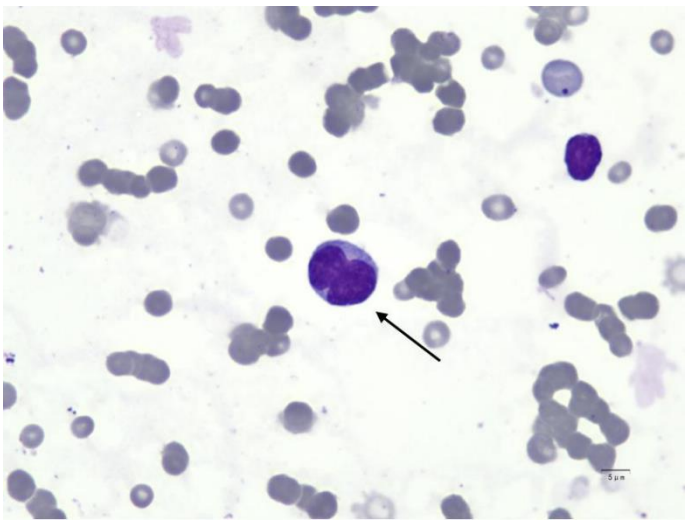

Fig.4 Bone marrow cytology smear of the cat（Wright-Giemsa staining，1 000×）

Arrow：binucleate cell

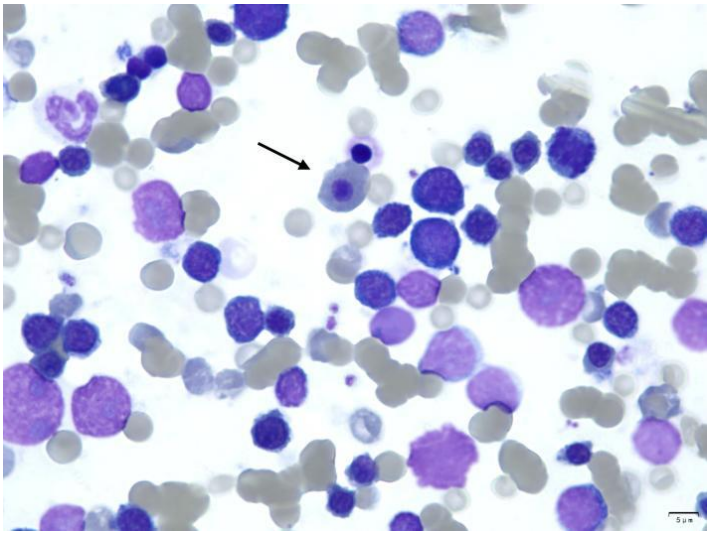

Fig.5 Bone marrowcytology smear of the cat（Wright-Giemsa staining，1 000×）

Arrow：asynchronous maturation between the nucleus and cytoplasm

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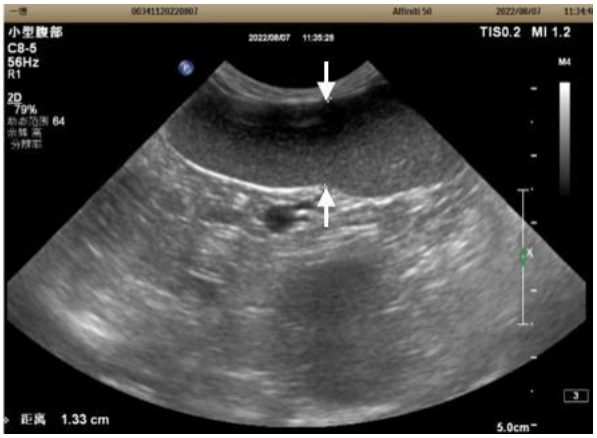

Fig.6 Longitudinal sonographic image of spleen

Arrow：Spleen diameter is approximately 1.33cm

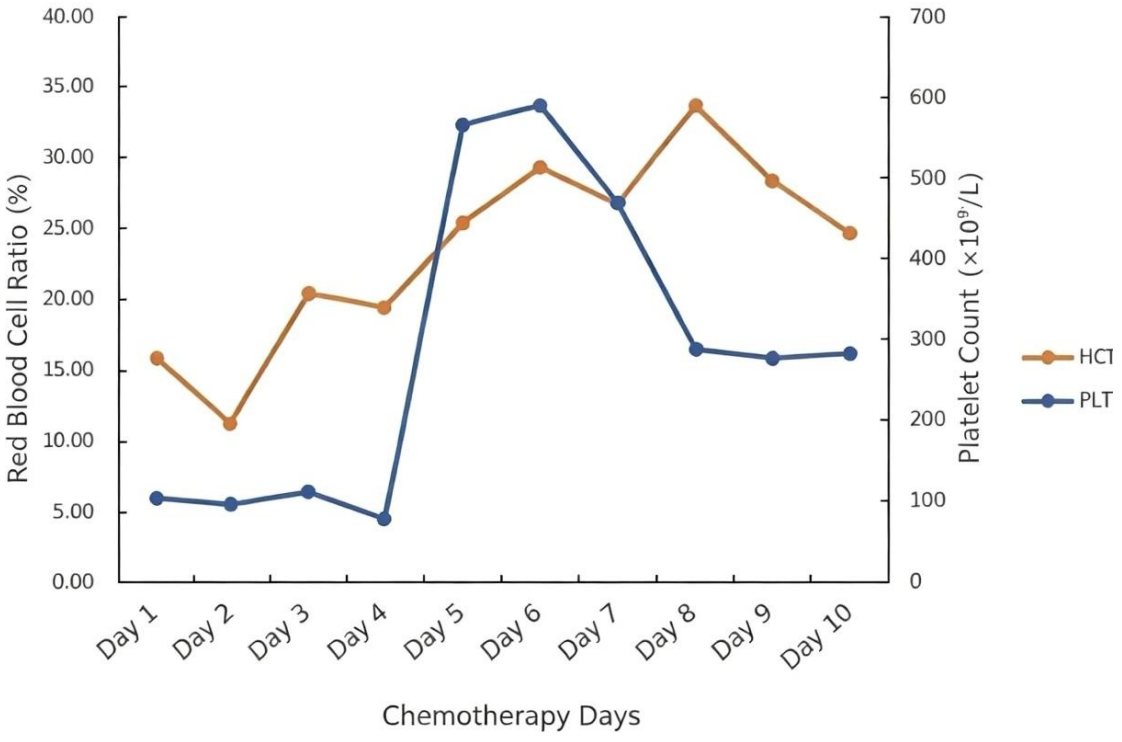

Fig.7 Trends of hematocrit and platelet count during three cycles of chemotherapy

Days ofchemotherapy；Hematocrit；Platelet count

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Pathological Mechanisms, Clinical Impacts, Management Strategies, and Advances in Innovative Drug Development for Feline Obesity: A Review

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Abstract: Feline obesity, as a prevalent multifactorial nutritional disorder, has seen a significant rise in incidence in recent years, posing serious threats to the health and quality of life of cats. Obesity not only triggers metabolic abnormalities such as insulin resistance and diabetes mellitus but is also closely associated with cardiovascular disease, renal dysfunction, respiratory impairment, and chronic inflammation. Current evidence indicates marked alterations in the gut microbiota composition of obese cats, suggesting a potential role of the microbiota in the pathogenesis of obesity. Furthermore, genetic factors, including variants in the MC4R and POMC genes, are linked to obesity susceptibility. Management strategies for obese cats include dietary modification, exercise intervention, and emerging pharmacotherapies. In recent years, breakthroughs in innovative drug development based on human weight-loss drug experience have been achieved, with GLP-1 receptor agonists, GLP-1/GIP dual-target agonists, SGLT2 inhibitors, and FGF21 agonists showing promising applications. Meanwhile, physical interventions such as peripheral focused ultrasound neuromodulation also offer new ideas for non-pharmacological management. However, challenges including species differences, safety concerns, and clinical trial design still need to be overcome. This review systematically summarizes the epidemiology, pathophysiology, clinical manifestations, diagnostic indicators, management strategies, and advances in innovative drug development for feline obesity, aiming to provide a scientific basis for clinical practice and future research.

Keywords: Feline obesity; metabolic abnormalities; gut microbiota; genetic variation; inflammation; weight management; GLP-1 receptor agonist; FGF21; innovative drugs

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1. Introduction

Feline obesity has become a major global challenge in pet health, particularly in the context of rapid urbanization. As human lifestyles and dietary habits change, weight management in cats has gained increasing attention. Statistical data show that the prevalence of obesity in cats exceeds 40%, which not only compromises their quality of life but may also lead to a range of serious health problems, including diabetes, joint diseases, and heart disease. According to the 2022 report of the Association for Pet Obesity Prevention (APOP), 61% of cats in the United States are overweight or obese, and over 40% of pet cats in the United Kingdom face the same problem. The number of pet cats in urban China has reached approximately 60 million, with an obesity rate of about 28.1% [1-3]. This high prevalence points to a significant increase in secondary health risks such as diabetes, heart disease, respiratory diseases, and joint problems.

The development of obesity often involves multiple interrelated factors, including genetic predisposition, environmental influences, and inappropriate dietary habits. Among these, lack of sufficient exercise and excessive intake of high-calorie foods are important contributors to obesity in cats. Additionally, as cats age, their basal metabolic rate gradually declines, further increasing the risk of obesity. As obligate carnivores, cats have unique glucose and lipid metabolism profiles, making them more prone to obesity compared to dogs. Studies have shown that for every additional kilogram of body weight, insulin sensitivity decreases by 30%, significantly increasing the risk of type 2 diabetes [4].

Currently, the management of feline obesity primarily relies on non-pharmacological approaches such as dietary control and exercise guidance; however, actual effectiveness is often constrained by multiple factors. Common issues include uncontrolled treat intake, overfeeding by owners in response to begging behavior, and failure to dynamically adjust feeding regimens based on individual metabolic differences. More critically, severe caloric restriction may induce fatal hepatic lipidosis, posing safety risks to non-pharmacological interventions [5]. These difficulties have prompted researchers to explore pharmacological intervention strategies. In recent years, breakthrough advances in human weight-loss drugs, particularly GLP-1 receptor agonists, have provided new research directions for obesity management in companion animals.

To effectively manage and prevent feline obesity, veterinarians and pet owners need to work together to develop scientifically sound dietary plans and exercise regimens. At the same time, individualized management strategies tailored to each cat's lifestyle, health status, and nutritional needs are particularly important. This review delves into the pathological mechanisms of feline obesity, evaluates its impact on feline health, summarizes existing management strategies, and highlights advances and challenges in innovative drug development, aiming to provide valuable references for pet owners and veterinarians.

2. Pathological Mechanisms, Clinical Impacts, and Management Strategies for Feline Obesity

2.1 Epidemiological Characteristics of Feline Obesity

2.1.1 Prevalence and Trends of Obesity by Age Group

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Data from large-scale U.S. veterinary hospitals between 2020 and 2023 show a significant upward trend in feline obesity rates. The data indicate that obesity prevalence in adult cats is approximately 15–25%, while in senior cats it exceeds 30%. This phenomenon is closely related to pets' lifestyles, dietary habits, and environmental factors. Especially during the COVID-19 pandemic, many cats were confined indoors, leading to reduced energy expenditure and worsening obesity. Moreover, clinical data show that obese cats have significantly higher veterinary visit rates and medical costs, indicating a strong correlation between obesity and health problems [6].

Obesity prevalence in cats varies markedly across age stages. Kittens during growth and development typically have higher nutritional demands and rarely exhibit obesity. However, as age increases—especially into middle and old age—cats' activity levels and metabolic rates decline significantly, raising obesity risk. Studies have shown that obesity in senior cats not only affects their quality of life but may also lead to a range of health issues, including diabetes, arthritis, and cardiovascular disease [7]. Therefore, appropriate management strategies tailored to different age groups are essential for obesity prevention.

2.1.2 Environmental and Behavioral Factors Influencing Obesity

Indoor lifestyle is a major factor contributing to feline obesity. Many cats are confined to the home, lacking sufficient exercise and thereby reducing energy expenditure. Meanwhile, many owners, due to busy schedules, opt for high-calorie, low-nutrition commercial cat foods, further exacerbating the imbalance between energy intake and expenditure. Studies indicate that indoor cats have significantly higher obesity rates than outdoor cats, and the problem worsened during the pandemic when activity time was further reduced [8].

Diet type and feeding practices also significantly influence obesity development. High-fat, high-sugar diets are closely associated with obesity. Many pet owners lack scientific knowledge about feeding, often giving treats or human food indiscriminately, leading to excessive caloric intake. Additionally, the absence of proper dietary plans and exercise schedules makes weight control more difficult. Research shows that comprehensive management strategies involving calorie restriction and increased physical activity can effectively prevent and control feline obesity [9].

2.2 Clinical Manifestations and Impact on Quality of Life in Obese Cats

2.2.1 Potential Impact of Obesity on Feline Quality of Life

Obesity has a significant negative impact on cats' quality of life, mainly reflected in reduced mobility, altered social behavior, and overall health deterioration. Quality-of-life studies indicate that obese cats generally exhibit lower quality of life than normal-weight cats. Pet owners often subjectively perceive reduced activity and health issues in obese cats but may underestimate the overall impact on well-being. According to research, obese cats frequently display reduced movement, lethargy, and social avoidance, which may diminish interactions with owners and other pets, thereby affecting emotional health [10].

Chronic inflammation and metabolic disorders associated with obesity undoubtedly exacerbate health problems, leading to complications such as diabetes, arthritis, and cardiovascular disease, which further impair quality of life. Obese cats often require longer recovery times and more complex treatment plans

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during veterinary assessments, increasing the financial and psychological burden on owners. Therefore, recognizing the potential impact of obesity on quality of life is crucial for veterinarians to provide effective management advice and measures.

2.2.2 Obesity-Related Changes in Respiratory Function

Respiratory function in obese cats is significantly affected, primarily due to mechanical breathing impairments caused by excess weight and metabolic changes. Studies have found that obese cats have lower resting respiratory rates and pulmonary function parameters than normal-weight cats, manifesting as dyspnea and reduced exercise tolerance [11]. Abdominal fat accumulation compresses the diaphragm and thoracic cavity, limiting lung volume and gas exchange efficiency.

Further analysis shows increased airway resistance and decreased lung compliance in obese cats, leading to reduced respiratory efficiency. Dyspnea is particularly pronounced during exercise and may lead to respiratory disorders such as sleep apnea syndrome. Obese cats also face higher respiratory risks during anesthesia and surgery, making them more prone to complications. Thus, veterinarians should integrate weight control with respiratory management when devising treatment plans for obese cats.

2.2.3 Relationship Between Obesity and Renal Function Indicators

Obesity is not only linked to respiratory issues but also closely associated with renal function. Studies indicate that obese cats have significantly elevated renal resistance indices (RI) and abnormal serum SDMA levels (an early marker of renal function), both important indicators for assessing kidney health [12]. Obesity affects renal health through multiple mechanisms, including increased tubular burden, hypertension, and metabolic syndrome-related inflammation.

Obese cats exhibit a clear association with high tubular load and glomerular hyperfiltration, especially when body weight is excessive. Research suggests that obesity may alter glomerular filtration function, thereby reducing the responsiveness to certain drugs and potentially affecting treatment choices and efficacy. Therefore, when managing renal issues in obese cats, veterinarians should prioritize weight management and renal function monitoring to enable early detection of kidney injury.

2.3 Metabolic Abnormalities and Inflammatory Status in Obese Cats

2.3.1 Abnormalities in Blood Pressure and Glucose Metabolism

Obese cats show significant metabolic abnormalities, especially in blood pressure and glucose levels. Studies have demonstrated a close relationship between obesity, hypertension, and hyperglycemia. Obese cats often exhibit metabolic syndrome, including insulin resistance, elevated blood glucose, and dyslipidemia. Specifically, weight gain leads to increased blood pressure, closely related to increased adipose tissue and associated metabolic changes. According to a study on metabolic syndrome, obesity increases cardiovascular risk factors, including hypertension and hyperglycemia, which interact in a vicious cycle [13].

Moreover, the hyperglycemic trend in obese cats should not be overlooked. Obesity-induced insulin resistance causes the pancreas to secrete more insulin to maintain normal blood glucose levels; however, over time, the pancreas' compensatory capacity declines, potentially leading to diabetes. This hyperglycemic state not only threatens overall health but may also trigger other complications such as cardiovascular and kidney

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diseases. Therefore, monitoring blood glucose and blood pressure levels in obese cats and intervening promptly is critically important.

2.3.2 Obesity-Related Chronic Low-Grade Inflammation and Oxidative Stress

Obese cats often exhibit a state of chronic low-grade inflammation closely related to obesity-associated metabolic abnormalities. Studies show that obesity not only increases adipose tissue but also triggers a series of inflammatory responses. Specifically, serum amyloid A (SAA) and other inflammatory markers are significantly elevated in obese cats, indicating ongoing inflammation. Additionally, antioxidant capacity is typically reduced in obese cats, making oxidative stress more frequent and further exacerbating inflammation [14].

The mechanisms of chronic low-grade inflammation are closely linked to cytokines, chemokines, and free fatty acids secreted by adipose tissue. These substances not only promote inflammation but may also affect overall metabolic health. Metabolic abnormalities in obese cats may lead to insulin resistance. Research indicates that oxidative stress levels in obese cats are significantly higher than in normal-weight cats, a phenomenon associated with metabolic dysregulation and reduced antioxidant enzyme activity. Therefore, studying and intervening in antioxidant capacity may improve metabolic status and overall health in obese cats.

2.3.3 Obesity and Pancreatic Function/Pancreatitis Risk

Obese cats also exhibit significant pancreatic abnormalities, particularly in the immunoreactivity of pancreatic lipase and trypsin. Studies have found that obesity leads to increased pancreatic fat deposition, which not only affects normal metabolic function but may also increase the risk of pancreatitis. Specifically, the expression levels of lipase and trypsin in pancreatic tissue of obese cats may change, thereby affecting fat and protein digestion and absorption [15].

Furthermore, pancreatic dysfunction in obese cats is characterized by structural changes and aggravated inflammatory responses, potentially leading to pancreatitis. Research shows that obesity induces pancreatic cell steatosis and apoptosis, ultimately affecting overall pancreatic function. Therefore, monitoring pancreatic function and assessing pancreatitis risk are important components of managing the health of obese cats. Targeted dietary interventions and appropriate exercise may help reduce these risks.

2.4 Changes in Gut Microbiota of Obese Cats and Their Significance

The gut microbiota plays a key role in metabolic regulation in obese cats. Research has shown that obese cats exhibit significant alterations in gut microbiota composition, which not only affect energy metabolism but may also be closely related to obesity development. The pathological mechanisms of obesity involve multiple factors, among which changes in the composition and function of the gut microbiota are considered critically important. Studying the gut microbiota of obese cats helps deepen our understanding of the causes of obesity and potential interventions.

2.4.1 Diversity and Compositional Changes of Gut Microbiota in Obese Cats

Obese cats show markedly reduced diversity and altered composition of gut microbiota. Studies indicate that the ratio of Firmicutes to Bacteroidetes increases significantly in obese cats, with an increase in

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Firmicutes abundance and a decrease in Bacteroidetes abundance, a change closely related to obesity [16-17]. Increased abundance of specific bacterial groups, such as certain Proteobacteria and Enterobacteriaceae, has also been observed in association with obesity. This microbial dysbiosis not only affects food digestion and energy absorption but may also increase the risk of various metabolic diseases.

Moreover, changes in gut microbiota are closely related to cats' dietary habits. High-fat diets significantly alter gut microbiota composition, further exacerbating the pathological process of obesity. Dietary modifications, such as increasing dietary fiber intake, can improve gut microbiota diversity, thereby counteracting obesity and its related metabolic diseases [18].

2.4.2 Association Between Gut Microbial Function and Energy Metabolism

Gut microbes not only affect intestinal health but also directly participate in regulating energy metabolism. The gut microbiota of obese cats influences fatty acid synthesis pathways through various mechanisms, thereby altering the host's energy metabolism. For example, microbial metabolites such as short-chain fatty acids (SCFAs) play an important role in fat metabolism by stimulating the secretion of gut endocrine hormones that regulate appetite and energy balance [19]. In obese cats, changes in gut microbiota may activate fatty acid synthesis pathways, exacerbating fat accumulation and energy imbalance. Microbes affect the host's energy acquisition and storage patterns through specific metabolites. Therefore, interventions targeting the gut microbiota, such as probiotics or dietary changes, may effectively improve the metabolic status of obese cats.

2.4.3 Impact of Weight Loss on Gut Microbiota

Standardized weight loss programs can significantly alter the abundance and diversity of gut microbiota in obese cats. Research has found that after weight loss intervention, the gut microbiota of cats develops toward a more diverse and healthier state, with an increase in Bacteroidetes abundance and a decrease in the Firmicutes ratio. These changes are closely associated with weight loss and metabolic improvement [17,19]. Further studies indicate that weight loss not only reduces body weight but also enhances intestinal health and overall metabolic function by modulating gut microbiota composition. Dietary intervention and appropriate exercise can effectively promote gut microbiota remodeling, playing an important role in obesity management. Therefore, future management of obese cats should consider gut microbiota modulation as a potential therapeutic strategy.

2.5 Research Progress on Obesity-Related Genes and Molecular Mechanisms

2.5.1 Association Between MC4R Gene Variants and Feline Obesity

The MC4R (melanocortin-4 receptor) gene plays an important role in the genetic study of obesity, particularly in feline obesity. Research has shown a significant association between MC4R gene variants (SNPs) and body mass index (BMI). According to a systematic review, over 200 MC4R variants have been documented, with a frequency of 1% to 6% in obese individuals [20]. Specific SNPs have been found to be closely related to appetite regulation and energy balance, and their functional relevance is strong. Variants may lead to increased appetite and reduced energy expenditure, thereby promoting obesity. For example, certain loss-of-function MC4R variants are closely associated with higher body weight and fat accumulation

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in cats. These findings not only provide important evidence for understanding the genetic basis of feline obesity but also offer potential genetic targets for precision therapy.

Further research indicates that abnormal activation of the MC4R signaling pathway is closely linked to obesity-related metabolic diseases such as diabetes and cardiovascular disease. These findings underscore the importance of MC4R in the pathophysiology of obesity and provide new perspectives for developing gene-based interventions.

2.5.2 Novel Variants in the POMC Gene and Their Potential Pro-Obesity Effects

The POMC (pro-opiomelanocortin) gene plays a key role in energy metabolism and body weight regulation. Recent studies have identified significant associations between POMC gene polymorphisms and obesity phenotypes. For instance, certain POMC variants may affect hunger and satiety sensations, leading to increased energy intake and weight gain [21]. Moreover, these variants may interfere with adipose tissue metabolism and inflammatory responses through neuroendocrine pathways, further exacerbating obesity development.

Studies in children and adolescents have found that certain POMC polymorphisms are closely related to BMI changes, suggesting that early identification of these genetic markers may help develop personalized obesity intervention strategies. This indicates that POMC polymorphisms play an important role not only in the pathogenesis of obesity but may also serve as potential therapeutic targets.

2.5.3 Changes in Obesity-Related Gene Expression and Metabolic Impact

In obesity, gene expression in muscle and adipose tissue undergoes significant changes closely related to metabolic disorders. Research shows that in obese individuals, the expression of pro-inflammatory genes in adipose tissue is significantly increased, while that of anti-inflammatory genes is decreased, creating a state of chronic low-grade inflammation [22]. This inflammation not only affects adipocyte function but also interferes with systemic metabolic balance.

In muscle tissue, obesity is associated with decreased expression of metabolism-related genes (such as AMPK, PGC-1α, etc.), which may lead to insulin resistance and reduced fatty acid oxidation capacity. Further studies have found that specific dietary and lifestyle interventions can partially restore normal expression of these genes, thereby improving metabolic status and reducing the risk of obesity-related complications. These findings provide new molecular targets and strategies for obesity management, emphasizing the importance of considering gene expression regulation in obesity treatment.

2.6 Hormonal Changes and Endocrine Effects in Obese Cats

Hormonal changes in obese cats are closely related to endocrine disorders, affecting their overall health. Obesity not only manifests as weight gain but also represents changes in metabolic status. Hormones play important roles in regulating energy balance, metabolism, and appetite, and alterations in hormone levels in obese cats may lead to a series of health problems, including diabetes and liver disease. Therefore, understanding hormonal changes and their endocrine effects is crucial for developing effective management strategies.

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2.6.1 Molecular Network of Appetite Regulation

The maintenance of food intake and energy balance relies on a complex signaling network, the core of which consists of two functionally antagonistic classes of peptide molecules: orexigenic peptides that promote appetite and anorexigenic peptides that suppress appetite. These molecules establish bidirectional communication between the central nervous system and peripheral organs, collectively maintaining the body's energy homeostasis [1,5].

Orexigenic peptides mainly include ghrelin, phoenixin, and asprosin. Among these, ghrelin, a 28-amino acid peptide hormone, not only stimulates appetite but also participates in the regulation of growth hormone secretion while directly targeting muscle cells to promote muscle protein synthesis, offering unique value in maintaining lean body mass [4]. Anorexigenic peptides are represented by glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), leptin, and nesfatin-1. GLP-1, secreted by intestinal L cells and released after meals, acts by delaying gastric emptying, promoting insulin secretion, and centrally suppressing appetite. GIP belongs to the same incretin family as GLP-1, and the two synergize to produce stronger metabolic improvement effects, which forms the theoretical basis for dual-target strategies [4].

2.6.2 Association of IGF-1 Levels with Obesity and Obesity-Related Diseases

Insulin-like growth factor-1 (IGF-1) is a polypeptide hormone synthesized by the liver and closely related to growth hormone. Studies have shown that IGF-1 levels are typically significantly elevated in obese cats, which is closely associated with increased body fat and metabolic disturbances. Elevated IGF-1 concentrations in non-diabetic obese cats may be due to the influence of cytokines and hormones secreted by adipose tissue on IGF-1 synthesis and metabolism. Moreover, the endocrine environment of obese cats may further exacerbate this process, and obese cats often exhibit pituitary enlargement, suggesting adaptive changes in the pituitary gland due to increased metabolic load.

Elevated IGF-1 is closely linked to the development of various obesity-related diseases. For example, IGF-1 may promote adipocyte proliferation and differentiation, exacerbating fat accumulation and thus obesity. IGF-1 is also considered to be associated with the development of diabetes; although elevated IGF-1 in non-diabetic obese cats does not directly cause diabetes, it may play a role in the development of metabolic syndrome. Changes in IGF-1 levels in obese cats are closely related to insulin resistance and hepatic steatosis. Therefore, monitoring IGF-1 levels can provide important biomarkers for the management of obese cats.

2.6.3 Metabolic Regulatory Role of FGF21 Pathway Activation

Fibroblast growth factor 21 (FGF21) is a newly discovered hormone involved in regulating various metabolic processes. FGF21 expression levels are typically elevated in obese cats, and its activation may be closely related to changes in energy metabolism. Research suggests that FGF21 may play a key role in regulating obesity and related metabolic diseases by influencing fatty acid oxidation and insulin sensitivity. Therefore, the study of the FGF21 pathway provides new ideas and potential therapeutic targets for obesity intervention. In recent years, metabolic regulators have gained increasing attention in feline obesity research. FGF21 plays an important role in energy metabolism, glucose homeostasis, and fatty acid oxidation. In obese cats, FGF21 expression levels typically change, which may be related to increased adipose tissue and altered

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metabolic load.

The application of FGF21 agonists has shown significant efficacy in studies of obese cats. Experimental results indicate that FGF21 agonists can effectively reduce body weight in obese cats and improve hepatic fat accumulation. FGF21 helps improve the metabolic status of obese cats by promoting fatty acid oxidation and inhibiting fat synthesis. Additionally, FGF21 can reduce insulin resistance by enhancing insulin sensitivity, providing a better metabolic environment for obese cats. In summary, FGF21 plays a key role in metabolic regulation in obese cats. Activating the FGF21 pathway not only helps reduce body weight but also improves endocrine disorders associated with obesity.

2.7 Nutritional Requirements and Dietary Management of Obese Cats

The management of obese cats is a complex process that requires in-depth exploration of their specific nutritional needs and dietary management strategies. Optimizing nutritional requirements not only aids weight loss but also improves overall health. As obesity becomes increasingly prevalent in cats, scientists are focusing on how dietary management can effectively control weight and improve quality of life.

2.7.1 Assessment of Essential Amino Acid and Vitamin Intake During Caloric Restriction

Assessing essential amino acid and vitamin intake in obese cats during caloric restriction is crucial. According to the National Research Council (NRC) recommendations, cats require specific amino acids and vitamins to maintain physiological functions. However, in practice, many cats' diets may not meet these needs, especially during weight loss. Studies have shown that deficiencies in certain essential amino acids (e.g., lysine, methionine) and vitamins (e.g., A and E) may lead to immune dysfunction, skin problems, and other health issues [6]. Therefore, when formulating weight loss plans, ensuring that the diet provides adequate nutrients is essential to avoid potential health risks.

Moreover, research indicates that caloric restriction in obese cats may affect amino acid metabolism, particularly during weight loss. Long-term caloric restriction may lead to loss of muscle mass, thereby affecting metabolic rate and health. Therefore, during weight loss programs, regular monitoring of body weight and nutritional status is recommended to adjust dietary plans promptly, ensuring that cats receive necessary nutrients while losing weight [23].

2.7.2 Application of Low-Carbohydrate, High-Protein Diets

Low-carbohydrate, high-protein diets are increasingly recognized in the management of obese cats. Studies show that this dietary pattern not only aids weight loss but also improves metabolic health. For cats with diabetes and obesity, excessive carbohydrates may cause blood glucose fluctuations, whereas high-protein diets provide a more stable energy source, helping control weight and blood glucose levels [24].

More importantly, low-carbohydrate, high-protein diets can promote fat oxidation, assisting in fat metabolism during weight loss. This dietary pattern may enhance satiety, reducing food demand and making weight control easier. Additionally, adequate protein intake helps maintain muscle mass, which is especially important for obese cats because preserving muscle tissue during weight loss helps stabilize basal metabolic rate [25].

2.7.3 Adjuvant Effects of Natural Anti-Inflammatory and Antioxidant Compounds

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The introduction of natural anti-inflammatory and antioxidant compounds shows positive potential in the management of obese cats. Research indicates that obese cats typically exhibit chronic low-grade inflammation, closely related to obesity-associated metabolic diseases. Incorporating natural anti-inflammatory and antioxidant compounds containing plant extracts and active ingredients can effectively alleviate obesity-induced inflammatory responses, thereby improving health and quality of life [8].

For example, certain plant extracts such as green tea extract and turmeric extract have been found to possess significant antioxidant and anti-inflammatory effects, helping reduce obesity-related inflammation. Furthermore, natural antioxidants can enhance the immune system and improve overall health. Combined with appropriate dietary strategies, the application of these natural compounds may provide additional health benefits for obese cats, aiding in weight management and metabolic function improvement. Therefore, considering the addition of these natural ingredients may be an effective adjunctive strategy when formulating dietary plans for obese cats [26]. Resveratrol, another natural polyphenol, has been shown in studies to improve lipid metabolism disorders in obese cats, but its weight-loss effect as a standalone intervention is limited [4].

2.8 Weight Management Strategies and Clinical Interventions for Obese Cats

2.8.1 Communication Strategies Between Veterinarians and Pet Owners

Effective communication between veterinarians and pet owners is crucial in managing obese cats. Research suggests that veterinarians should emphasize the impact of obesity on cats' life expectancy and prioritize this information in communication. Obesity not only reduces cats' quality of life but may also shorten their lifespan and increase the risk of chronic diseases such as diabetes and arthritis [6]. Therefore, veterinarians can help pet owners recognize the importance of weight management by providing detailed information on obesity-related diseases and preventive measures.

Additionally, veterinarians should employ appropriate communication techniques to help pet owners understand and accept their cats' obesity problems. Using simple language, charts, and examples, veterinarians can effectively convey the potential health hazards of obesity. At the same time, when advocating behavioral changes, veterinarians should respect pet owners' opinions and feelings, encouraging them to participate in the cat's management plan. Research shows that actively engaged owners are more likely to implement long-term dietary and exercise changes, thereby improving their cats' health [24]. Finally, regular follow-up and feedback are important components of communication strategies. Through regular check-ups and weight assessments, veterinarians can adjust management strategies in a timely manner and provide feedback to owners. This ongoing communication and support can enhance pet owners' confidence in the management plan, increasing their willingness and effectiveness in implementation.

2.8.2 Exercise Intervention and Behavioral Modification

Increasing physical activity is an important strategy for weight control in obese cats. Research shows that appropriate exercise can significantly increase energy expenditure and promote weight loss [25]. To achieve this goal, veterinarians can develop individualized exercise plans based on each cat's needs and lifestyle. Additionally, veterinarians should educate pet owners on how to increase their cats' activity levels in daily

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life. For example, using interactive toys, setting up obstacles, or engaging in play can effectively stimulate cats' interest in exercise.

Behavioral modification is also an important component of exercise intervention. Many cats are unwilling to exercise due to lack of interest or habitual behaviors, so veterinarians can help owners identify and change these undesirable habits. Taking small steps to gradually acclimate cats to new activity patterns can increase their participation. Additionally, using positive reinforcement (such as treats or praise) to encourage cats to exercise is an effective behavioral modification strategy.

Notably, exercise intervention should be combined with dietary management to ensure cats receive adequate nutritional support. When implementing exercise and behavioral modifications, veterinarians should regularly assess cats' health status to adjust plans as needed, ensuring safety and health [9].

2.8.3 Emerging Pharmacotherapies and Future Perspectives

With a deeper understanding of the pathological mechanisms of feline obesity, emerging pharmacotherapies are continuously being developed. Among novel drugs, GLP-1 receptor agonists, GLP-1/GIP dual-target agonists, SGLT2 inhibitors, and FGF21 agonists show promising application prospects.

(1) GLP-1 Receptor Agonists (Single Target)

GLP-1 receptor agonists are currently the most closely category in the field of human weight-loss drugs. Their mechanism of action involves reducing caloric intake through dual pathways—suppressing the appetite center and delaying gastric emptying—while improving insulin sensitivity and reducing the risk of diabetes complications [1]. Applying these drugs to pet obesity treatment has become an important direction for researchers. Currently, studies are underway to evaluate the weight-loss effects of GLP-1 receptor agonists in overweight and obese domestic cats. Preclinical data show that these compounds can safely and effectively limit food intake in experimental animals [4]. GLP-1 receptor agonists help achieve weight loss in cats by suppressing appetite and increasing energy expenditure [27].

(2) GLP-1/GIP Dual-Target Agonists

Dual-target agonists act on both GLP-1 and GIP receptors, aiming to achieve superior metabolic improvement through multi-pathway synergy. The design concept of these drugs originates from successful experiences in human medicine, and they have entered clinical research stages for feline obesity intervention. Available research data indicate that these drugs can achieve safe weight loss within a relatively short dosing period, providing preliminary clinical evidence for the application of dual-target strategies in cats [4].

(3) SGLT2 Inhibitors

SGLT2 inhibitors, as metabolic regulators, achieve dual effects of glucose lowering and weight loss by inhibiting renal glucose reabsorption and increasing urinary glucose excretion. They have entered clinical trials for feline diabetes and are expected to be extended for the treatment of simple obesity [1]. These drugs promote weight loss by increasing urinary glucose excretion and may improve the metabolic status of cats [28].

(4) FGF21 Agonists

As described in section 2.6.3, FGF21 agonists, as novel metabolic regulators, can help reduce body weight by improving insulin sensitivity and promoting fat oxidation [16]. Clinical research on these drugs is ongoing

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and shows potential for weight control in cats.

(5) Other Metabolic Regulators and Anti-Inflammatory Drugs

Based on the "inflamm-aging" pathological mechanism of feline obesity, drugs targeting inflammatory pathways and metabolic regulation have become important research directions. Resveratrol, a natural plant polyphenol, has been shown in studies to significantly decrease plasma triglycerides, free fatty acids, and serum amyloid A concentrations while increasing adiponectin concentrations in obese cats after four weeks of continuous supplementation; however, its weight-loss effect as a standalone intervention is limited [4].

Table 1 Comparison of Characteristics of Different Technological Approaches

Technological Approach	Route of Administration	Characteristics	Challenges
GLP-1/GIP dual-target agonist	Injection	Significant weight-loss effect, preliminary clinical data validation	Requires regular injection, high pet compliance requirements
Long-acting GLP-1 implant	Subcutaneous implantation	Stable dose release, high compliance	Implantation procedure required, higher cost
Oral small-molecule GLP-1 agonist	Oral administration	Convenient administration, high pet acceptance	Bioavailability challenges, difficult R&D
GLP-1 single-target agonist	Injection	Mature technology, good safety profile	Weight-loss effect may be weaker than dual-target
Natural product modulator	Oral	High safety, anti-inflammatory effects	Limited weight-loss effect as standalone

Overview of Global Research Progress

Currently, drug development for feline obesity is active worldwide. GLP-1 receptor agonists and their related derivatives are research hotspots in this field, with researchers in multiple countries conducting drug evaluations at various stages from preclinical to clinical. In terms of formulation innovation, research on long-acting sustained-release formulations is advancing, aiming to reduce dosing frequency and improve medication compliance. The development of oral small-molecule GLP-1 receptor agonists is also being explored, seeking to achieve non-injectable administration routes by improving bioavailability. Current research projects cover multiple stages from laboratory studies to clinical evaluations, with some candidate drugs having entered clinical trial phases. Primary evaluation indicators include changes in body weight, improvements in metabolic parameters, and safety profiles. Most study designs employ randomized

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controlled protocols to obtain reliable pharmacodynamic and safety data [1-4].

2.8.4 Physical Intervention: Peripheral Focused Ultrasound Neuromodulation (pFUS)

Peripheral focused ultrasound neuromodulation is an emerging non-invasive technique that modulates metabolic function by targeting peripheral sensory nerves. In the field of metabolic regulation, the target of pFUS is primarily the hepatic sensory nerves. One study explored for the first time the safety and potential efficacy of pFUS in cats. Phase 1 verified safety in healthy cats, showing no adverse events. Phase 2, conducted in overweight and obese cats, also showed no adverse events and observed a significant decrease in plasma glucose, with decreasing trends in interstitial glucose and triglycerides [4]. This study confirms the feasibility of pFUS in cats, offering a non-pharmacological option for future feline obesity management.

2.8.5 R&D Challenges and Safety Issues

Species Differences and Pharmacological Safety: Cats have significantly different physiological and metabolic characteristics from humans and dogs, rendering some human weight-loss drugs inapplicable. For example, long-term use of sulfonylurea oral hypoglycemic agents in cats leads to islet amyloid deposition [1]. Some studies have pointed out that GLP-1 receptor agonists may excessively stimulate insulin release while strongly inhibiting gastrointestinal emptying, leading to adverse reactions such as vomiting and anorexia [2]. Historical experience provides a scientific warning: a weight-loss drug for dogs was previously approved for marketing, which reduced appetite and lipid absorption by inhibiting microsomal triglyceride transfer protein. However, a considerable proportion of treated animals experienced vomiting and diarrhea, and some exhibited anorexia symptoms, ultimately leading to market withdrawal due to safety and tolerability issues [3,4]. Additionally, cats are highly sensitive to caloric restriction, and weight-loss drugs must precisely control the rate of weight loss to ensure a safe range of 0.5-1% weekly weight loss, thereby preventing complications such as hepatic lipidosis [1,5].

Clinical Trial Design and Execution Challenges: Pet drug clinical trials face multiple challenges including sample recruitment, cycle control, and standardization of execution. Clinical trials for feline obesity require strict control of variables such as diet and exercise, demanding high compliance from pet owners and increasing the complexity of trial execution [2]. Furthermore, according to relevant regulatory requirements, veterinary drugs for clinical trials must undergo inspection by specialized institutions and follow corresponding regulatory guidelines. Study design and implementation processes must meet rigorous scientific standards [3,4].

2.9 Comprehensive Management of Obesity-Related Diseases in Cats

Comprehensive management strategies are particularly important when dealing with obesity-related diseases in cats, including early screening for cardiovascular and renal diseases and the development of integrated treatment plans. Obesity not only affects cats' quality of life but also significantly increases the risk of cardiovascular disease (CVD) and chronic kidney disease (CKD). Studies show that obese cats commonly have hypertension, diabetes, and other metabolic diseases, which in turn exacerbate renal burden and lead to worsening renal function [29-30]. Therefore, early screening is crucial for identifying these potential risks. Regular blood tests and imaging assessments can help detect problems early. At the same

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time, comprehensive treatment plans for cardiovascular and renal diseases should include dietary control, appropriate exercise, and necessary pharmacological interventions.

2.9.1 Prevention of Obesity-Related Cardiovascular and Renal Diseases

Early screening and comprehensive treatment plans for obese cats are particularly important to promptly identify and address potential health risks. Monitoring obesity should incorporate multiple indicators such as body weight, heart rate, blood pressure, and renal function assessments. Research results indicate that the risk of cardiovascular disease in obese cats is significantly higher than in normal-weight cats, closely related to obesity-induced metabolic disorders [30]. Therefore, regular comprehensive health check-ups are recommended clinically, especially for middle-aged and senior cats, with a full examination every six months to enable early identification of potential cardiovascular and renal risks.

In comprehensive treatment strategies, dietary intervention is foundational. Research indicates that low-calorie, high-fiber diets aid weight loss and improve cardiovascular health. At the same time, appropriate exercise should not be overlooked, as it promotes metabolism and enhances cardiovascular function. Additionally, for hypertension and renal insufficiency caused by obesity, veterinarians may consider using ACE inhibitors to control blood pressure and reduce renal burden [29]. Treatment plans should be individualized and adjusted based on each cat's specific health status and response.

2.9.2 Association Between Obesity and Diabetes Mellitus and Key Management Points

The relationship between obesity and diabetes is primarily manifested through insulin resistance mechanisms. Excessive accumulation of adipose tissue in obese cats, especially visceral fat, often leads to impairment of insulin signaling pathways, resulting in insulin resistance [31]. This resistance reduces the efficiency of glucose utilization, ultimately leading to hyperglycemia and diabetes.

For this mechanism, management strategies should focus on weight loss and improving insulin sensitivity. Research shows that caloric restriction and increased exercise can significantly enhance insulin sensitivity in obese cats. Additionally, the use of specific drugs, such as GLP-1 receptor agonists, has shown potential for improving glycemic control [32]. Comprehensive management plans should include dietary adjustments, exercise programs, and possible pharmacotherapy to achieve better glycemic control and weight management.

2.9.3 Intervention in Chronic Inflammation and Metabolic Syndrome

Chronic inflammation plays a key role in the metabolic syndrome of obese cats, leading to a series of health problems such as diabetes and cardiovascular disease. Research indicates that adipose tissue in obese cats contains large amounts of inflammatory factors, which not only promote local inflammatory responses but also affect systemic metabolic status [33]. Therefore, anti-inflammatory treatment is an important measure to improve the health of obese cats.

Lifestyle modifications, including diet and exercise, are the foundation of anti-inflammatory treatment. Low-sugar, low-fat, high-fiber diets help reduce systemic inflammation levels. Additionally, increasing daily activity and reducing sedentary time have been shown to effectively alleviate inflammatory responses. Regarding pharmacotherapy, certain anti-inflammatory drugs or supplements, such as fish oil and antioxidants, may help alleviate chronic inflammation in obese cats [31]. The combined application of these

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measures can help improve the overall health of obese cats and reduce the risk of related diseases.

3. Conclusion

Feline obesity, as a complex multifactorial disease, is increasingly attracting attention in veterinary medicine. Through in-depth research into genetic, metabolic, inflammatory, and microbiota-related mechanisms, we can more comprehensively understand the impact of obesity on cats' quality of life and health. Obesity not only significantly reduces cats' activity levels and quality of life but also predisposes them to various complications such as diabetes, arthritis, and cardiovascular disease. These risks make obesity management an indispensable issue in veterinary practice.

Current research has revealed obesity-related gene variants (such as MC4R, POMC) and changes in the gut microbiota. These findings provide new therapeutic targets and may enable precision medicine. By integrating genomics and microbiome studies, we can better understand the biological basis of obesity and develop more effective interventions. Meanwhile, dietary regulation and exercise intervention remain core strategies for managing obese cats. Effective dietary plans must consider not only energy requirements but also nutrient balance to ensure cats' health during weight loss.

In terms of innovative drug development, GLP-1 receptor agonists and their related derivatives, based on human drug experience, are currently the most focused technological direction, with preliminary research data demonstrating their weight-loss potential. Diverse approaches, including GLP-1/GIP dual-target strategies, FGF21 agonists, SGLT2 inhibitors, long-acting formulations, oral formulations, and non-pharmacological physical interventions (such as pFUS), are all being explored. However, challenges including pharmacological safety issues due to species differences, difficulties in clinical trial execution, and lessons learned from historical drug development all indicate that cross-species drug research requires the establishment of independent evaluation systems tailored to feline metabolic characteristics.

The key to successful weight loss lies in effective communication between veterinarians and pet owners. Veterinarians need to provide scientific guidance and support, helping owners understand the health impact of obesity and develop practical weight loss plans. Pet owners should actively participate, regularly monitor their cats' weight and health status, and provide feedback to veterinarians to adjust management strategies. Only through such collaboration can the success rate of weight loss be improved.

Future research should further explore the molecular mechanisms of feline obesity and the clinical effects of interventions. We should focus on early identification and prevention of obesity to reduce its long-term impact on feline health. Additionally, as research progresses, novel pharmacotherapy strategies are expected to play a more active role in the weight loss process. Future feline obesity management may exhibit the following trends: multi-target combinations (developing from dual-target to triple-target agonists), long-acting formulations, oral administration routes, personalized therapy (combined with biomarker testing), and integrated interventions (combining drugs with prescription diets, weight monitoring, exercise guidance, etc., to form an integrated management model). Through scientific approaches including target optimization, formulation innovation, and combined interventions, feline obesity management is expected to move toward

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more precise and safer comprehensive treatment strategies.

In summary, the management of feline obesity requires multidisciplinary collaboration, advancing the field through the integration of scientific research and clinical practice. With a deeper understanding of feline obesity, we have reason to believe that the health and quality of life of cats will be significantly improved.

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Research Progress on the Molecular Mechanism and Regulatory Strategies of Abnormal Aggregation of α-Synuclein in Parkinson's Disease

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Abstract Parkinson's disease (PD) represents a multifaceted neurodegenerative condition, whose core pathological features include the gradual degeneration of dopaminergic neurons in the substantia nigra region, as well as the extensive deposition of aggregated alpha-synuclein (α-syn) within Lewy bodies distributed across the central nervous system[1]. Under normal physiological circumstances, α-syn belongs to the category of intrinsically disordered proteins, and it exerts indispensable regulatory functions in the processes of synaptic vesicle transport and neurotransmitter secretion[2]. Whereas in the pathological state related to PD, α-syn will experience conformational misfolding, oligomeric assembly, and eventually form insoluble amyloid fibrils that constitute the primary structural components of Lewy bodies[2]. This aggregation cascade not only serves as a core biomarker of PD pathological progression, but also has a close correlation with mitochondrial functional impairment, oxidative stress response and neuroinflammatory reaction, and these pathological events jointly drive the occurrence of neuronal injury and apoptosis[3][4][5].

Keywords Parkinson's disease; α-Synuclein protein; Aberrant aggregation; Molecular regulatory mechanism; Intervention strategies

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1. Introduction

The aberrant misfolding and subsequent aggregation of α-syn are widely acknowledged as core pathogenic factors driving the initiation and advancement of Parkinson's disease (PD)[1][6]. This aggregation process generally conforms to a nucleation-dependent polymerization paradigm: it commences with soluble monomeric forms, transitions through cytotoxic oligomeric intermediate states, and ultimately terminates in the generation of insoluble amyloid fibril structures[7]. Accumulating evidence indicates that soluble oligomeric species, instead of the fully assembled fibrils, serve as the main neurotoxic agents in disease pathogenesis[3][7]. These oligomeric assemblies are capable of impairing cell membrane integrity, disturbing normal mitochondrial functionality, and hindering intracellular transport processes, which ultimately triggers cellular dysfunction and degeneration[17]. The intercellular transmission of α-syn-related pathological alterations, commonly characterized as a "prion-like" mechanistic process, is broadly accepted as a prominent hallmark of PD progression[1][8][9]. Pathological α-syn aggregates can be secreted from an affected neuron into the extracellular milieu, and then internalized by adjacent neurons through pathways including extracellular vesicles (for instance, exosomes) or tunneling nanotube structures, thereby triggering the misfolding and aggregation of endogenously expressed normal α-syn[1][10]. This propagation mechanism offers a plausible explanation for the gradual spread of PD pathology from initially affected brain regions, such as the olfactory bulb and brainstem, to other functional domains of the nervous system[1][10].

2.Molecular Mechanisms of Abnormal α-Synuclein Aggregation in Parkinson's Disease

2.1 The Relationship between α-Synuclein Aggregation and Mitochondrial Dysfunction

Aberrant α-syn aggregation and mitochondrial impairment are closely interrelated, forming a vicious positive feedback cycle. Misfolded α-syn aggregates can target and accumulate within mitochondria, disrupting their normal physiological function through suppressing the activity of electron transport chain complex I, which subsequently causes a decline in ATP synthesis and elevated production of reactive oxygen species (ROS)[1][11][12][13]. Such mitochondrial functional defects conversely further promote the misfolding and aggregation process of α-syn[1][11][12]. Emerging studies have emphasized the pivotal function of mitochondrial dynamin-related protein 1 (Drp1) in the pathological progression of Parkinson's disease, as aberrant Drp1 activity is associated with α-syn-induced mitochondrial fission and neuronal death[14].

2.2 The Relationship between α-Synuclein Aggregation and Oxidative Stress

Oxidative stress serves as another pivotal element in the pathophysiological process of Parkinson's disease, exhibiting a close correlation with α-synuclein aggregation and mitochondrial dysfunction[3][5]. Reactive oxygen species produced by dysfunctional mitochondria further facilitate the covalent cross-linking

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as well as aggregation of α-synuclein[3]. On the contrary, aggregated α-synuclein itself can trigger oxidative stress and aggravate cellular injury via suppressing antioxidant defense systems, exemplified by the Nrf2-Keap1 signaling pathway[3][4]. Existing research has demonstrated that nuclease-dead Staphylococcus aureus Cas9 (dCas9) is capable of reducing α-synuclein expression, and alleviating mitochondrial DNA impairment as well as oxidative stress levels in stem cell models of Parkinson's disease derived from patients[15][16].

2.3 The Relationship between α-Synuclein Aggregation and Neuroinflammation

Neuroinflammation constitutes another core dimension of Parkinson's disease progression, which is regulated by the activation of microglia and astrocytes[17][18]. Aggregated α-syn is capable of activating microglia, inducing metabolic reprogramming in these cells, initiating the activation of the NLRP3 inflammasome, and prompting the secretion of pro-inflammatory cytokines including IL-1β, thus exacerbating the neuroinflammatory response[19][20][21][22]. Reactive astrocytes, especially those with NOX4 expression, further participate in the neuroinflammatory process in the hippocampus of PD patients via mediating the generation of pro-inflammatory cytokines and osteopontin[23][24]. Such a persistent neuroinflammatory microenvironment, conversely, facilitates α-syn aggregation and neuronal loss[1].

3.Regulatory Strategies Targeting Abnormal Aggregation of α-Synuclein

3.1 Small Molecule Inhibitors

Small molecule inhibitors are designed to disrupt the α-syn aggregation cascade via diverse modes of action, including stabilizing its non-pathogenic conformations, blocking aggregation-prone interaction interfaces, or facilitating the disassembly of preformed aggregates[7]. As an example, pyrroloquinoline quinone (PQQ) has been shown to modulate intracellular α-syn aggregate formation[27]. Bis-chalcone polyphenols have likewise exhibited disaggregation efficacy against both α-syn oligomers and mature fibrils[28]. Additionally, nanomaterials such as n-MTAB gold nanoparticles have been explored for their potential to suppress α-syn aggregation[29]. Contemporary investigations prioritize the development of small molecules functioning as pharmacological chaperones, which bind to the natively folded, physiological state of α-syn to decrease its propensity to transition into misfolded conformations[7].

3.2 Gene Editing and Gene Regulation Technologies

Gene editing and gene regulation technologies aim to directly modulate the expression levels of the SNCA gene, thereby reducing α-syn production[30]. CRISPRi technology, specifically using nuclease-dead Cas9 (dCas9), has been employed to downregulate α-syn gene expression, demonstrating reduced α-syn

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levels, decreased mtDNA damage, and oxidative stress in PD patient-derived stem cell models[15][16]. Additionally, the role of non-coding RNAs (ncRNAs) in regulating the SNCA gene and α-syn aggregation is gaining attention, offering new targets for genetic modulation[30].

3.3 Targeted Protein Degradation Techniques

Targeted protein degradation techniques, such as proteolysis-targeting chimeras (PROTACs), represent an emerging paradigm in drug discovery, designed to mediate the degradation of specific proteins via the ubiquitin-proteasome system[31]. While the application of PROTACs in PD is still in its early stages, their theoretical potential lies in selectively degrading pathological α-syn while preserving physiological α-syn[31]. Beyond PROTACs, liquid-liquid phase separation (LLPS) has also been implicated in regulating α-syn aggregation and mitophagy, providing new avenues for aggregate clearance[32].

4.Key Breakthroughs and Controversies in Basic Research

4.1 Key Breakthroughs

Structural polymorphism of α-syn: Recent progress in cryo-electron microscopy techniques has made it possible to resolve the structural polymorphs of different α-syn strains, uncovering structural variations across distinct Parkinson's disease subtypes. This provides valuable insights for the development of more targeted diagnostic and therapeutic approaches[7].

Dynamics of early folding intermediates: Single-molecule Förster resonance energy transfer (FRET) approaches have clarified the kinetic behaviors of α-syn’s early folding intermediate states, offering precise molecular insights into the triggering mechanisms of aggregation[7].

Role of astrocytes in propagation: Researches integrating humanized mouse models with microfluidic chip platforms have verified the pivotal function of astrocytes in the selective internalization and transmission of α-syn, laying a foundation for targeting glial cells to block pathological dissemination[17][33].

4.2 Existing Controversies

Dominant toxic species of pathological α-syn: No unified conclusion has been reached regarding which form of α-syn (oligomers, protofibrils, or mature Lewy bodies) exerts the strongest neurotoxic effect in PD. Although existing research findings mostly support soluble oligomers as the primary toxic entities[17], further exploration of the toxicity mechanisms underlying different aggregated species remains urgently required.

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Potential collateral damage to physiological α-syn function: A prominent hurdle for therapeutic strategies targeting α-syn lies in how to eliminate pathological aggregates while exerting no impact on the regular biological roles of endogenous α-syn, which exerts critical functions in synaptic plasticity and neurotransmitter release[10][26].

Peripheral origin hypothesis and the gut-brain axis: The "gut-first hypothesis", which puts forward that PD pathological changes might arise in the intestinal tract and transmit through the gut-brain axis, is attracting increasing focus[20]. Nevertheless, the spatiotemporal reliability of α-syn transmission in the intestinal tract and its direct association with cerebral pathological changes still need more evidence from single-cell tracking studies[20].

Clinical translation bottlenecks: While numerous small-molecule inhibitors have exhibited promising effects in cell-based assays and animal experimental models, the vast majority of such agents cannot achieve satisfactory therapeutic outcomes in clinical studies, which is primarily attributed to problems including inadequate drug concentration in human cerebrospinal fluid and unintended off-target pharmacological activities[7][26].

5. Conclusion

Taken together, the aberrant accumulation of α-syn in Parkinson’s disease constitutes a multi-stage process encompassing sophisticated molecular and cellular cascades, which is closely correlated with mitochondrial impairment, oxidative damage, and neuroinflammatory responses. Subsequent investigations will persist in centering on illuminating the exact molecular pathways underlying α-syn aggregation, formulating more selective and targeted intervention approaches, and resolving obstacles related to drug delivery and clinical transformation, in order to provide genuinely effective disease-modifying treatments for individuals suffering from PD.

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