Insights into nuciferine: A natural multifunctional bioactive alkaloid (Review)

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Abstract. Nuciferine (NF), an aporphine alkaloid extracted from the leaves of *Nelumbo nucifera* Gaertn., has attracted considerable attention due to its wide range of pharmacological properties. The present review elucidates the multifaceted biological activities of NF, which encompass immunomodulatory and antioxidative effects, neuroprotective, musculoskeletal-protective, cardioprotective, metabolism-regulating, antipsychotic and anticancer effects. Notably, the underlying mechanisms involve the modulation of key signaling pathways, such as AMP-activated protein kinase, peroxisome proliferator-activated receptor α, TGF-β1, Toll-like receptor 4/NF-κB and PI3K/Akt, which contribute to its metabolic regulation and anticancer properties. Furthermore, the present review discusses the findings of molecular docking simulations using an *in silico* approach, which offer valuable insights into the interactions of NF with various biological targets. However, despite its therapeutic potential, several challenges remain in translating the use of NF into clinical applications. These include concerns regarding its toxicity or undesirable effects, as well as issues associated with its bioavailability and drug delivery profile. Future research should focus on addressing these challenges to fully realize the therapeutic potential of NF across a range of diseases.

Contents

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Abbreviations: β_2-AR, β_2-adrenergic receptor; AMPK, AMP-activated protein kinase; AUC, area under the curve; BA, bile acid; BBB, blood brain barrier; COX-2, cyclooxygenase-2; EGCG, epigallocatechin-3-gallate; EMT, epithelial-to-mesenchymal transition; ER$^-$, estrogen receptor-negative; H_2O_2, hydrogen peroxide; HBXIP, hepatitis B virus X-interacting protein; HCC, hepatocellular carcinoma; HFD, high-fat diet; MCAO, middle cerebral artery occlusion; NAFLD, non-alcoholic fatty liver disease; NFEG-microgel, NF-EGCG double-encapsulated microgel; NF, nuciferine; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; OA, osteoarthritis; OSCC, oral squamous cell carcinoma; PC, pancreatic cancer; PCP, phencyclidine; PLA, polylactic acid; PPAR, peroxisome proliferator-activated receptor; RA, rheumatoid arthritis; PTGS2, prostaglandin-endoperoxide synthase 2; ROS, reactive oxygen species; SPR, surface plasmon resonance; STZ, streptozocin; TAS2R46, taste 2 receptor member 46; TFEB, transcription factor EB; TLR4, Toll-like receptor 4; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells

Key words: NF, biological activity, molecular mechanism, molecular docking, drug delivery system

7. Comparative analysis and integrative discussion
8. Conclusions, current challenges and future research directions

1. Introduction

Natural products have historically served as a notable reservoir for drug discovery, with plant-derived alkaloids representing one of the most successful classes of therapeutic agents (1). *Nelumbo nucifera* Gaertn., also known as sacred lotus, has served as a fundamental component in traditional Chinese medicine for >2,000 years to treat various disorders, including insomnia, hematuria and chronic dyspepsia (2). The medicinal properties of this plant are largely due to its diverse array of bioactive alkaloids, with nuciferine [NF; $C_{19}H_{21}NO_2$; Chemical Abstracts Service (CAS) no. 475-83-2] being a particularly notable aporphine-type compound that has shown promise in recent research (3).

NF (Fig. 1), also known as Sanjoinine E, VLT049 and (-)-NF, is a natural aporphine alkaloid widely used in traditional Chinese medicine. While *Nelumbo nucifera* Gaertn. remains the most extensively studied source of NF, this bioactive compound has also been detected in multiple other plant species, including *Annona crassiflora* Mart (4), *Michelia champaca* L (5), *Onychopetalum amazonicum* R.E.Fr (6) and Jujubae Fructus (https://www.tcmsp-e.com/molecule.php?qn=7213). Initially recognized for its sedative and anxiolytic properties, which align with its traditional medicinal uses, NF has recently garnered notable attention due to its diverse pharmacological effects (7). Over the past decade, preclinical research has uncovered its ability to modulate multiple critical pathways involved in various diseases (3,8). Accumulating evidence has demonstrated that NF modulates key pathophysiological pathways implicated in inflammatory diseases [including the Toll-like receptor 4 (TLR4)/NF-κB and NOD-like receptor family pyrin domain containing 3 (NLRP3) pathways] (9,10), neurodegenerative conditions (such as the JAK2/STAT3 pathway) (11), musculoskeletal degeneration (such as the MAPK/NF-κB pathway) (12), cardiovascular dysfunction [including thePI3K/Akt and nitric oxide (NO)/cGMP pathway] (13), metabolic disorders [such as the AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR) α pathways] (14,15) and oncogenesis (for example, the PI3K/Akt, Wnt/β-catenin and STAT3 pathways) (16-18). Furthermore, NF may combat obesity by modulating metabolic pathways and reducing fat accumulation (15). NF also effectively reduces lipid concentrations by inhibiting cholesterol synthesis and cholesterol esterase activity (19). Additionally, NF exhibits antidiabetic potential, regulating blood glucose levels and enhancing insulin sensitivity (20). The anti-inflammatory effects of NF are primarily mediated through its ability to regulate oxidative stress, metabolic signaling and gut microbiota (21). The neuroprotective properties of NF stem from its interactions with neurotransmitter receptors such as 5-HT_{2A}, 5-HT_{2C}, 5-HT_{2B} and D_2, which in turn modulate neurosignaling transduction (22). Furthermore, NF has been shown to suppress the proliferation and migration of melanoma cells, suggesting its potential as an antitumor agent (16). This expanding body of research highlights the multifaceted therapeutic potential of NF across a wide range of health conditions.

Despite this expanding body of evidence, the literature on NF remains fragmented and lacks synthesis, presenting several major challenges. First, the interactions of NF with multiple receptors, such as dopaminergic, serotonergic and adrenergic systems, and signaling pathways are well-documented; however, the relative importance of these targets in different disease contexts remains unclear. A number of studies have focused on isolated mechanisms without exploring how these pathways interact or integrate. Second, the clinical potential of NF is limited due to its low water solubility and modest oral bioavailability (~58% in rodents), as shown by Ye *et al* (23). Although researchers have tested new delivery systems (24-26), there is no thorough evaluation of their effectiveness or scalability for broader use. Third, safety concerns arise from NF-mediated inhibition of key cytochrome P450 (CYP) enzymes, including CYP2D6 (27) and CYP1A2 (28), which could lead to drug interactions, yet comprehensive toxicity studies and human pharmacokinetic data are still missing. Finally, while computational models have predicted numerous potential protein targets for NF (29-31), experimental validation is limited, leaving uncertainties about its true binding affinities and functional importance in biological systems.

The present review therefore offers a comprehensive analysis of NF, exploring its diverse biological activities and underlying molecular mechanisms across seven key therapeutic areas. The safety profile of NF is assessed by examining toxicity data and pharmacokinetic challenges while also evaluating innovative drug delivery approaches such as liposome formulations, poly lactic-co-glycolic acid (PLGA) nanoparticles and hydrogel scaffold systems. The discussion integrates computational docking predictions with existing experimental evidence, identifying areas where further validation is needed. Synthesizing these multifaceted aspects reveals the promising potential of NF as a novel therapeutic candidate for various medical conditions, facilitating the integration of traditional knowledge with modern pharmaceutical development.

2. Chemistry of NF

NF, also known as Sanjoinine E, is a natural alkaloid metabolite predominantly isolated from the leaves of the sacred lotus plant, *Nelumbo nucifera* Gaertn (3,8). This metabolite is characterized by the molecular formula $C_{19}H_{21}NO_2$ and possesses a molar mass of 295.4 g/mol (3). It is a colorless liquid with a pungent odor, and features a tetracyclic core, one nitrogen atom and a chiral center. The CAS registry number of NF is 475-83-2 (http://www.badd-cao.net:2345/browse/compound/C0586). The International Union of Pure and Applied ChemistrynameofNFis(6aR)-1,2-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo(de,g)quinoline (http://47.92.70.12/Detail/?v=HBIN037568&label=Ingredient). NF is notable for its high solubility in low-polarity organic solvents, such as benzene, ether, chloroform and halogenated alkanes. It also dissolves well in hydrophilic organic solvents, such as acetone and ethanol. However, its solubility in water is low or almost negligible, which can limit its bioavailability. NF exhibits a

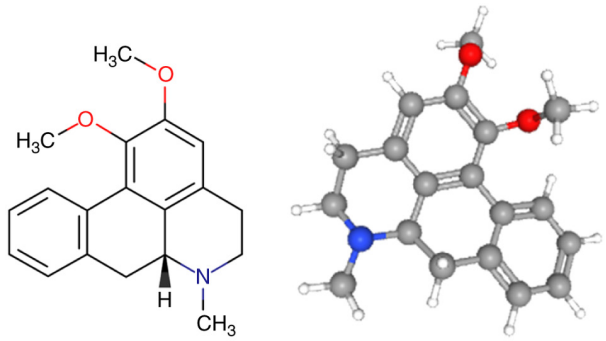

Figure 1. Structure of nuciferine.

characteristic melting point of 168˚C. Fig. 1 presents both the 2D and 3D structures of NF, which can be accessed via the PubChem database (https://pubchem.ncbi.nlm.nih.gov/compound/10146).

3. Multifunctional biological activities of NF

As a natural alkaloid metabolite, NF has garnered considerable attention for its diverse pharmacological effects, which encompass immunomodulatory and antioxidative effects, neuroprotection, osteogenic activity, cardiovascular protection, metabolic regulation, antipsychotic and anticancer activities. The diverse biological activities of NF are comprehensively summarized in Table SI and illustrated in Fig. 2.

Immunomodulatory and antioxidative effects. Inflammation represents a fundamental protective response that defends the human body from various infections agents (32). Nevertheless, chronic inflammation processes are frequently implicated in the pathogenesis of several inflammatory disorders, including acute kidney injury (33,34), acute lung injury (10), mastitis (35), ulcerative colitis (9,36) and cerebral ischemia-reperfusion injury (37). Given the key role of inflammation in disease pathology, NF has demonstrated considerable potential in therapeutics as an anti-inflammatory agent. In fructose-fed rats, NF mitigates renal injury by alleviating inflammatory responses via suppressing the TLR4/PI3K/NF-κB pathway and activation of the NLRP3 inflammasome (33). Similarly, in lipopolysaccharide (LPS)-induced acute lung injury, NF demonstrates anti-inflammatory effects by suppressing the TLR4-mediated pathway, thereby reducing inflammation and tissue damage (10). NF has also been shown to exhibit potential in mitigating LPS-induced mastitis in mice through suppression of the TLR4/NF-κB signaling pathway (35). In addition, in acute kidney injury models, it protects against folic acid-induced damage by inhibiting ferroptosis (34). Furthermore, NF attenuates inflammatory responses in LPS-stimulated macrophages and microglial cells via activation of PPARγ (38) and inhibition of p38 MAPK/activating transcription factor 2 signaling pathways (39). In an ulcerative colitis model, NF has been shown to modulate immune function and intestinal microbial composition, restoring the balance of T-cell subsets and improving colonic health (9). NF also suppresses MAPK/NF-κB and NLRP3/caspase 1 pathways, reducing cytokines and improving the disease activity index (DAI) and histological alternations in colitic mice (36). In cerebral ischemia-reperfusion injury, NF exerts its protective effects through modulation of actions via the PI3K/Akt/NF-κB pathway, reducing inflammation and improving cognitive and motor functions (37). These findings underscore the potential of NF as a therapeutic agent for various inflammatory diseases by modulating key signaling pathways and immune responses.

In addition to its immunomodulatory effects, NF has been reported to exhibit antiviral activity (40,41). For example, in a comprehensive structure-activity relationship investigation, Kashiwada *et al* (40) reported that NF exhibited potent anti-HIV efficacy, with an EC_{50} of 0.8 μg/ml and a favorable therapeutic window (therapeutic index, 36.3). NF has also been demonstrated to possess both direct virucidal and antiviral activities against the SARS-CoV-2 virus, with a virucidal EC_{50} of 13.24 μM, and an antiviral EC_{50} for inhibiting viral infection of 30.59 μM (41). These findings highlight the potential of NF in combating viral infections. Oxidative stress, defined by an overabundance of reactive oxygen species (ROS) and reactive nitrogen species, serves a substantial role in the aging process and the development of various diseases (42-44). The antioxidant properties of NF have also been extensively studied. NF has been shown to mitigate hydrogen peroxide (H_2O_2)-induced oxidative stress in cardiomyocytes and fibroblasts, demonstrating cardioprotective and anti-aging properties by downregulating pro-inflammatory cytokines and maintaining cellular homeostasis (45,46). In a mouse model, NF has been shown to improve the survival rate of random skin flaps through multiple functions (including promoting angiogenesis, reducing oxidative stress, inflammation and apoptosis), which effectively promotes vascular formation, mitigates oxidative damage and stimulates autophagy by mediating transcription factor EB (TFEB) nuclear translocation via the AMPK/mTOR signaling pathway (47). Nuciferine has also been reported to have applications in nutraceuticals as a gummy bear supplement with antioxidant and antiproliferative potential, by reducing endogenous ROS levels under oxidative stress (48). In summary, NF exhibits both immunomodulatory and antioxidant properties, making it a potential therapeutic agent for managing diseases associated with inflammation and oxidative stress.

Regulation of metabolism by NF. Emerging evidence has highlighted NF as a potential therapeutic agent for the management of diverse metabolic disorders, including obesity, hepatic steatosis, lipotoxicity, nephrotoxicity and hyperuricemia. Its diverse mechanisms of action involve the activation of key signaling pathways such as AMPK (15), PPARα (49) and TFEB (50) pathways, as well as the regulation of intestinal microbial composition and bile acid (BA) metabolism. These effects collectively contribute to its benefits in metabolic health.

NF has demonstrated a range of pharmacological properties, including the ability to stimulate insulin secretion in pancreatic β cells, which may offer a new therapeutic option for diabetes management (51). Additionally, NF has shown the anti-hyperuricemic and anti-inflammatory effects in reducing serum urate levels and interleukin-1β (IL-1β) secretion in mice, suggesting its potential use in treating hyperuricemia with

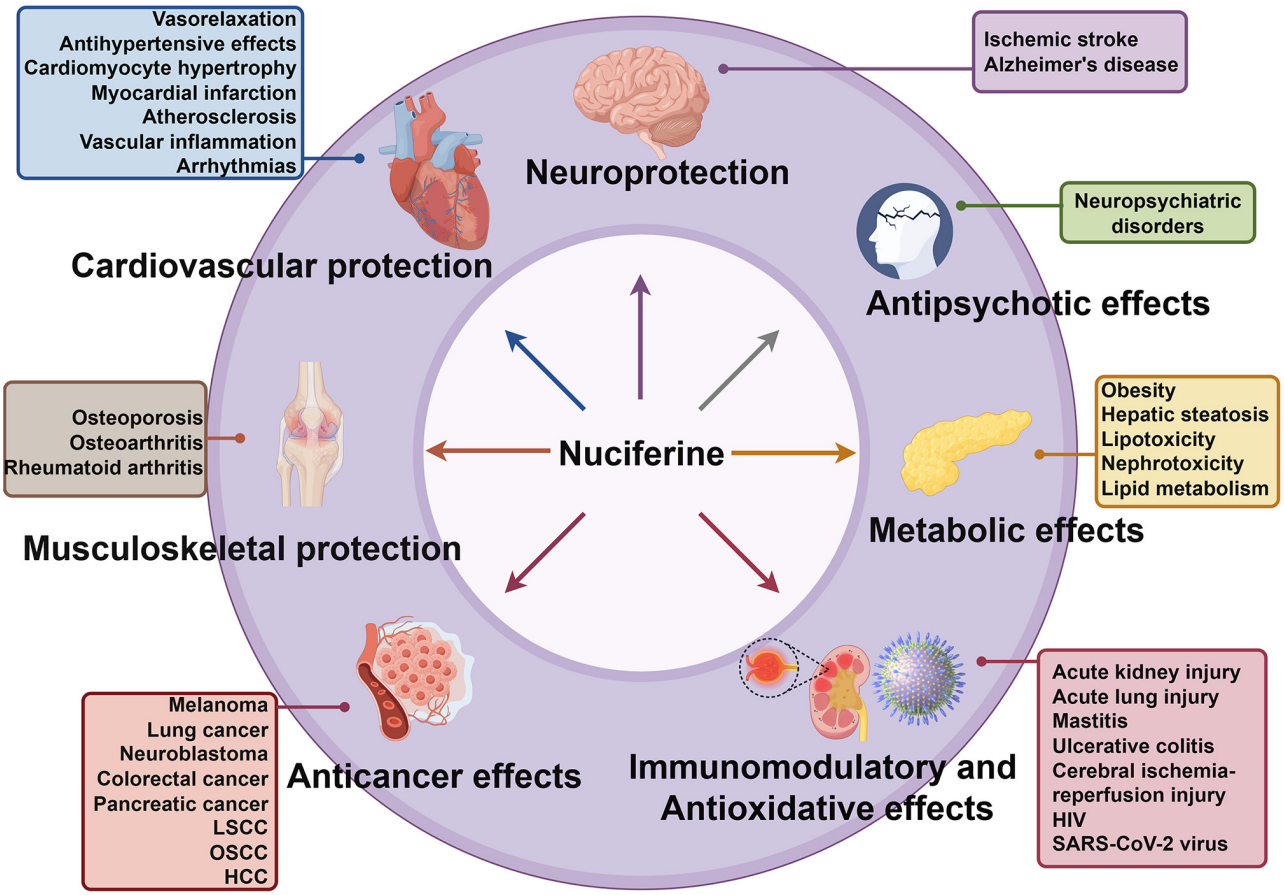

Figure 2. Multifunctional biological activities of nuciferine. This figure was drawn by Figdraw (https://www.figdraw.com). OSCC, oral squamous cell carcinoma; HCC, hepatocellular carcinoma; LSCC, laryngeal squamous cell carcinoma.

kidney inflammation (52). Metabolism studies have elucidated various phase I and II metabolites of NF in rats and mice, revealing key metabolic pathways such as oxidation, demethylation, glucuronidation and sulfation (53-55). Furthermore, the interaction of NF with metformin, a common antidiabetic drug, has been explored, indicating that NF may attenuate hepatic metformin accumulation, potentially affecting the glucose-lowering effect of metformin (56). Metabolomics and gut microbiota analyses have also elucidated the glycine, serine and threonine metabolism regulatory mechanisms of NF in hyperuricemia, highlighting its impact on metabolic pathways and gut microbiota (57).

NF has shown promising effects in managing obesity and hepatic steatosis. In high-fat diet (HFD)-fed mice, NF has demonstrated notable efficacy in attenuating body weight, fat accumulation and improving glycolipid profiles by activating the AMPK-mediated fatty acid synthase/hormone sensitive lipase pathway, promoting fatty acid oxidation in the liver and thermogenesis in white adipose tissue (58). Another study has demonstrated that NF ameliorates glucose intolerance, diminishes lipid accumulation and enhances glycogen storage in hepatocytes of C57BL/6J mice with HFD-induced gestational diabetes mellitus. Additionally, it may restore intestinal microbial balance by promoting the abundance of beneficial genera, including *Akkermansia*, *Lactobacillus* and *Bifidobacterium*, and suppressing pathogenic bacteria, such as *Staphylococcus* and *Escherichia-Shigella* (59).

NF may also protect against non-alcoholic fatty liver disease (NAFLD) by activating the TFEB-mediated autophagy-lysosomal pathway through direct interaction with the regulatory subunit hepatitis B virus X-interacting protein (HBXIP) and inhibiting mTORC1 activity, thereby reducing hepatic lipid accumulation and insulin resistance (60). In HFD-fed rats, NF has been reported to modulate BA metabolism and gut microbiota, altering the composition of colonic BA, promoting BA synthesis and excretion, and inhibiting BA reabsorption. It also reduces the abundance of bile salt hydrolase-producing and 7α-dehydroxylation bacteria, leading to increased conjugated BAs, which contributes to its protective effects against HFD-induced hepatic steatosis (61).

NF has been shown to mitigate non-esterified fatty acid-induced lipotoxicity in bovine mammary epithelial cells by activating the LKB1/AMPK signaling pathway, which is a key pathway for lipid metabolism and energy homeostasis (62). In another study, NF has been reported to block MIB2-mediated caspase recruitment domain protein family member 6 polyubiquitination and degradation, thereby reducing high fructose-induced lipid accumulation in hepatocytes, highlighting its potential in preventing fatty liver disease (63). Furthermore, NF alleviates hepatic steatosis and ferroptosis in NAFLD mice by modulating the PPARα signaling pathway, suggesting its therapeutic potential for NAFLD (49).

NF protects against obesity-induced nephrotoxicity by reducing lipid accumulation, inflammation and oxidative stress in kidneys and renal cells through the AMPK pathway (15). Additionally, NF may prevent obesity by activating brown adipose tissue through the TFEB/PPARλ coactivator 1-α (PGC-1α) pathway in excessive free fatty acid-induced oxidative injury model, enhancing energy expenditure and improving metabolic health (50,64).

NF has been extensively studied for its potential health benefits, particularly in the context of lipid metabolism and liver health (19-21,65-70). NF can markedly reduce body weight gain, liver and visceral fat weight, and improve serum and hepatic lipid profiles in HFD-induced hamster models (65). *In vitro* studies using L02 and HepG2 cells have demonstrated that NF reduces lipid accumulation and oxidative stress by activating the AMPK and PPARα pathways, suggesting its potential therapeutic applications for NAFLD (58,66). Further mechanistic studies have revealed that NF downregulates Per-Arnt-Sim kinase expression, which is associated with reduced lipogenesis and inflammation in HepG2 cells (67). Additionally, NF has been shown to inhibit lipogenesis and promote glucose uptake in insulin-resistant 3T3-L1 adipocytes by activating the AMPK signaling pathway (20). In a murine model of type 2 diabetes mellitus induced by HFD and streptozocin (STZ), NF has been shown to improve glucose tolerance, insulin resistance and hepatic steatosis through the PPARα/PGC-1α pathway (68). Similar protective effects have been observed in STZ-induced diabetic rats, where NF down-regulated lipogenesis associated genes (e.g. ACC2, PPAR-α and CPT-1α) and up-regulated lipolysis and fatty acid β-oxidation associated genes (e.g. SREBP-1c, LXR-a, ACC1, SCD-1, FAS, and DGAT-2) to reduce steatosis and liver injury (69). In broiler chickens, dietary NF reduces fat deposition by controlling triglyceride and cholesterol concentrations, highlighting its potential in animal nutrition (19). Furthermore, the anti-hyperlipidemic effects of NF have been associated with the liver steatosis-alleviating and anti-hyperglycemic abilities to modulate gut microbiota, particularly by enriching *Akkermansia muciniphila* (21). Finally, in 3T3-L1 preadipocytes, NF can inhibit cell proliferation and lipid accumulation by downregulating key lipogenic genes and promoting the expression of adipokines, such as FGF21 and ZAG, suggesting its potential as a therapeutic agent for obesity (70). In summary, the benefits of modulating lipid metabolism, and potential to improve liver health and enhance metabolic health, highlight the potential of NF as a novel therapeutic agent for the management of various metabolic disorders.

Neuroprotective activity of NF. The neuroprotective effects of NF are displayed in its potential to combat various neurological disorders, including ischemic stroke (71,72) and Alzheimer's disease (73). Its considerable brain penetration and potential as a neuropharmacological agent highlight its therapeutic potential.

Wu *et al* (72) elucidated the anti-ischemic stroke mechanism of NF in a rat model of middle cerebral artery occlusion (MCAO) by utilizing serum metabolomics. NF markedly improved neurological deficit scores (according to the Longa scoring system), reduced cerebral infarction and edema and modulated the metabolic pathways involved in energy metabolism, inflammation and lipid metabolism (72). Metabolic changes were analyzed using ^{1}H nuclear magnetic resonance spectroscopy, revealing 19 metabolites and nine key metabolic pathways involved in the therapeutic effects of NF, including amino acid metabolism, fatty acid metabolism and antioxidant pathways (11). Chen *et al* (74) further revealed that NF markedly alleviated neurological deficits, reduced infarct volume and regulated lipid metabolism pathways such as arachidonic acid metabolism, sphingolipid metabolism and the PPAR signaling pathway on MCAO-induced brain injury in rats through transcriptomic analysis. Li *et al* (71) demonstrated that NF maintained blood-brain barrier (BBB) integrity in ischemic stroke through suppression of the JAK2/STAT3 signaling pathway, thereby exhibiting neuroprotective properties. Mechanistically, NF was shown to protect the BBB structure via dual mechanisms: Attenuating endothelial cell apoptosis and mitochondrial impairment while simultaneously restoring tight junction protein balance (71). The findings of this previous study provide experimental evidence supporting the therapeutic efficacy of NF in improving energy metabolism and protecting neurons in ischemic stroke, thereby suggesting a pharmacological foundation for potential application in ischemic neurological disorders.

Khan *et al* (73) explored the anti-Alzheimer's disease effect of NF in alloxan-induced diabetic rats. NF markedly reduced blood glucose levels, improved body weight and enhanced antioxidant enzyme activities. It also inhibited lipid peroxidation and restored acetylcholinesterase activity in the brain, indicating potential therapeutic applications for diabetes and Alzheimer's disease. Ye *et al* (23) investigated the pharmacokinetics of NF and its associated metabolite N-nornuciferine in rats, revealing their rapid absorption and notable brain penetration. NF exhibited an oral bioavailability of 58.13%, whereas N-nornuciferine had an oral bioavailability of 79.91%. Both metabolites were found to have a relatively wide volume of distribution and slow elimination half-lives, suggesting their potential as neuropharmacological agents. In summary, the neuroprotective effects of NF are attributed to its ability to modulate multiple pathways and cellular processes. However, further research is required to elucidate its detailed mechanisms of action and to translate these findings into clinical applications.

Musculoskeletal protective effects of NF. Musculoskeletal diseases impose a considerable economic burden on individuals and social-care systems, encompassing conditions such as osteoporosis, osteoarthritis (OA), rheumatoid arthritis (RA), gout, lower back pain and psoriatic arthritis (75). Previous studies have extensively explored the therapeutic potential of NF in osteoporosis (76), OA (77,78) and RA (79,80), revealing its multifaceted benefits in these conditions.

NF has demonstrated notable promise in preventing bone loss in osteoporosis. In ovariectomized mice, NF has been reported to disrupt the maturation of multinucleated osteoclasts and enhance type H vessel formation through the inhibition of MAPK and NF-κB signaling pathways, both in *in vitro* and *in vivo* models (76). Additionally, NF suppresses glycolysis and ROS production by inhibiting the expression of glycolysis-related genes (such as hexokinase 2, pyruvate kinase M2 and lactate dehydrogenase A) and NADPH oxidase

1, while enhancing antioxidant enzyme expression during osteoclastogenesis (12). These mechanisms collectively contribute to the prevention of bone loss and the maintenance of bone health.

NF alleviates OA progression by inhibiting the production of inflammatory cytokines and targeting the PI3K/Akt/NF-κB signaling pathway. This results in reduced degradation of the extracellular matrix, decreased joint swelling and cartilage protection (77). Peng *et al* (78) further revealed that NF markedly reduced the production of inflammatory mediators, such as inducible NO synthase, prostaglandin E2 and IL-6 in IL-1β-induced chondrocytes through the PTEN/Akt/NF-κB signaling pathway. By modulating these pathways, NF effectively mitigated cartilage degradation and joint inflammation in OA.

In RA, NF has shown efficacy in reducing joint swelling, synovial hyperplasia, cartilage damage and inflammatory infiltration in rats by inhibiting the proliferation and invasion of fibroblast-like synoviocytes and rectifying the T-helper 17/T regulatory imbalance in collagen-induced arthritis (79). Kulhari *et al* (80) also demonstrated that NF treatment markedly reduced joint swelling, inflammatory cytokines (TNF-α and IL-1β) and oxidative stress markers (including malondialdehyde, superoxide dismutase and glutathione) in the paw tissue by inhibiting the TLR4/NF-κB/MAPK signaling axis in complete Freund's adjuvant (CFA)-induced arthritic rats. These findings highlight the ability of NF to modulate key inflammatory and immune pathways involved in RA. In conclusion, the advantages of NF in osteoporosis, OA and RA suggest its potential as a novel therapeutic agent for inflammation and bone related diseases.

Cardiovascular protective effects of NF. NF has emerged as a promising therapeutic agent for a wide range of cardiovascular conditions, demonstrating multifaceted benefits such as inducing vasorelaxation (81), antihypertensive effects (82), reducing cardiomyocyte hypertrophy (83), mitigating cardiotoxicity (84), protecting against myocardial infarction (13,85,86), regulating atherosclerosis (87), alleviating vascular inflammation (88) and arrhythmias (89). The present review summarizes the key findings and mechanisms underlying the cardiovascular effects of NF.

NF has been shown to induce vasorelaxation in rat mesenteric arteries through both endothelium-dependent and independent mechanisms. Specifically, it activates NO production and regulates calcium levels in vascular smooth muscle cells (VSMCs) (81). Similarly, NF exhibits vasodilatory effects on the rat thoracic aorta, mediated through the NO/cGMP signaling pathway and calcium regulation, indicating its potential as an antihypertensive agent (82).

In vitro and *in vivo* studies have revealed that NF reduces angiotensin II-induced cardiomyocyte hypertrophy by attenuating oxidative stress and apoptosis (45,83,90). Additionally, NF mitigates doxorubicin-induced cardiotoxicity by enhancing endogenous antioxidants and inhibiting caspase 3/7 activity (84). NF protects against isoproterenol-induced myocardial infarction in Wistar rats, normalizing heart rate and preventing pathological changes in heart and liver tissues (85). It also reduces vascular leakage and improves cardiac function in acute myocardial infarction by regulating the PI3K/Akt pathway, thereby preserving endothelial barrier function (13). Furthermore, NF enhances cardiac function in myocardial ischemia-reperfusion injury through the upregulation of PPARγ and the suppression of cardiomyocyte apoptosis (86).

NF shows potential in treating atherosclerosis. In apolipoprotein E (-/-) mice fed a HFD, NF has been shown to regulate the proliferation and migration of VSMCs by targeting the Calm4/MMP12/Akt pathway, thereby reducing atherosclerotic plaque formation (87). In the context of vascular inflammation, NF induces autophagy to alleviate vascular cell adhesion molecule 1 activation via the Akt/mTOR/AP1 pathway, thus protecting against cardiovascular events (88). NF analogs have demonstrated efficacy in treating arrhythmias by blocking calcium, voltage-gated sodium and potassium channels, thereby regulating the action potential (89). In conclusion, the broad-spectrum cardiovascular benefits of NF are attributed to its ability to regulate multiple pathways and cellular processes, making it a potential new therapeutic agent for the treatment of various cardiovascular diseases.

Antipsychotic effects of NF. The pharmacological profile of NF was comprehensively characterized by Farrell *et al* (22) through both *in vitro* and *in vivo* assays. The findings revealed that NF exhibited a complex pharmacological profile (e.g. blocking head-twitch responses and discriminative stimulus effects of a 5-HT2A agonist) similar to certain antipsychotic drugs, demonstrating potential antipsychotic-like effects in animal models. The aforementioned study emphasized the interactions of NF with multiple receptors and its impact on locomotor activity and prepulse inhibition, indicating potential therapeutic application for neuropsychiatric disorders. The receptor profile of NF shares similarities with aripiprazole-like antipsychotic drugs (22). Specifically, NF functions as an antagonist at 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, an inverse agonist at 5-HT_7 receptors, a partial agonist at D_5, D_2 and 5-HT_6 receptors, and an agonist at D_4 and 5-HT_{1A} receptors, while also inhibiting the dopamine transporter (VMAT2) (22). In rodent models relevant to antipsychotic pharmacology, NF has been reported to suppress head-twitch responses and discriminative stimulus effects elicited by a 5-HT_{2A} agonist, produce a clozapine discriminative stimulus, potentiate amphetamine-induced locomotor activity, attenuate phencyclidine (PCP)-induced locomotor activity and reverse PCP-induced disruption of prepulse inhibition, all without causing catalepsy. The receptor interaction profile of NF resembles, but is not identical to, that of several established antipsychotic agents, indicating that NF exhibits several properties consistent with an atypical antipsychotic profile (22). The pharmacological profile of NF suggests that it possesses atypical antipsychotic-like actions, making it a promising candidate for the treatment of neuropsychiatric disorders. Its ability to modulate multiple neurotransmitter systems while avoiding catalepsy is particularly noteworthy, as it may offer therapeutic benefits with fewer side effects compared with existing antipsychotic drugs.

Anticancer effects of NF. Increasing research has demonstrated that NF may exert considerable influence over various aspects of cancer biology, including cell proliferation, apoptosis, autophagy, metastasis, invasion, transcription and

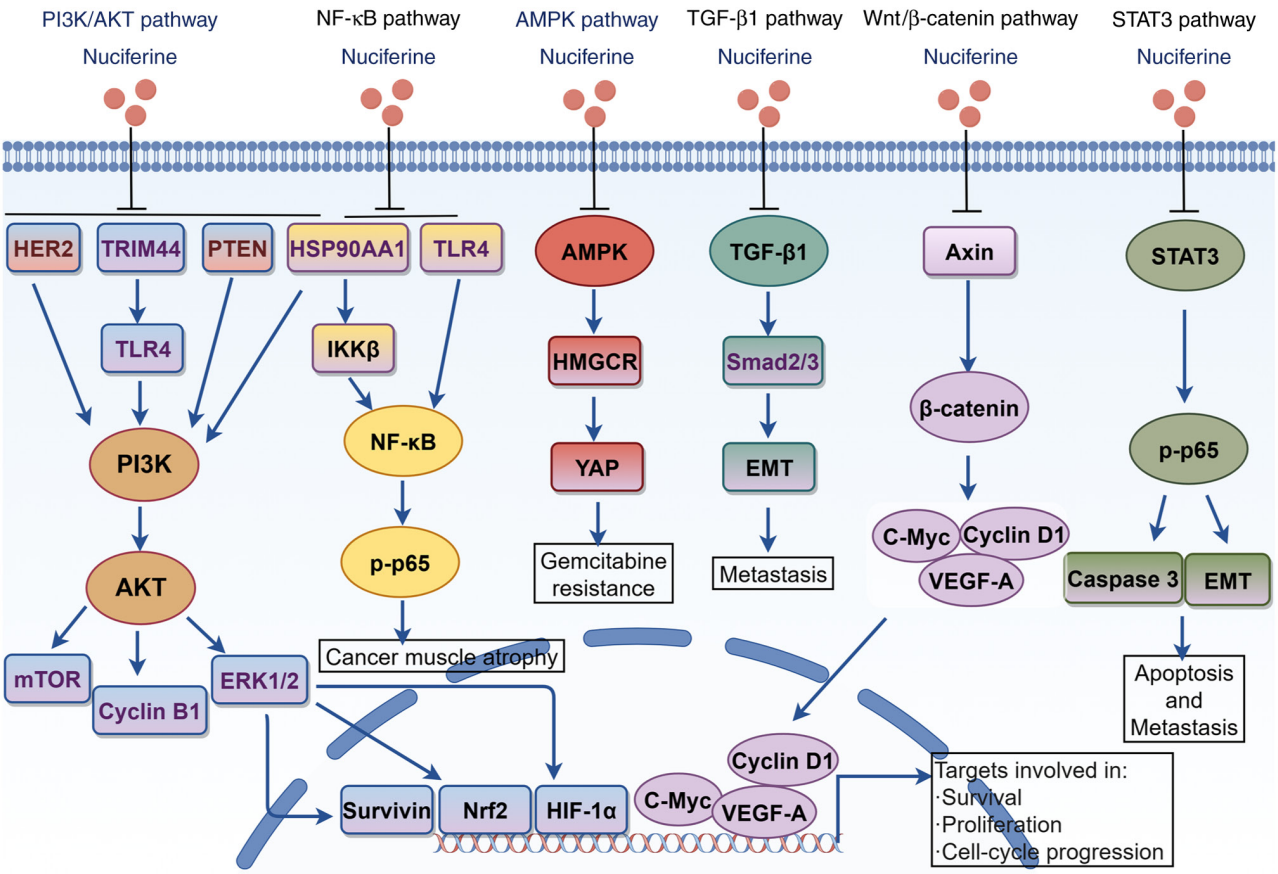

Figure 3. Anticancer effects of nuciferine in various types of cancer through different molecular signaling pathways. This figure was drawn by Figdraw (https://www.figdraw.com). TRIM44, tripartite motif containing 44; TLR4, Toll-like receptor 4; HSP90AA1, heat shock protein 90 α family class A member; p-, phosphorylated; AMPK, AMP-activated protein kinase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HIF-1α, hypoxia inducible factor-1α; YAP, yes-associated protein; Nrf2, nuclear factor erythroid 2-related factor 2; VEGF-A, vascular endothelial growth factor A; EMT, epithelial-mesenchymal transition.

drug-resistance. These effects have been observed across multiple types of cancer, such as melanoma (16,91,92), lung cancer (18,93,94), neuroblastoma (95), colorectal cancer (96,97), breast cancer (98-100), pancreatic cancer (PC) (101), laryngeal squamous cell carcinoma (102), oral squamous cell carcinoma (OSCC) (17) and hepatocellular carcinoma (HCC) (103). In these types of cancer, NF modulates several signaling pathways, such as the PI3K/Akt pathway in lung cancer and neuroblastoma (95,104), the NF-κB pathway in melanoma (16), the AMPK pathway in PC (101), the TGF-β1 signaling pathway in estrogen receptor-negative (ER^-) breast cancer (99), the Wnt/β-catenin signaling in non-small cell lung cancer (NSCLC) (18) and colon cancer (96), and the STAT3 signaling pathway in OSCC (17) (Fig. 3). NF also regulates the expression of different genes associated with factors, such as tumor cell proliferation, cell cycle progression, programmed cell death, autophagic pathways, metastasis and transcription (Fig. 4). Collectively, these above studies provide substantial evidence that NF is a promising multi-targeting agent for the prevention and treatment of various types of cancer. The mechanisms underlying the anticancer effects of NF are briefly summarized in Table SII.

PI3K/Akt signaling pathway. The PI3K/Akt signaling pathway serves as a fundamental regulatory axis governing a diverse array of cellular functions, including cell proliferation, survival, growth and metabolism (104). Its dysregulation is a hallmark of several types of cancer, contributing notably to tumorigenesis. The pathway is often activated by mutations or amplifications in its metabolites, leading to enhanced oncogenic signaling. For example, Liu *et al* (97) showed that NF combined with paclitaxel considerably inhibited lung cancer growth without causing notable toxicity, positioning NF as a promising multidrug resistance (including paclitaxel, doxorubicin, docetaxel and daunorubicin) sensitizer by suppressing the PI3K/Akt/ERK pathway, reducing the activation of hypoxia inducible factor-1α and nuclear factor erythroid 2-related factor 2 (Nrf2) in an A549/T xenograft mouse model.

An *et al* (105) revealed that NF exhibited protective effects against muscle wasting associated with lung cancer cachexia by modulating the Akt/mTOR signaling cascade through direct interaction with heat shock protein 90 α family class A (HSP90AA1). Qi *et al* (95) revealed that NF exerted its effects by suppressing the PI3K/Akt signaling pathway and lowering IL-1 concentrations in *in vitro* and *in vivo* models of neuroblastoma. Li *et al* (102) reported that NF reduced the expression of tripartite motif containing 44 and TLR4 proteins in a dose-dependent manner, inhibiting activation of the Akt signaling pathway. Li *et al* (103) demonstrated that NF inhibited HCC cell proliferation in a concentration-dependent

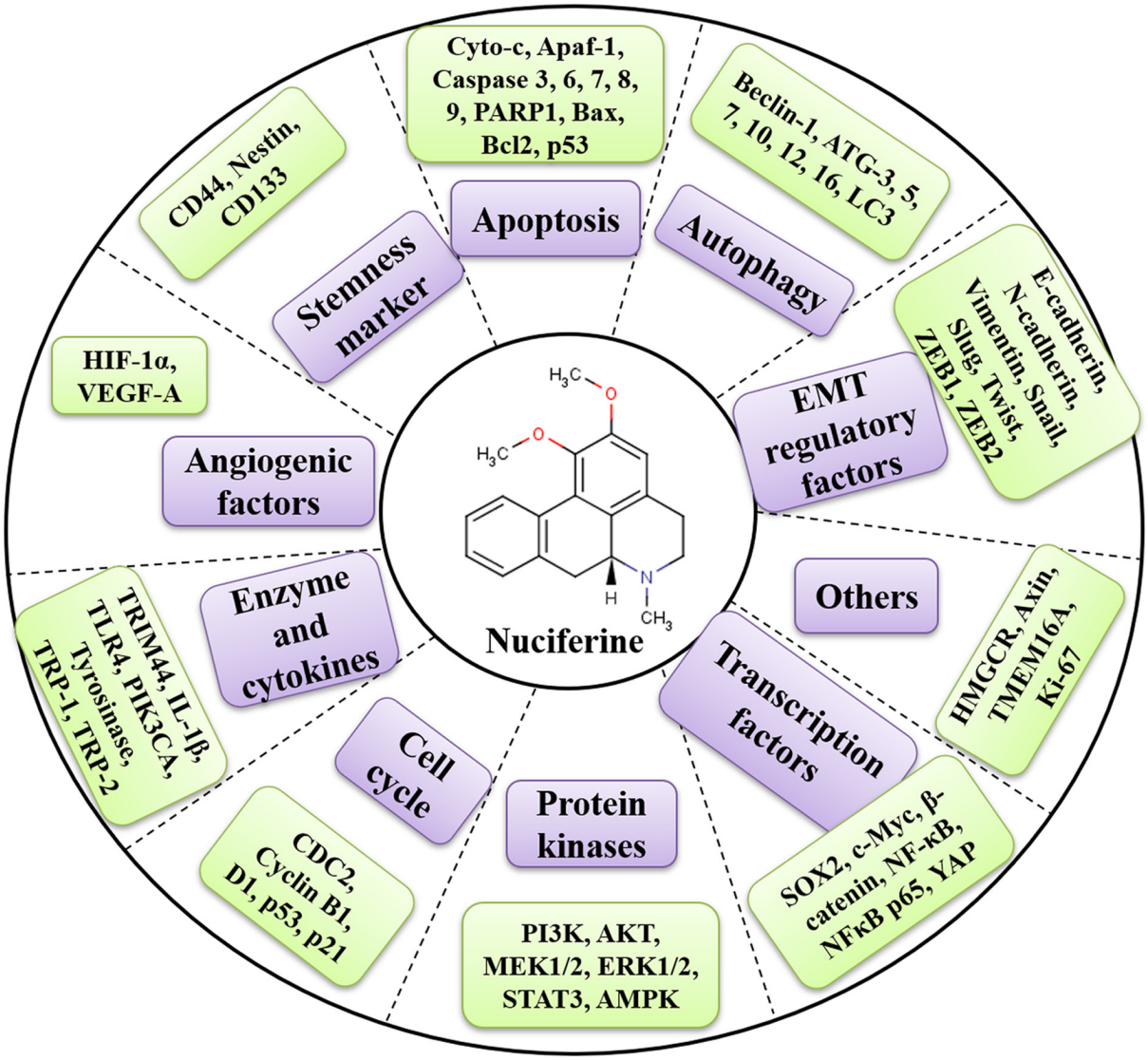

Figure 4. Various molecular targets modulated by nuciferine. HIF-1α, hypoxia inducible factor-1α; VEGF-A, vascular endothelial growth factor A; TRIM44, tripartite motif containing 44; TLR4, Toll-like receptor 4; TRP, tyrosinase-related protein; YAP, yes-associated protein; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; ZEB, zinc finger E-box binding homeobox; ATG, autophagy related; Cyto-c, cytochrome *c*; EMT, epithelial-mesenchymal transition.

manner through the induction of G_2/M cell-cycle arrest and the promotion of apoptosis, and suppressed tumor growth and angiogenesis by downregulating the HER2/PI3K/Akt/ERK signaling pathway. Collectively, the PI3K/Akt signaling pathway serves as a pivotal oncogenic pathway implicated in the pathogenesis of multiple malignancies. Its activation is associated with enhanced tumor growth, invasion and resistance to therapy, making it a key target for cancer treatment. The development of targeted therapies against this pathway, particularly in combination with other treatments, holds promise for improving outcomes for patients with cancer.

NF-κB signaling pathway. The NF-κB family comprises transcription factors that serve pivotal roles in modulating gene expression associated with immune responses, inflammation, cell proliferation and survival (106). Its dysregulation contributes to inflammatory disorders, metabolic disturbances and autoimmune diseases (107). The role of NF-κB in promoting oncogenesis, tumor cell proliferation, survival, metastasis, angiogenesis and therapy resistance highlights its potential as a therapeutic target for both inflammatory diseases and cancer (108). Xu *et al* (16) demonstrated that NF suppressed melanoma cell proliferation and tumor size by inhibiting the TLR4/NF-κB signaling pathway, Whereas An *et al* (105) showed that NF protected against muscle wasting in lung cancer cachexia by modulating the NF-κB signaling pathway via direct interaction with HSP90AA1.

AMPK signaling pathway. Gemcitabine, the current standard chemotherapeutic agent for advanced PC, frequently encounters notable drug resistance (109). NF has been identified as a potential therapeutic agent that may improve gemcitabine responsiveness in PC cells through modulation of the AMPK pathway. This activation leads to the downregulation of 3-hydroxy-3-methylglutaryl-CoA reductase, a key regulator of the mevalonate pathway essential for yes-associated protein activity (101). In a PANC-1 xenograft mouse model, the combination of NF and gemcitabine considerably reduced

tumor volume and weight without notable toxicity (101). Additionally, NF lowered the IC_{50} of gemcitabine in PC cell lines and exhibited synergistic cytotoxic effects when used in combination (101). These findings underscore the potential of NF as an effective adjuvant therapy for PC by leveraging the AMPK pathway to overcome gemcitabine resistance.

TGF-β1 signaling pathway. TGF-β1 serves as the archetypal cytokine within an extensive family of multifunctional secreted proteins. These molecules are pivotal in governing a wide array of cellular activities, including cell proliferation, differentiation and apoptosis via activation of the TGF-β1/SMAD signaling pathway (110). Given its modulation by various elements at different levels, this pathway is also closely involved in cancer development and progression (111). Gautam *et al* (94) revealed that NF exhibited potent therapeutic effects against pulmonary fibrosis induced by both TGF-β1 and bleomycin in both cellular and animal models, involving modulation of the TGF-β1/Smad2/3 signaling cascade and suppression of epithelial-mesenchymal transition (EMT) processes. Tong *et al* (99) indicated that NF markedly inhibited cell migration and metastasis of ER^- breast cancer cells by involving the TGF-β1 signaling pathway, the ERK1/2 and SMAD3 pathways and reducing intracellular H_2O_2 levels.

Wnt/β-catenin signaling pathway. The Wnt/β-catenin signaling pathway serves an essential role in development, tissue homeostasis and cell proliferation. However, its aberrant activation drives tumor initiation and progression, making it a promising target for cancer therapies (112). Liu *et al* (18) demonstrated that NF markedly reduced the proliferation of NSCLC cells, enhanced the stabilization of Axin and induced apoptosis by decreasing the Bcl-2/Bax ratio, and further demonstrated its efficacy in inhibiting tumor growth and alleviating nicotine-induced liver damage by the inhibition of Wnt/β-catenin signaling in *in vivo* experiments. Okayama *et al* (96) evaluated the anti-proliferative activities of NF against HT-29 human colon cancer cells and their cancer stem cells. Mechanistically, NF inhibited the expression of Wnt/β-catenin pathway target proteins, such as survivin, suggesting that its cytotoxic effects are mediated through inhibition of this pathway (96).

STAT3 signaling pathway. STAT3 is a central regulator of the antitumor immune response and is often hyperactivated in the tumor ecosystem, inhibiting immune activation and promoting immunosuppression (113). NF has been reported to inhibit the proliferation, migration and invasion of OSCC cells, while promoting apoptosis through suppressing the STAT3 signaling pathway (17). At the molecular level, NF increases the expression of pro-apoptotic markers cleaved-caspase 3 and Bax, enhances E-cadherin expression, and reduces Bcl-2 and vimentin levels, thereby promoting apoptosis and reversing the EMT in OSCC cells. However, colivelin, a potent STAT3 activator, can attenuate these effects by downregulating cleaved-caspase 3 and Bax, upregulating Bcl-2, and reversing changes in E-cadherin and vimentin expression, thereby reactivating the STAT3 signaling pathway and counteracting the antitumor effects of NF (17). In conclusion, the ability of NF to modulate multiple signaling pathways and molecular targets involved in cancer progression underscores its potential as a multi-targeting agent for cancer therapy.

4. Toxicity or undesirable effects of NF

While the pharmacological activities of NF have been extensively studied, it is essential to provide a more comprehensive understanding of its potential toxicity and undesirable effects (Table SIII). In addition to the aforementioned interactions with CYP enzymes and receptor antagonism, studies have begun to explore the broader toxicological profile of NF.

Previous *in vitro* studies have investigated the cytotoxic effects of NF on various cell lines. For example, a study by Li *et al* (103) evaluated the cytotoxicity of NF in human HCC (HepG2) cells using the MTT assay. The results indicated that NF exhibited time- and dose-dependent cytotoxicity, with an IC_{50} value of 101.88, 87.51 and 67.97 μM after 24, 48 and 72 h of treatment. Xie *et al* (17) investigated the impact of various concentrations of NF (0-120 μM) on the proliferation and viability of OSCC cells using the Cell Counting Kit-8 assay. Their findings demonstrated that NF effectively inhibited the proliferation of OSCC cells in a dose-dependent manner.

NF has been shown to have various interactions and effects with notable implications in the medical field. As reported by Ye *et al* (27) and Hu *et al* (28), the inhibition of CYP enzymes by NF suggests a potential for drug-drug interactions. NF potently inhibits CYP2D6, with an IC_{50} value of 3.78 μM and also inhibits CYP2C9 and CYP2C19, with IC_{50} values of 94.88 and 29.0 μM, respectively. Given the key role of CYP2D6 in the metabolism of several clinically important drugs, this interaction is particularly concerning. This could lead to increased plasma levels of co-administered drugs, potentially resulting in adverse effects or therapeutic failure; thus, careful consideration of these interactions is necessary in clinical settings.

Beyond these CYP-related interactions, NF has demonstrated specific antagonistic activity against the β_2-adrenergic receptor (β_2-AR), which holds potential therapeutic benefits for conditions such as hypertension, heart failure, glaucoma and infantile hemangioma. In human epidermoid carcinoma A431 cells, NF was reported to exhibit an IC_{50} value of 15.8±2.6 μM and a *Ki* value of 0.091 μM, highlighting its efficacy as a β_2-AR antagonist (114).

Heng *et al* (115) further explored the inhibitory effects of NF. Using a TGF-α shedding assay, this previous study assessed the impact of NF on human 5-HT_2 and adrenergic α1 receptor subtypes. The results showed that NF effectively inhibited 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, with IC_{50} values of 7.18±0.03, 7.51±0.21 and 7.44±0.01 nM, respectively. Additionally, it exhibited strong inhibition against α_{1A}, α_{1B} and α_{1D} receptors, with IC_{50} values of 7.42±0.07, 7.22±0.01 and 6.78±0.01 nM, respectively.

Liu *et al* (29) investigated the inhibitory effects of NF on *Mucor miehei* lipase, revealing an IC_{50} value of 0.194 mg/ml. NF acts as a non-competitive inhibitor with a *Ki* value of 0.16 mg/ml. Moreover, Guan *et al* (116) demonstrated that NF can act as a potent inhibitor of TNF-α with an IC_{50} value of 61.19 μM. These multiple inhibitory effects of NF across different targets suggest its complex pharmacological profile and diverse potential applications in medicine.

These findings highlight the potential for NF to interact with various enzymes and receptors, which may have both therapeutic and adverse effects. The inhibition of CYP enzymes by NF suggests the possibility of drug-drug interactions, which need to be carefully considered in clinical settings. Additionally, the antagonistic activity against β_2-AR and other receptors indicates potential therapeutic applications, but also underscores the need for further investigation into the safety profile of NF. Future research should focus on further elucidating the toxicological profile of NF. Comprehensive *in vitro* and *in vivo* studies are needed to fully understand its potential adverse effects, particularly at higher doses and with long-term exposure. Additionally, clinical trials should be designed to evaluate the safety and efficacy of NF in humans, with a focus on identifying potential drug-drug interactions and mitigating strategies.

5. Molecular docking simulation of NF through an *in silico* approach

Molecular docking simulations have emerged as a powerful tool to predict the binding modes and affinities between NF and its potential targets such as PI3K (30), prostaglandin-endoperoxide synthase 2 (PTGS2) (31), taste 2 receptor member 46 (TAS2R46) (117), JAK2 (71), *Mucor miehei* lipase (29), CYPs (55), ARs (85), α-glycosidase and α-amylase (73), HBXIP (60), cyclooxygenase-2 (COX-2) (118), URAT1 (119) and TNF-α (116), providing valuable insights into their interactions. Various computational methods, such as AutoDockTools software and SYBYL-X 2.0 software have been employed to achieve this (120-124). Protein structures were sourced from the Protein Data Bank (https://www.rcsb.org/), while the chemical structure of NF was obtained from the PubChem database (PubChem CID: 10146). Docking parameters were set with a grid box size of 40 Å centered on the active site of each protein and binding affinities were calculated using the default scoring function of AutoDockTools software (Table SIV).

PI3K. The binding affinity of NF to PI3K was calculated to be -6.33 kcal/mol, indicating strong interactions with key residues such as Ser594 and Asn634 (30).

PTGS2. Similarly, NF exhibited a binding affinity of -9.33 kcal/mol with PTGS2. Its key amino acids, including Gln203, His207 and His388, serve a key role in forming interactions and contributing to the non-competitive binding site (31).

TAS2R46. Ding *et al* (117) confirmed the specific target binding ability of NF to TAS2R46 through molecular docking. The results indicated that NF effectively interacted with the Ser248 residue of TAS2R46, with a binding affinity of -8.20±0.28 kcal/mol, suggesting a stable binding interaction.

JAK2. Li *et al* (71) demonstrated a strong binding affinity between NF and JAK2, with a binding energy of -7.5903±0.7926 kcal/mol. NF was effectively accommodated within the kinase active pocket of JAK2, forming a hydrogen bond with the Gly993 residue.

Mucor miehei lipase. Liu *et al* (29) reported that NF can bind to the catalytic pocket of *Mucor miehei* lipase, forming two hydrogen bonds (O_2-Arg169 and N-Asp238), and interacting with Tyr195 and Pro194 through hydrophobic and stacking actions by molecular docking analysis. The binding energy was -6.13 kcal/mol, primarily contributed by van der Waals forces and hydrogen bonds. The methyl and benzene ring structures of NF are key for binding, and its inhibitory mechanism involves both active center insertion and external region binding, inducing conformational changes in the lipase and reducing its activity.

CYPs. Gao *et al* (55) investigated the interaction between NF and CYPs using ADMET Predictor 9.0 and SYBYL-X 2.0 software. NF was predicted to be a substrate of nine CYP family isoenzymes (CYP1A2, 2C9, 2B6, 2A6, 2C8, 2C19, 2E1, 2D6 and 3A4), with potential sites of metabolism located at various carbon and nitrogen atoms. Molecular docking revealed hydrogen bonds and hydrophobic interactions between NF and these enzymes, with specific binding modes varying among different enzymes. For example, NF can form one hydrogen bond (with Arg106) and seven hydrophobic contacts when binding to CYP1A1 and one hydrogen bond (with Thr321) and 10 hydrophobic contacts when binding to CYP1A2 (55).

ARs. Harishkumar and Selvaraj (85) reported that NF exhibited binding energies of -8.46 and -5.02 kcal/mol with the β_1- and β_2-ARs, respectively, which were higher than those of isoproterenol (-5.27 and -4.3 kcal/mol). NF can bind to the β_1-AR at residues Val122, Thr126 and Ser211, and to the β_2-AR at residues Lys140, Gln229 and Glu1005 (85). These differences in binding residues may account for its antagonistic activity against isoproterenol-mediated interactions.

α-glycosidase and α-amylase. Khan *et al* (73) demonstrated that NF exhibits considerable inhibitory activity against α-glycosidase and α-amylase. NF was successfully docked into the active sites of both enzymes. Specifically, it forms a π-π interaction with Trp484 and a metal-ligand interaction with a calcium ion at position 701, in α-glycosidase, interacting with key residues such as Glu173, Glu474, Glu456 and Glu480 (73). In α-amylase, the oxygen atom at position 39 of NF forms a bond with Lys35, and its six-membered ring participates in a π-π interaction with Trp396 (73).

HBXIP. Du *et al* (60) confirmed that NF directly interacts with HBXIP, binding to a conserved potential pocket that includes residues such as His87, Ile74, Gly72, His41, Ile45, Glu40, Val44 and Thr36. This interaction effectively disrupts the assembly of the Rag GTPase-Ragulator complex, leading to the inhibition of mTORC1 activity and the subsequent activation of TFEB-mediated autophagy.

COX-2 and URAT1. Zhang *et al* (118) reported a binding energy of -5.78 kcal/mol between NF and COX-2, mediated through hydrogen bonds with Lys328. Additionally, NF exhibited a binding energy of -7.44 kcal/mol with URAT1, forming a hydrogen bond with Lys393 and a π-π interaction with Phe364 (119).

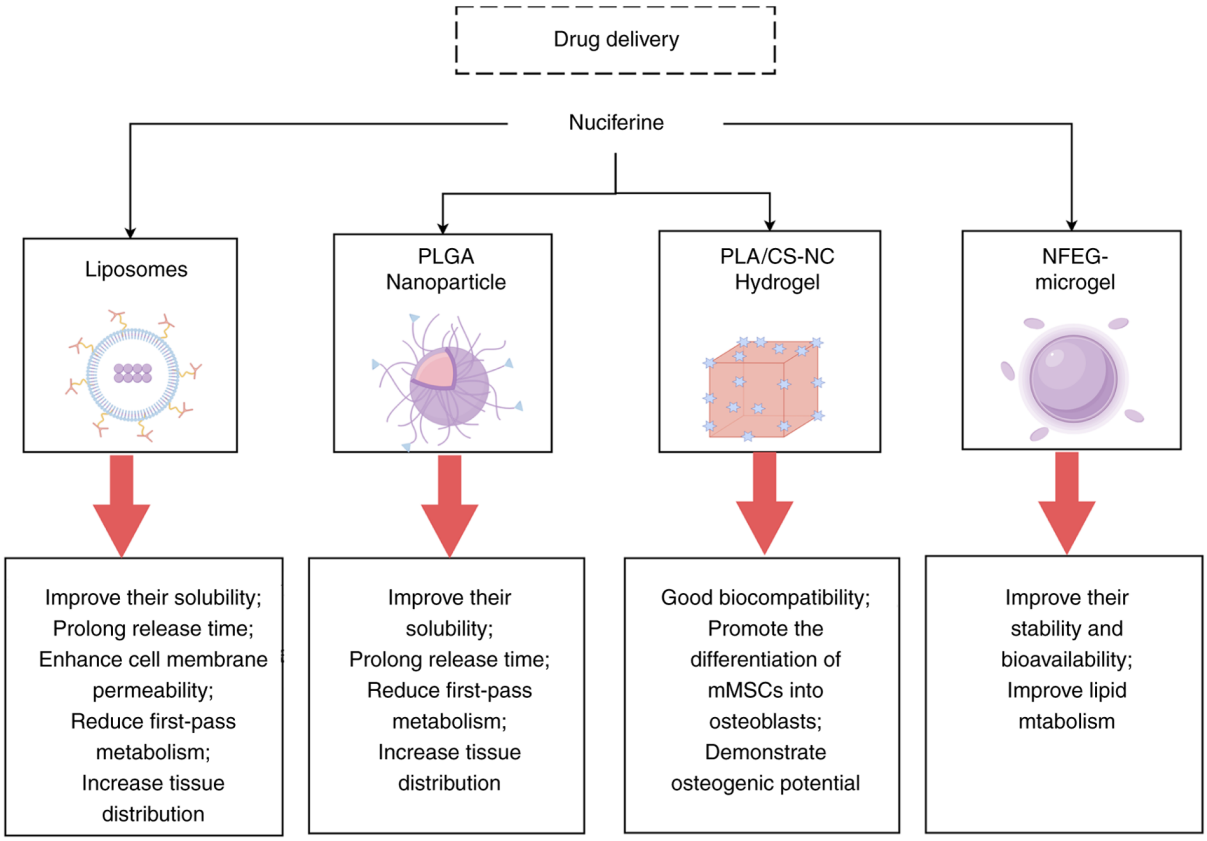

Figure 5. Drug delivery systems of nuciferine. This figure was drawn by Figdraw (https://www.figdraw.com). PLGA, poly lactic-co-glycolic acid; PLA, polylactic acid; NFEG, nuciferine-epigallocatechin-3-gallate double-encapsulated microgel; CS-NF, nuciferine-loaded chitosan hydrogel; mMSCs, mouse mesenchymal stem cells.

TNF-α. Guan *et al* (116) investigated the binding interactions between NF and TNF-α, revealing a binding energy of -8.4 kcal/mol. NF formed a carbon-hydrogen bond with Ser60 and engaging in two π-π interactions with Tyr119. Surface plasmon resonance (SPR) assays confirmed a strong affinity for TNF-α, with a dissociation constant of 61.19 μM (116).

Summary of the molecular docking simulation of NF. The molecular docking simulations of NF detailed in the present review reveal its interactions with multiple biological targets, providing information on potential pharmacological mechanisms and a basis for developing more effective derivatives. These simulations identify key binding affinities and interactions, demonstrating the versatility of NF as a promising natural therapeutic compound. However, these computational findings are preliminary and require experimental validation to confirm their biological relevance. Future studies should combine computational predictions with laboratory techniques, such as site-directed mutagenesis, ligand-protein interaction assays and cell-based functional tests, to verify the proposed mechanisms.

6. Bioavailability and drug delivery of NF

NF, a hydrophobic metabolite, exhibits poor solubility in water, which considerably limits its bioavailability. To address this challenge, various advanced drug delivery systems capable of encapsulating NF have been developed. These include liposomes (125), PLGA nanoparticles (24), 3D-printed polylactic acid (PLA) scaffolds incorporating chitosan (CS)-NF hydrogel (25) and NF-epigallocatechin-3-gallate (EGCG) double-encapsulated microgel (NFEG-microgel) (26) (Table SV; Fig. 5). These innovative carriers have demonstrably enhanced the aqueous solubility and bioavailability of NF.

Liposomes notably enhance the bioavailability of NF through multiple mechanisms, including improving its solubility, prolonging release time, enhancing cell membrane permeability, reducing first-pass metabolism and increasing tissue distribution. Specifically, NF liposomes exhibit smaller and more uniform particle sizes, slower release rates conforming to a first-order release model and notably increased pharmacokinetic parameters, such as half-life ($T_{1/2}$), mean residence time and area under the curve (AUC), while reducing clearance and peak concentration (125). For example, a pharmacokinetic study of NF liposomes demonstrated a notable increase in bioavailability compared with free NF. The $T_{1/2}$ of NF liposomes was extended to 6.46 h, compared with 3.15 h for free NF. The AUC increased by 2-fold, indicating enhanced absorption and distribution (125). These characteristics enable NF liposomes to function more effectively in the body, thereby enhancing their therapeutic efficacy.

PLGA nanoparticles notably enhance the bioavailability of NF by improving its solubility, prolonging release time,

reducing first-pass metabolism and increasing tissue distribution. Specifically, the nanoparticles have small and uniform particle sizes, slower release rates with sustained release characteristics and higher release efficiency in simulated intestinal fluid compared with simulated gastric fluid. Pharmacokinetic parameters show extended T1/2, markedly increased AUC and a 3.3-fold increase in relative bioavailability, with sustained release characteristics over 24 h (24). These features enable NF-PLGA nanoparticles to function more effectively in the body, thereby enhancing therapeutic efficacy.

Bharathi *et al* (25) developed a NF-loaded PLA scaffold using 3D printing technology and chitosan hydrogel for bone tissue engineering. The results of the study showed that this composite scaffold has good biocompatibility and can promote the differentiation of mouse mesenchymal stem cells into osteoblasts, demonstrating osteogenic potential at both cellular and molecular levels. Specifically, NF is released in a sustained manner, with ~70% released over 21 days. Moreover, the NF-treated scaffolds considerably enhance alkaline phosphatase (ALP) activity, increase calcium deposition and upregulate the expression of osteogenesis-related genes (such as RUNX family transcription factor 2, ALP, COL-1 and OC). These findings suggest that the NF-loaded PLA/chitosan scaffold is a promising material for bone tissue engineering.

Zhu *et al* (26) successfully encapsulated NF and EGCG into a microgel system, improving their stability and bioavailability. In HFD-induced rats, NFEG-microgel intervention effectively reduced body weight and serum lipid levels by modulating key lipid metabolism genes and specific microRNAs (miRs), such as miR-30b-5p and miR-126a-5p, in serum extracellular vesicles (26). It also enhanced gut microbiota diversity, enriching beneficial short-chain fatty acid-producing bacteria while reducing harmful ones, thereby improving lipid metabolism through intestinal flora regulation. These results highlight NFEG-microgel as a promising delivery system and therapeutic strategy for lipid metabolism disorders.

To further enhance the bioavailability of NF, future research should prioritize optimizing nanoparticle formulations through strategies such as surface modification with polyethylene glycol, which can improve stability and reduce immunogenicity. Additionally, exploring targeted delivery systems such as antibody-drug conjugates could enable more precise delivery of NF to diseased tissues, minimizing off-target effects. These advanced drug delivery approaches show notable potential for overcoming the solubility and bioavailability challenges of NF, ultimately improving its therapeutic efficacy.

7. Comparative analysis and integrative discussion

NF demonstrates a marked capacity to regulate the PI3K/Akt pathway, which is evident in both its metabolic regulation and anticancer activities. In the context of metabolic disorders, NF activates the AMPK pathway, thereby enhancing lipid metabolism and reducing inflammation (58). In cancer models, the inhibition of the PI3K/Akt pathway by NF has been shown to suppress tumor growth and enhance chemotherapy sensitivity (97). These overlapping mechanisms suggest that NF could have broad therapeutic applications by targeting common signaling pathways involved in both metabolic and oncogenic processes.

NF has also demonstrated clinical potential. For example, in immunomodulation and antioxidant effects, the ability of NF to regulate inflammatory pathways (such as TLR4/NF-κB) and reduce oxidative stress is associated with the management of chronic inflammatory diseases and age-related diseases. NF shows potential in the treatment of acute kidney injury, cerebral ischemia-reperfusion injury and ulcerative colitis. In metabolic regulation, its ability to regulate lipid metabolism and improve metabolic health by activating AMPK and PPARα pathways has attracted attention, indicating that it may become a valuable drug for the treatment of obesity, liver steatosis, type 2 diabetes and other metabolic diseases. In musculoskeletal protection, its ability to inhibit osteoclastogenesis and reduce cartilage degradation in osteoporosis and OA is notable, with the potential to address musculoskeletal diseases through a single drug. In anticancer effects, its ability to regulate key pathways involved in cancer cell proliferation, apoptosis and metastasis suggests it could be a valuable addition to cancer treatment.

Despite the encouraging preclinical research results, the application of NF in clinical practice remains a considerable challenge. In preclinical studies, there is a notable difference in the concentrations of NF. In *in vitro* studies, its concentration typically ranges from low micromolar (1-10 μM) to higher levels (30-200 μM), while in *in vivo* studies, its concentration is typically between 1 and 50 mg/kg. Although these concentrations have shown biological effects *in vitro* and in animal models, achieving such levels in humans may face notable challenges. For example, to achieve effective concentrations in target tissues without causing toxicity or adverse reactions, careful consideration of pharmacokinetics, bioavailability and potential drug interactions is required. At the same time, detailed mechanistic studies are required to comprehensively elucidate the downstream effects of NF on various signaling pathways.

In addition, the studies included in the present review collectively demonstrate the diverse interactions of NF with a range of biological targets, including enzymes, receptors and protein complexes. These interactions are not only indicative of the potential therapeutic applications of NF but also provide a detailed understanding of its molecular mechanisms. For example, the strong binding affinities observed between NF and key targets, such as PI3K, PTGS2 and TNF-α, suggest potential roles in modulating signaling pathways and inflammatory responses. Similarly, interactions with enzymes such as α-glycosidase and α-amylase highlight its potential as an antidiabetic agent. The docking results also reveal specific binding modes and key residues involved in these interactions, which can guide the design of more potent NF derivatives. However, the present review appreciates that these *in silico* findings are a key first step and must be complemented by experimental validation. Future research should focus on integrating computational predictions with wet-lab techniques, such as site-directed mutagenesis, ligand-protein interaction assays and cell-based functional studies, to confirm the mechanistic relevance of these interactions.

Although there have been several reviews on NF in the past 5 years, these have primarily focused on summarizing specific aspects of NF activity. For example, Huang *et al* (126) comprehensively summarized extensive knowledge on chemistry and biology of NF including separation technology, structural modification, total synthesis, structure-activity relationship, as well as *in vivo* metabolism, biological activity and biosynthesis. Zhao *et al* (3) critically summarized the information regarding the structure-activity relationship of NF, its biological activity and clinical application in inflammation-related diseases (such as diabetes, obesity, cardiovascular diseases, liver diseases and cancer), as well as its potential mechanisms. Ren *et al* (8) provided a comprehensive overview of the chemical properties, pharmacological activities (such as improving hyperlipidemia, relaxing smooth muscles, vasodilatation, stimulating insulin secretion, antiarrhythmic activity, inducing hypotension, as well as anti-HIV and antibacterial activities) of NF and their potential regulatory mechanisms. Zhao *et al* (127) summarized studies on the neuroprotective mechanisms of alkaloids derived from *Nelumbo nucifera*, which encompass anti-inflammatory and antioxidant effects, modulation of ion channels and calcium signaling, promotion of neurogenesis and regulation of key neurotransmitter systems. However, the present review consolidates and synthesizes a broader range of data, including previous studies on immunomodulation, metabolism regulation, neuroprotection, musculoskeletal protection, cardiovascular benefits, antipsychotic effects and anticancer activities. Secondly, the present review gives a detailed analysis of the potential applications of NF in fields such as molecular docking simulation and drug delivery. The latest research results on the molecular mechanism of NF *in vivo* and *in vitro* in recent studies have also been included, and put forward novel views on the challenges and future directions of NF research, distinguishing the present work from prior reviews.

8. Conclusions, current challenges and future research directions

Conclusions and challenges. NF, a natural alkaloid derived from the lotus plant (*Nelumbo nucifera* Gaertn.), exhibits a wide range of biological activities, positioning it as a promising candidate for therapeutic applications. Its ability to modulate multiple signaling pathways and interact with various molecular targets underscores its potential in treating diverse diseases, including inflammatory conditions, metabolic disorders, neurodegenerative diseases and several types of cancer. The present review has elucidated the multifaceted biological activities of NF, highlighting its potential as a novel therapeutic agent.

To advance NF from bench to bedside, several key challenges must be addressed. Firstly, the lack of standardized extraction and purification protocols has led to notable variability in the yield, purity and composition of NF across studies. Factors such as solvent type, extraction time and plant source all influence the final product, which may affect biological activity and reproducibility (3,26). Future studies should adopt standardized, reproducible extraction methods and include rigorous quality control measures, such as high-performance liquid chromatography and mass spectrometry fingerprinting, to ensure consistency and comparability of results.

Secondly, species differences in metabolism, receptor expression and pharmacokinetics limit the direct translational relevance of findings from animal models. For example, the oral bioavailability and tissue distribution of NF may differ markedly between rodents and humans (24-26,125). To bridge this gap, cross-species pharmacokinetic studies, human-relevant *in vitro* models and organoid or organ-on-chip systems should be employed to improve the ability to predict human responses.

Thirdly, inconsistent findings across studies, such as variable efficacy in inflammation or cancer models, highlight the need for greater standardization in experimental design. This includes dose selection, treatment duration and endpoint assessment. Publication bias and underreporting of negative results may also skew the literature. Meta-analyses, systematic reviews and transparent data reporting are essential to reconcile contradictions and identify true effect sizes.

Fourthly, while molecular docking provides useful hypotheses about the binding of NF to target proteins, these predictions remain speculative without experimental validation. Several docking studies lack biophysical confirmation (29,60,73), such as SPR, isothermal titration calorimetry and crystallography, or functional assays to verify binding affinity and downstream effects. Future research should integrate computational predictions with wet-lab validation, using techniques such as site-directed mutagenesis, ligand-protein interaction assays and cell-based functional readouts to confirm mechanistic relevance.

Comprehensive toxicology studies are also lacking, making it difficult to assess the safety profile of NF. Long-term studies are needed to evaluate potential chronic effects, and identify biomarkers for monitoring treatment efficacy and safety. Conducting comprehensive toxicology studies, including acute and chronic toxicity assays, will be key to establish a safety profile. Developing biomarkers to monitor treatment efficacy and safety in clinical trials is also essential.

The poor solubility and bioavailability of NF limit its therapeutic potential. Advanced drug delivery systems are needed to enhance their solubility and targeted delivery. Developing advanced drug delivery systems, such as liposomes, PLGA nanoparticles and prodrug strategies, can enhance the solubility and bioavailability of NF. Optimizing nanoparticle formulations to improve cellular uptake and reduce off-target effects will further improve its therapeutic efficacy. Comparative studies with standard drugs are limited, making it difficult to assess the relative efficacy and potential advantages of NF. Conducting comparative studies with standard drugs to evaluate the efficacy and safety of NF is essential. Exploring synergistic effects of NF with existing drugs, such as metformin or chemotherapeutics, could enhance therapeutic outcomes.

Lastly, as the current research on NF mainly focuses on cellular and animal models, or molecular docking techniques, comprehensive pharmacokinetics, toxicology and phase I trials are necessary steps before considering any clinical translation. Designing human trials that accurately reflect the therapeutic potential of NF requires careful consideration of dosing, patient selection and endpoint assessment. Phase I trials should

be designed to assess safety, tolerability and pharmacokinetics in healthy volunteers. Using biomarker-guided trials to stratify patient populations and monitor therapeutic response will be key. Considering adaptive trial designs to optimize dosing and treatment duration based on interim results will also enhance the efficiency and success of clinical trials. Addressing these challenges will be essential to unlock the full therapeutic potential of NF and advance its clinical application.

Therapeutic prospects and future research directions. To fully realize the therapeutic potential of NF, several key priorities should guide future research. Firstly, the anti-inflammatory and antioxidant properties of NF position it as a promising therapeutic agent for various conditions, including acute kidney injury, acute lung injury and ulcerative colitis. The ability of NF to modulate key signaling pathways, such as TLR4/NF-κB and Nrf2, further suggests its potential for managing chronic inflammatory diseases. Additionally, the effects of NF on lipid metabolism and glucose regulation indicate its therapeutic potential in metabolic disorders, such as obesity, type 2 diabetes and NAFLD. By activating AMPK and PPARα pathways, NF shows promise in addressing metabolic syndrome.

Moreover, the neuroprotective effects of NF demonstrated in ischemic stroke and Alzheimer's disease models highlight its potential in neurodegenerative and psychiatric disorders. Its ability to penetrate the BBB and modulate neurotransmitter signaling underscores its promise in central nervous system disorders. In the field of oncology, the anticancer effects of NF, mediated through the modulation of signaling pathways such as PI3K/Akt, NF-κB and Wnt/β-catenin, suggest its potential as a multi-targeting agent for various types of cancer. Its ability to inhibit tumor cell proliferation, induce apoptosis and overcome drug resistance further highlights its therapeutic potential in cancer therapy.

To advance the clinical application of NF, it is essential to conduct detailed mechanistic studies to elucidate the molecular mechanisms underlying its therapeutic effects. This includes investigating its interactions with specific receptors and signaling pathways, as well as identifying downstream targets. Comprehensive toxicity studies are also required to fully understand the safety profile of NF, including long-term studies to assess potential chronic effects and the development of biomarkers to monitor treatment efficacy and safety.

The development of advanced drug delivery systems, such as liposomes and nanoparticles, should be prioritized to enhance the bioavailability of NF and reduce its hydrophobicity. These systems should be designed to improve targeted delivery and minimize off-target effects. Well-designed clinical trials are necessary to translate the therapeutic potential of NF into clinical practice, focusing on specific disease indications such as metabolic disorders, neurodegenerative diseases and different types of cancer to establish its efficacy and safety in humans.

Lastly, investigating the potential of NF in combination with existing therapies could enhance its therapeutic effects. For example, combining NF with chemotherapeutic agents or metabolic regulators could provide synergistic benefits in cancer and metabolic diseases. Overall, addressing these priorities will be important in identifying the full therapeutic of potential of NF and advancing its clinical application.

In conclusion, NF demonstrates considerable potential as a versatile natural compound with broad therapeutic applications, but its transition to clinical use demands thorough standardization, mechanistic understanding and proven delivery methods. Overcoming these obstacles through collaborative, interdisciplinary efforts and translational research will be essential to fully realize the benefits of NF in modern medicine. Future research should focus on comprehensive toxicology studies, advanced drug delivery approaches, comparisons with existing treatments, and carefully designed human trials to ensure the safety and efficacy of NF in clinical practice.

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Availability of data and materials

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Authors' contributions

YL, XL and XX prepared the original draft. XL, BH and XL drew figures and tables, and participated in the concept and design of the manuscript. BY and XX reviewed and revised the manuscript. YL, XX, LZ and HM were responsible for conceptual design. HM and LZ carried out supervision and management. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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