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Review article

A systematic review: Sinomenine

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ABSTRACT

Sinomenine (SIN), an alkaloid derived from the traditional Chinese medicine, *Caulis Sinomenii*, has been used as an anti-inflammatory drug in China for over 30 years. With the continuous increase in research on the pharmacological mechanism of SIN, it has been found that, in addition to the typical rheumatoid arthritis (RA) treatment, SIN can be used as a potentially effective therapeutic drug for anti-tumour, anti-renal, and anti-nervous system diseases. By reviewing a large amount of literature and conducting a summary analysis of the literature pertaining to the pharmacological mechanism of SIN, we completed a review that focused on SIN, found that the current research is insufficient, and offered an outlook for future SIN development. We hope that this review will increase the public understanding of the pharmacological mechanisms of SIN, discover SIN research trial shortcomings, and promote the effective treatment of immune diseases, inflammation, and other related diseases.

1. Introduction

In the 1920s, Sinomenine (SIN) was first isolated from the stems of the Chinese medicinal plants *Sinomenium acutum* (family Menispermaceae) and *Caulis Sinomenii* by Ishiwari [1]. As a natural compound, SIN has a sedative effect similar to that of morphine [2]. Continuous research on SIN in China and Japan has demonstrated that it has extremely strong anti-inflammatory capabilities. SIN injections and sustained-release tablets were approved for the first time in the 1990s, and it was indexed in the Chinese Pharmacopoeia in 2005. Over the past 40 years, clinical research has verified SIN efficacy in RA and nephritis treatment. A total of 1505 relevant research articles published from 1963 to last year were obtained in the study of PubMed, Web of Science, Embase, NKI, Google Scholar, and other databases with “Sinomenine” as the keyword, including a total of 493 articles on pharmacological research, and 186 related

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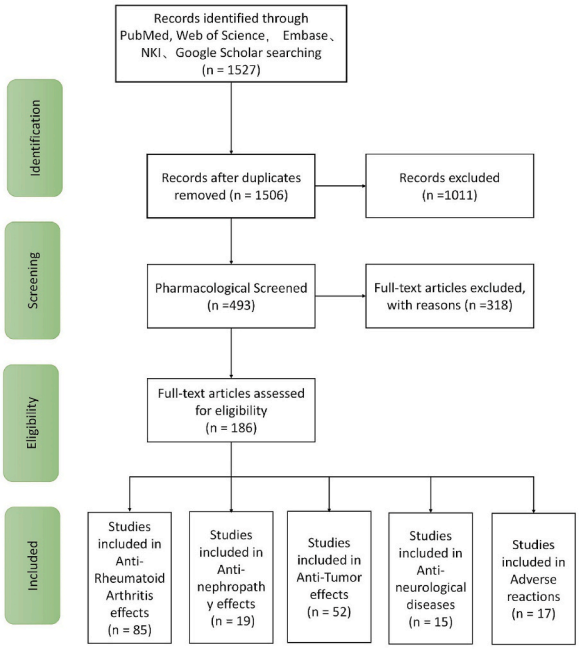

Fig. 1. Flowchart of literature screening.

articles were further screened, including 84 on anti-RA effects, 19 on anti-nephrotic effects, 52 on anti-cancer articles, 15 on anti-neurological diseases, and 17 on adverse reactions (Fig. 1).

Nuclear factor-κB (NF-κB) is an important factor in regulating gene transcription and is involved in the pathological processes of diverse diseases, such as inflammatory response [3]. NF-κB signalling pathway is a classic pathway in RA. When used in combination with methotrexate (MTX) to treat RA [4], SIN can block NF-κB/TLR4 signalling pathway by downregulating miR-155 expression, upregulating SOCS1 [5,6], or upregulating IκB expression to inhibit NF-κB activity [7–9]. SIN reduces RANKL expression, downregulates NF-κB activation, reduces p38 and JNK phosphorylation, and inhibits AP-1 and nuclear factor of activated T cell (NFAT) transcription to suppress osteoclast activation and inflammation [10]. SIN downregulated NF-κB-p65 phosphorylation thereby reducing pro-inflammatory cytokines expression [11–13]. SIN inhibits the migration and invasion of pancreatic cancer cells by inhibiting the NF-κB signalling passage [14]. SIN inhibits the NF-κB signalling pathway to inhibit inflammation development and achieve the effect of treating Alzheimer's disease (AD) and epilepsy. Migraine symptoms are alleviated by SIN through NF-κB signalling pathway inhibition.

Tumour necrosis factor-α (TNF-α) is an important pro-inflammatory factor in the body, secreted by monocytes, lymphocytes, and immune-activated endothelial cells. If the body experiences immune disorders or inflammatory reactions, the expression level of TNF-α increases. Our research group has long been committed to studying the pharmacological effects of SIN in IgA nephropathy (IgAN) treatment and has now made preliminary findings: SIN downregulates the level of the pro-inflammatory cytokine TNF-α to achieve the effect of treating nephritis. *In vivo* experiments have suggested that SIN can significantly curb the expression level of pro-inflammatory factor TNF-α in the serum of collagen-induced arthritis (CIA) rats and exert anti-inflammatory effects [15]. SIN downregulates LPS-induced 7nAChR expression to reduce TNF-α protein synthesis and inhibit NO production [16]. TNF-α and IL-1β regulated by Ras signal pathway are hepatocarcinoma-promoting factors in the hepatocellular microenvironment, activating transcription factor C/EBPβ binding in the foster region of COX-2 and iNOS genes and contributing to tumourigenesis. SIN inhibited the Ras signalling pathway, reduced TNF-α and IL-1β expression to disrupt the tumour microenvironment, and decreased C/EBPβ protein expression to inhibit tumourigenesis [17]. For colon cancer cure, SIN blocked the cell cycle process and inhibited cancer cell proliferation along with the exudation of inflammatory cytokines TNF-α, IL-23, and β-catenin expression [18–20], disrupted the tumour microenvironment and curbed cancer cells proliferation [21]. The treatment of Parkinson's disease (PD) by SIN is achieved by reducing TNF-α level.

SIN achieves the effect of treating diseases by inhibiting the NF-κB pathway and reducing the pro-inflammatory factor TNF-α levels. The purpose of this review is to elucidate the current research progress in SIN treatment of diseases, predominantly focusing on the study of the pharmacological mechanisms of action. By elaborating the pharmacological mechanisms of SIN in treating diseases, readers can enhance their understanding of its pharmacological effects. Simultaneously, we propose the limitations of this SIN research progress and look forward to future development trends. While it is convenient for readers to comprehend the pharmacological mechanism of SIN, we have also supplemented our own research projects in the summary. This article discusses RA, nephritis, tumours, and neurological diseases, explores the pharmacological effects of SIN on diverse diseases, combines current research trends and results, identifies deficiencies, and looks forward to future development directions.

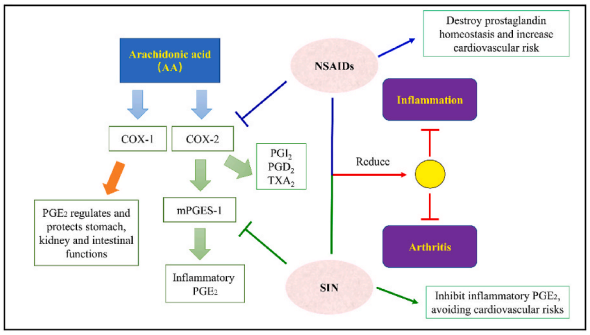

Fig. 2. SIN selectively inhibits mPGES-1, thus inhibiting the production of PGE_2 while having no effect on COX-2. SIN selectively inhibited mPGES-1, down-regulated the secretion of inflammatory PGE_2, suppressed inflammation and joint destruction. It has no inhibitory effect on COXs, avoids adverse cardiovascular effects, and has a better safety profile than NSAIDs.

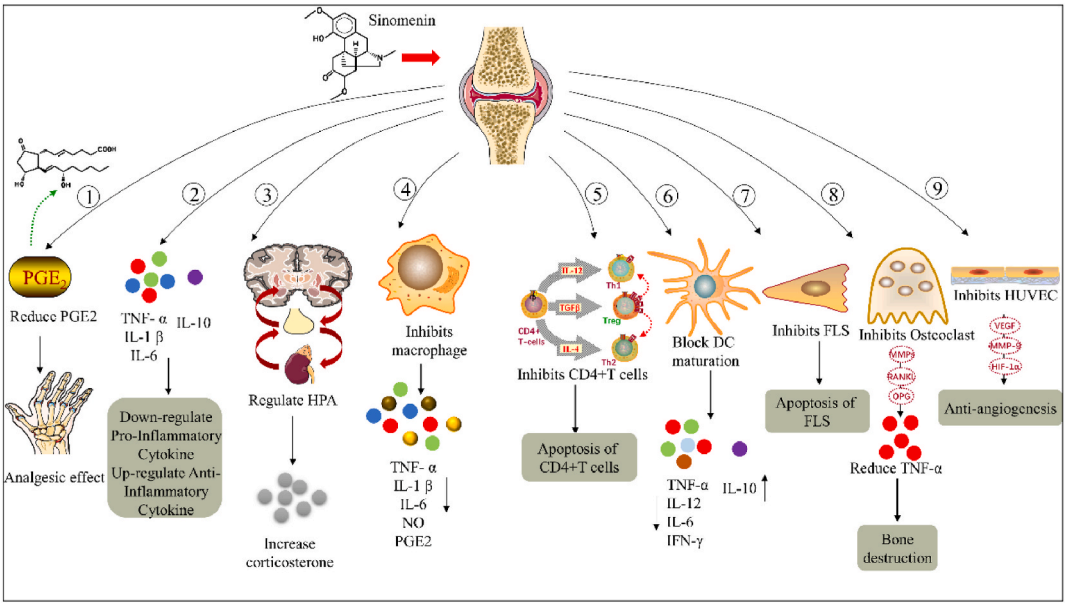

Fig. 3. Summary of the pharmacological mechanism of SIN against RA. (1) SIN produced analgesic effects by blocking the p38MAPK–NF–κB pathway and decreasing PGE_2 levels. (2) SIN decreased the production of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and increases IL-10. (3) SIN regulated the dysfunction of hypothalamic-pituitary-adrenal (HPA) axis in RA patients, increases the synthesis and secretion of corticosterone, and exerts anti-inflammatory effects. (4) SIN inhibited the proliferation of macrophages and induces their apoptosis. (5) SIN up-regulated Treg cells and down-regulates Th17 cells, restores the balance of Treg and Th17 cells, and induced apoptosis of $CD4^+$ T cells by activating Caspase-3. (6) SIN inhibited DC differentiation and maturation, reduces the release of inflammatory cytokines such as IFN-γ, TNF-α and IL-12, and decreases the expression of costimulatory molecules such as CD80 and CD86. (7) SIN inhibited the proliferation of FLS and induces apoptosis. (8) SIN down-regulated MMP and RANKL, up-regulates OPG, inhibits the secretion of inflammatory cytokine TNF-α, and reduces inflammation. (9) SIN inhibited the proliferation, migration and invasion of HUVEC, decreased the expression of HIF-1α, VEGF and MMP-9 in synovial membranes to inhibit angiogenesis.

2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterised by small-joint deformation and bone destruction [22]. The global prevalence of RA is between 0.5 and 1 %, and most patients are women [23]. Non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GC), and anti-rheumatic drugs (DMARDs) are the primary drugs for RA [24] and biologics, but the side effects of these drugs are relatively large [25]. NSAIDs [26] directly inhibit COX-1 or COX-2 to release prostaglandins (PGs) and reduce inflammation and pain [27]. Compared with NSAIDs, SIN inhibits NF-κB signalling pathway and has no cardiovascular adverse effects. Recent studies have demonstrated that MTX combined with SIN can enhance this effect and reduce adverse reactions [28]. Yi et al. reported that SIN acts on the GC receptor (GR) and has an anti-inflammatory effect similar to that of GC [29]. Rheumatoid arthritis (RA) is an autoimmune disease. SIN can regulate the balance of the immune cell phenotype and T lymphocytes multiplication, including the maturation and differentiation of DCs, macrophages activation, and autoantibodies production. With anti-RA effects

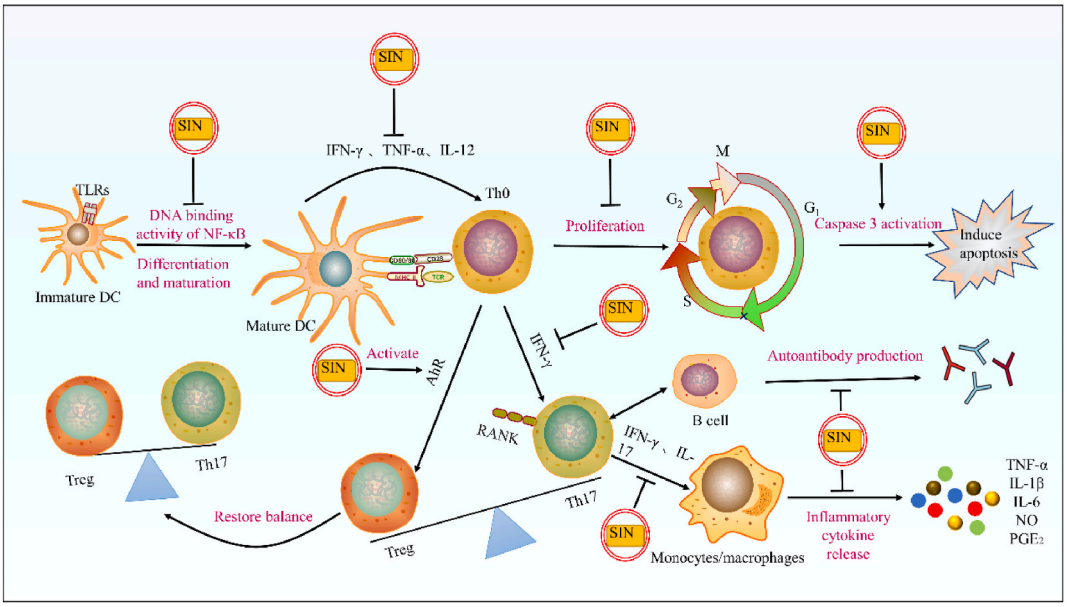

Fig. 4. SIN regulates immune system balance. SIN regulates immune system balance. SIN up-regulated Treg cells by activating AhR, down-regulated Th17 cells by inhibiting IFN-γ, restoring the balance between Treg cells and Th17 cells, thereby inhibiting the production of autoantibodies by B lymphocytes, the activation of macrophages and the release of inflammatory cytokines. It also inhibited the differentiation and maturation of DCs, reduced the release of IFN-γ, TNF-α, IL-12 and other inflammatory cytokines, and suppressed the expression of CD80, CD86 and other costimulatory molecules.

similar to those of commonly used clinical drugs and no adverse cardiovascular reactions, SIN will gradually become a popular drug for RA treatment.

2.1. Present use

Recently, a new SIN mechanism in RA treatment was reported. SIN can activate aromatic hydrocarbon receptors by regulating tryptophan metabolism and activity regulated by intestinal microbiota to achieve the therapeutic effect in RA [30]. SIN selectively inhibits NF-κB signalling pathway to reduce generation of pro-inflammatory cytokines TNF-α and IL-6, inflammatory mediators mPGES-1, iNOS, PGE_2, and NO [31,32]. Recent research has demonstrated that SIN selectively inhibits mPGES-1 downstream of the NF-κB pathway to inhibit PGE_2 production (Fig. 2) [33,34]. The selective inhibition of SIN downregulates mPGES-1 to reduce PGE_2 production for anti-inflammatory purposes [34,35]. Inflammation is frequently accompanied by pain. SIN produces analgesic effect through non-μ opioid receptor mechanism, which can significantly relieve joint pain [36]. SIN stimulates GABA receptors to trigger neuronal hyperpolarisation and reduce pain [37]. The alleviation of inflammation is achieved indirectly through IL-2 expression inhibition by SIN, which inhibits the production of the membrane interleukin-2 receptor (mIL-2R) [38]. Joint swelling accompanied by inflammation is a typical RA symptom. SIN suppresses inflammation by reducing CD14/TLR4 expression and free calcium ion concentration and activating the JAK2/STAT3 pathway (Fig. 3) [39]. Diverse SIN concentrations significantly inhibited the proliferation of the mice synovial cell line RSC-364 induced by IL-1β in a dose-dependent form, and the expression level of inflammatory factors IL-6 and MMP-3 were also significantly reduced [40]. SIN also inhibits inflammation development by reducing TLR2/TLR4 and downregulating MyD88 expression [41–45]. SIN promotes adrenal cortex function and increases corticosterone synthesis and secretion, thereby exerting anti-inflammatory effects [46]. T cell-mediated cellular immunity affects RA pathogenesis. Mature T cells can be divided into $CD4^+$ and $CD8^+$T cells. SIN inhibits $CD4^+$T cell propagation and induces apoptosis [47]. Th17 cells produce a crucial inflammatory cytokine, IL-17, which promotes the incidence of RA. Regulatory T lymphocytes (Tregs) are the primary cells that release IL-10 anti-inflammatory cytokines. SIN upregulates Treg cells by sensitising the aryl hydrocarbon receptor (AhR) and simultaneously inhibits γ-interferon (IFN-γ) secretion. SIN downregulates Th17 cells to treat RA [48,49]. Monocytes are key cells involved in the occurrence, maintenance, and high activity of RA Synovitis [50]. SIN, which inhibits splenic lymphocytes proliferation induced by LPS and PMA in vivo, not only inhibits macrophage proliferation, but also activates ERK to increase P27 and Bax levels, leading to apoptosis [51,52]. SIN has an immunosuppressive function in RA, and apoptosis induction may be one of its immune mechanisms (Fig. 4) [53]. In general, rheumatic disease pathogenesis is related to abnormal immune responses in the body [54]. Dendritic cells can activate T cells [55]. SIN participates in DC differentiation and maturation by negatively regulating NF-κB activity [56], SIN inhibits DCs differentiation and maturation, reduces the release of IFN-γ, TNF-α, IL-12 and other pro-inflammatory cytokines, and decreases CD80, CD86, and other costimulatory molecules expression [57,58]. It also inhibits T cell activation and differentiation by reducing the antigen expression levels in DC [59]. SIN causes abnormal T cell sensitisation [60,61]. Moreover, SIN suppresses the secretion of

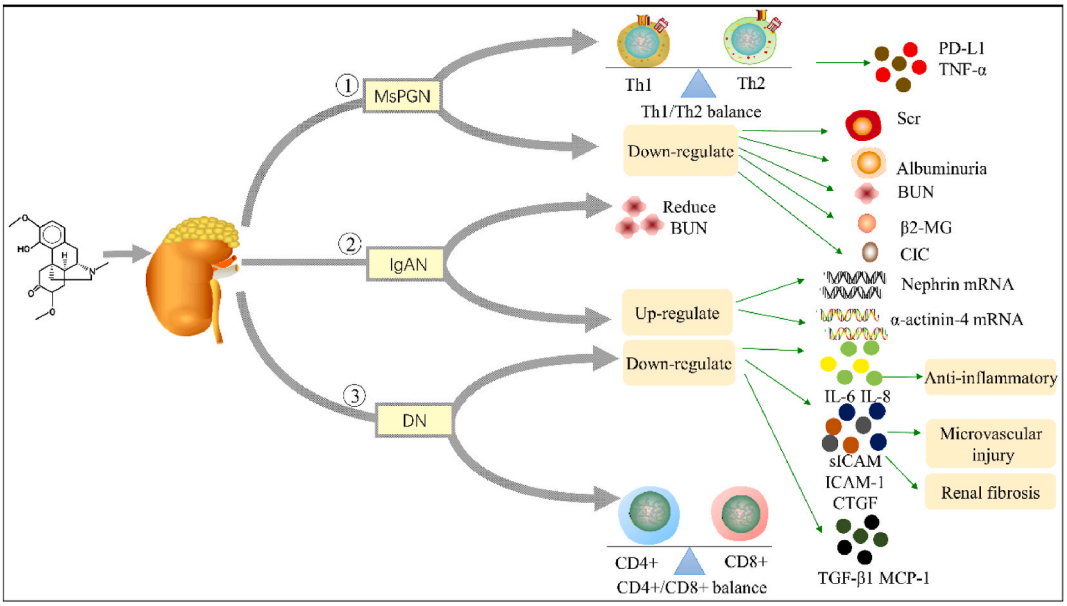

Fig. 5. Summary of the pharmacological mechanism of SIN in the treatment of nephropathy. (1) The effect of SIN on membranous glomerulonephritis. SIN significantly decreased albuminuria, BUN, Scr, β2-MG, CIC to alleviate renal damage, and regulated the balance of Th1 and Th2, thereby down-regulating PD-L1 and TNF-α. (2) The effect of SIN on IgAN. SIN significantly reduced BUN, promoted mRNA expression of Nephrin and α-actin-4, attenuated glomerular podocyte injury, and improved renal pathology in IgAN. (3) The effect of SIN on diabetic nephropathy. SIN reduced IL-6 and IL-8 to exert anti-inflammatory effects, decreased the expression of sICAM, CTGF and ICAM-1 to reduce microvascular injury and renal fibrosis, corrected the imbalance of $CD4^+/CD8^+$ to improve the immune status.

the chemokines CXCL9 (MIG) and CXCL10 (IP10), thus preventing T cells aggregation, differentiation, and activation [62]. SIN can also attenuate DC-mediated inflammatory responses by blocking cytokine secretion, which is beneficial for RA treatment [63]. The major pathological feature of RA is inflammatory cells infiltration [64]. This inhibitory effect was more pronounced when combined with MTX [65]. It also blocks the cell cycle and leads to apoptosis in synovial cells by downregulating bcl-2 protein expression [66–69]. Therefore, it is important to suppress multiple bones destruction in RA patients. Synovial over-expansion leads to local hypoxia in the synovium. Inhibiting the content of hypoxia-inducible factor-α (HIF-α) is helpful for RA treatment [70]. SIN may reduce PGE_2 expression level in mesenchymal stem cells (MSCs), increase the OPG/RANKL ratio, and reduce osteoclast differentiation [71]. SIN inhibits MyD88 and TRAF-6 proteins expression in RA-FLS by affecting TLR signal transduction channels and delaying FLS multiplication [72]. The pannus phenomenon is the major pathological phenomenon in RA, and the inhibition of its occurrence has become an important strategy [16]. As critical factors in angiogenesis, VEGF, MMP-9, and SIN strongly affect its generation [73]. SIN prevents RA-induced bone damage by inhibiting FLS proliferation, inflammatory cell infiltration, and MMPs activity, making it a preferred drug for preventing bone damage during RA pathogenesis. SIN can inhibit the adhesion and infiltration of synovial and inflammatory cells by inhibiting CYR61 [74]. The inhibitory effect of SIN on activated macrophages has become the primary reason for its resistance to RA, which is the major focus of our research. We verified the anti-inflammatory and anti-RA effects of SIN using an activated macrophage model. Exploring the pharmacological mechanism of SIN in other immune system cells, including mast cells and fibroblast-like synoviocytes, will be the major focus of our future research. The excellent therapeutic effect of SIN on RA deserves a lot of effort to explore.

2.2. Shortcomings

SIN significantly inhibits late complications in RA patients. In advanced RA patients with severe atherosclerosis, SIN further inhibits fibroblast growth factor (bFGF)-induced proliferation, migration, and invasion of human umbilical vein endothelial cells (HUVEC) by blocking the cell cycle [75]. Currently, research on the pharmacological mechanism of SIN in treating RA is ongoing, and the mechanisms by which SIN prevents late complications of RA have not been elucidated. Researchers suggest that SIN reduces α7nAChR representation and inhibits synovial cell proliferation by restraining the ERK/Egr-1 signalling pathway [76–79]. However, when HIF-α expression is inhibited, large amounts of oxygen radicals are generated [80], causing oxidative damage to biological macromolecules for instance amino-containing proteins and nucleic acids and promoting lipid peroxidation of polyunsaturated fatty acids (LPO) [81]. SIN was found to inhibit HIF-α expression, scavenging free radicals and anti-LPO [82]. Devastation of articular cartilage and bone damage results in disability in RA patients, and osteoclasts are the main cells [83]. Currently, there is limited research on the mechanism of action of SIN in osteoclasts. When SIN was administered in combination with MTX, systemic OPG levels increased, and RANKL expression in the synovial tissue decreased [84]. Co-administration of SIN and aconitine can synergistically

reduce RANKL content in activated T cells and indirectly inhibit osteoclastogenesis [85], thereby decreasing MMP-3, MMP-13, and IL-17 expression levels; however, both alone failed to downregulate IL-17 expression [86,87]. With the rise in combination therapy, the effective treatment of RA has been enhanced. However, research on the specific pharmacological mechanisms of combined administration and clinical data support need to be improved. Therefore, the safety of SIN in combination with other effective anti-RA drugs must also be considered. SIN also inhibits osteoclast formation by reducing TLR4/6 expression and downstream signalling [88].

2.3. Future directions

Macrophages are the primary target cells for RA treatment. With the rise in targeted drug delivery therapy, our research group has committed to using modified nanomaterials to target activated macrophages to treat RA. Clinically, SIN combined with acupuncture and moxibustion has demonstrated obvious therapeutic effects in RA treatment [89]. The combination of traditional Chinese medicine treatment methods and targeted preparations is expected to become a popular research topic. SIN combined with MTX protects bone from destruction in RA patients [90]. Research on the use of modified SIN-targeting agents in combination with commonly used anti-RA drugs to treat RA is gradually increasing. Allergic reactions to SIN are associated with mast cells [91]. After discovering the cause of allergy, we successfully prepared a nanoformulation that directly targeted the arthritis site. Therefore, it is important to reduce the adverse reactions caused by SIN without affecting its efficacy. SIN reduced HIF-1α generation in synovial membranes, including VEGF and MMP-9 expression, thereby inhibiting angiogenesis [92]. As a selective mPGES-1 inhibitor, SIN inhibited angiogenesis without causing adverse cardiovascular effects. SIN treatment alleviated later complications in RA patients.

3. Nephropathy

Kidney disease is a chronic inflammatory disease with fibrosis being a common characteristic. SIN has anti-renal fibrosis effect [93]. SIN promotes TGF-β secretion to inhibit Th1 and Th2 immune responses and has the greatest impact on Th1 [94,95]. Th1 and Th2 cells regulation by SIN is the major mechanism underlying its function in nephritis. In recent years, research has been conducted on kidney diseases treatment with SIN, predominantly focusing on three kidney diseases: mesangial proliferative glomerulonephritis (MsPGN), IgA nephropathy and diabetic nephropathy (Fig. 5).

3.1. Present use

MsPGN is a renal illness characterised by renal mesenchymal cells proliferation and accumulation and expansion of the extracellular matrix in the interstitial region [96]. An imbalance between Th1 and Th2 in the renal tissue can promote MsPGN occurrence [97]. Studies have found that SIN is involved in interfering with the development of MsPGN [98,99] and downregulating the expression of declined cell death protein 1 ligand 1(PD-L1), which promotes the development of inflammation [100], and cytokines TNF-α which causes mesenchymal proliferation and sclerosis [101]. Water-soluble hydrochlorides in SIN have a strong therapeutic effect on MsPGN rats [102]. SIN alleviates kidney damage in MsPGN [103]. IgAN is the most usual junior glomerular illness around the globe [104,105]. Studies have found that SIN can treat a variety of autoimmune nephropathies, including IgAN [106,107]. SIN significantly reduced the urinary protein concentration in rats with IgAN [108]. As a form of α-actinin protein, α-actinin-4 maintains podocytes integrity. SIN promotes the mRNA expression of α-actinin-4 to reduce glomerular podocyte injury and improve renal pathology in IgAN [109]. Diabetic nephropathy (DN) is the major manifestation of end-stage renal disease worldwide [110]. SIN significantly downregulated the expression of connective tissue growth factor (CTGF) and ICAM-1, thereby reducing renal fibrosis [111]. Connective tissue growth factor (MCP-1) is elevated in DN as a potent chemokine for monocytes and macrophages [112]. MCP-1 induces macrophages to migrate to kidney tissues [113], and SIN downregulates MCP-1 expression to play a therapeutic role [114]. TGF-β1 promotes extracellular matrix aggregation, renal fibrosis, and glomerulosclerosis in DN patients, while SIN inhibits TGF-β1 expression level in renal tissues [115,116].

3.2. Shortcomings

Although research into SIN treatment in kidney disease has been conducted for several years, clinical data are still lacking. Currently, research on SIN treatment for kidney disease focuses only on the above three kidney diseases, and there is almost no research on its effectiveness in other kidney diseases. Therefore, further research is required to determine whether SIN can replace other effective drugs for treating kidney disease.

3.3. Future directions

Post SIN administration, albuminuria, serum creatinine (Scr) and circulating immune complex (CIC), and blood urea nitrogen (BUN) and β2-microglobulin (β2-MG) in the blood and urine of MsPGN patients decreased [117]. For effective MsPGN treatment, in the future, more focus should be placed on the specific reasons why SIN reduces protein levels in plasma and urine, including its direct targets. In recent years, our research group has been investigating the pharmacological mechanism of SIN in IgAN treatment, and the results will be supplemented in the future. SIN not only reduces 24-h urinary protein excretion and renal pathological changes in DN rats but also reduces IL-6 and IL-8 to exert anti-inflammatory effects [118]. A previous study reported that SIN causes allergies [119]. While treating DN with SIN, avoiding allergic reactions should be considered.

4. Tumours

4.1. Present use

4.1.1. Cervical cancer

Cervical cancer is the fourth most constant malignancy in females globally, with approximately 600,000 new examples of cervical cancer and approximately 300,000 women dying from its lesions each year [120]. To effectively treat cervical cancer, it is essential to explore the regulatory mechanisms of SIN during its pathogenesis. Bcl-2 is a proto-oncogene that inhibits apoptosis, and studies have found that SIN inhibits its expression [121]. PI3K/Akt signalling pathway and protease caspase-3 play crucial roles in apoptosis. SIN inhibits Akt synthesis, enhances Caspase-3 activation, and promotes apoptosis in cancer cells [122]. The combination of SIN and cisplatin was found to produce significant synergistic suppression of cancer cell proliferation, presumably by inhibiting mitosis through DNA polymerase activity inhibition [123]. SIN may also inhibit cancer cell proliferation by affecting cell cycle distribution and promoting apoptosis during cervical cancer treatment [124]. Recently, Wang et al. found that SIN could suppress the proliferation and aggression of effective cervical cancer SiHa cells cultured *in vitro* [125]. SIN effectively treated cervical cancer by inhibiting cervical cancer cells proliferation and promoting apoptosis. Existing research demonstrates that SIN can be used to treat cervical cancer; however, its specific pharmacological mechanism has not been elucidated.

4.1.2. Lung cancer

In China, lung cancer has a high mortality rate. Therefore, it is crucial to identify a suitable drug for treatment. SIN inhibited cancer cell proliferation by reducing the oncogenes p53 and p16 expression levels [126]. SIN inhibits the expression of A2A and α7 nicotinic acetylcholine receptor (α7nAChR), which may be the mechanism of inhibiting cancer cells multiplication [45,127]. SIN downregulates Bcl-2, upregulates Bax expression, releases cytochrome C, and activates caspase-9 and caspase-3 to induce apoptosis in lung cancer cells apoptosis [128,129]. As an important tumour cell apoptosis regulator, the important p53 inhibitor is that iASPP can inhibit the transcriptional activation of p53 downstream antioxidant target genes, thereby promoting tumour cell apoptosis. Sensitisation of the Akt and ERK1/2 pathways is often associated with cell proliferation and survival [128]. SIN inhibits ERK phosphorylation and iASPP expression [130]. It can also be used in combination with PI3K/Akt and MEK/ERK signalling pathway inhibitors to enhance apoptosis in lung cancer cells [131]. The effect of SIN on lung cancer can be summarised as cancer cell proliferation inhibition and apoptosis induction.

4.1.3. Liver cancer

Liver cancer, the third deadliest cancer in the world, significantly interferes with the function of the body of a patient and requires specific drugs. China has the highest morbidity and mortality rates of liver cancer. Both Fas and Bcl-2 regulate apoptosis in liver cancer cells. SIN enhances the representation of Fas, diminishes Bcl-2 content, and promotes apoptosis in liver cancer cells [132]. DR4 and DR5 are apoptotic receptor ligands found in liver cancer cells. With an increase in SIN concentration, the protein expression levels of DR4 and DR5 increased in a dose-dependent manner to promote apoptosis in liver cancer cells [133]. SIN can also block hepatoma cells in G1 phase by mediating DNA damage via the ATM/CHK2 pathway, resulting in apoptosis [134]. The major effect of SIN on liver cancer cells was apoptosis. SIN restrained cancer cells proliferation and metastasis [135,136]. CASP3 and CASP9 are apoptotic proteins, while CAV1 and SOX2 seriously affect human hepatoma cell metastasis. SIN increases CAV1, CASP3, and CASP9 content, and reduces SOX2 expression, thereby inducing liver cancer cells apoptosis and suppressing their invasion and metastasis. Similarly, SIN inhibits cell reverse transcriptase activity and blocks DNA replication in hepatocellular carcinoma cells, thereby inhibiting cell proliferation [137]. P21 and P27 are cell cycle-related proteins that decelerate the cell cycle. SIN regulates P21 and P27 protein expression and blocks the cell cycle to inhibit cancer cell growth [138]. Therefore, SIN is essential for tumour invasion.

4.1.4. Gastric cancer

Gastric cancer is a malignant tumour with a high recurrence rate, rapid invasion and metastasis, and low cure rates [139]. SIN targets miR-141 to curb gastric cancer cell proliferation, invasion, and metastasis [140]. SIN inhibits IL-6 expression to suppress the M2 phenotype in the tumour microenvironment, remodel the tumour environment, and reduce tumour cell proliferation [141]. SIN alters the Bcl-2/Bax protein expression ratio, thereby inhibiting cancer cell growth [142].

4.1.5. Glioblastoma

Glioblastoma is the most common and lethal idiopathic brain tumours in grownups [143]. Currently, there is no specific cure for glioblastoma, and its prognosis is extremely poor. SIN downregulates the NF-κB signalling pathway to inhibit MMP-2/-9 expression [144]. SIN can inhibit glioblastoma xenograft growth by inducing autophagy through proactive oxygen species ROS-mediated Akt/mTOR and JNK-dependent pathways to inhibit cancer cell growth and promote lysis by activating transcription factor EB (TFEB) [145]. The inhibitory effect of SIN on glioblastoma is predominantly mediated by the NF-κB signalling pathway.

4.1.6. Breast cancer

Breast cancer is a malignant tumour that occurs in breast epithelial cells and has a high degree of spatiotemporal heterogeneity [146]. SIN inhibits the sensitisation of NF-κB and SHh pathways and regulates MMP-2 and vimentin to inhibit cancer cell proliferation and migration [147]. SIN regulates the miR-29/PDCD-4 axis to inhibit cancer cell proliferation, migration, and invasion; promote apoptosis [148]; and reduce IL-8/CXCR1 and c-inhibits breast cancer-induced osteolysis and Fos/NFATc1 signalling [149]. SIN

Table 1
Roles of SIN in cancer.

Cancer	Roles of SIN in cancer		
Cervical cancer	Inhibit proliferation	Induce apoptosis	
Lung cancer	Inhibit proliferation	Induce apoptosis	Inhibit migration and erosion
Liver cancer	Inhibit proliferation and metastasis	Induce apoptosis	
Gastric cancer	Inhibit proliferation	Induce apoptosis	
Glioblastoma	Inhibit proliferation	Induce apoptosis	
Breast cancer	Inhibit proliferation, migration, invasion	Induce apoptosis	Inhibit IL-6
Pancreatic cancer	Inhibit proliferation, migration, invasion	Induce apoptosis	
Leukemic tumor	Induce apoptosis		
Colon cancer	Inhibit proliferation	Inhibit TNF-α, IL-23, β-catenin	

Table 2
Mechanism of SIN in inducing apoptosis.

Cancer	Mechanism of SIN in inhibiting cell proliferation
Cervical cancer	Block cancer cells in G1 phase and induce apoptosis. Inhibit the proliferation of cancer cells through inhibition of DNA polymerase activity and mitosis.
Lung cancer	Regulate cell cycle ratio and inhibit cancer cell proliferation by reducing the expression of p53 and P16. Inhibit the effect of NNK and the expression of A2A and α7nAChR.
Liver cancer	Inhibit cell growth by inhibiting the activity of reverse transcriptase and blocking DNA replication in. Inhibits Ras signal pathway, decrease expression of TNF-α and IL-1β leads to the destruction of tumor microenvironment, decrease expression of C/EBP β protein inhibits tumorigenesis. Up-regulate P21 and P27 protein expression, induce cell cycle arrest, inhibit cell growth.
Gastric cancer	Block the G1 phase of the cell cycle, up-regulate P21 protein. Targeting miR-141 through metastasis-associated MALAT1.
Glioblastoma	Inactivation of NF-κB inhibits the expression of MMP-2/-9. Reversal of endogenous EMT by endoplasmic reticulum stress-mediated autophagy. Tumor inflammatory microenvironment stimulation reverses exogenous EMT.
Breast cancer	Reduce the expression and release of VEGF. Inhibits the activation of NF-κB and SHh pathway and then regulates MMP-2 and vimentin to affect cancer metastasis. Regulating angiogenic factor bFGF, anti-angiogenic factor PF-4 and chemokine GM-CSF to induce vascular normalization Regulating the miR-29/PDCD-4 axis.
Colon cancer	Block the cell cycle and inhibit the proliferation of cancer cells. Inhibit the secretion of inflammatory factors TNF-α, IL-23 and the expression of β-catenin, destroy the tumor microenvironment.

Table 3
Mechanism of SIN in inducing apoptosis.

Cancer	Mechanism of SIN in inducing apoptosis
Cervical cancer	Inhibit the expression of bcl-2 Inhibit the synthesis of Akt, up-regulate caspase-3
Lung cancer	Inhibit the expression of bcl-2, increase the expression of Bax, accompanied by the collapse of mitochondrial membrane potential, cytochrome C release, activate caspase-9, caspase-3 Activate Akt and REK Decrease the phosphorylation of ERK protein and inhibit the expression of iASPP
Liver cancer	Inhibit the expression of bcl-2, increase the expression of Apo2.7 and Fas gene Inhibit the expression of P21 protein, activate caspase cascade Increase the protein expression levels of DR4 and DR5, activate caspase cascade block hepatoma cells in G1 phase through DNA damage mediated by ATM/CHK2 pathway
Gastric cancer	The combination of SIN and 5-FU can enhance the function of 5-FU in inducing apoptosis through mitochondrial pathway.
Glioblastoma	Down-regulates SIRT1 and increases the expression of p53 protein, which promotes the apoptosis of cancer cells
Breast cancer	Inhibit the proliferation, migration, invasion and induce apoptosis of cancer cells by regulating the miR-29/PDCD-4 axis
Pancreatic cancer	Inhibit EMT to reduces the expression of F-actin and β-tubulin, thus inhibiting the invasion and metastasis of cancer cells
Leukemic tumor	regulating the proportion of Bcl-2/Bax protein and activating Caspase-3, induce early apoptosis of leukemic tumor cells

decreases VEGF expression and release and inhibits cancer cell proliferation [150]. SIN curbs breast cancer metastasis by inhibiting epithelial-mesenchymal transition (EMT) and cancer stem cell (CSC) properties owing to the lack of significant hepatotoxicity or nephrotoxicity [151]. Wu et al. found that SIN alone was more effective than in combination with 5-fluorouridine (5-FUR) in breast cancer treatment. It may be that 5-FUR undergoes a series of reflections within the body, resulting in DNA synthesis blockade [152]. With the continuous deepening of SIN research, progress in the effective treatment of breast cancer will be accelerated (Tables 1–3).

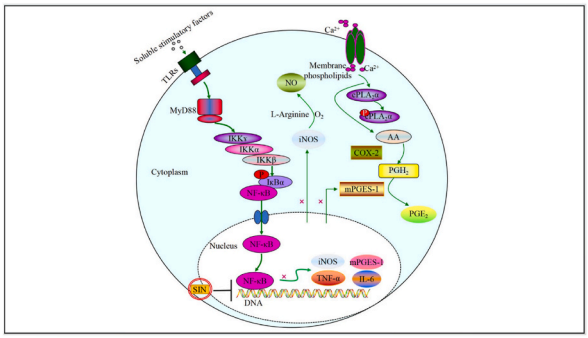

Fig. 6. The anti-inflammation effect and mechanism of SIN. SIN selectively inhibited DNA-binding activity of NF-κB downstream of the NF-κB signaling pathway, reduced the production of pro-inflammatory cytokines TNF-α and IL-6, inflammatory mediators mPGES-1, iNOS, PGE_2 and NO.

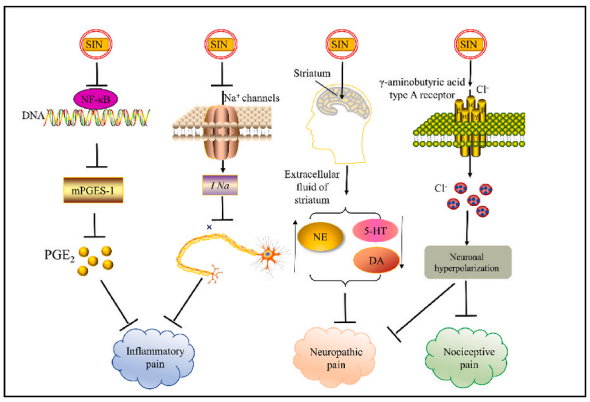

Fig. 7. Summary of the pharmacological mechanism of SIN in the treatment of neurological diseases. SIN produced a wide range of analgesic effects through non-μ opioid receptor mechanisms, does not addiction, dependence and depress respiration as opioid analgesics.

4.2. Shortcomings

The current results indicate that SIN has a significant inhibitory effect on cancer, but its direct target of action has not yet been elucidated (Fig. 6). Although SIN can treat cancer, there is a lack of cases in clinical practice that support its effective treatment success. Only with sufficient clinical data can SIN be used in cancer treatment. Overall, the current research on SIN for cancer treatment must be conducted.

4.3. Future directions

However, the pharmacological mechanism of SIN in cancer treatment requires further investigation. Dual validation of therapeutic effects of SIN on cancer using in vivo cancer models and *in vitro* experiments is essential for future research. ZQFTN is currently the major form of the SIN formulation. Li et al. statistically evaluated 204 adverse reactions cases caused by ZQFTN injection, including 9 cases of anaphylactic shock, 197 local allergic rash cases, and 19 systemic allergic rash cases [153]. After exploring the pharmacological mechanisms of SIN in cancer treatment, it is essential to consider the direct transport of modified SIN-targeted nanomaterials to cancer cells. The preparation of new targeted nanomaterials will help overcome the adverse reactions caused by ZQFTN.

5. Psychoneurological disease

5.1. Present use

Alzheimer's disease (AD) is a highly age-related degenerative disorder of the central nervous system characterised by progressive cognitive impairment and memory damage. Neuroinflammation is an substantial factor in AD progress and SIN significantly inhibits NF-κB activity, suppresses inflammation, and reduces neuronal cells apoptosis [154]. Parkinson's disease (PD) is a gradual neurodegenerative disorder of the central nervous system characterised by progressive extrapyramidal dysfunction. Microglia are easily over-activated and produce abundant pro-inflammatory cytokines under pathological conditions. SIN significantly reduces TNF-α, PGE_2, and ROS produced by microglia [155]. Epilepsy is one of the most common chronic neurological diseases in paediatric patients

and is characterised by repetitive and paroxysmal central nervous system dysfunction. SIN inhibits epilepsy by inhibiting neuronal apoptosis in the CA1 and CA3 regions and activates caspase-3 by regulating Bcl-2/Bax protein expression [156]. During migraines, c-fos and c-jun are abnormally expressed in several parts of the brain. SIN inhibits c-fos and c-jun expression in the brainstem of patients with migraines and upregulates 5-HT activity to treat migraines [157,158]. Periaqueductal grey matter (PAG) contains all kinds of inflammatory cytokines associated with migraine, and SIN reduces NF-κB and COX-2 expression in the PAG area and upregulates 5-HT activity [159,160]. SIN also treats neuropathic pain by inhibiting IL-17A/CaMKii/CREB pathway activation [161]. SIN plays a role in psychiatric neuropathy treatment by inhibiting the inflammatory pathway and reducing proinflammatory cytokines production. As the fundamental component of amyloid plaques in the brain of AD patients, Aβ oligomers can induce neuronal death. Aβ can lead to inflammation and the release of toxic molecules for instance of reactive oxygen species (ROS) and NO. SIN can prevent the generation of reactive oxygen species, NO, and inflammation-related molecules in the β-amyloid-induced astrocyte line C8D1A, resulting in neuroprotection [162]. Post SIN intervention, the number of tyrosine hydroxylase (TH)-positive neurones and TH protein expression increased significantly, which played a neuroprotective role [163]. SIN reduces the levels of inflammasome complex (NLRP1) and inflammatory cytokines IL-1β, IL-18, IL-6, and TNF-α in a dose-dependent style [164]. During epilepsy healing, SIN reduces oxidative stress damage to the hippocampal structure and plays a significant role in reducing oxidative stress, inflammation, and apoptosis [165]. SIN markedly declined IL-1β and TNF-α expression in inflammatory cells around subarachnoid minor vessels and brainstem. The mechanisms and regulatory factors of SIN in psychiatric disorders require more detailed experimental exploration (Fig. 7).

5.2. Shortcomings

Low-dose SIN inhibits allergic mediator production in mast cells, inhibits the trigger of mast cells and reduces inflammatory cytokines expression level by upregulating SIRPα performance [166,167]. Few cases of adverse haematological effects caused by SIN have been reported. To date, four agranulocytosis cases, one of autoimmune haemolytic anaemia [168], one of aplastic anaemia [169], one of thrombocytopenia [170], and one of allergic purpura [171] have been reported. The effect of SIN on the blood has been less studied. As there are few studies on anti-nervous system diseases of SIN and that SIN has adverse reactions, it cannot be used in the clinical treatment of neurological diseases. However, in *vitro* cell models have not demonstrated the ability of SIN to treat neurological diseases. However, in *vitro* experiments and animal models have not indicated the dose at which SIN can treat neurological diseases without causing side effects. Currently, the methods for constructing animal models, including AD, are too simple. Multiple approaches and animal models should be used to verify the therapeutic effects of SIN on neurological diseases.

5.3. Future directions

To treat neurological diseases more effectively, it is crucial to determine the appropriate clinical dosage of SIN. SIN directly induces mast cell degranulation which releases histamine and causes hypersensitivity responses [172,173]. Low concentration of SIN (100 μmol/L) curbs mast cell proliferation, promotes their apoptosis, and inhibits their activation and degranulation. High SIN concentrations directly induce mast cell degranulation. Differences in SIN concentrations exhibit a bidirectional regulatory effect on mast cells [174]. SIN reduces cardiomyocyte excitability and causes arrhythmia [175]. There were two menstrual irregularity cases caused by the use of ZQFTN (60 mg BID) in 44-year-old women, and menstruation returned to normal post drug discontinuation [176]. Future studies on SIN in neurological diseases must determine a dose that avoids adverse effects.

6. Side effects

At present, the main SIN preparation in domestic clinical application is ZQFTN, which is mostly used to treat RA, and the incidence of adverse reactions is about 14.2 % [177]. The allergic reaction of SIN has been proved to be related to mast cells, and the activation of mast cells releases all kinds of pro-inflammatory and vasoactive substances, which participate in allergic reactions [178]. Addressing the adverse effects of SIN will expand its clinical use. Our research team has now prepared an active targeting system to avoid its effect on mast cells. At the same time, there are also a few reports stating that SIN reduces the excitability of cardiomyocytes and causes arrhythmia [179]. There were two cases of SIN causing irregular menstruation, but menstruation returned to normal after stopping the drug [180]. The specific mechanism of adverse reactions caused by SIN has not yet been elucidated, and specific methods to avoid its adverse reactions have not yet been implemented.

7. Emerging research directions

With advancements in technology and medicine, SIN for treating diseases is no longer limited to ZQFTN. Recently, researchers have attempted to modify SIN to directly target activated macrophages and achieve anti-inflammatory effects. In situ LCs laden with SIN and 5-FUR realise the desired drug precision, targeting, and sustained release for liver cancer treatment [181]. The use of new materials or conjugates for targeted SIN delivery achieves a sustained release effect, improves bioavailability, and reduces side effects [182]. Autoimmune rejection also makes the clinical treatment of SIN difficult. The nano-PB NPs complex offers a good carrier for the controlled discharge and targeted SIN aggregation at the site of arthritis and facilitates immune escape [183]. SIN is an effective anti-inflammatory drug, but it has the disadvantage of short half-life. The study found that the pharmacokinetic distribution of SIN in rats has significant gender differences [184]. The current research hotspot is to extend the half-life of SIN and enhance its

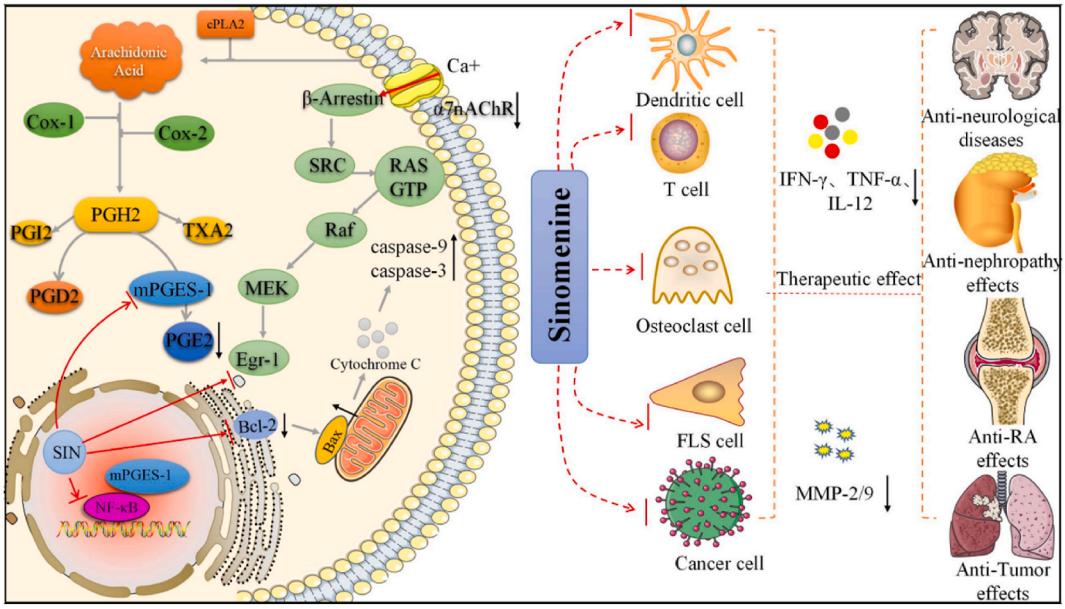

Fig. 8. Summary of pharmacological effects of SIN. (1) SIN selectively inhibited the DNA-binding activity of NF-κB downstream of the NF-κB signaling pathway, inhibited DCs, T cell, FLS cell, Ostcoclsat cell, Cancer cell, reduced pro-inflammatory cytokines and MMP-2/9 to act against RA, cancer, kidney disease, neurological diseases, etc. (2) SIN inhibited the ERK/Egr-1 signaling pathway, reduced the expression of α7nAChR, and inhibited the proliferation of synovial fibroblasts and cancer cells. It also induced apoptosis of synovial cells and cancer cells by downregulating Bcl-2, raising Bax expression, activating caspase-9 and caspase-3 protein expression, blocking synovial cells and cancer cell cycles.

bioavailability through modern nanotechnology means. Our team successfully prepared an SIN active targeting drug delivery system (FA–SIN–HSA NPs) to achieve a direct therapeutic effect on RA. Through FA and HSA modification, SIN can directly target and activate macrophages. Therefore, allergic reactions caused by SIN-induced mast cell degranulation must be considered. As research into the pharmacological effects of SIN continues to increase, and new preparations loaded with SIN are expected to undergo clinical trials.

8. Sinomenine derivatives

There are currently few studies on SIN derivatives. Current research has found that the derivatives of SIN are S1a-S1f and $C_{(26)}H_{(28)}FNO_{(4)}\cdot 1.5H_{(2)}O$, etc. Zhao et al. found that SIN derivatives have anti-inflammatory activity similar to SIN by constructing an acute inflammation model [185,186]. Research on other pharmacological mechanisms of its derivatives has not yet been covered. The discovery of SIN derivatives will bring hope to the control of inflammation and the treatment of other inflammatory diseases.

9. Summary

This article reviews the mechanism of action of SIN in diverse diseases and current research results (Fig. 8). SIN plays a crucial role in treating RA and other inflammatory diseases by inhibiting other inflammatory pathways, such as NF-κB pathway. *In vivo* and *in vitro* experiments have suggested that SIN has strong therapeutic effects in cancer treatment, and the future market for SIN anticancer drugs requires several clinical trials. As an alkaloid derived from traditional Chinese medicine, SIN has strong analgesic and anti-inflammatory effects owing to its structural characteristics, which are key to its treatment of psychiatric and neurological diseases. While treating diseases, SIN also has side effects, including allergies and menstrual irregularities. With continuous research on targeted preparations, it is possible to overcome the adverse reactions caused by SIN while producing the same therapeutic effect. Targeted delivery of SIN and combination of SIN with other drugs will reduce its side effects. Current research on SIN side effects has only revealed its effect on mast cells; its adverse effects on other cells have not yet been discovered. The mechanism of adverse reactions caused by SIN has not yet been elucidated, which makes it difficult to research the pharmacological effects of SIN and the targeted treatment of RA. Our research group prepared FA–SIN–HSA NPs to overcome the allergic reaction to SIN, but other side effects of SIN have not yet been resolved, which still require the efforts of scientific researchers.

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Data availability statement

This study is a review and the raw data are available in references studies.

CRediT authorship contribution statement

Shan Jiang: Writing – original draft. **Shuang Li:** Writing – original draft. **Siyuan Pang:** Writing – review & editing. **Mei Liu:** Visualization. **Huifeng Sun:** Formal analysis. **Ning Zhang:** Writing – review & editing, Resources. **Jianxin Liu:** Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:The authors reported no declarations of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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