

A review on anti-inflammatory mechanism and delivery systems of genistein

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Abstract Genistein is a phytoestrogen with multiple biological activities. Studies have shown that genistein can exert anti-inflammatory activities through various pathways, and an in-depth study of its mechanism of action could develop more effective anti-inflammatory drugs. The poor solubility and stability of genistein limit its application. Researchers have developed a variety of novel delivery systems, such as nanocarriers, liposomes, and microemulsions, which can improve the solubility, stability, and *in vivo* distribution of genistein and enhance its therapeutic activity. The study presents the recent investigation on genistein's effects on the anti-inflammatory mechanisms and delivery formulation of genistein.

Keywords: genistein; anti-inflammatory; delivery system

1 Introduction

Genistein is an isoflavones of natural plant origin^[1], alias 5,7,4'-trihydroxyisoflavone, mainly found in legumes, and widely distributed in legume foods as well as seeds, fruits and vegetables, such as soybeans and alfalfa^[2]. The molecular formula of genistein is C₁₅H₁₀O₅ with molecular weight of 270.241 g/mol and structure is shown in Fig. 1^[3]. Genistein exerts a variety of biological activities, including antibacterial, anti-tumor, anti-inflammatory, neuroprotection, estrogen-like effect, metal chelation, etc., but the disadvantages of poor water solubility, poor lipid solubility and low bioavailability of it limits the clinical application^[4, 5]. Therefore, suitable drug delivery systems are needed to improve the solubility and bioavailability of genistein. This paper

summarizes the anti-inflammatory effect of genistein and the drug delivery system.

Inflammation is a local defense response of the body to injury or infection, usually with symptoms^[6].

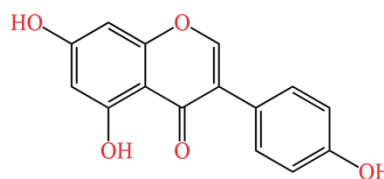


Fig. 1 Chemical structure of genistein

When the body meets external stimulation, the immune system is activated to produce a series of physiological responses to remove pathogens and to promote tissue repair. Inflammation is categorized into acute inflammation and chronic inflammation^[7]. Among them, chronic inflammation, may persist for a longer period of time due to the continuous production of cytokines^[8, 9], and is strongly associated with many chronic diseases^[10-12]. Cytokines mainly

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include interleukin (IL), tumor necrosis factor (TNF), intercellular cell adhesion molecule (ICAM), growth factor (GF), interferon (IFN) ^[13, 14]. In most cases, inflammation is a normal response of the body to protect itself, but excessive or prolonged inflammation can lead to tissue damage and disease. Therefore, controlling the inflammatory response is important for maintaining good health.

At present, many inflammatory conditions and their induced diseases still deeply affect human health. The anti-inflammatory therapies currently in use are nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying agents for rheumatoid diseases (DMARDs) ^[15]. However, long-term use can produce various side effects such as gastrointestinal bleeding, cardiovascular problems, endocrine problems, liver and kidney damage ^[16-18]. Thus, there is a need for novel natural medicines with high safety profile and wide sources to treat inflammation.

2 Anti-inflammatory mechanism of genistein

Genistein can be used as a natural anti-inflammatory drug for the prevention and treatment of inflammation-related diseases, such as nephritis, arthritis, asthma, gastroenteritis, osteoporosis, and heart disease ^[19]. The anti-inflammatory activities of genistein have been demonstrated in many experimental studies, and its mechanisms of action include inhibiting the production and release of inflammatory mediators, regulation of inflammatory signaling pathways, inhibiting the activity of inflammatory cells, and inhibition of oxidative stress ^[20]. Genistein is also a potent inhibitor of arachidonic acid (AA), phospholipase A2, cyclooxygenase (COXs), nitric oxide synthase (NOS), and lipoxygenase (LOXs), which reduces the production of key inflammatory substances prostaglandins (PGs), leukotrienes, and NO ^[21, 22]. Genistein also reduces the release of arachidonic acid metabolites and chemokines, thereby reducing leukocyte infiltration and edema and modulating immune cell activity. It also suppresses the activation of inflammatory cells

and reduces the levels of proinflammatory cytokines such as IL-6, IL-8, TNF- α , IL-1 β , and monocyte chemoattractant protein-1 (MCP-1) ^[22]. Inhibition of proinflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) ^[23]. Genistein also regulates many pathways, such as mitogen-activated protein kinase (MAPK), phosphoinositide 3 kinase (PI3K) / Akt, and extracellular signal-regulated kinase (ERK), to inhibit the activation of nuclear factor (NF- κ B) ^[24-26], and inhibit the activity of MPO and COX-2 through the NF- κ B pathway ^[27-32].

2.1 Cartilage diseases

2.1.1 Osteoarthritis

Osteoarthritis (OA) is a common chronic and degenerative bone and joint disease in middle-aged and elderly people. With the advent of aging in China, its incidence has increased significantly, and its pathogenesis is still unclear ^[33]. It mainly affects articular cartilage, and common parts include knee, hip, spine, fingers and wrist joints. Osteoarthritis leads to changes in subchondral bone and progressive erosion of articular cartilage, characterized by degeneration of articular cartilage, subchondral osteonecrosis, and irregular hyperplasia of bone. Usually, it causes joint pain, swelling, stiffness, and movement disorders.

The causes of osteoarthritis may include aging, joint damage, being overweight, genetic factors, and repetitive movements of the joints. The main reasons may be related to inflammation, oxidative stress, cell damage, and apoptosis in chondrocytes and synoviocytes ^[34]. Among them, NF- κ B is a key transcription factor in the inflammatory and immune response processes, involved in the OA pathology activated by pro-inflammatory cytokines ^[35]. The production of cytokines such as interleukin IL-1 β , tumor necrosis factor TNF- α , IL-6, matrix metalloproteinases (MMPs), iNOS and prostaglandin E2 in joints is also closely related to osteoarthritis, involved in the development of OA and leading to the

destruction of cartilage ^[36].

Genistein has an estrogen-like activity in the prevention of osteoporosis and osteoarthritis ^[28]. An estrogen-like phenomena is combined with the presence of two estrogen receptors (ER- α and ER- β) on articular chondrocytes to prevent the development of osteoarthritis ^[37]. Genistein can reduce ROS secretion in LPS treated chondrocytes, oxidative stress levels, inhibit the expression of inflammation-related genes IL-1 β , IL-6, TNF- α , MMP-MMP-13, MMP-1, inducible nitric oxide synthase iNOS, and transcriptional regulator p53 in cells, and reduce joint inflammation ^[38, 39]. It can also inhibit signaling pathways such as NF- κ B activated by protein kinase MAPK, which can reduce the ratio of apoptotic gene Bax/Bcl-2, thereby inhibiting chondrocyte apoptosis ^[35, 40]. Genistein increases Sox9, type II collagen and proteoglycan expression in chondrocytes by inhibiting MMP levels ^[28]. Genistein is also an inhibitor of tyrosine kinase in protein kinases that can regulate the differentiation and appreciation of chondrocytes ^[41]. It has been shown that genistein can also stimulate the expression of Ho-1 to activate the Nrf 2 signaling pathway and inhibit the activation of NF- κ B and inflammatory cytokines ^[42]. It can also inhibit the generation of catabolic factor nitric oxide synthase 2 (NOS-2), cyclooxygenase 2 (COX-2), MMPs induced by inflammatory factor IL-1 β , and reduce the development of osteoarthritis ^[43]. In conclusion, genistein mediates the inflammatory response to fight chondrocytic apoptosis and restore cartilage balance in the treatment of osteoarthritis ^[44]. Therefore, genistein can be used for remission and treatment of OA.

2.1.2 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, autoimmune disease, which is more common in women than in men ^[45]. The main manifestations are joint inflammation, pain, stiffness, swelling and dysfunction, resulting to impaired motor function ^[46]. Many RA patients are not suitable to use existing drugs to control disease progression. Therefore, finding safer and more effective treatments is crucial

for patients with rheumatoid arthritis.

The onset of rheumatoid arthritis may be due to genetic and environmental, the development of RA is associated with synoviocytes proliferation, increased angiogenesis, inflammatory cell infiltration, and progressive joint erosion, with an increased number of synovial cell layers in response to inflammation ^[28]. Among them, NLRP 3 inflammasome is an important factor promoting the progression of RA, and non-phagocytes such as T cells can activate inflammasome NLRP 3, and secrete cytokines IL-1 and IL-8 to promote the development of inflammation ^[47]. Studies have shown that the development of rheumatoid arthritis has a great relationship with monocytes, macrophages and T cell function ^[48], and is a marker of disease progression ^[49]. Induction of IL-17 A and TNF- α expression by Th 17 cells caused cartilage damage, whereas Tregs exhibited anti-inflammatory activity, and abnormal control between Treg/Th 17 cells caused an inflammatory response in RA ^[50]. These inflammatory factors stimulate synoviocytes, osteoclasts, and activate some MMPs ^[46], destroying bone and chondrocytes, and eventually forming rheumatoid arthritis.

The researchers designed bovine collagen type II (CII) emulsion and an incomplete Freund's adjuvant (IFA) in DBA / 1 mice, induced CIA (collagen-induced arthritis). Giving genistein 5 mg / kg daily for 10 days reduced the serum levels of IL-1 β , IL-6, and TNF- α in mice, inhibited the expression of vascular endothelial growth factor (VEGF), reduced angiogenesis in the articular synovial ^[51]. It also inhibited the expression of MMP-9 and MMP-2 induced by IL-1 β and TNF- α ^[52]. Tumor necrosis factor TNF- α is the main mediator of inflammation in RA and can target VE-cadherin to alter vascular permeability. Experiments demonstrate that genistein inhibited TNF- α -induced tyrosine phosphorylation of VE-cadherin and delayed the progression of RA ^[53]. In addition, genistein can inhibit tyrosine phosphatase activity, downregulate NO synthase in chondrocytes, reduce the redness and swelling of the joints of CIA rats, significantly inhibit the collagen damage in rats, and delay the progression of rheumatoid arthritis in

rats^[54]. Because IL-6 stimulates the JAK 2 / STAT 3 signaling pathway, it promotes VEGF expression in rheumatoid arthritis synovial fibroblasts (MH7A)^[55], and increases angiogenesis. Genistein reduced the levels and expression of STAT 3, IL-6, and VEGF in IL-6-stimulated MH7A, inhibited JAK 2 / STAT 3 signaling downstream of IL-6, and inhibited IL-6 to induce vascular endothelial cell migration and blood vessel formation in EA.hy926 cells^[56]. The activation of osteoclasts is also an important factor in rheumatoid arthritis, and related genes TRAP, NFATc1, c-Fos are expressed, resulting in the development of RA. Genistein can inhibit the activation of osteoclasts in CIA mice by inhibiting NF- κ B signaling pathway and the expression of downstream transcription factors NFATc1 and c-Fos; it also increases the plasma expression of IgG glycosylation genes (B4gal1, St6gal1), increases IgG glycosylation and reduces arthritis symptoms^[57]. Genistein also modulates the Th 1-cell-dominated immune response, reducing the levels of IFN- γ and enhancing the secretion of the anti-inflammatory factor IL-4^[58], showed potent anti-inflammatory activity of genistein. In conclusion, genistein inhibits synovial cell proliferation and the activation of osteoclasts, reduces angiogenesis and inflammatory infiltration, reduces bone and cartilage damage, and delays the disease process of rheumatoid arthritis.

2.2 Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a common form of chronic inflammation, including ulcerative colitis (UC) and Crohn's disease (CD)^[59]. IBD causes prolonged, recurrent ulceration, bleeding, and inflammation of the colonic lining, causing symptoms such as diarrhea, abdominal pain, anemia, and weight loss, which can eventually lead to colon cancer^[60]. At present, the incidence rate is increasing year by year worldwide, which seriously affects the quality of life of patients. However, some anti-UC drugs including anti-inflammatory, immunosuppressants and antibiotics have side effects and allergic reactions, so UC patients need more safe and effective drugs^[61].

The etiology of IBD is not clear, which may be

due to the combination of environmental, genetic, immune system and other factors. Among them, the dysregulation of immune response of intestinal microbiota, destruction of mucus layer and epithelial cells of intestinal mucosal barrier, abnormality of intestinal cytokines, and massive release of reactive oxygen species may be important factors in the development of IBD. These factors lead to the barrier damage to the intestinal mucosa^[62]. The serum levels of TNF- α , IL-1, IL-6, IL-17A and IL-23 in IBD patients were altered^[63], with IL-17 associated with the severity of untreated UC^[64]. The differentiation of helper T cells 17 (Th 17) cells increases the secretion of IL-17, and the imbalance between helper T cells (Th) and regulatory T cells leads to the onset of ulcerative colitis^[65]. JAK / STAT, NF- κ B, and Nrf 2 are important signal pathways in intestinal cells related to the development of IBD. Oxidative stress also promotes the development of the disease, with massive release of reactive oxygen species (ROS), and nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) further damage the intestinal mucosa by inhibiting the antioxidant system and upregulating free radicals^[66]. In addition, a large number of intestinal cell apoptosis destroys the homeostasis of the intestine, stimulates the intestinal microbiome to cause inflammatory response, increases the damage in the intestine^[67], and accelerates the development of UC disease.

It was shown that genistein can inhibit the activation of NF- κ B, reduce the levels of inflammatory cytokines IL-6, TNF- α , and improve the activity of SOD^[68, 69]. The NLRP 3 inflammasome plays an important role in the production and development of colitis^[70], which induces the secretion of the inflammatory cytokine IL-1 β . The researchers found that genistein reduced the infiltration of inflammatory cells in dextran sodium sulfate (DSS) -induced colitis, inhibited NLRP 3 inflammasome by activating TGR 5-cAMP signal in macrophages, reduced the levels of cytokines IL-1 β , TNF- α , IL-18 in colon inflammatory cells and serum, reduced caspase-1 levels, and normalized colon length and body weight in mice^[71]. It can also polarize M1 macrophages to M2, reduce the secretion of some cytokines, and

reduce the symptoms of colitis ^[72]. This study found that genistein reduced the acetate (AA) -induced colon histopathological score in UC rats, inhibited INF- γ / JAK 1 / STAT 1 and INF- γ / TLR-4 / NF- κ B signaling pathway, regulated IRF-1 / iNOS / NO and IL-6 induced JAK 2 / STAT 3 / COX-2 pathway, reduced NF- κ B activated ^[73] TNF- α , IL-6 and IL-1 β levels, increased the number of goblet cell GCs, and maintained the function and integrity of colon cells ^[74]. It can also inhibit the immunohistochemical expression of caspase-3 and attenuate the apoptosis of colon cells, thus restoring body weight and reducing colon edema in rats ^[75]. New studies show that acetic acid (AA) -induced UC in rats, treated by genistein injection, reduced the level of apoptotic gene BAX *in vivo*, and significantly increased the expression of PGC-1, TFAM, Nrf 2, HO-1 and BCL 2, indicating the therapeutic effect of genistein on UC ^[76].

2.3 Psoriasis

Psoriasis is a common immune-mediated chronic skin disease characterized primarily by erythematous, scaly, itchy, painful skin with prominent blood vessels ^[77]. It usually appears on the scalp, knees, elbows and back. Its typical symptoms are red plaques covered with silvery-white scales that flake off easily, revealing underlying erythema and punctate hemorrhages when peeled off. Most psoriasis is scalp psoriasis and is prone to recurrence ^[78].

The etiology of psoriasis is not fully understood and may be related to a variety of factors such as genetics, immunity, and the environment. Stress, lifestyle, infections, sun exposure, and certain medications such as beta blockers can exacerbate the disease ^[79], and diseases including obesity, diabetes, hypertension, and hyperlipidemia are also inherent risk factors for psoriasis ^[80]. Nerve growth factor (NGF) is an important factor in the pathogenesis of psoriasis and has been linked to the Koebner phenomenon ^[81], which is the fact that only a very small amount of trauma is needed to cause damage to the skin. TRM cells, which are converted from T cells, have also been implicated in the Koebner phenomenon and also

produce psoriasis-associated cytokines and contribute to psoriasis production and flare-ups ^[82]. IFN- α and IFN- β , TNF- α , IL-23, and IL-17 are also important factors in causing and developing psoriasis ^[83], and IFN in turn activates the STAT1 pathway resulting in the expression of keratin K17 in cells. In addition obesity may also contribute to the development of psoriasis, adipose tissue can secrete various mediators such as pro-inflammatory factors TNF- α , IL-6 leading to an inflammatory state ^[84]. TNF-alpha-regulated VEGF promotes angiogenesis in the dermis, and levels are significantly elevated in psoriatic skin tissues, with VEGF concentrations reflecting psoriasis severity ^[85].

Previous studies have shown that genistein significantly inhibited IFN-induced K17 expression ^[86]. The researchers further investigated the anti-inflammatory mechanism of genistein for psoriasis using imiquimod IMQ-induced psoriasis mice and found that genistein improved the Psoriasis Area Severity Index (PASI) score of the skin of psoriasis mice, reduced the levels of inflammatory mediators such as IL-1 β , IL-6, TNF- α , chemokine ligand 2 (CCL2), IL-17 and IL-23, reduced epidermal thickness, and alleviated psoriasis symptoms in mice ^[87]. *In vitro* studies also showed that genistein inhibited TNF- α -induced expression of inflammatory factors and chemokines IL-6, IL-1 β , IL-8, IL-20, IL-23, VEGF A, and CCL2 mRNA in HaCaT cells, and blocked IL-17A and TNF- α -induced STAT3 and NF- κ B signaling pathways, inhibited ROS activation, and decreased the TNF- α -induced cell proliferation and keratinocyte inflammation. TNF- α -induced cell proliferation and inflammatory response of keratinocytes reduced psoriasis symptoms ^[87, 88]. It also reduced intracellular MAPK activity, decreased the phosphorylation level of its downstream molecule ERK1/2, and significantly inhibited IL-17a-induced PI3K activation ^[89]. In conclusion, genistein reduces the thickness of the stratum corneum, decreases the rate of angiogenesis, and can play a role in the treatment of psoriatic lesions.

This part mainly describes the pharmacological effects of genistein. Table 1 summarizes the anti-inflammatory mechanism of genistein.

Table 1 The anti-inflammatory mechanism of genistein

Inflammation type	Symptom	Anti-inflammatory mechanism	References
Osteoarthritis	Degeneration of articular cartilage, subchondral osteonecrosis, and irregular hyperplasia of bone, causes joint pain, swelling, stiffness, and movement disorders	IL-1 β ↓, IL-6↓, TNF- α ↓, MMP-13↓, MMP-1↓, iNOS↓, p53↓, NF- κ B↓, MAPK↓, COX-2↓, Bax / Bcl-2↓, Nrf2↑ Sox9, type II collagen and proteoglycan expression in chondrocytes↑	[35] [38] [39] [40] [42] [43]
Rheumatoid arthritis	Joint inflammation, pain, stiffness, swelling and dysfunction, resulting to impaired motor function	IL-1 β ↓, IL-6↓, TNF- α ↓, VEGF↓, MMP-9↓, MMP-2↓, STAT3↓, IFN- γ ↓, NF- κ B↓ IL-4↑	[51] [52] [53] [55] [58]
Inflammatory bowel disease	Prolonged, recurrent ulceration, bleeding, and inflammation of the colonic lining, causing symptoms such as diarrhea, abdominal pain, anemia, and weight loss	IL-6↓, TNF- α ↓, IL-1 β ↓, IL-18↓, caspase-1↓, caspase-3↓, MPO↓, Bax / Bcl-2↓ SOD↑, PGC-1↑, TFAM↑, Nrf2↑, HO-1↑, polarize M1 macrophages to M2	[68] [69] [70] [71] [72] [74] [76]
Psoriasis	In the scalp, knees, elbows, back and other parts of the skin erythema, scaly, itching, pain, prominent blood vessels	Inhibited IFN-induced K17 expression, PASI score↓, IL-1 β ↓, IL-6↓, TNF- α ↓, CCL2↓, IL-17↓, IL-23↓, IL-8, IL-20↓, VEGF A↓, epidermal thickness↓, STAT3↓, NF- κ B↓, MAPK↓, ROS↓	[86] [87] [88] [89]

3 Delivery system of genistein

Dietary supplements and drugs containing genistein are used for the prevention and treatment of a wide range of diseases. However, the high activity of the phenolic hydroxyl group of genistein results in poor water solubility, rapid metabolism and low systemic absorption, which affects its bioavailability and its clinical application. Therefore, the use of effective drug delivery systems to enhance the bioavailability and bioactivity of genistein is the focus of current research. Different techniques such as particles, nanoparticle formulations, liposomal vesicles, solid dispersions, inclusion complexes and micelles are used to increase the bioavailability of genistein and deliver it to the site of action ^[20], enhances its anti-inflammatory effects.

3.1 New dosage form of genistein

Novel drug delivery systems are expected to improve the solubility and bioavailability of genistein. For example, the use of extended and controlled release dosage forms, targeted formulations to improve the bioavailability of drugs, reduce the frequency of

administration, improve the dissolution and absorption of drugs in the gastrointestinal, enhance the stability of the drug, and improve the bioavailability. It can also be prepared as an extracorporeal transdermal formulation to avoid the gastrointestinal and hepatic first-pass effects. Yan, et al. ^[90] applied the film dispersion method to produce nanoscale liposomes using soy lecithin and cholesterol as raw materials. In addition, liposomes were used to encapsulate the fat-soluble active substance, soy isoflavone genistein, to obtain genistein nano-liposomes (GEN-Lip). GEN-Lip was observed to have a sustained-release effect by in vitro simulated digestion system, and cell experiments found that nanoliposomes could improve the anti-inflammatory effect of GEN. Researchers have developed microemulsion of genistein using various components of oil, surfactant and co-surfactant ^[91]. The results showed that formulation factors such as HLB value, and combination of surfactant and co-surfactant had a significant effect on the solubility and penetration of dynein lignin and good compatibility with the skin. Shete, et al. ^[92] prepared phospholipid@90H complex (GPLC) of genistein to improve its biopharmaceutical properties and anti-inflammatory activity, which was confirmed by the study to be stable, significantly

improved the solubility of genistein, increased the half-life of the drug, and increase its oral bioavailability. Shao, et al. [93] used a solvent evaporation method to prepare a genistein Gen-adenine drug complex, which improved the dissolution and release of the drug and

was stable, and was a novel formulation to effectively improve its bioavailability. These new dosage forms provide new ideas and methods for the clinical application of genistein. Table 2 shows the study of the new dosage forms of genistein.

Table 2 The new dosage forms of genistein

Drug delivery system	Characteristic	References
Nano-liposomes	Have a stronger anti-inflammatory effect, control drug release, reduce the frequency of drug administration	[90]
Microemulsion	Improve the solubility, permeability and bioavailability of genistein, good compatibility with the skin	[91]
Phospholipid@90H complex of genistein	Improve the genistein biopharmaceutical properties and anti-inflammatory activities, improved the solubility of genistein, increased the half-life of the drug, and increase its oral bioavailability	[92]
GEN-adenine drug complex	Improved drug dissolution, release, and strong stability. Effectively improve genistein bioavailability	[93]

3.2 Challenges and directions for the development of novel formulations of genistein

However, the novel delivery system of genistein may meet some challenges, among which the complex preparation process and high cost may limit its large-scale production and application. The carrier materials in the novel delivery system may raise safety issues the metabolism and clearance process of genistein in the delivery system may also affect its bioavailability. The new dosage form of genistein could be further validated the efficacy and safety *in vivo*. It is necessary to explore multifunctional delivery systems, combining targeting, extended release and other functions to improve therapeutic effects. It also is possible to enhance the combined application with other drugs or therapeutic methods.

4 Conclusions

In this review, the discussions were focused on the mechanisms of anti-inflammatory activities and delivery systems of genistein. The anti-inflammatory mechanisms include inhibition of the production and release of inflammatory mediators and modulation of immune cell activity, which provide a theoretical basis

for its use in the treatment of inflammation-related diseases. However, the solubility of genistein is low and difficult to absorb, and an appropriate delivery system could improve the bioavailability of genistein. The development of new dosage forms is important to improve the bioavailability and therapeutic potencies of genistein and to improve the biocompatibility of the dosage forms. New dosage forms such as nanocarriers and liposomes can improve the solubility, stability of genistein with targeting effects. The study of the anti-inflammatory mechanism and new dosage forms of genistein provides new ideas and methods for its use in the treatment of inflammatory diseases.

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