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Anti-neurodegenerative, anticancer, anti-inflammatory, and antiobesity activities of theaflavin and its derivatives

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ABSTRACT

Polyphenol metabolites have several hydroxyl groups on aromatic rings. Flavonoids are the main natural groups of polyphenols with numerous therapeutic effects. Theaflavin and its derivatives (theaflavin 3-gallate, theaflavin 3,3′-digallate, and theaflavin 3′-gallate) as one of the major polyphenols of black tea have shown promising anticancer, anti-inflammatory, antiobesity, and anti-neurodegenerative activities. This bioactive compound has the potential capacity to ameliorate coronary heart disease and a healing impact on the density of bone minerals. The emergence of drug resistance in cancer cells and bacteria has caused more endeavors to find novel effective anticancer and antibacterial agents. In addition, recent studies aim to reduce severe side effects associated with chemotherapy and antimicrobials. In the case of neurodegenerative diseases such as Alzheimer's, multiple sclerosis, and Parkinson's, the low efficiency of current expensive drugs is the main problem with therapy for these disorders. In this regard, discovering and designing new anti-neurodegenerative drugs is dispensable.

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Introduction

The drug resistance and severe side effects in cancer therapy have led to more endeavors for finding and designing novel effectual anticancer and antimicrobial agents [1]. Low efficiency of anti-neurodegenerative and anti-inflammatory drugs also has resulted in the necessity of smart discovery of novel therapies, specifically based on combination therapy [2-4]. Polyphenol compounds with several hydroxyl groups on aromatic rings have abundant therapeutic activities [5-7]. Theaflavin and its derivatives (theaflavin 3-gallate, theaflavin 3,3′-digallate, and theaflavin 3′-gallate) are the main polyphenols of black tea that illustrate significant anticancer, anti-inflammatory, antioxidant, anti-aging, antiobesity (by assistance in lipid digestion), and anti-neurodegenerative activities (Figure 1) [8-10]. Oolong tea is semifermented tea having its metabolites involving the properties of black (fermented) and green (unfermented) tea [11]. These metabolites are higher (−)-epigallocatechin, (−)-gallocatechin-3-gallate, and (−)-epigallocatechin-3-gallate compared to theasinensins and theaflavins [12]. The characteristic theaflavins have been presented in Figure 2. The main hindrance to clinical application of theaflavin is poor systematic bioavailability, in which only a small concentration of theaflavins can be found in the urine and plasma samples [13]. Therefore, new biocompatible formulations in both micro and nanoscale are required to increase the bioavailability of theaflavin and its derivatives, which this review has tried to cover this issue.

Anti-neurodegenerative effects

Memory and learning deficiency may be caused by cellular oxidative stress as a common pathomechanism in multiple age-related disorders and age-related neurodegenerative disorders [14]. Theaflavin-3,3′-digallate with potential phytochemical antioxidant

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ability can ameliorate these diseases by reduction of cellular oxidative stress. Treatment animal model by this metabolite down-regulated antioxidant genes superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPX1), nuclear factor E2-related factor 2 (NRF2), and peroxiredoxin 2 (Prx 2) in brain tissue [15]. As a main mechanism in neurodegenerative diseases, high-level production of hydroxyl and superoxide radicals can lead to apoptosis in neural cells by oxidative stress [16]. Theaflavins in a concentration of 10 μM protected PC12 neural cell lines from oxidative stress caused by 200 μM hydrogen peroxide (H_2O_2). Downregulation of the ratio of pro-apoptosis Bcl-2-associated X protein (BAX)/anti-apoptosis Bcl-2 (B-cell lymphoma 2) proteins was found the major neuroprotective effect of theaflavins [17].

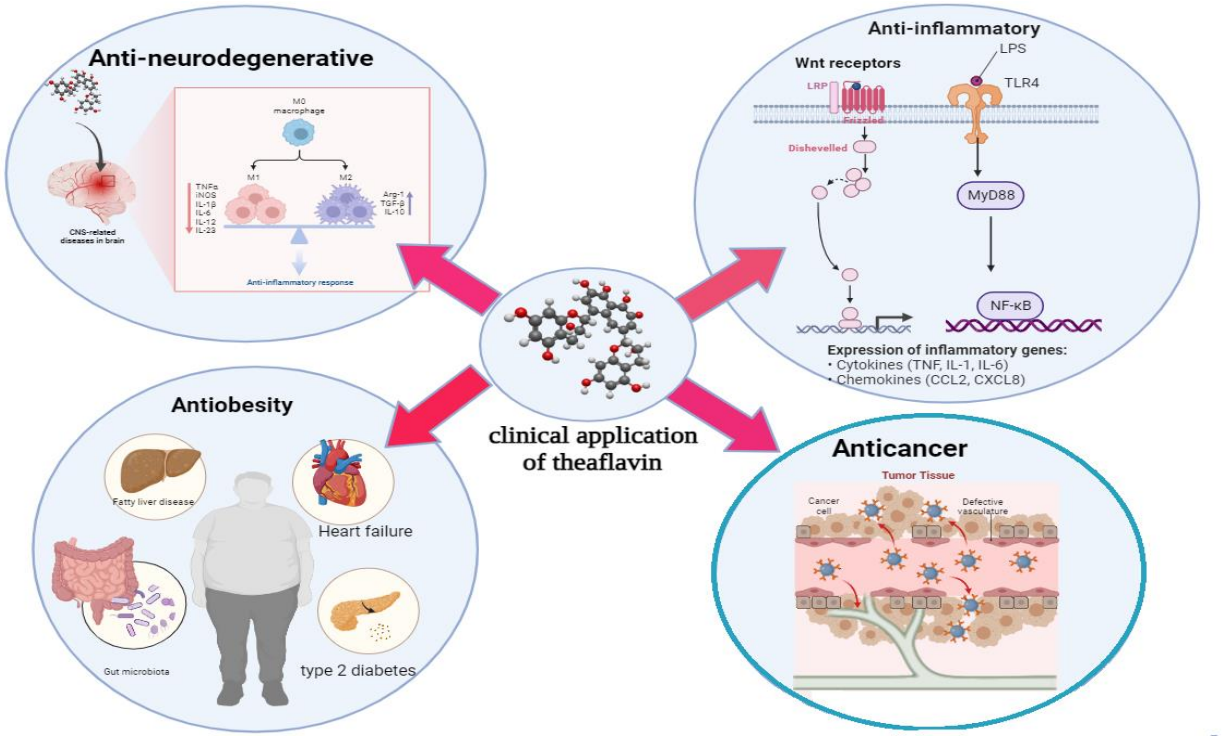

Fig. 1. The main therapeutic activities of theaflavin and their derivatives (Source: BioRender.com).

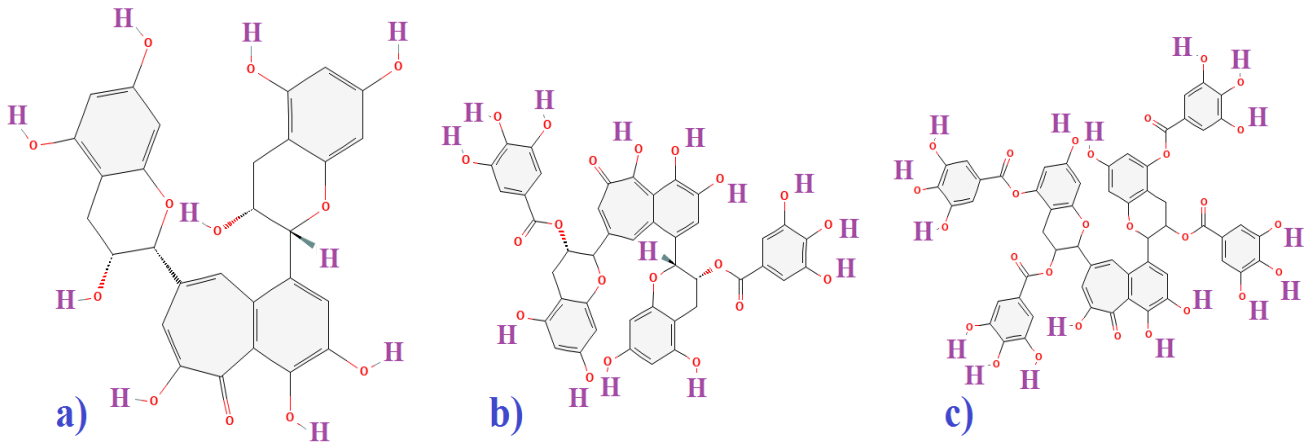

Fig. 2. Chemical structures of theaflavin (a), theaflavin digallate (b), and theaflavin tetragallate (c) (Source: PubChem database).

Some studies have explored the effects of theaflavins on macrophage polarization, The balance between these two states plays a crucial role in regulating immune responses and inflammation in the body. Theaflavins may promote the polarization of macrophages, M1 (pro-inflammatory) toward the M2 (anti-inflammatory) state. This modulation can help maintain immune homeostasis and promote tissue repair and healing [18, 19].

Anticancer activity

As the main anticancer mechanisms, theaflavins can modulate growth transcription factors, cell-migration-related proteins, cell-cycle regulatory proteins, and apoptosis-related proteins [20]. Theaflavins exhibited anticancer activity by radical-scavenging ability and hindering the cell proliferation of human colon cancer SW620 cell lines and human colon adenocarcinoma cancer SW480 cell lines with half maximal inhibitory concentration (IC_{50}) < 32.0 μM. The probable anticancer mechanism was the induction of cell cycle arrest without high toxicity against healthy cells by a safety index in the range of 1.89–6.26 [21]. As explained in the introduction section, various organic or inorganic nanomaterials (NMs) can be employed as carriers or nanoconjugates of theaflavins and other polyphenols [22]. For instance, conjugation of theaflavin with gold nanoparticles (AuNPs) as a nanoconjugate was used to passively target ovarian cancer cells. The existance of a quinone motif in conjugates of AuNP@theaflavin led to the apoptosis process in ovarian cancer cells by the depolarization of mitochondria and the production of reactive oxygen species (ROS) at a high level [23]. Green synthesized metallic NPs have illustrated remarkable therapeutic effects compared to pristine NPs. Biosynthesis of silver NPs (AgNPs) with a mean diameter size of 9 nm in spherical shape by black tea leaf extract demonstrated a significant anticancer effect on the HeLa cervical cancer cell line in a dose-dependent way [24]. NRF2, a transcription factor, is a main regulator of genes associated with oxidative stress and antioxidant response elements such as cytoprotective proteins and antioxidant enzymes [25]. A combination therapy composed of cisplatin drug upon pre-treatment with theaflavin-rich black tea deregulated NRF2 in cell line A549 of lung adenocarcinoma dependent on duration of treatment and concentration [26].

Anti-inflammatory activity

The inflammation process as a defensive response is caused by various stress factors or harmful stimuli [27]. Lipopolysaccharide (LPS) of Gram-negative bacteria cell walls such as *Escherichia coli* can lead to activation of cells of the innate immune system including macrophages and neutrophils, which synthesize proinflammatory factors, such as free radicals, matrix metalloproteinases (MMPs), interleukin-1β (IL-1β), and tumor necrosis factor (TNF) causing secondary inflammation response [28, 29]. The expression level of IL-6, IL-1 beta, and TNF-α in RAW 264.7 cell lines and phorbol myristate acetate -primed U937 as well as the severity of LPS-induced acute lung injury in mice were reduced by theaflavin-3,3′-digallate [30]. In a similar study, reduction of TNFα, IL-1β, chemokine (C-X-C motif) ligand 8, MMP-9, MMP-8, and MMP-3 was found for black tea theaflavins treatment of a gingival keratinocyte monolayer upon stress of *Porphyromonas gingivalis* bacteria [31]. Theaflavin-3,3'-digallate may activate MAPK, Wnt (Wingless-related integration site)/β-Catenin, and bone morphogenetic protein (BMP)/Smad (the fusion of *Caenorhabditis elegans* Sma genes and the Drosophila Mothers against dpp protein) signaling pathways, which are inhibited by TNF-α, and promote the transcription of osteogenic-related factors, including Runt-related transcription factor 2 (Runx2) and osterix, ultimately promoting the differentiation and maturation of osteoblasts [32]. A study found that theaflavin-3'-gallate had anti-inflammatory effects during influenza virus infection. As a result of inhibiting the TLR4 (Toll-like receptor 4)/MAPK (mitogen-activated protein kinase)/p38 pathway, and reducing lung inflammation, theaflavin-3'-gallate improved survival rates in mice infected with influenza virus. Theaflavin-3'-gallate also had synergistic effects with the antiviral drug oseltamivir [33]. Theaflavins, can potentially have anticancer effects by inhibiting the Wnt signaling pathway, which is overactivated in cancer and promotes tumor growth. They may also regulate β-catenin, a key protein in the Wnt pathway, influencing its levels and activity to impact Wnt signaling [9].

In 2004, Aneja and his coworkers investigated the effects of theaflavin on IL-8 gene expression through TNF in A549 cells. A549 cells were tested with different concentrations of theaflavin and were evaluated for TNF-α-mediated IL-8 gene expression [33]. The results of these experiments showed that theaflavin prevents the expression of the IL-8 gene by TNF. The results of these studies proved that this effect probably involves the inhibition of IL-8 transcription because theaflavin prevented the activation of the IL-8 promoter by TNF in cells transiently transfected with IL-8 promoter-luciferase reporter plasmid. The results of these investigations also proved that theaflavin also significantly reduced TNF-α-mediated DNA binding of activating protein-1 [33].

In the same year, enzymatic synthesis of tea theaflavin derivatives was done and the anti-inflammatory properties of these derivatives were evaluated. The results of the investigations showed that some of these compounds inhibit TPA-induced rat ear edema, and arachidonic acid release via LPS-stimulated RAW 264.7 cells. The results of this research showed that compounds related to synthesized theaflavin inhibit inflammation compared to epigallocatechin gallate, which is the main catechin compound in green tea. Therefore, it can be concluded that black tea polyphenols have similar biological properties to green tea polyphenols [34]. After that in 2006, Cai and colleagues investigated cerebral ischemia-reperfusion injury through the anti-inflammatory effect of theaflavin compound. This research proved that theaflavin compound significantly suppresses the inhibition of inflammation-related pro-oxidative enzymes (Inducible-NO synthase (iNOS) and cyclooxygenase-2 (COX-2)) in the ischemic brain via reducing the phosphorylation of signal transducer and activator of transcription 1 (STAT1) [35]. In another investigation in 2012, the anti-influenza virus and anti-inflammatory activities of theaflavin derivatives were measured. The results of this research proved that theaflavin derivatives also reduce the expression level of the inflammatory cytokine IL-6 during viral infection, which expression probably leads to tissue damage and apoptosis. This research showed that theaflavin derivatives are potential compounds to prevent the multiplication of influenza virus and have anti-inflammatory activities [36]. Then in 2017, the effect of theaflavins in black tea on *Porphyromonas gingivalis* and the anti-inflammatory activity of these compounds were investigated. The results of this research showed that black tea theaflavins have the effects of reducing the secretion of IL-1β, TNF-α, and MMP-9 by *P. gingivalis*-stimulated macrophages. In general, it can be concluded that black tea theaflavins prevented the degradation of gelatin by MMP-9 [31]. The anti-inflammatory properties of theaflavin-3,3′-digallate on lipopolysaccharide-induced inflammation were investigated by Wu and his coworkers. In this study, theaflavin-3,3′-digallate compound suppressed the LPS-induced phosphorylation of c-Jun N-terminal kinase. In addition, this group exhibited that theaflavin-3,3′-digallate hindered the TNF-α expression phorbol myristate acetate -primed U937 and RAW 264.7 cells [30].

Recently in a research done in 2023 anti-inflammatory properties of theaflavin-3′-gallate during influenza virus infection were measured. These results proved that theaflavin-3′-gallate significantly inhibited virus replication and reduced pneumonia damage. The antiviral effect of this compound is probably related to the reduction of inflammatory cytokines caused by the influenza virus by regulating the TLR4/MAPK/p38 signaling pathway [37].

Gastric ulceration therapy

Indomethacin as a nonsteroidal anti-inflammatory drug can cause gastric ulceration via protein oxidation, lipid peroxidation, and reduction of prostaglandin E (PGE), thiol-defense, and mucin in the gastric tissues [38]. Treatment of the mouse model by theaflavins decreased the oxidative effects of indomethacin and promoted the PGE synthesis through increasing the expressions of cyclooxygenases 1 and 2 [39]. Treatment by theaflavins at a concentration of 1 mg/kg for 3 days can lead to remarkable ulcer healing (78–81%) by reversing the parameters related to indomethacin-induced stomach ulceration [40].

Inhibiting obesity

Theaflavins have been studied for their potential to influence metabolic processes in the body. Some research suggests that they may enhance energy expenditure and promote the oxidation of fat, potentially leading to weight loss or preventing weight gain [41]. Improving insulin sensitivity is important for

preventing and managing obesity. Some studies have indicated that theaflavins may enhance insulin sensitivity, potentially reducing the risk of obesity-related conditions like type 2 diabetes [42].

Theaflavins can modulate glycolipid metabolisms by several characteristic mechanisms. In obese mice induced through a high-fat diet, theaflavins hindered the synthesis and accumulation of lipids in the liver by activation of the sirtuin 6 (SIRT6)/ adenosine monophosphate-activated protein kinase (AMPK)/sterol regulatory element-binding protein-1 (SREBP-1)/fatty acid synthase (FASN) signaling pathway [43]. In addition, theaflavins can regulate fecal metabolome in high-fat diet-fed mice model. In this regard, Huangjinya black tea showed a reduction in lipogenic and adipogenic gene expression, adipocyte expansion, and an increase in lipolytic gene expression. Huangjinya black tea regulates bile acid metabolism, augments short-chain fatty acids synthesis, and decreases phosphocholines and carnitines [44]. Modulation of gut microbiota has been indicated by black and green teas in hyperglycemic mice via the increase of the number of *Turicibacter*, *Allobaculum*, and *Lactobacillus* as non-pathogenic bacteria and decrease the number of *Bacteroides* and Clostridiales as pathogenic bacteria [45]. In a similar study, treated rats with oolong tea extract exhibited a remarkably higher number of *Hydrogenoanaerobacterium* and *Candidatus arthromitus* compared to rats fed with a high-fat diet with a lower number of *Odoribacter*, *Ruminococcus1*, and *Oscillibacter* [12].

Nonalcoholic fatty liver disease may lead to cirrhosis, hepatitis, and hepatic carcinoma [46]. A reduction of fat vacuoles was found in liver tissue of leptin-deficient obese mice with nonalcoholic fatty liver disease upon treatment by theaflavin-3,3′-digallate at a concentration of 10 mg/kg body weight (M-TF3), and a concentration of 20 mg/kg body weight (H-TF3) (Figure 3) [47].

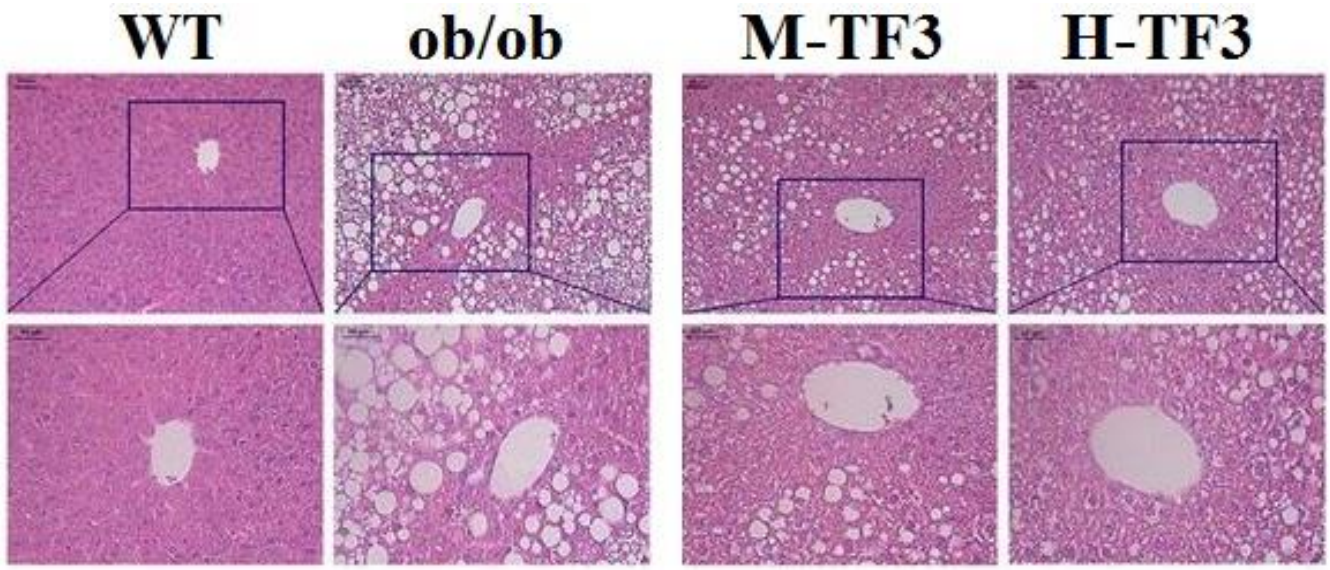

Fig. 3. Histological changes as a decrease of fat vacuoles in liver tissue of leptin-deficient obese mice upon treatment (ob/ob) compared to wild mice under treatment of M-TF3 (The dose of 10 mg/kg body weight) and H-TF3 (The dose of 20 mg/kg body weight) (Adapted and modified from [47]).

Tea, especially green and black tea is known for its cardiovascular benefits due to its polyphenols like theaflavins and catechins, which have strong antioxidant properties. Recent studies have identified tea compounds such as epigallocatechin gallate, kaempferol, and gallic acid that can prevent pathological cardiac hypertrophy (PCH) by influencing signaling pathways and reducing oxidative stress. This research focuses on theaflavin-3,3'-digallate, a black tea pigment, and its potential role in preventing PCH induced by angiotensin II (ANGII). The study uses H9c2 cells to establish an *in vitro* PCH model and aims to elucidate theaflavin-3,3'-digallate molecular mechanisms in hypertrophic signal transduction [48].

Conclusions

Theaflavin polyphenols as the major metabolites of black tea have been widely acknowledged for their

therapeutic properties. Anti-neurodegenerative effects of theaflavin-3,3′-digallate can result from its antioxidant capacity via reduction of the cellular oxidative stress. As the characteristic anticancer mechanisms, theaflavins modulate growth transcription factors, cell-migration-related proteins, cell-cycle regulatory proteins, and apoptosis-related proteins. Moreover, this polyphenol can show anticancer activity via radical-scavenging ability and hindering effect on the cell proliferation of human colorectal cancer cell line. A combination therapy can increase the anticancer activity of chemotherapeutic drugs. For instance, cisplatin plus theaflavin-rich black tea demonstrated NRF2 reorientation in cell line A549 of lung adenocarcinoma dependent on duration of treatment and concentration. Theaflavins modulate glycolipid metabolisms by hindering the production and accumulation of lipids in the liver by activation of the SIRT6/ AMPK/SREBP-1/FASN signaling pathway. Moreover, theaflavins can regulate fecal metabolome in high-fat diet-fed mice model via a reduction in adipogenic and lipogenic gene expression, adipocyte expansion, and an augment of lipolytic gene expression. Theaflavin-3,3′-digallate reduces fat vacuoles in liver tissue of leptin-deficient obese mice at doses of 10 and 20 mg/kg body weight.

Study Highlights

- Theaflavins modulate growth transcription factors, cell-migration-related proteins, cell-cycle regulatory proteins, and apoptosis-related proteins in cancer cells.
- Anti-neurodegenerative effects of theaflavin-3,3′-digallate result from its antioxidant capacity via reduction of the cellular oxidative stress.
- These metabolites regulate glycolipid metabolisms by inhibiting the production and accumulation of lipids in the liver by activation of the SIRT6/ AMPK/SREBP-1/FASN signaling pathway.
- Theaflavins decrease adipogenic and lipogenic gene expression, adipocyte expansion, and augment lipolytic gene expression.

Abbreviations

AMPK: Adenosine monophosphate-activated protein kinase
ANGII: Angiotensin II
BAX: Bcl-2-associated X protein
Bcl-2: B-cell lymphoma 2
BMP: Bone morphogenetic protein
COX-2: Cyclooxygenase-2
FASN: Fatty acid synthase
GPX1: Glutathione peroxidase 1
IC_{50}: The half maximal inhibitory concentration
IL-1β: Interleukin-1β
iNOS: Inducible-NO synthase
LPS: Lipopolysaccharide
MAPK: Mitogen-activated protein kinase
MMPs: Matrix metalloproteinases
NMs: Nanomaterials
NPs: Nanoparticles
NRF2: Nuclear factor E2-related factor 2
PCH: Pathological cardiac hypertrophy
PGE: Prostaglandin E
Prx 2: Peroxiredoxin 2
ROS: Reactive oxygen species
Runx2: Runt-related transcription factor 2
SIRT6: Sirtuin 6
Smad: The fusion of *Caenorhabditis elegans* Sma genes and the Drosophila Mothers against dpp protein
SOD1: Superoxide dismutase 1
SREBP-1: Sterol regulatory element-binding protein-1
STAT1: Signal transducer and activator of transcription 1
TLR4: Toll-like receptor 4
TNF: Tumor necrosis factor
Wnt: Wingless-related integration site

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

All authors: conceptualization, preparing the first draft, and editing.

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