

# Antioxidant, Anti-Inflammatory and Anti-Apoptotic Activities of Nesfatin-1: A Review

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**Abstract:** Nesfatin-1, a newly identified energy-regulating peptide, is widely expressed in the central and peripheral tissues, and has a variety of physiological activities. A large number of recent studies have shown that nesfatin-1 exhibits antioxidant, anti-inflammatory, and anti-apoptotic properties and is involved in the occurrence and progression of various diseases. This review summarizes current data focusing on the therapeutic effects of nesfatin-1 under different pathophysiological conditions and the mechanisms underlying its antioxidant, anti-inflammatory, and anti-apoptotic activities.

**Keywords:** antioxidant, anti-inflammatory, anti-apoptotic, nesfatin-1, anorexigenic

## Introduction

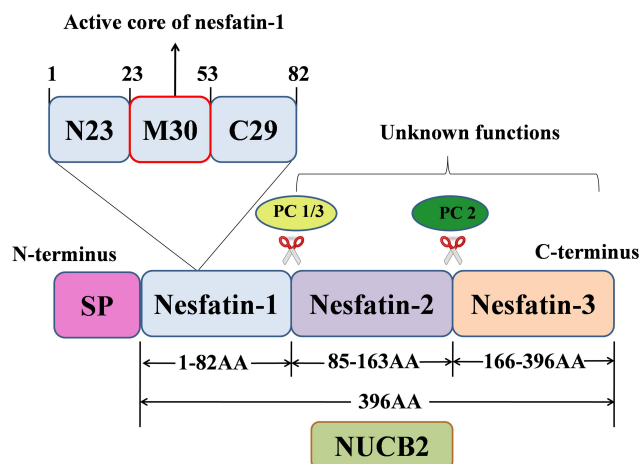
Nesfatin-1 was first discovered in the hypothalamic nuclei and was initially reported to reduce food intake.<sup>1</sup> Studies have shown that nesfatin-1 is widely expressed in central and peripheral tissues and has pleiotropic effects.<sup>2</sup> More recent evidence indicates that nesfatin-1 exerts antioxidant, anti-inflammatory, and anti-apoptotic effects in different inflammation-related diseases.<sup>3,4</sup> In this review, we provide a brief account of the structure, localization, and functions of nesfatin-1, and mainly focus on the experimental evidence for the antioxidant, anti-inflammatory, and anti-apoptotic effects of nesfatin-1 and its possible mechanism.

## Structure and Localization of Nesfatin-1

Nesfatin-1, an 82-amino acid peptide discovered by Oh-I in 2006, is derived from the precursor protein nucleobindin-2 (NUCB2).<sup>5</sup> The product of the *NUCB2* gene is a peptide with 420 amino acid (AA), which is composed of a 396 AA long precursor peptide and a 24 AA long signal peptide (SP). The precursor peptide is cleaved into three different parts by prohormone/proprotein convertase (PC) 1/3 and PC 2: nesfatin-1 (AA 1–82), nesfatin-2 (AA 85–163), and nesfatin-3 (AA 166–396).<sup>5</sup> The structure of nesfatin-1 can also be divided into three segments, namely N23, M30, and C29,<sup>6</sup> among which M30 is critical for its anorexigenic action.<sup>7,8</sup> However, no obvious biological activity has been detected for nesfatin-2 or nesfatin-3.<sup>9</sup> Figure 1 shows a schematic representation of nesfatin-1 processing from its precursor, NUCB2.

Initially, the paraventricular nucleus (PVN), arcuate nucleus (ARC), supraoptic nucleus (SON), and lateral hypothalamic area (LHA) in the hypothalamus were thought to be the main sites of nesfatin-1 expression.<sup>5</sup> Subsequent studies have shown that nesfatin-1 is widely expressed in other regions of the brain also, like

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**Figure 1** Schematic representation of the production of nesfatin-1 from its precursor NUCB2.

**Abbreviations:** AA, amino acid; NUCB2, nucleobindin-2; PC, prohormone/protein convertase; SP, signal peptide.

brainstem, including dorsal vagal complex (DVC), Edinger-Westphal nucleus, locus coeruleus (LC), lateral parabrachial nucleus, ventrolateral medulla (VLM),<sup>10,11</sup> insular cortex, central amygdala, ventrolateral medulla, cerebellar Purkinje cell, pterygopalatine parasympathetic preganglionic neurons, and spinal cord at the lumbar and sacral region.<sup>11</sup> In addition to being widely expressed in the central nervous system, nesfatin-1 is also expressed in peripheral tissues, like esophagus,<sup>12</sup> stomach, small intestine,<sup>13</sup> colon, pancreas,<sup>14</sup> liver, adipocytes,<sup>15</sup> cardiomyocytes,<sup>16</sup> testes,<sup>17</sup> ovaries,<sup>18</sup> uterus and epididymis.<sup>19</sup>

## Functions of Nesfatin-1

As an energy-regulating peptide, nesfatin-1 is widely expressed in both central and peripheral tissues.<sup>20</sup> This, along with the fact that nesfatin-1 can cross the blood-brain barrier,<sup>21,22</sup> suggests that nesfatin-1 may have pleiotropic effects. In addition to maintaining the feeding balance, this peptide plays an important role in glucose homeostasis,<sup>23</sup> lipid metabolism,<sup>24</sup> modulation of gastrointestinal functions,<sup>25</sup> cardiovascular,<sup>9</sup> and reproductive functions.<sup>26</sup> It may also be involved in epilepsy,<sup>27</sup> psychological disorders, including stress,<sup>28</sup> sleep disorders,<sup>29</sup> anxiety,<sup>30</sup> and depression.<sup>30</sup>

## Antioxidant, Anti-Inflammatory, and Anti-Apoptotic Activities of Nesfatin-1 in Multiple Diseases

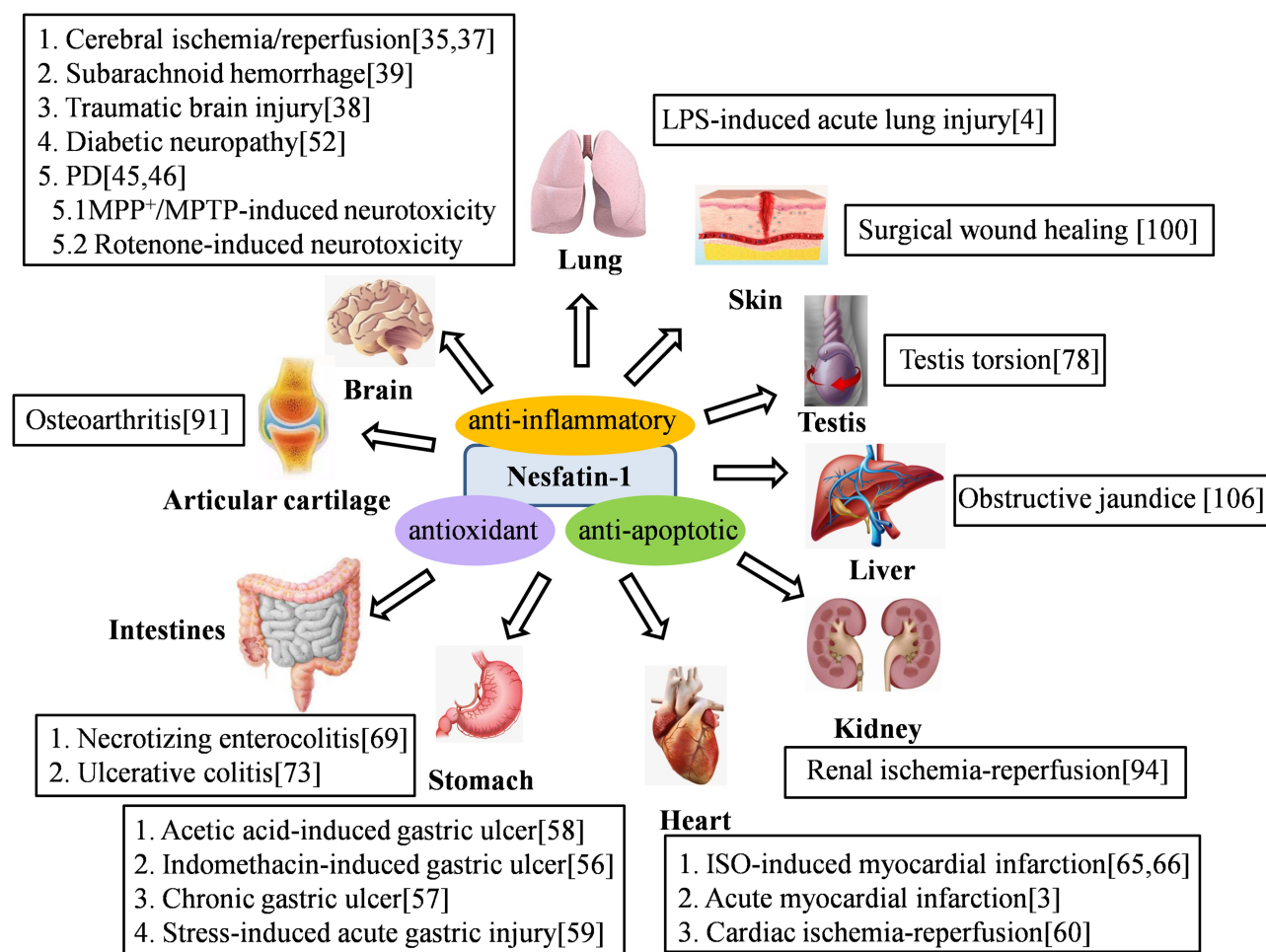
Besides its anorexigenic and anti-hyperglycemic effects, nesfatin-1 has recently been reported to have potent

anti-inflammatory, anti-apoptotic, and anti-oxidative capabilities, which can ameliorate the symptoms of several diseases (Figure 2).

## Brain-Related Diseases

As cerebral ischemia/reperfusion (I/R) leads to neuroinflammation and neuronal apoptosis,<sup>31,32</sup> prevention of these processes is recommended as a treatment to compensate for the brain damage.<sup>33</sup> Erfani et al<sup>34</sup> showed that nesfatin-1 could significantly improve the memory impairment caused by cerebral I/R by reducing the activity of caspase-3, an apoptosis-associated protein, in the pyramidal cells in CA1 area of the hippocampus, and decreasing the number of Iba-1 positive cells.<sup>34</sup> Iba-1 is an immunohistochemical marker for activated microglia.<sup>35</sup> Consistent with these results, another study<sup>36</sup> demonstrated the usefulness of nesfatin-1 in the treatment of cerebral I/R through inhibition lipid peroxidation, increase in the expression of anti-apoptotic protein Bcl-2, and reduction of the Bax-mediated neuronal apoptosis. The neuroprotective effects of nesfatin-1 through its anti-inflammatory and anti-apoptotic activities has also been reported in two other brain-related diseases; reduction of caspase-3-mediated nerve cell apoptosis and inhibition of release of mediators of inflammation in the brain damage through trauma<sup>37</sup> and through subarachnoid hemorrhage.<sup>38</sup>

Parkinson's disease (PD), a neurodegenerative disease, is characterized by the loss of dopaminergic neurons in the substantia nigra of the brain.<sup>39</sup> Increasing evidence indicate that PD is related to mitochondrial dysfunction through multiple pathways, including free radical generation, inflammation, and apoptosis.<sup>40,41</sup> Numerous studies have shown that apoptosis, induced by mitochondrial dysfunction, plays a vital role in the incidence and development of PD,<sup>42,43</sup> suggesting that inhibition of apoptosis may be one of the treatment strategies for PD. Recently, rotenone-treated MES23.5 dopaminergic cells, a cellular model of PD, were used to study the neuroprotective effect of nesfatin-1 in PD and to understand the underlying mechanisms. The results indicated that treatment with nesfatin-1 inhibited the production of rotenone-induced reactive oxygen species (ROS), release of mitochondrial cytochrome C, and subsequent activation of caspase-3.<sup>44</sup> This suggested that nesfatin-1 exerts a neuroprotective effect in PD through its antioxidant and anti-apoptotic properties. More recently, the neuroprotective effect of nesfatin-1 in PD was further confirmed through in vivo and in vitro experiments, which showed that the anti-apoptotic C-Raf-extracellular signal-regulated protein kinase



**Figure 2** Nesfatin-1 exerts antioxidant, anti-inflammatory and anti-apoptotic effects in various diseases.

**Abbreviations:** ISO, isoproterenol; LPS, lipopolysaccharide; PD, Parkinson's disease.

1/2 (ERK1/2) signaling pathway mediates the protective effect of nesfatin-1 on dopaminergic neurons against 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced neurotoxicity in C57BL/6 mice and 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>)-induced cytotoxicity in MES23.5 cells.<sup>45</sup>

Diabetic neuropathy (DN), one of the most debilitating outcomes of diabetes mellitus, is thought to be the consequence of oxidative stress,<sup>46</sup> inflammation,<sup>47</sup> and neural apoptosis.<sup>48</sup> More specifically, increased glucose levels damage the mitochondrial membrane and respiratory chain, resulting in the production of large amounts of ROS,<sup>49</sup> which accelerate the damage of lipids, proteins, and nucleic acids, and eventually lead to inflammation and neural apoptosis.<sup>50</sup> Due to its antioxidant, anti-inflammatory, and anti-apoptotic activities, nesfatin-1 may have an ameliorating effect on DN. It has been reported<sup>51</sup> that nesfatin-1 inhibits intracellular ROS

overproduction and reduces apoptotic cell death in PC12 cells following high-glucose exposure, a widely used in vitro model for DN, which makes nesfatin-1 a potential drug for the treatment of DN against high glucose-induced cell death.

## Gastric Diseases

Expression of nesfatin-1 in the stomach is reported to be 20 times higher than that in the brain tissues in rats.<sup>52</sup> Lipopolysaccharide (LPS) administration is known to increase the production and release of gastric NUCB2/nesfatin-1.<sup>53</sup> Due to its anti-inflammatory properties, nesfatin-1 may have a protective effect against gastric injury.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat various ailments. However, serious side effects of these drugs, such as bleeding, acute injury, and gastric ulcers, have been widely reported.<sup>54</sup> Recently, potential anti-ulcer and anti-inflammatory effects

of nesfatin-1 in a model of gastric ulcer induced by indomethacin, an NSAID with analgesic, antipyretic, and anti-inflammatory effects, were studied.<sup>55</sup> The results showed that nesfatin-1 alleviated the indomethacin-induced gastric injury, by supporting the balance of oxidant and antioxidant systems and inhibiting the production of proinflammatory mediators.<sup>55</sup> Gastro-protective effect of nesfatin-1 was confirmed using acetic acid-induced gastric ulcer model. Nesfatin-1 promoted the healing of chronic gastric ulcers induced by acetic acid by accelerating the gastric blood flow and mucosal repair, and partially reversing the downregulation of superoxide dismutase (SOD) mRNA.<sup>56</sup> Moreover, nesfatin-1 treatment healed the acetic acid-induced gastric injury by inhibiting neutrophil infiltration and proinflammatory cytokine release, and promoting the antioxidant activity.<sup>57</sup>

Intraperitoneal injection of nesfatin-1 is shown to decrease the gastric lesions induced by water immersion and restraint stress (WRS), probably by inhibiting the secretion of gastric acid and attenuation of the expression and release of proinflammatory cytokines, including interleukin-1 $\beta$  (IL-1 $\beta$ ), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>58</sup>

## Cardiac Diseases

Detection of nesfatin-1 protein and mRNA in rat cardiac extracts by Western blotting and qRT-PCR<sup>59</sup> suggests a physiological role for nesfatin-1 in cardiac myocytes. Myocardial I/R injury often causes oxidative stress and inflammation, which in turn, leads to apoptosis and necrosis of cardiomyocytes.<sup>60,61</sup> Nesfatin-1 can prevent this injury by reducing the infarct size and post-ischemic contracture, and by inhibiting the release of lactate dehydrogenase<sup>59</sup> through its antioxidant properties. Myocardial infarction (MI) is one of the most common life-threatening diseases, which may lead to other diseases through oxidative stress and inflammation.<sup>62</sup> Previous studies have suggested that the plasma level of nesfatin-1 in patients of acute myocardial infarction (AMI) was significantly lower than that in healthy controls.<sup>63</sup> Moreover, a negative correlation was reported between the levels of plasma nesfatin-1, and high-sensitivity C-reactive protein and neutrophils in AMI patients,<sup>63</sup> indicating that reduced nesfatin-1 levels may abet the pathogenesis of AMI through inflammatory mechanisms. In vivo studies also confirmed the cardioprotective effect of nesfatin-1. Isoproterenol (ISO)-induced MI in rats is a commonly used experimental model to evaluate the protective effect of various cardioprotective agents against human MI.<sup>64,65</sup>

Intraperitoneal administration of nesfatin-1 (10  $\mu$ g/kg/day) conferred significant cardioprotection against the induced MI in this model by lowering the levels of proinflammatory cytokines and reducing the number of apoptotic and necrotic cells in the myocardium.<sup>3</sup>

## Intestinal Diseases

Necrotizing enterocolitis (NEC), a leading cause of gastrointestinal morbidity in premature infants, is an inflammatory disease with systemic repercussion.<sup>66</sup> It is characterized by excessive inflammatory infiltration of intestinal mucosa, resulting in the destruction of the intestinal barrier.<sup>67</sup> Therefore, drugs with anti-inflammatory effects are likely to contribute to healing and prevent the development and progression of the disease. Nesfatin-1 ameliorated the survival rate and oxidative damage of NEC-induced neonatal intestine by supporting the balance of the oxidative/antioxidant system, inhibiting the NF- $\kappa$ B-65 pathway, and reversing NEC-induced dysbiosis.<sup>68</sup>

Ulcerative colitis (UC), an idiopathic inflammatory bowel disease, leads to bloody diarrhea and inflammatory alterations mostly in the large intestine, and affecting the colon and rectum.<sup>69</sup> Overproduction of ROS and consequent inflammation of the mucosa are the important causes of tissue injury in UC.<sup>70</sup> Recent studies have found that some peptide hormones may have a healing effect on UC. For instance, the anti-inflammatory effect of ghrelin is demonstrated in various types of chronic inflammation, including UC.<sup>71</sup> Similarly, intracerebroventricular injection of nesfatin-1 can restore the oxidative damage in the model of UC, probably through its anti-inflammatory action, by preventing neutrophil infiltration into the tissue, and its antioxidant activity, by suppressing free radical formation.<sup>72</sup>

## Other Diseases

Testicular torsion is a urological emergency that may cause an ischemia-reperfusion injury to the testes.<sup>73</sup> Testicular ischemia leads to over-generation of ROS,<sup>74</sup> while the exhaustion of antioxidants, activation of neutrophils, increased production of pro-inflammatory cytokines and adhesion molecules, lead to testicular lipid peroxidation and apoptosis,<sup>75,76</sup> eventually damaging germ cells and sperm. Tamer et al<sup>77</sup> recently demonstrated the antioxidant, anti-inflammatory, and anti-apoptotic effects of nesfatin-1 on impaired testicular function induced by testis torsion. Treatment with nesfatin-1 reduced the pro-inflammatory cytokine expression, depressed apoptosis,

degeneration of seminiferous tubules, and ameliorated the oxidative damage and preserved spermatogenic cells in torsioned rat testes.<sup>77</sup> Moreover, nesfatin-1 promotes puberty, spermatogenesis and steroid production in pre-pubertal male mice by directly acting on the testes, accompanied by reduced oxidative stress.<sup>78</sup> Similarly, the stimulatory effects of nesfatin-1 on spermatogenesis and steroidogenesis may be related to its antioxidant and anti-apoptotic activities.<sup>79</sup> Further, it ameliorates the type-2 diabetes mellitus (T2DM)-associated testicular dysfunction and decreases the production of antioxidative enzymes in mice with T2DM.<sup>80</sup> In addition, nesfatin-1 is also expressed in the reproductive organs of female mice and has been reported to be indispensable for the onset of normal puberty in female rats.<sup>81</sup> Expression level of nesfatin-1 decreased significantly in pregnant rats, indicating the important role of nesfatin-1 in pregnancy and fetal development.<sup>82</sup> Detailed study showed that serum levels of nesfatin-1 were negatively correlated with levels of IL-17A in both normal pregnancy and abortion model mice.<sup>83</sup> IL-17A is a landmark cytokine secreted by the helper T cell subset Th17 cells, which plays an important role in the pathogenesis of inflammation, autoimmune diseases, and allogeneic organ rejection. Further studies have confirmed that compared to normal pregnant mice, in abortion model mice serum levels of anti-inflammatory cytokines, such as IL-4, IL-13, and IL-1ra were reduced, and the expression levels of nesfatin-1/NUCB2 in the implantation sites in the uterus were significantly increased.<sup>84</sup> These results suggest a close relationship between nesfatin-1 and inflammatory cytokines in female reproductive physiology and pathology, but more studies are needed to support the anti-oxidative, antiapoptotic, and anti-inflammatory roles of nesfatin-1 in female reproductive function.

Osteoarthritis (OA) is a painful joint condition, characterized by the breakdown of the cartilage matrix, progressive degeneration of the articular cartilage, inflammation of the synovial membrane, and osteophyte formation in the joints.<sup>85</sup> Increasing evidence suggest that apoptosis of chondrocytes, the cellular component of the cartilage, plays a crucial role in the pathogenesis and development of OA,<sup>86–88</sup> making apoptosis a potential target for OA treatment. A previous study has shown that the levels of nesfatin-1 in articular cartilage and serum of patients with OA were significantly higher than in healthy controls.<sup>89</sup> Moreover, serum nesfatin-1 levels were positively correlated with high-sensitivity C-reactive protein

levels, and synovial nesfatin-1 levels were also positively correlated with IL-18 levels.<sup>89</sup> These results indicate a potentially pivotal role of nesfatin-1 in the pathophysiology of OA. More recently, Jiang et al investigated the potential effect of nesfatin-1 on the rat OA model and IL-1 $\beta$ -stimulated chondrocytes, a useful model of OA chondrocytes.<sup>90</sup> The results revealed that nesfatin-1 not only inhibits matrix metalloproteinase (MMP) expression and chondrocyte inflammation but also reduces apoptosis in rat chondrocytes,<sup>90</sup> indicating a protective effect of nesfatin-1 in OA through its anti-inflammatory and anti-apoptotic activities.

Renal I/R causes severe oxidative damage to tissues and organs, the mechanisms of which may be related to oxidative stress, necrosis, apoptosis, adenosine triphosphate depletion, and calcium dyshomeostasis.<sup>91,92</sup> An *in vivo* study conducted by Jiang et al<sup>93</sup> showed that intraperitoneal administration of nesfatin-1 can significantly improve the renal function and mitigate the cellular damage caused by I/R injury in murine model. Moreover, after nesfatin-1 treatment, the malondialdehyde (MDA) level decreased, while SOD and catalase (CAT) activities increased in the experimental rats, compared to untreated rats,<sup>93</sup> suggesting that nesfatin-1 ameliorated renal I/R injury by inhibiting oxidative stress. Furthermore, the anti-apoptotic activity of nesfatin-1 was also thought to be involved in the kidney protection it provides, as indicated by a significant decrease in apoptotic tubular cells, as well as a decrease in caspase-3 activity and an increase in the Bcl-2/Bax ratio.<sup>93</sup> Therefore, nesfatin-1 has a therapeutic potential to prevent renal IR injury.

Acute lung injury (ALI), a major cause of morbidity and mortality in both humans and animals, is characterized by strong pulmonary inflammation, resulting in inflammatory cell infiltration, alveolar capillary injury, abnormal release of ROS characterized by excessive oxidative stress, and apoptosis of alveolar epithelial cells.<sup>94</sup> Inhibition of these processes is considered to be the key to relieve ALI.<sup>95,96</sup> In an animal experiment, recombinant nesfatin-1 significantly ameliorated the symptoms of ALI and reduced the level of inflammation and oxidative stress in lung tissue of mice treated with LPS.<sup>4</sup> Similar therapeutic effects of nesfatin-1 were observed in the human alveolar epithelial cell line BEAS-2B incubated with LPS, an ALI cell model.<sup>4</sup>

Hyperglycemia affects and delays wound healing, but the specific underlying mechanism is still unclear.<sup>97</sup> It has been suggested that prolonged



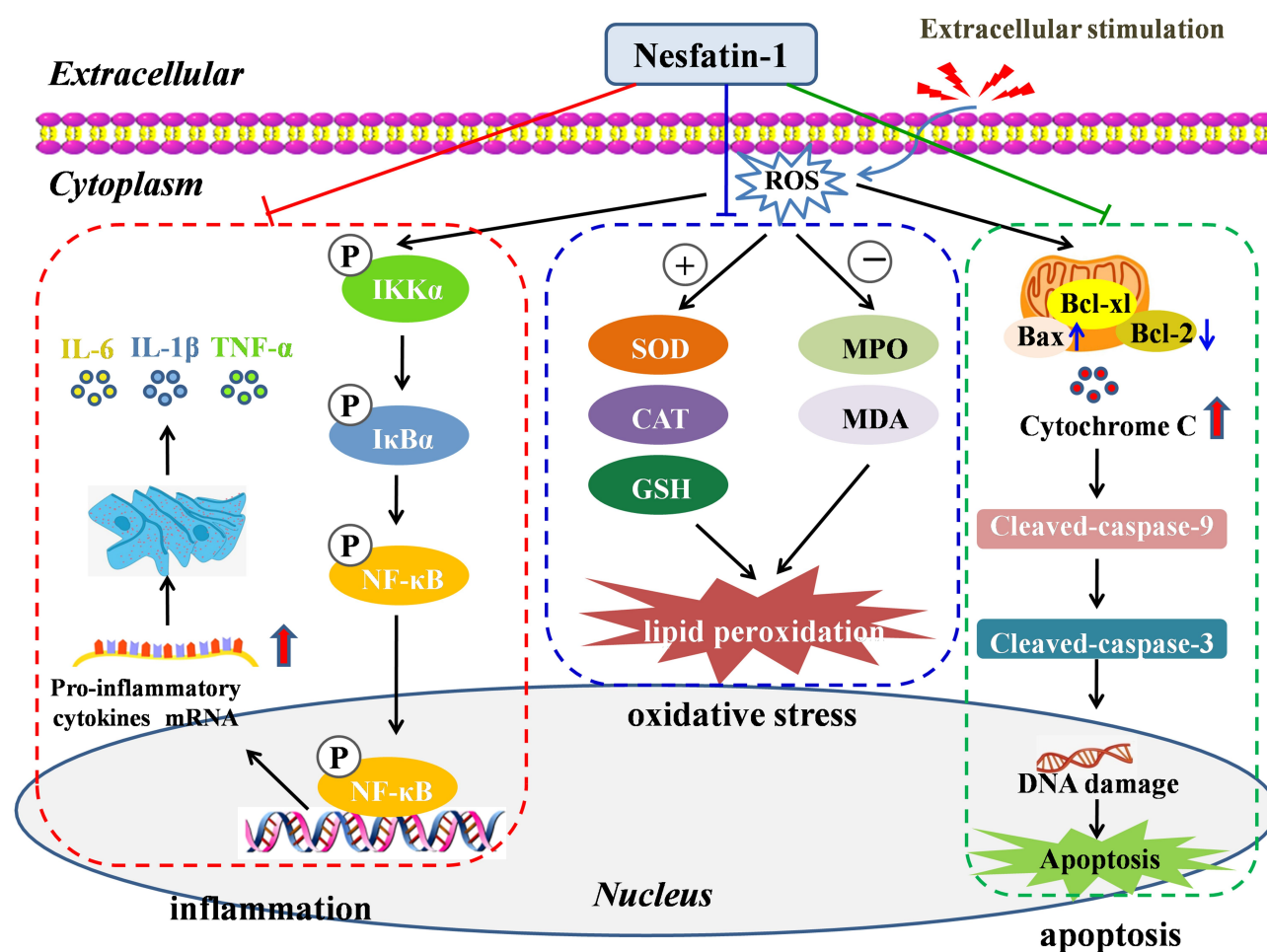
inflammation, delayed re-epithelialization, and consistent oxidative stress may correlate the high blood glucose levels with impaired wound healing.<sup>98</sup> Treatment for three consecutive days with nesfatin-1 (2 µg/kg/day) inhibited apoptosis and oxidative stress in the skin, decreased the plasma levels of inflammatory factors IL-1β and interleukin-6 (IL-6), and improved surgical wound healing in both normoglycemic and hyperglycemic rats.<sup>99</sup> This indicates that nesfatin-1 may play a potent role in promoting wound healing through its antioxidant, anti-inflammatory, and anti-apoptotic potential.

Obstructive jaundice is a medical condition caused by blockage of the body's biliary system.<sup>100</sup> The main causes of the obstructive jaundice and the consequent liver damage are persistent inflammation and oxidative stress.<sup>101</sup> Because of this, various antioxidants have been tested in experimental obstructive jaundice models.<sup>102–104</sup>

Solmaz et al<sup>105</sup> found that nesfatin-1 reduced the oxidative damage of the liver through its anti-inflammatory and antioxidant effects,<sup>105</sup> and may become a potential drug for the treatment of obstructive jaundice.

## Mechanisms and Pathways That Mediate the Antioxidant, Anti-Inflammatory, and Anti-Apoptotic Effects of Nesfatin-1

Increasing evidence indicate the role of ROS as secondary messengers in the initiation and amplification of cell signaling, which have key roles in cell proliferation, apoptosis, oxidative damage of cells, and inflammation.<sup>106,107</sup> More specifically, imbalances in ROS homeostasis may lead to oxidation-anti-oxidation imbalance, increase oxidative stress, and result in oxidative damage to biological macromolecules such as lipids,



**Figure 3** Mechanisms and intracellular processes through which nesfatin-1 exerts its antioxidant, anti-inflammatory and anti-apoptotic effects.

**Abbreviations:** CAT, catalase; GSH, glutathione; IL-1β, interleukin-1β; IL-6, interleukin-6; MDA, malondialdehyde; MPO, myeloperoxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α.

**Table 1** Mechanisms of Nesfatin-1 Exerting Antioxidant, Anti-Inflammatory and Anti-Apoptotic Effects

Diseases	Mechanisms	Effects	Literature
cerebral I/R	decrease the number of Iba-1-positive cells maintain the balance of oxidant/antioxidant systems decrease Caspase-3 activity and increase Bcl-2/Bax ratio	anti-inflammatory antioxidant anti-apoptotic	34,36
subarachnoid hemorrhage	inhibit neutrophil infiltration and subsequent release of inflammatory mediators	anti-inflammatory/anti-apoptotic	38
traumatic brain	inhibit NF- $\kappa$ B pathway lessen Caspase-3 activity	anti-inflammatory anti-apoptotic	37
diabetic neuropathy	inhibit intracellular ROS overproduction and reduce the apoptotic cell death	antioxidant/anti-apoptotic	51
PD (MPP <sup>+</sup> /MPTP-induced)	activate c-Raf-ERK1/2 pathway	anti-apoptotic	45
PD (rotenone-induced)	inhibit the release of cytochrome C from mitochondria, ROS production and Caspase-3 activation	antioxidant/anti-apoptotic	44
acetic acid-induced gastric ulcer	modulation of oxidant-antioxidant balance, inhibit neutrophil infiltration and proinflammatory cytokine release by a COX-dependent mechanism	antioxidant/anti-inflammatory	57
indomethacin-induced gastric ulcer	support the balance in oxidant and antioxidant systems inhibit the generation of pro-inflammatory mediators	antioxidant anti-inflammatory	55
chronic gastric ulcers	downregulation of SOD mRNA	antioxidant	56
stress-induced acute gastric injury	inhibit expression and release of proinflammatory cytokines	anti-inflammatory	58
myocardial infarction cardiac I/R	activate Akt/GSK-3 $\beta$ pathway inhibit the release of lactate dehydrogenase	anti-inflammatory/anti-apoptotic antioxidant	3 59
necrotizing enterocolitis	inhibit NF- $\kappa$ B-65 pathway and maintain the balance of oxidant/antioxidant systems	antioxidant/anti-inflammatory	68
ulcerative colitis	suppress the free radical formation prevent neutrophil infiltration	antioxidant anti-inflammatory	72
testis torsion	the AKT and CREB signaling pathways	anti-inflammatory/anti-apoptotic	77
osteoarthritis	inhibit NF- $\kappa$ B, MAPK, and the Bax/Bcl-2 signal pathway	antioxidant/anti-inflammatory /anti-apoptotic	90
renal I/R	decrease Caspase-3 activity and increase Bcl-2/Bax ratio maintain the balance of oxidant/antioxidant systems	anti-apoptotic antioxidant	93
LPS-induced AMI	inhibit HMGB1/p38MAPK/NF- $\kappa$ B-65 pathway	antioxidant/anti-inflammatory	4
skin injury	maintain the intracellular antioxidant pools	antioxidant/anti-inflammatory	99
obstructive jaundice	decrease malondialdehyde levels prevent neutrophil infiltration	antioxidant anti-inflammatory	105

**Abbreviations:** AMI, acute myocardial infarction; COX, cyclooxygenase; I/R, ischemia/reperfusion; LPS, lipopolysaccharide; MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium ion; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; ROS, reactive oxygen species; SOD, superoxide dismutase.

DNA, and proteins.<sup>108</sup> ROS have also been reported as key mediators of inflammation.<sup>109</sup> By activating the NF- $\kappa$ B pathway and enhancing the sensitivity of IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, ROS can induce cellular

inflammation.<sup>110</sup> Promotion of apoptosis is another crucial feature of ROS.<sup>111</sup> ROS promote apoptosis by increasing mitochondrial membrane permeability, mediating cytochrome C release, and enhancing caspase 9

activation and formation of apoptosis complex.<sup>112</sup> The intracellular processes of ROS-induced oxidative stress, inflammation, and apoptosis are summarized in Figure 3.

Some therapeutic agents can target an interconnected network of signaling pathways to treat diseases. For example, selenium nanoparticles contribute to neuronal survival by targeting different cellular signaling pathways that regulate cellular metabolism, oxidative defense system, inflammatory reactions, autophagy, and apoptotic cell death.<sup>113</sup> Nesfatin-1 plays a protective role in a variety of diseases by regulating ROS-induced oxidative stress, inflammation, and apoptosis (Figure 3). Nesfatin-1 treatment exerts its antioxidant effect by inhibiting intracellular ROS overproduction and maintaining the balance of oxidant/antioxidant systems, by decreasing the levels of lactate dehydrogenase, MPA, and MDA, and increasing the levels of SOD, CAT, and glutathione (GSH), as well as suppressing the free radical formation. Nesfatin-1 exerts its anti-inflammatory effects through several mechanisms. (1) Regulation of inflammatory cells. Nesfatin-1 inhibits inflammation by inhibiting neutrophil infiltration, decreasing the number of Iba-1-positive cells, and inhibiting astrocyte activation. (2) Decreasing the subsequent release of inflammatory mediators. (3) Modulation of various inflammation-related signaling pathways, including the NF- $\kappa$ B pathway, Akt/GSK-3 $\beta$  pathway, and CREB signaling pathway.

The anti-apoptotic effect of nesfatin-1 is relevant to the inhibition of mitochondria-associated apoptotic signaling via caspase-dependent pathways by decreasing the loss of mitochondrial membrane potential, increasing the Bcl-2/Bax ratio, inhibiting the release of cytochrome C from mitochondria, and decreasing caspase-3 activity. Additionally, activation of the C-Raf-ERK1/2 pathway is reported to be involved in the protective effects of nesfatin-1 against apoptosis. Table 1 shows the cellular, molecular, and biochemical mechanisms of nesfatin-1 exerting antioxidant, anti-inflammatory, and anti-apoptotic effects in multiple diseases.

## Conclusion

The reviewed data suggest that nesfatin-1 plays an ameliorative role in different pathophysiological conditions through its antioxidant, anti-inflammatory, and anti-apoptotic properties. Because the receptor of nesfatin-1 has not yet been identified, the exact mechanisms involved in the biological effects of nesfatin-1 are still unclear. Detailed understanding of the biological processes underlying the antioxidant, anti-inflammatory, and anti-

apoptotic effects of nesfatin-1 may pave the way for the design of new promising drugs.

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## Disclosure

The authors declare no conflicts of interest for this work.

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