Review Article

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A Review of the Beneficial Effects of Hesperidin on Urban Diseases

Chutamas Wunpathe PhD[1], Anongnard Kasorn PhD[1]

[1] *Department of Basic Medical Science, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok 10300, Thailand*

ABSTRACT

The urban environment is increasingly recognized as a key determinant of health, influencing lifestyles that can either promote or hinder well-being. This review aims to summarize recent studies (2020-2024) on the potential therapeutic effects of hesperidin, a flavonoid derived from citrus fruits, in addressing urban-related diseases worsened by pollution, sedentary habits, poor nutrition, and chronic stress. These health conditions include cardiovascular diseases respiratory issues, metabolic disorders, neurodegenerative diseases, mental health challenges, infectious diseases, and cancer. Hesperidin's anti-inflammatory, antioxidant, and immunomodulatory properties have shown promise in improving cardiovascular health, reducing oxidative stress, enhancing insulin sensitivity, protecting against neurodegeneration, alleviating mental health symptoms, reducing respiratory inflammation, and inhibiting cancer cell growth. While preclinical studies show encouraging results, clinical evidence remains limited, underscoring the need for further research to validate its safety, efficacy, and optimal dosage for urban health interventions.

KEYWORDS: antioxidant, flavonoid, hesperidin, urban diseases

INTRODUCTION

Urban-associated diseases are illnesses that become either more common or more severe due to urban living or are projected to rise due to future urbanization trends[1]. Urban diseases encompass a range of health conditions, including diseases of immune dysfunction such as allergies, asthma, and autoimmune disorders; lifestyle and chronic diseases such as cardiovascular disease and obesity; and infectious diseases such as respiratory infections. Together, these conditions constitute a significant portion of the global health burden[1].

In recent times, bioactive compounds, phytochemicals naturally found in edible plants and food, have gained significant importance in drug discovery and disease treatment. Technological advancements and global collaboration have driven research into the anti-inflammatory, antimicrobial, and antioxidant properties of plant extracts. Techniques such as chromatography, spectroscopy, and genomic tools are extensively employed to identify bioactive compounds and investigate phytochemical biosynthesis[2]. Plant extracts are increasingly utilized in the management of chronic conditions such as diabetes, cancer, and neurodegenerative diseases (NDGDs). These natural substances and their active compounds have been shown to mitigate oxidative stress and inflammation, while also aiding in the management of cardiovascular and neurological disorders[3-7]. Therefore, medicinal plants offer a promising alternative to conventional medicine, often with fewer side effects, and continue to be a key focus in high-impact research.

Corresponding author: Anongnard Kasorn, anongnard@nmu.ac.th
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Hesperidin, a naturally occurring flavonoid mainly found in citrus fruit peels and other citrus plants, has been reported to have beneficial health effects[8]. Hesperidin has been incorporated into traditional Chinese medicine for the treatment of various health conditions[9]. These citrus plants are widely available and easy to include in daily diets, making them a practical source of hesperidin beneficial for all ages. Apart from citrus fruits, hesperidin has been discovered in mint plants (*Mentha*), honeybush (Cyclopia maculata), and aromatized tea[10]. Hesperidin possesses diverse pharmacologic properties, including antioxidative and anti-inflammatory effects[11]. It has been reported to improve neurologic disorders, including NDGDs, mental disorders, demyelinating diseases, and ischemic–reperfusion and brain injury[12]. In addition, hesperidin has shown effective anticancer properties through the regulation of a variety of cell-signaling molecules. Hesperidin's anticancer effect is evidenced by its effect on inflammation, cell-cycle regulation, apoptosis, and angiogenesis[13]. However, there are currently no studies gathering data on the effects of hesperidin on urban-associated diseases. Therefore, this review aims to summarize the underlying biological mechanisms and potential therapeutic benefits of hesperidin in these conditions.

THE EFFECT OF HESPERIDIN ON URBAN DISEASES

Allergies and asthma

Urban environments typically have higher levels of pollutants, including vehicle emissions, industrial waste, and environmental smoking exposure, which can exacerbate respiratory conditions[14]. In addition, the consumption of fast foods and fried meats is common in densely populated cities, contributing to the increased prevalence of allergy. Studies have shown that children and adults in urban settings are at a higher risk of developing and experiencing more severe symptoms of allergies and asthma compared with those in rural areas[15,16]. Hesperidin has shown significant potential in the management of allergies and asthma, largely due to its anti-inflammatory properties. Various experimental models have shown hesperidin to alleviate airway inflammation and hyperresponsiveness, which are common symptoms of asthma. These effects are mediated through its influence on nuclear factor kappa B (NF-κB), which reduces the production of proinflammatory cytokines and chemokines, thus mitigating the inflammatory cascade that exacerbates asthma symptoms[17]. A recent study demonstrated that hesperidin in three different doses effectively mitigated the effects induced by mechanical ventilation. This was evidenced by the reduced infiltration of inflammatory cells into the airways, decreased levels of inflammatory markers, and diminished oxidative damage, all of which are involved in asthma development[18]. Hesperidin notably reduced the increase in transforming growth factor–beta (TGF-β), tumor necrosis factor–alpha (TNF-α), interleukin-5 (IL-5), and immunoglobulin E levels in ovalbumin (OVA)–induced bronchial asthma. Moreover, it attenuated cellular infiltration, mitigated damage to alveolar sacs, decreased disruption of the bronchiole walls, and reduced neuronal cell nucleus pyknosis. These effects suggest that hesperidin, potentially through its anti-inflammatory and immunoregulatory effects, may offer protection against OVA-induced asthma[19]. Overall, recent research underscores hesperidin's potential as a complementary treatment for managing allergies and asthma, primarily through its action on the TGF-β, TNF-α, and NF-κB pathway associated with the production of proinflammatory cytokines. These findings highlight the importance of further clinical studies to establish the efficacy and safety of hesperidin in human populations.

Autoimmune and inflammatory diseases

Autoimmune and inflammatory diseases in urban areas are influenced by various

environmental factors including pollution and lifestyle habits in urban settings[20]. These factors can contribute to the increased incidence and severity of conditions such as rheumatoid arthritis[21] and inflammatory bowel disease[20]. Hesperidin exhibits potent anti-inflammatory and antioxidant properties, which are crucial in modulating inflammatory responses. In rats with collagen-induced arthritis, hesperidin was shown to be effective in reducing the severity of rheumatoid arthritis by lowering the arthritic score, arthritis index, and serum levels of TNF-α, IL-6, IL-17A, and C-reactive protein[22]. In addition, hesperidin exhibited an antiarthritic property by reducing scavenging free radicals and inhibiting glycation processes[23], modulating serum interferon gamma and IL-4 levels, and providing protection against oxidative damage[11]. Furthermore, the administration of hesperidin in rats with cyclosporine A–induced nephrotoxicity reduced the expressions of TNF-α, B-cell lymphoma-2 (Bcl-2)–associated X protein, and NF-κB, resulting in the attenuation of pathological kidney damage with an increase in nuclear factor erythroid 2–related factor 2 (Nrf2) expression in the kidney[24]. Thus, these findings suggest the role of hesperidin as an immunomodulatory agent.

LIFESTYLE AND CHRONIC DISEASES

Cardiovascular disease

Previous study indicated that cardiovascular diseases are the leading cause of mortality in urban areas and worldwide[25]. Recent studies have explored various aspects of the effects of urban living on cardiovascular health. In urban areas, patients with ST-elevation myocardial infarction exposed to high concentrations of nitrogen dioxide (NO_2) and particles with a diameter of 10 microns or less (PM_{10}) experience a greater risk of readmission for heart failure[26]. Nevertheless, individual factors such as dietary habits, educational level, and physical activity influence the prevalence of cardiovascular disease. Hesperidin has garnered attention for its potential cardiovascular benefits. Previous studies suggested that hesperidin exhibits antioxidant, anti-inflammatory, and antiapoptotic effects, which contribute to its protective effects against cardiotoxicity[27]. Similarly, hesperidin prevents cardiotoxicity via modulation of the gene expression levels of the Phosphoinositide 3-kinase/ Protein kinase B (Akt)/ mammalian target of rapamycin (mTOR) signaling pathway[28], and proapoptotic Bcl-2-associated X protein and caspase-3, and it also improves the expression of the pathway proteins p62 and Nrf2[29]. Hesperidin also enhances cholesterol reverse transport by increasing the upregulation of adenosine triphosphate-binding cassette protein A1 (ABCA1)[30] which is a crucial factor in the development and progression of cardiovascular disease. Hesperidin also prevented vascular alterations induced by L-NG-Nitroarginine Methyl Ester in rats, possibly by suppressing the activation of the renin-angiotensin system, inhibiting TGF-β1 expression, and reducing oxidative stress[5]. It also improved symptoms of metabolic syndrome and cardiac dysfunction in a rat model of diet-induced metabolic syndrome, likely through the insulin receptor substrate/ Akt/Glucose transporter type 4 signaling pathway[4]. In addition, hesperidin protected against varenicline-enhanced oxidized low-density lipoprotein uptake in RAW 264.7 cells by blocking the upregulation of cluster of differentiation 36 (CD36) and lectin-like oxidized low-density lipoprotein receptor-1 scavenger receptors and preventing the downregulation of ABCA1 and adenosine triphosphate-binding cassette sub-family G member 1 cholesterol efflux transporters[31], further reducing the risk of atherosclerosis and related cardiovascular events. Therefore, hesperidin provides substantial cardiovascular protection via its antioxidant, anti-inflammatory, and antiapoptotic properties by modulating key signaling pathways, lowering blood pressure, enhancing lipid profiles, and safeguarding against cardiotoxicity, metabolic syndrome, and atherosclerosis.

Neurodegenerative diseases

Air pollution in urban areas poses a serious threat to public health and the environment. The major sources of air pollution include vehicle emissions, industrial discharges, and construction activities, leading to elevated levels of PM, carbon dioxide, and NO_2[32]. These pollutants contribute to cardiovascular diseases as well as NDGDs[33]. Air pollution is increasingly recognized as a significant contributor to NDGDs such as Alzheimer's disease (AD) and Parkinson's disease (PD). Pollutants such as PM and heavy metals can trigger neuroinflammation and oxidative stress, leading to neuronal damage. Data from a recent review indicated that individuals in polluted areas face a higher risk of NDGDs, highlighting the critical need for strategies to reduce air pollution and protect brain health[34]. There has been a growing interest in recent studies on NDGDs and the potential therapeutic effects of hesperidin, with evidence suggesting that hesperidin may offer neuroprotective benefits. NDGDs, such as AD, PD, and amyotrophic lateral sclerosis, are characterized by the progressive degeneration of the nervous system, leading to cognitive and motor impairments. Hesperidin has been shown to exhibit antioxidant, anti-inflammatory, and neuroprotective properties, which could potentially help in mitigating the underlying mechanisms of neurodegeneration[35,36]. Recent research highlighted the role of hesperidin in improving cognitive functions and reducing amyloid beta aggregation, α-synuclein aggregation[37] and decreasing oxidative/nitrosative stress[38], which are key features in AD. In addition, researchers also reported dopaminergic neuronal protection and stabilization of cellular calcium homeostasis by hesperidin, suggesting its potential role as a complement treatment for PD[39,40]. Moreover, hesperidin has been shown to affect several signaling pathways involved in neuronal survival, making it a promising candidate for drug development[41, 42]. Although preclinical studies have shown promising results regarding the neuroprotective effects of hesperidin, additional clinical trials are necessary to confirm its efficacy in human populations and to optimize treatment protocols. Continued investigation into hesperidin's mechanisms of action and its therapeutic potential could pave the way for novel interventions in the management of NDGDs, ultimately improving patient outcomes and quality of life.

Cancer

The incidence of cancer in urban areas has been a growing concern, particularly because of the interplay of environmental and lifestyle factors prevalent in densely populated regions. Residents of urban environments are often exposed to higher levels of air pollution, which has been linked to an increased risk of lung cancer and other respiratory malignancies[43]. In many Asian cities, including Bangkok, urban air pollution from traffic is a significant issue. This pollution mainly arises from incomplete fossil fuel combustion and includes carcinogenic compounds such as polycyclic aromatic hydrocarbons and benzene. It has been reported that Bangkok schoolchildren are exposed to total polycyclic aromatic hydrocarbons at levels 3.5 times higher than children in rural areas are, while their exposure to benzene is about twice as high as that of schoolchildren in rural regions[44]. In addition, a previous study reported high incidences of other types of cancer in urban areas, including ovarian cancer[45], thyroid and colorectal cancers, lung cancer, prostate cancer, kidney cancer, bladder cancer, lymphoma, and leukemia[46]. However, variations in individual lifestyle factors, such as diet, exercise, and the prevalence of smoking and alcohol consumption, also influence the risk of developing cancer.

In the past few years, various studies have reported the promising anticancer properties of hesperidin, which exerts its effects through multiple mechanisms including antioxidant activity, modulation of inflammatory pathways, and induction of apoptosis in cancer cells. In the preclinical setting, hesperidin was shown to

abolish the growth and metastasis of breast cancer[47], prostate cancer[48], lung cancer[49], oral cancer[50], intrahepatic cholangiocarcinoma[51], leukemia cancer[52], and colorectal cancer[53]. Furthermore, hesperidin also inhibited cancer cell progression via modulation of the p53 signaling pathway[54], inhibition of the Mitogen-Activated Protein Kinase Kinase Kinase 2 (MEKK2)/Mitogen-Activated Protein Kinase Kinase 5 (MEK5)/Extracellular-signal-regulated kinase 5 (ERK5) signaling pathway activation[51], and inhibition of programed death ligand 1 expression via downregulation of Akt and NF-κB signaling[55]. In addition, hesperidin also suppressed the phosphorylated signal transducer and activator of transcription 1 and signal transducers and activators of transcription 3, leading to cell-cycle arrest in cancer cells[50]. Hesperidin also promotes apoptotic cancer cell death via reactive oxygen species (ROS)–driven cell necrosis[48] and targeting of the microRNA-132/zinc finger Ebox binding homeobox 2 signaling pathway[49].

A recent study demonstrated that a combined treatment with hesperidin and chlorogenic acid produced a synergistic effect by regulating mitochondria and production of adenosine triphosphate through the estrogen receptor pathway in breast cancer cells. This finding suggests that, when used alongside chemotherapy drugs, hesperidin and chlorogenic acid could be effective as adjunctive therapies for breast cancer patients[56]. Moreover, hesperidin also enhances the efficacy of conventional therapies such as chemotherapy, potentially by protecting normal cells from treatment-induced damage[57]. Overall, hesperidin represents a potent bioactive compound with significant potential in cancer prevention and treatment. The compound's antioxidant and anti-inflammatory properties further contribute to its protective effects against cancer. Despite promising preclinical findings, more clinical trials are needed to confirm the safety, optimal dosage, and therapeutic potential of hesperidin in cancer treatment.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition characterized by chronic inflammation and irreversible airflow obstruction, primarily caused by long-term exposure to irritants such as cigarette smoke and air pollutants[58]. Inflammation is a pervasive factor in numerous respiratory diseases, such as COPD[59]. Hesperidin, a prominent polyphenol, has been shown to inhibit key transcription factors and regulatory enzymes involved in the mediation of inflammation, including NF-κB, inducible NO synthase, and cyclooxygenase-2. Moreover, hesperidin enhances cellular antioxidant defenses via the activation of the ERK/Nrf2 signaling pathway, suggesting its potential therapeutic utility in managing the inflammatory aspects of respiratory diseases[17]. The effect of hesperidin on COPD currently remains unclear. Nevertheless, a recent study demonstrated that hesperidin effectively mitigated inflammation and oxidative stress in mice with COPD induced by cigarette smoke extract. This beneficial effect is likely mediated through the modulation of the sirtuin 1/peroxisome proliferator-activated receptor gamma coactivator 1-alpha/NF-κB signaling pathway[60]. This suggests that hesperidin might be a potential therapeutic option for managing COPD.

Obesity and diabetes mellitus

Obesity and diabetes mellitus (DM) are common in the urban areas of developing countries[61]. Previous studies have highlighted hesperidin's potential benefits in managing obesity and DM due to its anti-inflammatory, antioxidant, and lipid-lowering properties, resulting in improvements in metabolic profiles and insulin resistance[62,63]. An in-silico study showed that the administration of hesperidin significantly improved leptin and insulin resistance in a high-fat diet (HFD)–induced obese experimental animal model[62]. Moreover, researchers also reported a substantial reduction in serum amylase and lipase activities,

a significant increase in insulin levels, and improvement in the pancreatic antioxidant defense system in cadmium-induced pancreatitis rats[64]. Moreover, several lines of evidence have suggested the antidiabetic effects of hesperidin. In HFD-fed rats, the administration of hesperidin improved blood glucose, insulin level, liver enzymes, lipid profile, and oxidative profile[65] and normalized the expression levels of insulin signaling and glucose metabolism–related genes in the liver[63]. In rats fed an obesogenic diet, hesperidin supplementation decreased total cholesterol, low-density lipoprotein cholesterol, and free fatty acids[66]. In addition, the highest dose of hesperidin used in this study also improved blood pressure and insulin sensitivity and reduced markers of arterial stiffness and inflammation. A recent study in patients with gestational DM and obesity showed that hesperidin significantly inhibited the autophagy proteins and m6A level in LPS and glucose-induced human villous trophoblasts isolated from these patients[67]. Overall, the evidence from recent studies suggests that hesperidin could be a valuable component of therapeutic strategies aimed at managing obesity and diabetes, promoting overall metabolic health, and reducing the risk of associated complications.

Mental health

Urban environments present a unique set of challenges that can contribute to the development and exacerbation of depression among residents. Several factors such as social isolation and environmental stressors including noise and pollution contribute to mental health conditions[68], which can exacerbate and lead to physical diseases that diminish the overall quality of life. Hesperidin has been reported to effectively slow the progression of mental health conditions, especially depression. Hesperidin administration in chronic unpredictable mild stress (CUMS) depressed mice significantly alleviated depressive symptoms and expression levels of key components in the proptosis pathway including caspase 1, IL-18, IL-1β, and nucleotide-binding and oligomerization domain-like receptor protein 3[69]. A similar effect was observed when hesperidin was administered to CUMS-induced rats[70]. Moreover, hesperidin could ameliorate depression and anxiety-like behaviors in diabetic rats by enhancing glyoxalase-1, potentially via the activation of the Nrf2/ antioxidant responsive element (ARE) pathway[71]. Researchers have also reported the protective role of hesperidin against depression. Pretreatment with hesperidin significantly reduced depressive behavior; increased the levels of CD4, CD25, forkhead box P3, IL-10, dopamine, serotonin, and neurotrophin-3; and improved the motor function of OVA-induced bronchial asthma rats, suggesting its protective roles against OVA-induced asthma and depression[19]. It also exerted anxiolytic-like and antidepressant-like effects in the neurotoxin 6–hydroxydopamine model of PD by modulating cytokine production, neurotrophic factor levels, and dopaminergic innervation in the striatum[72]. In addition, hesperidin has shown antidepressant effects in animal models of posttraumatic stress disorder by decreasing the 5-hydroxyindoleacetic acid/5-hydroxytryptamine ratio, monoamine oxidase A activity, and tryptophan hydroxylase-1 expression[73]. In the clinical setting, coronary artery bypass graft patients who had mild depression exhibited a reduction in depressive symptoms after 12 weeks of 200 mg/day hesperidin[74]. Overall, these results indicate that hesperidin is a promising therapeutic option for treating depressive disorders.

Infectious diseases

Urban areas, which are characterized by high population density and frequent social interactions, are particularly vulnerable to the rapid spread of infectious diseases. Studies have shown that a high density of people and frequent social contact contribute to an increased risk of a range of infections, including respiratory illnesses such as coronavirus disease 2019 (COVID-19) and influenza, as well as vector-borne diseases[75,76].

Hesperidin has been demonstrated to exert its antiviral and anti-inflammatory effects, particularly in relation to COVID-19 and other infectious diseases, through a variety of mechanisms. It inhibits viral replication by modulating key viral proteins and cellular signaling pathways. For instance, hesperidin has been reported to interfere with the entry of severe acute respiratory syndrome coronavirus 2 into host cells by affecting the interaction between the virus spike protein and angiotensin-converting enzyme 2[77,78]. In addition, an in-silico study showed that the combination of hesperidin with zinc oxide nanoparticles exhibited high antiviral activity against mRNA hepatitis A virus, indicating that this combination might be a promising candidate for the treatment of COVID-19[79]. In nonvaccinated patients with COVID-19, 1,000 mg of hesperidin daily for 14 days could reduce the key symptoms of COVID-19, such as fever, shortness of breath, cough, and anosmia. Although it slightly alleviated anosmia, the most persistent symptom, further research with longer treatment periods or higher doses is required[80]. Hesperidin also exhibited strong inhibitory effects on the Chikungunya virus[81] and hepatitis C virus nonstructural protein 3 protease[82] with half-maximal inhibitory concentration values of 10 and 11.34 μg/mL, respectively.

Moreover, infectious diseases can also be caused by bacterial infection. A recent study reported hesperidin's antivirulence effects against *Aeromonas hydrophilia* (*A. hydrophilia*), a rod-shaped, gram-negative bacterium present predominantly in drinking water, wastewater, sewage, and food. The transmission of *A. hydrophilia* from fish to humans via the consumption of raw seafood can cause diseases such as gastroenteritis, septicemia, and skin diseases. Hesperidin methylchalcone decreased the development of biofilm and the production of the virulence factor of *A. hydrophilia*, suggesting its role as a possible treatment for *A. hydrophilia*–related infections in humans[83]. These findings suggest the potential role of hesperidin as a supportive therapeutic agent in the management of viral and bacterial infections. Although the current results are promising, further studies are needed to establish the comprehensive efficacy and safety profiles of hesperidin. Longer treatment periods, higher doses, and diverse experimental conditions should be conducted to evaluate its effectiveness and optimal usage.

CONCLUSION

In this review based on studies conducted from 2020 to 2024, we have highlighted the possible mechanisms and therapeutic benefits of hesperidin as a promising treatment for urban diseases (Table 1). Hesperidin demonstrates multiple mechanisms that can address various urban diseases. It inhibits key inflammatory pathways, particularly by modulating NF-κB signaling. This reduces the production of proinflammatory cytokines (such as TNF-α, IL-6, IL-1β) and chemokines, which are crucial in conditions like asthma, COPD, and autoimmune diseases. It also acts as an antioxidant by activating the Nrf2 pathway, which helps combat oxidative stress in cardiotoxicity. In metabolic syndrome, hesperidin improves cardiac function by influencing insulin receptor substrate/Akt/insulin-responsive glucose transporter signaling pathway. It also enhances insulin sensitivity and regulates glucose metabolism in diabetes and obesity. Hesperidin stabilizes calcium homeostasis, prevents amyloid beta aggregation, and decreases dopaminergic neuronal damage. These effects are beneficial for conditions like PD and AD. Its anticancer properties are linked to the regulation of cell progression through p53, and MEKK2/MEK5/ERK5 signaling pathway pathways. Regarding mental health, hesperidin reduced depressive symptoms in CUMS mice and rats by lowering proptosis markers. It also improved depression and anxiety in diabetic rats via the Nrf2/ARE pathway and showed antidepressant effects in post-traumatic stress disorder models

by reducing key biochemical markers. In infectious diseases, hesperidin inhibits viral replication and bacterial virulence factors. Hesperidin inhibits the entry of viruses like SARS-CoV-2 into host cells. This is done by modulating the interaction with the angiotensin converting enzyme-2 receptor. Its broad mechanisms position hesperidin as a potential therapeutic agent for managing urban-related diseases. While preclinical studies have demonstrated promising results, further clinical research is needed to fully validate the therapeutic efficacy and safety of hesperidin in humans. Additionally, optimal dosing regimens and long-term effects require further investigation. Nonetheless, hesperidin holds considerable promise as a natural therapeutic option for managing a variety of urban-associated health challenges, offering a potential complementary approach to current medical treatments and preventative health strategies.

Table 1 The major targets of hesperidin and their associated signaling pathways on urban diseases

Diseases	The major targets and possible mechanism of action	Model	References
Allergies and asthma	Decreased levels of TNF-α, IL-5, and IgE	OVA-induced bronchial asthma in rats	19
Autoimmune and inflammatory diseases	Reduced TNF-α, IL-6, IL-17A, and C-reactive protein	Collagen-induced arthritis in rats	22
	Reduced serum TNF-γ and IL-4 levels	Complete Freund's adjuvant-induced arthritic rats	11
	Suppressed TNF-α, Bcl-2–associated X protein, and NF-κB, upregulated Nrf2 expression	Cyclosporine-induced nephrotoxicity in rats	24
Cardiovascular disease	Upregulated IRS/Akt/GLUT4	HFD-induced MS in rats	4
	Decreased renin-angiotensin system activation and TGF-β1 expression	L-NAME rats	5
	Modulated PI3K/Akt/mTOR signaling pathway, inflammatory parameters (Beclin 1, LC3A, LC3B, NF-κB, IL-1β, TNF-α), and apoptotic genes (caspase-3, -6, -9, Bax, Bcl-2, p53, cytochrome c)	Sodium fluoride-induced cardiotoxicity in rats	28
	Increased p62-Keap1-Nrf2 signaling pathway	Cisplatin-induced cardiotoxicity in mice	29
	Increased ABCA1 upregulation	Apoe-deficient mice	30
	Decreased CD36 and LOX-1 scavenger receptors upregulation, but increased ABCA1 and ABCG1 cholesterol efflux transporters upregulation	Apoe KO mice	31
Neurodegenerative diseases	Reduced beta amyloid and α-synuclein	*In vitro* model of AD	37
	Reduced NOx and protein carbonyl levels	Streptozotocin-induced AD rat model	38
	Stabilized cellular calcium homeostasis	SH-SY5Y cellular model of Parkinson disease	39
	Decreased Fe levels	Parkinson-like disease in Drosophila melanogaster	40
Cancer	Increased miR-132 expression and decreased ZEB2 expression	Non-small cell lung cancer	49
	Inhibited MEKK2/MEK5/ERK5 signaling pathway activation	Intrahepatic cholangiocarcinoma	51
	Modulated p53 signaling pathway	Breast cancer stem cells	54

Table 1 The major targets of hesperidin and their associated signaling pathways on urban diseases (continued)

Diseases	The major targets and possible mechanism of action	Model	References
	Downregulated Akt and NF-κB signaling	Breast cancer cells	55
	Inactivated STAT1 and STAT3 signaling molecules	Oral cancer cells	50
	Induced ROS–driven cell necrosis	Prostate cancer cells	48
Chronic obstructive pulmonary disease	Modulated SIRT1/PGC-1α/NF-κB signaling pathway	COPD mice	60
Obesity and diabetes mellitus	Increased insulin-mediated phosphorylations of Akt and GSK3β	PA-treated HepG2 cell	63
	Normalized expression levels of hexokinase-II, enolase-1, and PI3 kinase p110δ	HFD-induced obese mice	63
	Decreased iNOS, NF-κB, IL-6 and TNF–α levels	Cadmium-induced pancreatitis rats	64
	Suppressed autophagy proteins and m6A levels	LPS and glucose-induced human villous trophoblasts	67
Mental health	Regulated the NLRP3 pathway	Chronic unpredictable mild stress depressed mice	69, 70
	Activated Nrf2/ARE/Glyoxalase 1 pathway	Diabetic rats	71
	Modulated cytokine production, neurotrophic factor levels, and dopaminergic innervation	6-OHDA Parkinson's model	72
	Decreased 5-HIAA/5-HT ratio, MAO-A activity, and tryptophan hydroxylase-1 expression	Animal model of post-traumatic stress disorder	73
Infectious diseases	Interfered the binding of the SARS-CoV-2 S protein to the ACE2 receptor	in silico methods	77
	Decreased the interaction between the spike protein and ACE2, as well as ACE2 and TMPRSS2 expression	VeroE6 cells	78

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; ABCA1, ATP-binding cassette transporter A1; ABCG, ATP binding cassette subfamily G member; ACE2, angiotensin-converting enzyme 2; AD, Alzheimer's disease; Akt, protein kinase B; ApoE, apolipoprotein E; ARE, arrestin-related protein; Bax, Bcl-2-associated X protein; Bcl2, anti-apoptotic protein; CD36, cluster of differentiation 36; COPD, chronic obstructive pulmonary disease; ERK5, extracellular signal-regulated kinase 5; Fe, iron; GLUT4, glucose transporter type 4; GSK3β, glycogen synthase kinase 3 beta; HepG2, human hepatoblastoma cell line; HFD, high fat diet; IgE, immunoglobulin E; IL, interleukin; iNOS, inducible nitric oxide synthase; IRS, insulin receptor substrate; Keap1, Kelch-like ECH-associated protein; KO, knock out; LC, microtubule-associated protein light chain; L-NAME, N-nitro-L-arginine methyl ester; LOX-1, elctin-like oxidized low-density lipoprotein receptor 1; LPS, lipopolysaccharide; MAO-A, monoamine oxidase A; MEK5, mitogen-activated protein kinase kinase 5; MEKK2, mitogen-activated protein kinase kinases kinase 2; miR, microRNA; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-kappa B; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; NOx, nitrogen oxides; Nrf2, nuclear factor erythroid 2-related factor 2; OHDA, 6-hydroxydopamine; OVA, ovalbumin; PA, palmitate; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; ROS, proto-oncogene tyrosine-protein kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SH-SY5Y, a thrice-cloned subline of the human neuroblastoma cell line SK-N-SH; SIRT1, sirtuin 1; STAT, signal transducers and activators of transcription; TGF-β1, transforming growth factor beta 1; TMPRSS2, transmembrane serine protease 2; TNF-α, tumor necrosis factor-alpha; TNF-γ, tumor necrosis factor-gamma; ZEB2, zinc finger E-box binding homeobox 2

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