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Review

Prospective multifunctional roles and pharmacological potential of dietary flavonoid narirutin

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ABSTRACT

Plant-based phytochemicals are now being used to treat plenty of physiological diseases. Herbal drugs have gained popularity in recent years because of their strength, purity, and cheap cost-effectiveness. Citrus fruits contain significant amounts of flavanones, which falls to the category of polyphenols. Flavanones occupy a major fraction of the total polyphenols present in the plasma when orange juice is taken highly or in moderate states. Narirutin is a disaccharide derivative available in citrus fruits, primarily dihydroxy flavanone. From a pharmacological viewpoint, narirutin is a bioactive phytochemical with therapeutic efficacy. Many experimental researches were published on the use of narirutin. Anticancer activity, neuroprotection, stress relief, hepatoprotection, anti-allergic activity, antidiabetic activity, anti-adipogenic activity, anti-obesity action, and immunomodulation are a couple of the primary pharmacological properties. Narirutin also has antioxidant, and anti-inflammatory activities. The ultimate goal of this review is to provide the current scenario of pharmacological research with narirutin; to make a better understanding for therapeutic potential of narirutin, as well as its biosynthesis strategies and side effects. Extensive literature searches and studies were undertaken to determine the pharmacological properties of narirutin.

1. Introduction

Phytochemicals derived from natural resources are used as alternative therapeutics for various diseases. Regardless of significant advances in contemporary medicine, a persistent insufficiency of acceptable and potential therapeutics has remained [1]. It is noted that substantial physiological complications may result due to drug-induced toxicity; thereby leading towards death. So, most of the pharmaceuticals with toxicological properties are being withdrawn from the market [2,3]. Herbal medications have gained in relevance and appeal in recent years as a result of their potency, purity, and low cost-effectiveness [4].

Flavanones are natural phytochemicals with anti-inflammatory, antioxidant, anti-allergic, and anti-proliferative effects [5–8]. The structural configuration and hydrogen-donating competences of their phenolic groups confer these pharmacological attributes [9]. Flavanones; mainly narirutin is highly present in citrus fruits [10]. Plants contain enormous quantities of phenolic compounds. Due to their bioactivity, secondary metabolites provide a wide range of multifunctional health benefits, such as the ability to inhibit the growth of microorganisms, and to reduce inflammation in the body. They can remove radicals, chelate and heavy metals, and may work as ion or hydrogen donors. Some phenolic compounds have significant antioxidant potential as pure molecules, whereas others require synergy to carry out their protective functionalities [11,12]. Narirutin constitute the majority of the flavonoids that occur naturally in citrus fruits [13]. Citrus peels are the main source of many important flavonoids, flavanones (hesperidin and narirutin), and polymethoxyflavones (PMFs; sinensetin, nobiletin, and tangeretin) [14]. More studies on narirutin and other flavonoids demonstrate that they have antihypertensive, cholesterol-lowering, and insulin-stimulating properties, which account for their ability to reduce atherosclerosis in animal models [15]. Several experimental investigations have proven that narirutin supplementation is useful in the

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treatment of obesity, type 2 diabetes, high blood pressure, and metabolic syndrome [16].

The purpose of this study is to convey the current status of pharmacological research, using narirutin as a focus. To establish the pharmacological characteristics of narirutin, extensive literature searches and reviews were attempted. The goal of this review is to better understand the therapeutic application of narirutin, as well as its biosynthetic challenges and side effects.

2. Methodology

To pick up the most relevant articles (available in the most well-known medical/biology/chemical databases such as Scopus, PubMed, and Web of Science) for this review as precisely as possible are considered. The following terms are used as keywords: "Narirutin, flavanones, pharmacological properties, and bioactive phytochemical". An algorithm exacted by the flow chart displayed in Fig. 1 (according to Page et al. recommendations [17,18]) was used, which inserted all of the steps/selection requisite for the necessary material in the literature.

3. Structure and classification of narirutin

Narirutin is a flavanone-7-O-glycoside that is present in orange juice and is made up of the flavanone naringenin bound to the disaccharide rutinose. The molecular formula of narirutin is $C_{27}H_{32}O_{14}$ with molar weight of 580.539 g/mol [19]. It is a disaccharide compound formed when (S)-naringenin is replaced at position 7 by a 6-O-(6-deoxy--alpha-L-mannopyranosyl)-beta-D-glucopyranosyl moiety through a glycosidic linkage. It works as an anti-inflammatory, antioxidant, and metabolite [20].

Flavonoids are polyphenols that humans are unable to produce. The structural properties of the six families of flavonoids (flavanones, flavonols, flavones, anthocyanins, isoflavonoids, and flavans) surrounding the heterocyclic oxygen ring were determined using reverse-phase LC–DAD–ESI–MS–MS analysis. Citrus fruits possess most of the flavanones, whereas herbs include flavones, legumes contain isoflavonoids, fruits contain anthocyanins and catechins, and other fruits and vegetables contain flavonols [21,22]. There are several citrus-derived flavonoid glycosides, such as eriocitrin, narirutin, hesperidin, isorhoifolin, diosmin, rosmarinic acid, and 5, 7-dihydroxycromone-7-O-rutinoside [23]. In sour orange juice, seven flavonoids and a furocoumarin were discovered for the first time, featuring two O-glycosides (narirutin 4′-glucoside and rhoifolin 4′-glucoside) [24]. HPLC and NMR were used to characterize citrus peel-extracted narirutin [25].

In flavonoids like narirutin, several hydroxyl groups have the least favorable effect. The biggest promoter of β-carotene absorption is O-glycosylation at C_7 of the A ring. O-Glycosylation at C7 has a greater affinity for the cell membrane, which causes the cell membrane to fluidize. Aglycone molecules generate temporary increases in paracellular permeability by modulating the activity of tight junction proteins (ZO-1, claudin-1). Citrus flavanones also serve as ligands of peroxisome proliferator-activated receptor (PPAR)-gamma, increasing the production of scavenger receptor class B type I (SR-BI). The catechol composition in the B-ring inhibited SR-BI expression activation. The stimulating function of citrus flavanones on β-carotene cellular absorption is mechanistically associated with structure-dependent membrane potential and regulation of particular membrane proteins [26].

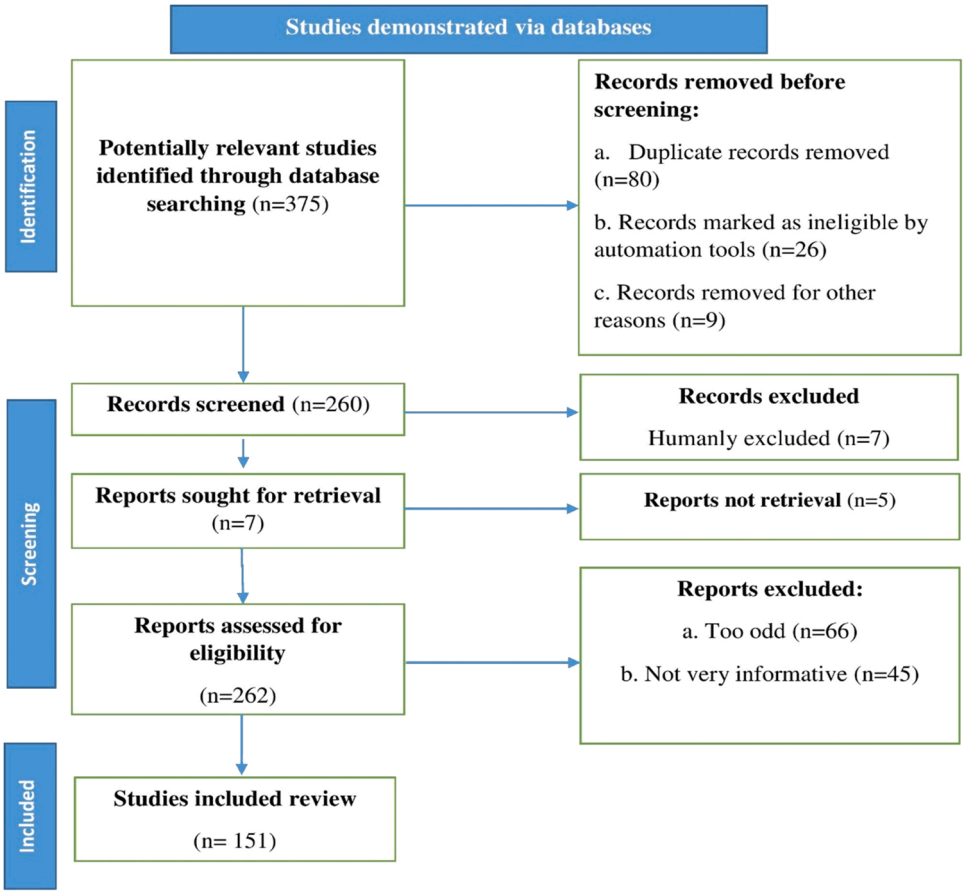

Fig. 1. Flow diagram showing the search strategy, the number of records identified and the excluded and included literature; n = number of literature.

4. Sources of narirutin

Rutaceae citrus plants, including oranges, mandarins, and grapefruits are grown worldwide. Fruit and juices from these plants contain flavonoids, including narirutin and naringin in grapefruits [27]. Narirutin has been discovered in most of the plants and fruits, such as grapefruit, sour orange, bergamot, tart cherries, tomatoes, Greek oregano, cocoa, water mint, and beans [28]. Researchers found various flavanones, flavones, and aglycones in the grapefruit juice sample. Specifically, the flavanones narirutin, naringin, hesperidin, poncirin, and neohesperidin have been discovered. Total flavonoids were found in concentrations ranging from 310 to 390 mg/L juice [29]. Citrus peels were effectively pulled out for narirutin utilizing subcritical water extraction (SWE). The highest yields was achieved using SWE at 160 °C for 10 min, with narirutin yields more than 3.7-fold greater than those obtained using hot water [13]. For better extraction of narirutin from *Aurantii fructus* and many other Citrus plants, deep eutectic solvent may be used as a green solvent. At ideal extraction conditions, the extraction efficiency of narirutin was 8.39 ± 0.61 [30]. Another research indicated that orange juice carries between 15 and 85 mg narirutin/l, and 200 and 600 mg hesperidin/l, while a single glass of orange juice may include between 40 and 140 mg flavanone glycosides [31]. The sources of narirutin are shown in Table 1.

5. Biosynthesis of narirutin

The body produces flavanones in response to various stressors. Naringin, hesperidin, narirutin, quercetin, didymin, poncirin, and neohesperidin are some of the flavanones found in Citrus. The phenylpropanoid route, which also produces tannins, lignins, flavonoids, stilbenes, and coumarins, is used to make flavonoids. The common precursor, phenylalanine, is the preliminary stage in the phenylpropanoid pathway. Phenylalanine ammonia-lyase (PAL), the first enzyme in the biosynthetic pathways, converts phenylalanine to cinnamate. To begin with, 4-coumaroyl-CoA (four-coumaroyl-CoA) is turned into narin chalcone, which is further converted into flavanone by chalcone isomerase (ChI), the initial enzyme in flavonoid biosynthesis (CHI). All flavanone aglycones begin with naringenin, which is then converted to naringenin 7-O-glucoside by 7-O-glucosyltransferase. 1,2-rhamnosyltransferase (2RT) converts naringenin-7-Oglucoside to naringin, whereas 1,6-rhamnosyltransferase (6RT) converts naringenin-7-Oglucoside to narirutin [50]. The biosynthesis of narirutin is shown in Fig. 2.

6. Pharmacological activities

6.1. Anticancer effect

Cancer is a severe physiological complication characterized by abnormal cell proliferation with the ability to infiltrate or spread to other regions of the body. Unlike malignant tumors, benign tumors do not spread [51]. Carcinogenesis is a multistage process caused by genetic modifications that activate many signaling pathways and result in the gradual transformation of a healthy cell into a cancer cell. Polyphenolic compounds, owing to their capacity to influence the activity of many targets implicated in carcinogenesis, are used to inhibit the proliferation of cancer cells. Polyphenols used for anticancer medicines have the ability to affect several signaling transduction pathways associated with cancer [52]. There are many forms of cancer in the human body, including breast cancers, prostate cancers, leukemia, melanoma, and lymphoma as well as bladder cancers, thyroid cancers, and pancreatic cancers [53]. The possible cancer treatment options are chemotherapy, surgery, radiation therapy, hormone therapy, etc. However, a patient's prognosis is significantly influenced by short- and long-term adverse effects associated with treatment. Novel therapeutics produced from natural products, including plant-derived bioactive chemicals, has been the subject of an increasing number of researches in recent years. Narirutin has been demonstrated to inhibit several malignancies through several methods, including malignant cell growth inhibition, apoptosis induction, and cell cycle arrest, and control of oxidative stress (OS), inflammation, and angiogenesis via the regulation of multiple cellular signaling cascades [54]. Grapefruits and oranges contain naringin (NG) and its aglycone naringenin (NGE). Numerous cell signal cascades have been implicated in their anti-carcinogenic effects. Combination treatment including NG and NGE with existing anti-cancer medicines has recently shown tremendous synergistic benefits as compared to monotherapy, as shown by recent studies. It has also been observed that NG and NGE can overcome the primary impediment to clinical therapy, multidrug resistance, which is caused by many cancer defensive mechanisms [54]. Narirutin demonstrated the most powerful prevention of cell damage by blocking the apoptosis route via the JNK-p53-caspase pathway. Thus, citrus fruits offer a great natural source of biologically active phytochemicals with health advantages for prospective use in functional meals. Narirutin suppressed significant NO generation in LPS-stimulated monocytes (IC_{50} =65 μM) and was the best inhibitor [27]. MicroRNAs (miRNAs) play a role in cancer progression by degrading messenger RNA's 3′untranslated region (3′UTR) in a

Table 1
Sources of narirutin and region of abundance.

Family	Genus	Species	Plant part used	Region of abundance	References
Rutaceae	*Citrus*	*Citrus sinensis* (Sweet orange)	Fruit, peel	Asia, the Mediterranean, Africa, and both South and North America	[32]
Rutaceae	*Citrus*	*Citrus limon* (Lemon)	Fruit, peel	Asia, primarily Northeast India (Assam), Northern Myanmar or China	[32,33]
Rutaceae	*Citrus*	*Citrus aurantifolia* (Lime)	Fruit, leaf, peel	South eastern Asia	[32,34]
Rutaceae	*Citrus*	*Citrus reticulate* (Mandarin)	Fruit, leaf, peel	Mainly in Asia but also in Brazil, Portugal, Spain, Italy, Greece, Morocco, Turkey and Egypt	[32,35]
Rutaceae	*Citrus*	*Citrus unshiu* (Satsuma Mandarin)	Fruit, peel	China, Japan	[36,37]
Rutaceae	*Citrus*	*Citrus paradise* (Grape fruit)	Fruit, peel	USA, Barbados, Cuba, Mexico, Argentina, Brazil, South Africa and India	[32,38]
Rutaceae	*Citrus*	*Citrus hassaku*	Fruit	Japan	[39,40]
Rutaceae	*Fortunella*	*Fortunella margarita*	Fruit, peel	China, Japan, and Philippines	[41,42]
Zingiberaceae	*Boesenbergia*	*Boesenbergia pulchella*	Root, rhizome	Southeast Asia, India, Sri Lanka, and Southern China	[42,43]
Fabaceae	*Cyclopia*	*Cyclopia subternata (honeybush)*	Leaves, Flowering top	South Africa	[44]
Rutaceae	*Eremocitrus*	*Eremocitrus glauca*	Fruit	Australia	[45,46]
Rutaceae	*Citrus*	*Aurantii Fructus* (unripe fruit of *Citrus aurantium* Linn)	Fruit juice, pulp, peel	Southeast Asia	[30,46]
Daisy family	*Cynara*	*Cynara cardunculus* (Cardoon)	Leaves, Flower bud	Western part of the Mediterranean basin, California and Australia	[47,48]
Lamiaceae	*Menthae*	*Peppermint Menthae × piperitae folium*	Leaves, Flower	China, The United States, Northern Africa and the Mediterranean	[49]

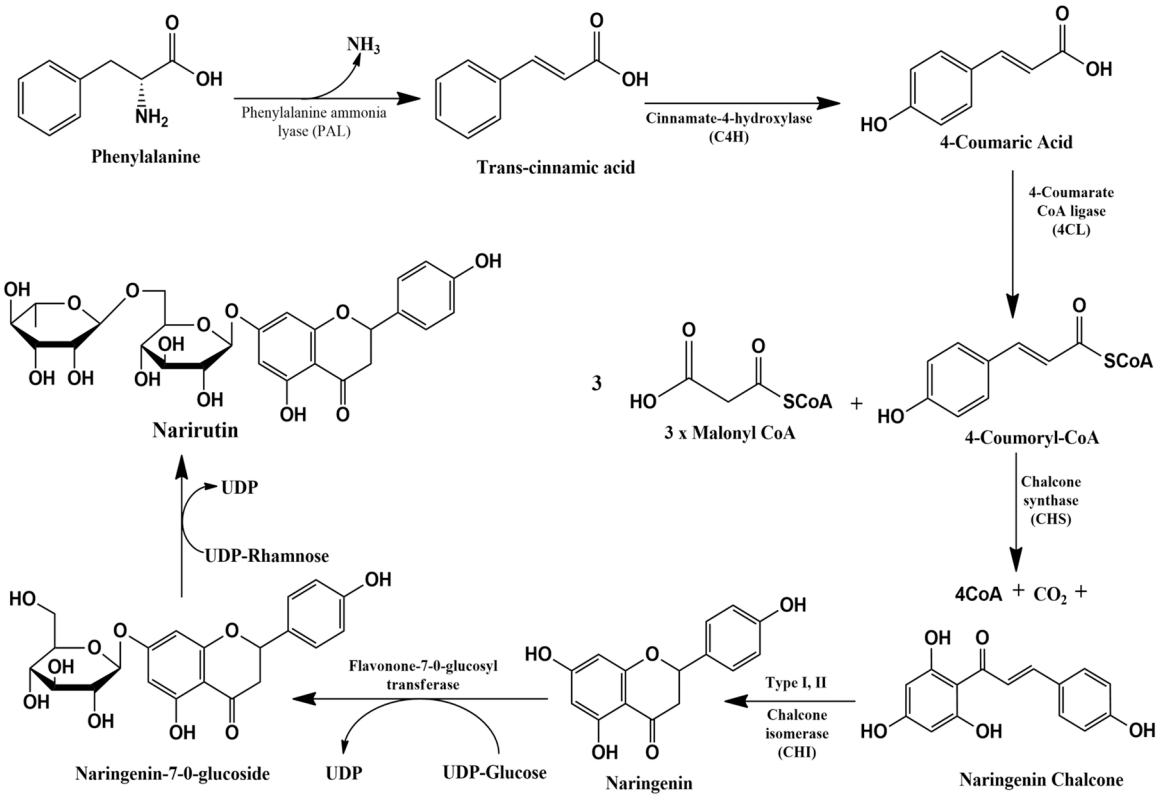

Fig. 2. Step wise biosynthesis of narirutin.

sequence specific manner (mRNA). Narirutin binds to pre-miRNA and disrupts the priRNA structure, resulting in a lack of DICER pre-miRNA connections by inhibiting pre-miRNA production and so altering miRNA processing. Further pharmacokinetics and toxicity prediction demonstrated that it is noncarcinogenic, nonmutagenic, and does not block CYPs activity. Thus, narirutin acts as an antagonist of carcinogenic miRNAs and thus useful for miRNA targeted cancer prevention and treatment [55]. At 50–500 g/mL doses, water extracts of sweet orange peel suppressed the tert-butyl hydroperoxide–induced cytotoxicity of HepG2 cells and inhibited TBARS formation, raised mitochondrial membrane potential and the Bcl-2:Bax ratio, and lowered caspase-3 [56].

6.1.1. *Lung cancer*

Lung cancer develops when abnormal cells proliferate out of control in the lungs. They have the capacity to infiltrate and cause cancer in surrounding tissues. Narirutin and other flavonoids are quite efficient against various cancers and tumors [57]. In an Ovalbumin (OVA)--sensitized NC/Nga mouse model, narirutin at 0.1, 1, or 10 mg/kg prevents lung cancer. In a mouse model of allergic eosinophilic airway inflammation, it also decreased inflammation, eosinophil levels in the peripheral circulation and bronchoalveolar lavage fluid (BALF), interleukin (IL)−4 levels in BALF, and IgE levels in serum by boosting IL-4 and IgE. Therefore, narirutin has the potential to be a new useful tool in the management of bronchial asthma [6].

6.1.2. *Pancreatic cancer*

Pancreatic cancer is a disease in which healthy cells in the pancreas stop working normally and undergo uncontrolled proliferation. These cancerous cells can cluster together to form a tumor [58]. According to an in vitro research, narirutin was combined with naringenin and hesperidin in various ratios to suppress the proliferation and migration of human pancreatic cancer cells (Miapaca-2, Panc-1, Detroit551, and SNU-213 cells) through the stimulation of caspase-3 cleavage and reduced expression of the FAK and p38 signaling cascades [59]. Similarly, In pancreatic cancer cell lines AsPC-1, Miapaca-2, SNU-213, and Panc-1, narirutin was employed at a concentration of 5 mg/mL. Narirutin produced from Citrus unshiu peel extract (eCUP) reduced pro-angiogenic effects in HUVECs while maintaining a promising anticancer activity through the AK and MAPK signal transduction pathways [60]. If fCUP (fermented extract of Citrus unshiu peel) can be developed into a safe and effective anticancer medication for pancreatic cancer, this can be a suitable option. Experiments were conducted on pancreatic cancer cells using 2.5–5 mg/mL fCUP. Caspase-3 cleavage in human pancreatic cancer cells was induced by narirutin, which is the primary ingredient in this study. Intracellular signaling cascades including MKK3/6 and P38 inhibit the migration of human pancreatic cancer cells [61]. Inhibition of Glycogen Synthase Kinase-3 (GSK-3) leads to a reduction in pancreatic cancer cell growth and survival. Additionally, citrus flavonoids' narirutin inhibits GSK-3 activity directly by binding to the enzyme's active site, suggesting that it has the ability to reduce pancreatic cancer tumor growth in pancreatic cancer cells (Panc-1 and BxPC-3) in vitro [62].

6.1.3. *Prostate cancer*

Prostate cancer is mainly caused by mutations in the DNA of the prostate cells [63]. An in vitro research found that citrus fruits containing narirutin at 1 mg/mL dose blocked the growth of prostate cancer PC-3 and LNCaP cells. Narirutin inhibited cell cycle re-entry in inactive PC-3 cells by decreasing the PI3K/AKT and ERK/MAPK signal transduction cascades and stimulating the PTEN pathway [64] In human prostate cancer (LNCaP) cells, narirutin inhibited cell growth and has differential antioxidant activity [65].

6.1.4. *Thyroid cancer*

Thyroid cancer is a pathological state in which carcinogenic cells originate in the tissues of the thyroid gland which normally generates thyroid hormone, which regulates the body's metabolism. Thyroid

cancer is classified into four main types: papillary, medullary, follicular, and anaplastic [66]. Naritutin was extracted from the juice of a Mandarin orange (MJe) Thyroid cancer was treated by inhibiting the growth of CAL-62,8505 C, and C-643 cells at concentrations of upto 0.5 mg/mL. Downregulation of the metalloproteinase MMP-2, as well as inhibiting the G2/M stage of the cell cycle, are among the mechanisms, which are associated with reduced cell mortality due to autophagic death [67].

6.1.5. Leukemia

Leukemia is a cancerous, progressive disease that causes the bone marrow to form an abnormally high number of immature leucocytes. These inhibit normal blood cell synthesis, resulting in anemia and other symptoms [68]. Experiments on leukemia protection have been carried out in many ways. Pure flavonoids extracted from *Citrus paradisi* Macfad peel demonstrated anti-leukemic activity in human myeloid leukemia cellsHL-60, Kasumi-1, and K562. Here, narirutin at different doses decreased leukemia cell growth and induced Kasumi-1 cell apoptosis by raising the levels of stimulated poly adenosine diphosphate-ribosepolymerase and caspase-3/-9, while decreasing Mcl-1 expression [69]. Additionally, studies using the human leukemia cell lines HL-60 and MCF-7 (adenocarcinoma of the breast) as well as the human chronic myelogenous leukemia cell line K562 were done. *Citrus sinensis, C. deliciosa, C. clementina, C. reticulate,* and *C. aurantium* fruit juices were shown to be antiproliferative in this study. By boosting IL-4, inhibiting ERK/MAPK, and also PI3K/AKT signaling pathways, narirutin present in the juice was able to achieve this effect [70]. Furthermore, varying concentrations of narirutin inhibited leukemia through degranulation in mice immune cell leukemia RBL-2H3 cells. The process comprises the regulation of MAPK pathway signals as well as the decrease of allergy symptoms by reducing Akt phosphorylation, which is accountable for the inhibition of cytokinesis [71].

6.1.6. Colon cancer

Colon cancer initiates in the intestinal tract (colon) as tiny, noncancerous (benign) aggregates of cells called polyps, which may grow into colon tumors over time [72]. In human colon cancer HCT116 cells and malignant human melanoma cells (A375), various concentrations (0–400 μg/mL) of hydrolyzed citrus residues comprising narirutin were applied for 24, 48, and 72 h, demonstrating anti-cancer and antiproliferative activities by free radicals, as well as retardation of aging processes [73]. A substantial number of enzymatically hydrolyzed leftovers are created as waste material during the bioethanol manufacturing process using citrus peels. In human carcinoma A375 and colon cancer HCT116 cells, this enzymatically degraded residue demonstrated antiproliferative action and sub-G1 arrest. These findings indicate that a new use for hydrolyzed citrus extracts in the functional food, cosmetic, and pharmaceutical sectors [73]. *Citrus bergamia* juice extracts (BJe) containing narirutin inhibit colorectal cancer cell proliferation in many ways. Low BJe concentrations inhibit the MAPKs pathway and change apoptosis-related proteins, causing cell cycle arrest and apoptosis in HT-29 cells. Instead, excessive quantities of BJe cause OS, leading to DNA damages [74]. Malignant human melanoma cells (A375) and colon cancer (HCT116) cells were treated for 24, 48, and 72 h with different concentrations (0–400 g/mL) of hydrolysis residues of citrus peel extract containing narirutin. In A375 cells and colon cancer (HCT116) cells, they showed a strong growth inhibitory effect. After treatment with enzymatically hydrolyzed citrus peels, the number of viable cells reduced marginally, and cell viability decreased by 18–30% at 400 g/mL [75].

6.1.7. Gastric cancer

Gastric cancer is a condition in which malignant (tumor) cells grow in the stomach lining. Most of the stomach cancers (90–95%) are adenocarcinomas which start from the mucosa cells of the stomach [76]. SGC-7901, AGS, and BGC-823 gastric cancer cell lines were treated with 35 Citrus (*Citrus reticulata* Blanco) up to 200 L. In this study, narirutin was shown to have antioxidant and cytotoxicity effects against stomach cancer. The radical scavenging activity of ferric reducing antioxidant power (FRAP), 2,2-diphenyl-1-picrylhydrazyl (DPPH), cupric reducing antioxidant capacity, and oxygen radical absorbance capacity (ORAC) were used to assess anticancer effects [77].

6.1.8. Brain tumor

Brain cancer is the formation of malignant cells in the tissues of the brain, and narirutin plays a pivotal role in its prevention [78]. *Citrus bergamia* juice (BJ) at a concentration of 2 micro-liters is effective in the treatment of brain tumors. BJ containing narirutin lowered cell adhesion strength, invasion of SK-N-SH and LAN-1 cells, and the number of pulmonary metastases in a metastatic neuroblastoma mice model. Knocking down E- and P-selectins, inhibiting intracellular signaling pathways in the metastatic process, and modulating critical molecules involved in metastasis development are all part of the approach [79]. *Citrus kawachiensis* dried peel powder contained naringin (NGIN; 44.02 0.491 mg/g), narirutin (NRTN; 4.46 0.0563 mg/g), and auraptene (AUR; 4.07 0.033 mg/g) and when this dried peel powder was orally administered at the dose of 1.2 or 2.4 g/kg/day for 7 days into lipopolysaccharide injected mice model, it suppressed activation of microglia and astrocytes in the hippocampus and expression of cyclooxygenase-2 [79]. The anticancer properties of narirutin are shown in Fig. 3.

6.1.9. Renal tumor

Renal tumor is an abnormal development of the kidneys. When it comes to kidney cancer, renal cell carcinoma (RCC) is the most prevalent diagnosis. RCC is also known as renal cell adenocarcinoma. The vast majority of kidney malignancies are renal cell carcinomas, which account for around 90% of cases. Citrus containing narirutin at a dose of 3 and 30 mg/mouse weight (kg) reduced the development of kidney tumor cells by increasing cytokines such as IFN-γ and TNF-α, promoting immune-mediated anti-tumor effects in tumor-bearing mice [80] (Table 2).

6.2. Neuroprotective effect

Neuroprotection is the capacity to inhibit neuronal cell death by interfering in and suppressing the pathogenetic cascade that leads to cell malfunction and finally death [127]. Narirutin has been shown to have neuroprotective properties in several studies [128]. In a structure-based screening model for 2-D QSARs, BACE-1, narirutin causes the protein to change conformation. Narirutin has a high Aβ aggregation inhibitory potential as well as antioxidant properties. Thus, narirutin has a neuroprotective effect since it was identified as a multi-potent hit utilizing the multi-target screening approach, inhibits BACE1, Aggregation substantially, and has modest antioxidant action. The use of a multi-target screening technique in the development of Alzheimer's disease therapies is thus established, and the discovered hit, narirutin, has high multi-potent efficacy [81]. Narirutin is used to treat cerebral ischemia by lowering oxidative damage and improving neurobehavioral abnormalities. Narirutin-rich fraction (NRF) demonstrated neuroprotective effects at dosages of 150 and 300 mg/kg via discharging nitrosative and OS through ROS and activating voltage-gated potassium channels, and also inhibiting the caspase pathway by preventing the release of cytochrome-c and glutamate [82]. Again, narirutin in *Citrus kawachiensis* dried peel powder decreased neuroinflammation-related brain disorders in LPS-injected rats at dosages of 1.2 or 2.4 g/kg/day. Loss of body weight, activation of astrocytes, and microglia in the hippocampus through cyclooxygenase (COX)-2 production are all part of the pathway [83]. A prominent issue in aging populations is dementia, which is defined by a gradual deterioration in cognitive function over time. 42 individuals in a trial that got enriched (6.0 mg/day of auraptene) test juice, while the other participants received a placebo juice and Narirutin form of auraptene. As AUR is able to cross the blood–brain barrier, it

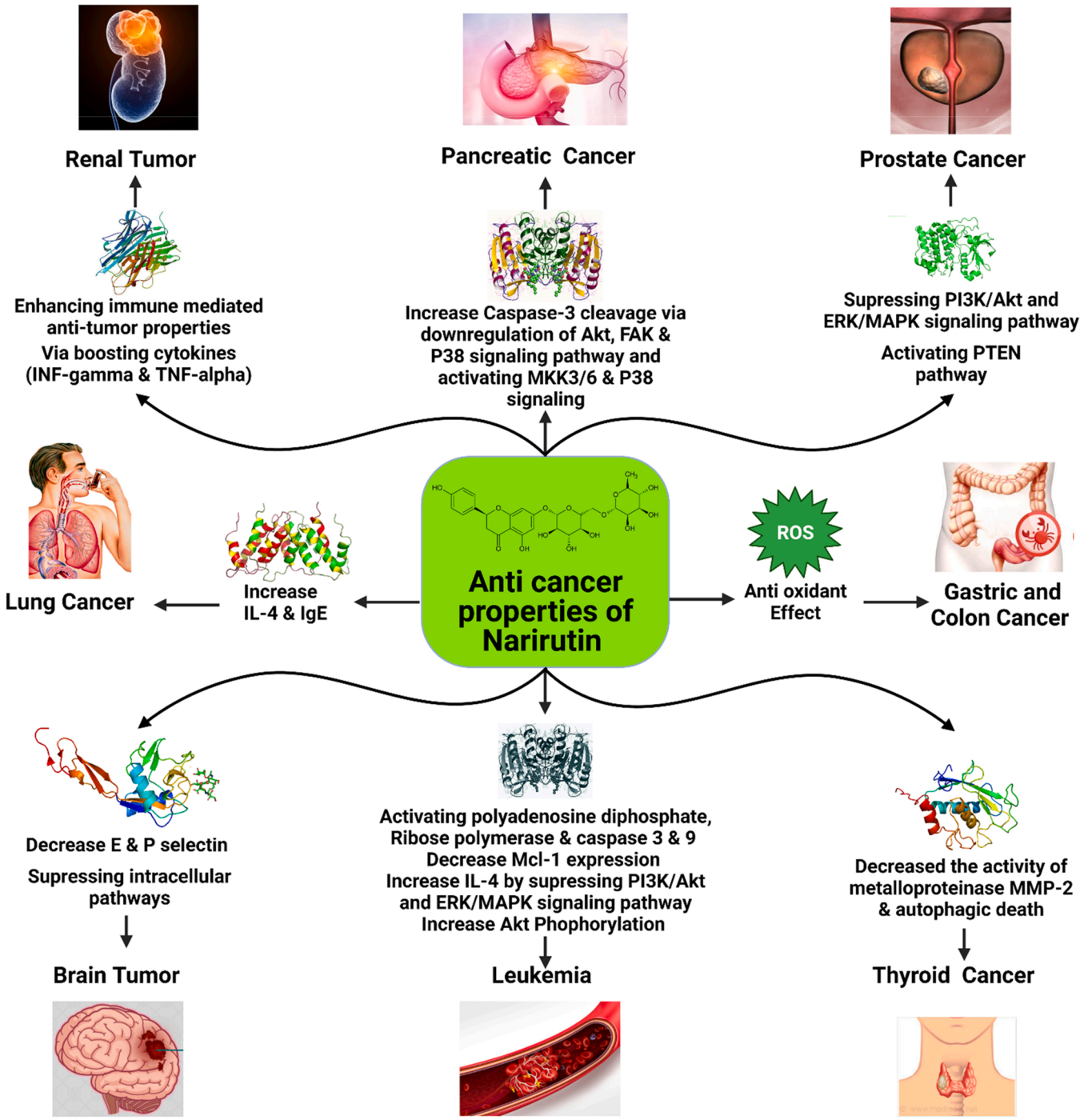

Fig. 3. Anticancer properties of narirutin.

directly affects the brain's inflammation. AUR inhibited microglial activation, COX-2 production in astrocytes, and COX-2 mRNA translation in the hippocampus, and after 60 min of intraperitoneal treatment, it was still detectable in the brain [84]. In healthy, young individuals, consuming flavanone-rich orange juice in typical proportions may dramatically increase blood flow to the brain. An acute, single-blind, randomized, cross-over design was used with two 500-mL drink conditions, on a high-flavanone (HF; 705 mg) drink (containing narirutin) and an energy-, and vitamin C-matched, zero-flavanone oversee over twenty-four healthy young adults aged 18–30 years, and the impacts of narirutin on cognitive performance and cerebral blood were proven [129].

6.3. *Anti-inflammatory effects*

Anti-inflammatory agents are substances that reduce inflammation (swelling, pain) in the body. They are used to treat various health issues by blocking particular chemicals in the body that produce inflammation [130]. Narirutin (at the concentration up to 100 μg/mL) suppressed the production of NO synthase (iNOS) and cyclooxygenase-2 in mouse macrophage cell line RAW 264.7, by inhibiting the LPS-mediated activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPKs) [36]. In another research, narirutin was shown to suppress degranulation in rat basophilic leukemia cells (RBL-2H3) at various doses (0–200 μM). The processes include lowering NF-κB signaling route transduction, inhibiting phosphorylation of MAPK signal

Table 2
Preclinical experimental findings on the use of narirutin on different pharmacological targets.

Field of Study		Subject	Dose	Results	Mechanism of Action	References
Anticancer effect	Lungs cancer	*(In vitro)* Ovalbumin (OVA)-sensitized/ challenged NC/Nga mice	0.1, 1 or 10 mg/kg	Diminish inflammation, reduced eosinophil counts in the peripheral blood and bronchoalveolar lavage fluid (BALF), interleukin (IL)−4 levels in BALF and IgE levels in serum	Increasing IL-4 and IgE in a murine model of allergic eosinophilic airway inflammation.	[6]
	Pancreatic cancer	*(In vitro)* Miapaca-2, Panc-1, SNU-213, and Detroit551 cells	Combination therapy with different ratio.	Inhibit growth and migration of human pancreatic cancer cells	Through induction of caspase-3 cleavage and via down regulation of FAK and p38 signaling pathway.	[59]
		(In vitro) AsPC-1, Miapaca-2, Panc-1, and SNU-213 pancreatic cancer cell lines.	5 mg/mL	Soothed the pro-angiogenic effect in HUVECs while retaining a strong anti-cancer effect	AK and MAPK signaling pathway is responsible for the effect of eCUP treatment inhuman pancreatic cancer *in silico* and in vitro.	[60]
	Prostate cancer	*(In vitro)* PC-3 and LNCaP cells.	1 mg/mL, citrus acid	Exhibited negligible cell cycle re-entry inhibitory effect on quiescent PC-3 cells	Inhibition of PC-3 cells from re-entering cell cycle mainly by suppressing PI3K/ AKT and ERK/MAPK signaling pathways and activating PTEN pathway.	[64]
	Pancreatic cancer	*(In vitro)* Human pancreatic cancer cells.	2.5–5 mg/mL of fCUP	Inhibited the growth of human pancreatic cancer cells, blocked the migration of human pancreatic cancer cells	Through induction of caspase-3 cleavage. Migration of human pancreatic cancer cells is blocked through activation of intracellular signaling pathways such as MKK3/6 and P38.	[61]
	Thyroid Cancer	*(In vitro)* 3 human anaplastic thyroid carcinoma (ATC) cell	Up 0.5 mg/mL concentration after 48 h	Proliferation of CAL-62, C-643, and 8505 C cells, measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, was significantly reduced	Decreasing activity of the metalloproteinase MMP-2, also blocking in the G2/M phase of the cell cycle, accompanied by low cell mortality owed to autophagic death.	[67]
	Leukemia	Human myeloid leukemia cells Kasumi-1, HL-60 and K562	Hesperidin and Narirutin found in various concentrations	Inhibited leukemia cell proliferation and triggered Kasumi-1 cell apoptosis	Increasing the levels of activated poly adenosine diphosphate-ribosepolymerase and caspase-3/-9, but reducing the levels of Mcl-1 expression in Kasumi-1 cells.	[69]
		K562 (human chronic myelogenous leukemia), HL-60 (human leukemia) and MCF-7 (human breast adenocarcinoma) cell lines	Hesperidin and Narirutin found in various concentration	Showed anti-proliferative activity	Increasing IL-4, by suppressing PI3K/ AKT and ERK/MAPK signaling pathways	[70]
		Rat basophil leukemia RBL-2H3 cells	Different concentrations of narirutin, hesperetin	Showed inhibitory activity against the degranulation	By suppression of pathway signals and reduce the symptoms of allergy by inhibiting phosphorylation of Akt, which leads to the suppression of cytokines.	[71]
	colon cancer	Malignant human melanoma cells (A375) and human colon cancer HCT116 cells	Various concentrations (0–400 μg/mL) of hydrolysis residues for 24, 48 and 72 h	Show antioxidant, anticancer activities and antiproliferative effects	By free radicals and retardation of ageing processes.	[73]
	Gastric cancer	Three gastric cancer cell lines, SGC-7901, BGC-823 and AGS	Upto 200 μL citrus extractions	Show antioxidant capacities and the cytotoxicity effects.	Significant cytotoxicity. Antioxidant effects were determined through 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, ferric reducing antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC) and cupric reducing antioxidant capacity (CUPRAC)	[77]
	Brain tumor	(*In vitro*) in a spontaneous metastatic neuroblastoma SCID mouse model	2 μL	Reduces cell adhesiveness, invasion of LAN-1 and SK-N-SH cells and the number of pulmonary metastases.	Knocking-out of E- and P-selectins, suppressing intracellular pathways involved in the metastatic process and through modulation of key molecules implicated in the processes of metastasis formation.	[79]
	Renal tumor	Tumor-bearing mice with renal carcinoma cell, Renca	Various doses of SM content and peel extracts (3 and 30 mg/mouse weight (kg)	Inhibited the growth of tumor cells	Via boosting cytokines such as IFN-γ and TNF-α, enhancing immune-mediated anti-tumor properties.	[80]
Neuroprotective effect		Structure-based screening model for BACE-1, 2-D QSARs	Not mentioned	Induces conformational transition of the protein. Narirutin possesses strong Aβ aggregation inhibitory potential & antioxidant property	Narirutin sieves out as multi-potent hit using the multi-target screening protocol. Narirutin strongly inhibits BACE1, Aβ aggregation and possesses moderate antioxidant activity.	[81]

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Table 2 (*continued*)

Field of Study	Subject	Dose	Results	Mechanism of Action	References
	Male Wistar rats (180–200 g)	NRF (150, 300 mg/kg, oral) for 7 days	In the treatment of cerebral ischemia by improving neurobehavioral alterations and reducing oxidative damage	By releasing nitrosative and OS via ROS and activation of voltage-gated potassium channels. Also inhibiting caspase pathway by inhibiting cytochrome c release and glutamate release.	[82]
	lipopolysaccharide-(LPS-) injected mice	1.2 or 2.4 g/kg/day for 7 days	For the reduction of neuroinflammation-related brain diseases.	Inducing loss of body weight, activating microglia and astrocytes in the hippocampus, inducing expression of cyclooxygenase (COX)-2	[83]
	84 adult volunteers	auraptene enriched (containing 6.0 mg/day of auraptene)	Auraptene in the Peels of Citrus Kawachiensis Contributes to the Preservation of cognitive function	AUR passes through the blood–brain barrier and directly exerts anti-inflammatory effects in the brain. It also suppressed microglial activation, COX-2 expression in astrocytes, and COX-2 mRNA expression in the hippocampus	[84]
Anti-inflammatory effects	Mouse macrophage cell line RAW 264.7	Narirutin fraction upto 100 μg/mL LPS(1 l μg/mL)	Narirutin fraction inhibited the release, by lipopolysaccharide (LPS)-stimulated macrophages, of nitric oxide (NO) and prostaglandin E_2 (PGE_2). Narirutin fraction inhibited the LPS-mediated activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinases (MAPKs)	Suppressing the expression of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2)	[36]
	Rat basophilic leukemia (RBL-2H3) cells	Different concentrations of narirutin (0–200 μM) for 20 h	Inhibit RBL-2H3 cells degranulation	Inhibiting Ca^{2+} influx by suppressing the phosphorylation of Syk, LAT and PLCγ1 signaling pathway transduction, decreasing NF-κB signaling pathway transduction, suppressing phosphorylation of MAPK signaling pathways by decreasing the expression of P-p38, P-ERK and P-JNK	[85]
	Human THP-1 cells (1×10^6 cells/mL)	narirutin (10^{-9} to 10^{-5} M) in 96-well plates for 24 and 48 h	Reduce inflammatory disease by suppressing IP-10 via epigenetic regulation	Suppress IP-10 production in M1 macrophage cells through nuclear receptors including ERs, AhRs, PPAR-α and PPAR-γ receptors at different degrees.	[86]
	The murine macrophage-like cell line, RAW 264 (RCB0535),	1 μg/mL of LPS and 50, 100, and 200 μM of narirutin for 24 h.	Narirutin exhibited following inhibitory effects: nitric oxide synthesis (IC50 = 105 μM), Interleukin-6 synthesis (IC50 = 65 μM), and inducible soluble epoxide hydrolase activity (IC50 = 267 μM)	Suppressing nuclear factor κB (NF-κB) pathway, working as an enzyme inhibitor, synthesizing NO, IL-6 and TNF-α NO and iNOS induction	[87]
	Eight-week-old male Sprague–Dawley rats	3.83 mg/mL	The protective effects against NSAID-induced small intestine disease	Narirutin Promoted autophagy through the PI3K/Akt signaling pathway. It inhibits the production of inflammatory mediators via NF-kB and MAPKs in lipopolysaccharide	[88]
	UVB irradiated hairless mice	ICP containing 22.9 μg hesperidin, 7.2 μg narirutin/100 g	Improve the damage caused by UV exposure and loss of skin hydration, increase of transepidermal water loss	By suppressing epidermal cell mortality and BM destruction. It suppressed MMP-1 production in human dermal fibroblasts, MMP-2 expression in UVB-irradiated hairless mice.	[89]
	Atopic dermatitis (AD) model mice.	Narirutin 3.2 mg/day and 10–20 mg·kg-1/day, 5% CJ powder	Safe and useful for the patients with atopic dermatitis	have anti-inflammatory potentials to inhibit productions of nitric oxide (NO) and interleukin-6 (IL-6), and to inhibit enzymatic activities of soluble epoxide hydrolase (sEH) and hyaluronidase	[90]
	Human umbilical vein endothelial cells	Different dosages of AECUP	Induced cellular migration and capillary tube formation	Via increasing the phosphorylation of FAK and ERK1/2 through the integrin signaling pathway.	[91]
Antidepressant-like effects	Sixty male ICR mice (with a 5% attrition rate), weighing 22–24 g	NR was dissolved in saline and was injected once daily for 7 continuous days within the dose range of 3–10 mg/kg	NR exerted potential antidepressant-like and anxiolytic-like effects	By neuroimmune mechanism also blocking the CMS-induced anxiety-like behaviors.	[92]
	female offspring rats	Kaempferol-3-O-glucoside (15 mg/kg bw) and narirutin (30 mg/kg bw).	Reverts depression-like behavior in rat female offspring	By enhanced anti-inflammatory effects via up-regulation AKT/β-catenin cascade activity.	[93]
					[94]

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Table 2 (*continued*)

Field of Study	Subject	Dose	Results	Mechanism of Action	References
	Depression-like model mice.	Oral administration of Koso-san (1.0 g/kg/body wt./day, 9 days	Shows the antidepressant-like effect by shortening the duration of immobility	Through suppressing the hyperactivity of the HPA (hypothalamic–pituitary–adrenal) axis.	
	SPF male Sprague–Dawley rats	Narirutin (5720 ng/mL), ZQ extract at a dose of 20 g/kg	show antidepressant effects by decreasing the immobility time	Not mentioned	[95]
	Males aged 30–65	240-mL FR orange juice,0.25 μM hesperetin and 0.12 μM naringenin in the plasma at 6 h	Reduced risk of neuropsychological disease, attenuation of aging-induced cognitive decline and maintenance of optimal cognitive facilities	Via increasing CBF, as a result of enhancing endothelial function and increasing bioavailability of nitric oxide. Also by the synthesis of proteins and enzymes in the brain such as cAMP-response element-binding protein (CREB), which affect neuronal signal transduction and increasing the expression of brain-derived neurotrophic factor (BDNF)	[96]
Hepato-protective effect	male C57BL/6 mice(*in vivo*) human LX-2 cells (*In vitro)*	TFCH at 25 mg/kg, 50 mg/kg, 200 mg/kg, respectively, for successive 8 weeks	Anti-apoptosis effect, increase the antioxidant ability and reduce the oxidative damage	Through Nuclear factor erythroid 2-related factor 2 (Nrf2)- antioxidant response elements pathway	[97]
Antioxidant effect	Human leukemia HL-60 cell line.	Different concentrations of the bioactive compounds	Show antiproliferative activity and antioxidant activity	Not mentioned	[98]
	Normal rat liver cells	Narirutin and hesperidin contents in the peel extracts were 8.8 and 7.5 mg/100 g, respectively	Show Antioxidant and anti-inflammatory properties	Preventing (H_2O_2)-induced OS, reducing expression of the inflammatory markers (NF-κB) and phosphorylated IκBα (p-IκBα) in A549 human lung carcinoma cells, and inhibiting Lipopolysaccharide (LPS)-induced THP-1 monocyte differentiation to an extent of 85%	[99]
	Rat hyperlipemia model.	0.24–1.2 mg/mL for antioxidant effect,50–200 mg/kg for antihyperlipidemic activities	TFCB with the highest flavonoid contents has the strongest antioxidant-associated activities	Because of hydrogen-donating ability of their phenolic groups. Also peroxidation ofLDL, triggering oxygen free radicals (O_2, OH, H_2O_2)	[100]
Stress reliever	Male Sprague-Dawley (SD)-rats	(500 μg/mL)	Protective effects on OS and restraint stress	Decreasing ROS levels, and vascular protection	[101]
	HepG2 cells	concentrations ranging from 2.5 to 100 μM	Provide a significant cytoprotective effect against OS.	Increasing reactive oxygen species and decreasing glutathione levels observed	[102]
	12 patients with stage I hypertension	5-week period	reduces blood pressure (BP)	Endothelial nitric oxide synthase (eNOS) gene expression was unregulated	[103]
Anti-inflammatory effects	Obesity-induced non-alcoholic fatty liver disease (NAFLD) model of rats.	Total flavonoids of QZK (TFCH) were given orally for 8 weeks. Low dose (25 mg/kg), intermediate-dose (50 mg/kg), high-dose (100 mg/kg)	exerted hepatoprotective and anti-inflammatory effects	By suppression of phosphorylated NF-κB and MAPKs, indicating a mechanism associated with NF-κB and MAPK signaling pathways.	[104]
	10 weeks old male ICR mice.	325 mg CFs/kg mouse. G-CFs and CFs-glc fed groups were fed with 714 mg G-CFs or 236 mg CFs-glc/kg 93 mouse/day.	Prevent Alcoholic liver disease (ALD) by suppressing increases in prognostic parameters of a hepatocellular injury	Through preventing excessive lipid formation, protecting the antioxidant system and suppressing induction of inflammation in hepatocytes.	[105]
	(In vivo) ICR mice	Four groups; normal diet control, ethanol control (6.5 g ethanol/kg), low-CNF (ethanol + 150 mg CNF/kg) and high-CNF (ethanol + 300 mg CNF/kg) groups	CNF suppress severe liver damage with increases in prognostic indicators such as aspartate transaminase, excessive accumulations in liver TG and TC	Through preventing lipid formation, protecting antioxidant system and suppressing productions of pro-inflammatory cytokines such as nuclear factor (NF)-κB, tumor necrosis factor (TNF)-α and interleukin (IL)−1β in liver	[106]
Antidiabetic property	*Twenty-five rats were divided into five groups(male Wistar rats)*	groups III, IV, and V were given sweet orange peel extract doses of 125, 250, and 500 mg/kg body weight (BW)	antidiabetic and antihypercholesterolemic activities of sweet orange fruit peels extract was found at doses from 125 to 500 mg/kg BW	Decreasing the activities of glucose-6-phospate and phosphoenol pyruvate, via antiperoxidation, inhibiting α-amylase enzyme activity, inhibiting HMG-CoA reductase and acetyl-coenzyme A acetyltransferase	[107]
	Male CD1 mice	8-week treatment with RLE (120 mg/kg/day^{-1}). Narirutin (60 mg/kg/day^{-1})	Reduction in glucose, cholesterol and triglycerides levels in the blood, with positive effects on regulation of hyperglycemia and lipid metabolism.	Scavenge free radicals, affecting transmembrane protein CD36, and the glucose transporters SGLT1 and GLUT2, reducing basophil degranulation, reducing triglycerides, total cholesterol, and glucose blood levels	[108]

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Table 2 (*continued*)

Field of Study	Subject	Dose	Results	Mechanism of Action	References
	In vitro	Neohesperidin (72.96–116.50 mg/ 100 mL), hesperidin (55.24–69.52 mg/ 100 mL) and narirutin (7.21–12.13 mg/ 100 mL)	Show hypoglycemic and antioxidant properties.	By inhibiting carbohydrate hydrolyzing enzymes such as α-amylase and α-glucosidase and activating c-Jun NH2-terminal kinase (JNK)	[109]
	Female C57BL/6 mice	1% w/w CIE for 8 weeks	Lower blood glucose level and improve glucose tolerance	Decreasing mRNA expression levels of peroxisome proliferator-activated receptor γ (PPARγ) and its target genes, decreasing expression of liver X receptor (LXR) α and β which are involved in lipid and glucose metabolism	[110]
	Hyperlipemia rats	Oral administration of TFCB started from 50 m to 200 mg/kg	Shows antioxidant and antihyperlipidemic activities. TFCB at 0.24–1.2 mg/mL possessed the most significant antioxidant effects	Not mentioned	[100]
Anti-adipogenic effects	3T3-L1 preadipocytes cells	0.5 mg/mL	Adipocyte differentiation was inhibited in CU-C group	By modulation of adipocyte differentiation and lipid metabolism.CU-C markedly suppressed the protein expression of CCAAT/enhancer-binding protein α (C/EBPα) and peroxisome proliferator-activated receptor gamma (PPARγ) as well as the mRNA levels of CEBPα, PPARγ, and sterol regulatory element binding protein 1c (SREBP1c)	[111]
	3T3-L1 cells	Hesperidin (2,13% w/ w), narirutin (0.07% w/ w), 2.5, 5, 10, 25 μM of anthocyanins	Antioxidant and anti-adipogenic activities during adipocyte differentiation of 3T3-L1 pre-adipocytes	Influences the adiposity by inhibiting 3T3-L1 differentiation, by down-regulating both adipogenic gene and enzymes and adiponectin secretion and by increasing leptin release. (ROS are involved in adipocyte differentiation)	[112]
	3T3-L1 murine pre-adipocytes	Narirutin and hesperidin (4.52 67 and 3.61 g/ 100 g, respectively)	Regulation of adipocyte differentiation and lipid accumulation	Inhibiting DPPH radical and reactive oxygen species, demonstrating a strong radical scavenger activity.	[113]
	3T3-L1 Cells	100 μg/mL	Ameliorate Adipocyte Differentiation of 3T3-L1 Cells Exposed to TNFα	By Down-Regulating miR-155 Expression and increasing both C/Ebpβ and Creb mRNA and protein levels.	[114]
Anti-obesity effect	C57BL/6 mice	(300 mg/kg, CP) treated orally for 12 weeks.	CP treatment reduced body weight gain, decreased epididymal fat, mesenteric fat, plasma and hepatic TG levels.	Up-regulation of specific lipolysis enzymes such as HSL and AMPK and down-regulation of adipogenesis related genes such as C/EBPα and ACC.CP also decreases proinflammatory cytokines, TNF-α and IL-6, which are the key factors for regulation of inflammation.	[115]
	3T3-L1 cells	Various concentration	Inhibited lipid accumulation and ROS production during adipocyte differentiation.	Via the regulation of lipid metabolism-associated factors and ROS-generating enzymes. CU suppressed three adipogenic transcription factors, including PPARg, C/ EBPa, and Sterol regulatory element-binding protein-1c (SREBP-1c) in adipocyte differentiation.	[116]
	zebrafish	OJe (5 mL/L in fish water)	Decreased both BW and BMI values and lowered the visceral adipose tissue.	Lipolyticaction via modulating some obesity-related genes, such as leptin A, ghrelin, orexin, pro-opiomelanocortin (POMC), and neuropeptide Y (NPY), in both gut and brain	[117]
	3T3-L1 adipocytes	different amount of Jeju HallabongTangor Peel Extracts	Show anti-obesity effects through inhibition of adipocyte differentiation or induction of adipolytic activity	Reducing insulin-induced mRNA levels of CCAAT/enhancer-binding protein and sterol regulatory element-binding protein 1c (SREBP1c)	[118]
Immunomodulatory effect	11 fish and five food-related pathogenic bacteria	Total flavonoid contents in the methanol extracts from the CPCs were 477.4 mg/100 g, 463 mg/100 g, and 624 mg/100 g	Strong antibacterial activity against pathogenic bacteria	Binding to the surface of bacterial cells, preventing target points, and changing biochemical processes in the bacterial cells. It leads to uncoupling of oxidative phosphorylation, restraints from on active transport, reductions in metabolites and disruption of nucleic acid, protein, lipid, and polysaccharide synthesis	[119]
	36 laying hens	(0.2% ECL+ 0.4% OP) or (0.2% ECL+ 0.2% OP) showed the best result	Increase egg production, egg quality and improve immune response	Inhibiting many bacterial strains, destroying some pathogenic protozoa and scavenging free radicals	[120]

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Table 2 (*continued*)

Field of Study	Subject	Dose	Results	Mechanism of Action	References
	Twelve rabbits	(1.0 μg/mL)	Showed bacteriostatic activity, increase cellular immune response and phagocytosis	Inducing macrophages for phagocytosis; performing as secretory cells, producing nitric oxide, producing lysosome enzymes and cytokines	[121]
	Male Wistar rats (180–230 gms)	100 mg/kg and 200 mg (/kg, *p.o.*)for 3-days	NRF is very much effective against isoproterenol induced myocardial infarction in rats.	Treatments with NRF have reduced the levels of plasma CK-MB, LDH, AST and ALT and have also reduced the levels of antioxidant enzymes like SOD and CAT	[122]
	Virtual screening of phytochemical database NPACT. Narirutin was selected for in vitro anti-tubercular study.	not mentioned	Show anti-tuberculosis potency. The phytochemical is tested for its antitubercular activity in vitro. It has MIC99 62.5 μg/mL against the MtbH37Rv strain	Via Shikimate pathway	[123]
	Male Wistar rats (180–230 gms)	(100 mg/kg and 200 mg/kg, *p.o.*)for 3-days	Preventing cardiotoxicity	Treatments with NRF have reduced the levels of plasma CK-MB, LDH, AST and ALT and have also reduced the levels of antioxidant enzymes like SOD and CAT	[122]
	Eight-week-old male Sprague–Dawley rats	3.83 mg/mL	The protective effects against NSAID-induced small intestine disease	Narirutin Promoted autophagy through the PI3K/Akt signaling pathway. It alsoinhibits the production of inflammatory mediators via NF-kB and MAPKs in lipopolysaccharide	[88]
Anti-allergic activity	Rodent with allergic asthma,	Different concentration of flavonoids	Reduce airway hyper responsiveness	Lowering inflammatory mediators such as histamine and cytokines, and cell infiltration. Preventing (IgE) synthesis and mast cell degranulation	[124]
	patients with allergic asthma or rhinitis	Different concentration of flavonoids	Show anti-allergic activities	Lowering expression of IgE receptor, modulation of calcium influx, and the downregulation of particular signaling pathways that eventually produces lower primary and secondary mediator release	[124]
	Mouse and guinea pig models	Different concentration of UMEP	Show anti-allergic activity	Reversing the peripheral blood flow, suppressing late phase of nasal airway resistance, inhibiting compound 48/80-induced scratching behavior	[125]
	RBL-2H3 cells and in mice	HXZQ-OL (263.8, 527.6 and 1055 mg/kg/d) or dexamethasone (5 mg/kg/d, positive control) for 7 days	Show anti-allergic actions	Inhibiting degranulation of mast cells (IC_{50}, 123 μg/mL)	[126]

transduction pathways by decreasing the expression of P-ERK, P-p38, and P-JNK, and inhibiting Ca^{2+} influx by reducing the phosphorylation of LAT, Syk, and PLC1 signaling pathways [85]. Narirutin (10^{-9}–10^{-5} μM) for 24–48 h in human THP-1 cells (1 106 cells/mL) decreased inflammation by lowering IP-10 through epigenetic regulation. A variety of nuclear receptors, including AhRs, ERs, PPAR-alpha, and PPAR-gamma receptors, are involved in suppressing IP-10 synthesis in M1 macrophage cells [86]. Another in vitro investigation used a murine macrophage-like cell line with 1 μg/mL of LPS and 50, 100, and 200 μM of narirutin over 24 h. NF-κB pathway, acting as an enzyme inhibitor, and generating NO, IL-6, and TNF-α dependent NO and iNOS production, demonstrate an anti-inflammatory effect [87]. Plenty of experimental research has shown the anti-inflammatory properties of narirutin, including one in which pure total flavonoids from citrus (PTFC) at a concentration of 3.83 mg/mL exhibited protective role against NSAID-induced small intestinal illness in male Sprague–Dawley rats. The anti-inflammatory action of narirutin is mediated through the PI3K/Akt signal transduction pathway, which is activated by narirutin. It also suppresses the NF-kB and MAPK-dependent synthesis of inflammatory mediators in lipopolysaccharide (LPS) [88]. A narirutin-rich extract of immature *Citrus unshiu*, which enhanced the effects of UV exposure on hairless mice's skin hydration and transepidermal water loss, was also found. BM destruction and epidermal cell death are both inhibited as a result of this approach. In human dermal fibroblasts, it reduced the synthesis of MMP-1 [89]. The anti-inflammatory properties of narirutin are shown in Fig. 4.

6.4. Antidepressant effects

Depression is a very debilitating and sometimes fatal mental conditions characterized by dysregulation of the peripheral and central immune systems. One of the active compounds extracted from this plant is narirutin, which possesses antioxidant and anti-inflammatory properties and can be a powerful antidepressant for living beings [92]. Immune system malfunction is often shown to be associated with depressive disorders, making them very severe; even life-threatening. Narirutin extracted from Citrus has anti-inflammatory and anti-depressant properties [92]. In 60 adult ICR mice (with a 5% attrition rate) weighing 22–24 g, narirutin was dissolved in saline and administered orally once daily for seven consecutive days at a dosage of 3–10 mg/kg. The neuroimmune mechanism of narirutin exhibited potential antidepressant and anxiolytic effects and blocked the anxiety-like behaviors caused by CMS [64]. Narirutin's antidepressant-like behavioral, neurochemical, and neuroendocrine effects in mice is mediated via interactions with neuroendocrine and neurochemical systems [131]. The anti-inflammatory effects of narirutin (30 mg/kg bw) and kaempferol-3-O-glucoside (15 mg/kg bw) on female offspring rats through an increase in AKT/β-catenin cascade activity also reverse depression-like behavior [93]. After 9 days of oral treatment of Koso-San (1.0 g per kilogram of body weight per day) on depression-like rats, the antidepressant effect is shown by reducing their immobility period. The HPA (hypothalamic–pituitary–adrenal) axis is suppressed by narirutin, which is the primary ingredient responsible for this action [66]. Also, narirutin (5720 ng/mL) and ZQ extract at a dosage of 20 g/kg demonstrated antidepressant effects by reducing the immobility period in SPF

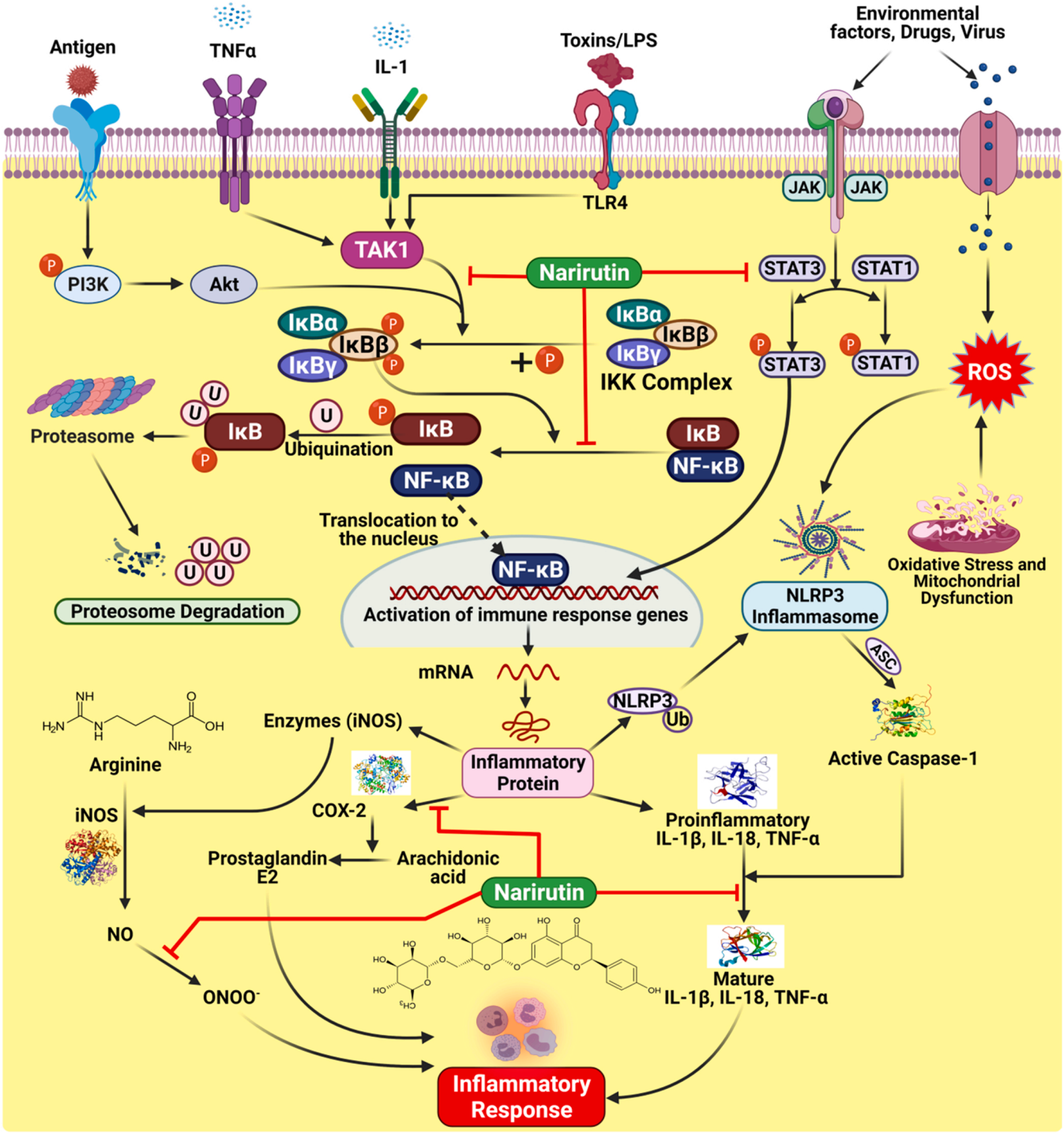

Fig. 4. Anti-inflammatory properties of narirutin.

adult Sprague–Dawley rats [95].

6.5. Antioxidant effect

Antioxidants inhibit cell damage caused by free radicals, the unstable molecules produced in the body in response to environmental and other stresses [132]. ABTS radical dot+ and DPPH radical dot radical scavenging tests were used to determine the antioxidant property of sour orange juice containing narirutin [24]. Narirutin, a flavanone subclass, serves as an antioxidant, free-radical scavenger, and antiapoptotic agent, as well as protecting plasma vitamin E levels, lowering total cholesterol levels, improving lipid metabolism, and lowering OS [93]. Anti-apoptosis, antioxidant, and oxidative damage reduction effects of total flavonoids (including narirutin) from *Citrus paradisi* fruit extracts at 25, 50, and 200 mg/kg for 8 weeks were observed in males C57BL/6 mice (in vivo) and human LX-2 cells (in vitro). This hepatoprotective activity of narirutin is due to the Nrf2-antioxidant response elements pathway [70]. It has been shown that the orange peel extracts containing narirutin may inhibit the proliferation of human leukemia cells [98]. Furthermore, the citrus peel extracts included narirutin (8.8 mg/100 g) that had antioxidative and anti-inflammatory properties in normal rat liver cells. An 85% reduction in the formation of THP-1

monocytes after exposure to LPS was observed as a result of the mechanism, which includes the prevention of OS, decrease of the activation of proinflammatory markers NF-κB and p-κIB, and inhibition of lipopolysaccharide (LPS)-induced THP-1 differentiation [99]. In another research, the total flavonoid content with the greatest level of naringin demonstrated the most antioxidant-associated activities in a rat hyperlipidemic model (0.24–1.2 mg/mL for antioxidant impact, 50–200 mg/kg for antihyperlipidemic activities.). Hua Ju Hong (peels of *Citrus grandis* (L.) Osbeck), a traditional Chinese medicine, is high in naringin and has antioxidative properties due to the hydrogen-donating capacity of its phenolic groups. In addition, peroxidation of Lipoprotein and the generation of oxygen radicals (O, OH, H_2O_2) play a role in the process [100].

6.6. Stress relieve

One way to manage inflammation is to reduce OS [133]. Chronic stress elevates inflammation; therefore, upraises cortisol levels in the blood. Cortisol's ability to control the inflammatory and immunological responses is impaired due to these changes [134]. Many researches have shown that naringin has stress-relieving properties. Citrus-based mixed drinks (CBMDs) comprising naringin at 500 μg/mL dose demonstrated protective effects on OS and restricted it by reducing ROS levels, as well as vascular defense [76]. In HepG2 cells, naringin at doses ranging from 2.5 to 100 μM offered considerable cytoprotection against OS by raising reactive oxygen species and lowering glutathione levels [102]. Additionally, naringin from sweetie fruit juice (a cross between grapefruit and pummelo) reduced blood pressure in 12 individuals with stage I hypertension during a 5-week period. Endothelial nitric oxide synthase (eNOS) gene expression level is upregulated as part of the process [103].

6.7. Hepato-protective effect

Hepatoprotection is the ability to protect the liver by a chemical substance via restoring the function of catalase, glutathione peroxidase, and superoxide dismutase to normal levels [135]. The peel of *Citrus changshan-huyou* containing naringin demonstrated hepatoprotective and anti-inflammatory activities in a rat model of obesity-induced non-alcoholic fatty liver disease. For 8 weeks, total flavonoids from QZK (TFCH) were administered orally in three doses: low (25 mg/kg), intermediate (50 mg/kg), and high (100 mg/kg). The mechanism involves the inhibition of phosphorylated MAPKs and NF-κB, which are linked to corresponding signaling pathways [104]. In another research, 10 weeks old male ICR mice were given citrus flavonoids (CFs) and EM-CFs (325 mg CFs/kg animal) that had been enzymatically changed. The G-CFs and CFs-glc groups were given 714 mg G-CFs and 236 mg CFs-glc/kg, respectively. The compound CFs, which included 60% hesperidin and 40% naringin, protected alcoholic liver disease (ALD) by reducing elevations in hepatocellular damage prognostic indicators. Excess lipid synthesis is prevented, the antioxidant system is protected, and inflammation in hepatocytes is suppressed [105]. Moreover, Citrus plants containing 75% naringin were given into four groups; normal diet control, ethanol control (6.5 g ethanol/kg), low-CNF (ethanol + 150 mg CNF/kg), and high-CNF (ethanol + 300 mg CNF/kg) groups of ICR mice. Naringin extracted from Citrus reduces severe liver damage by increasing prognostic markers including aspartate transaminase and excessive TG and TC buildup in the liver. In the liver, naringin inhibits the production of pro-inflammatory cytokines such as NF-κB, tumor necrosis factor (TNF)-α, and interleukin (IL)−1 by preventing lipid formation, protecting the antioxidant system, and suppressing the production of nuclear NF-κB, TNF-α, and interleukin-1β [106]. *Citrus sunki* extract, which is a good source of naringin reduced body weight gain, adipose tissue weight, serum total cholesterol, and TG, as well as serum concentrations of aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) in high-fat diet–fed mice and prevented liver steatosis at a dose of 150 mg/kg/d [136,137]. *Citrus unshiu* extract also reduced hepatic steatosis and hypertriglyceridemia in the liver by inhibiting gene expression and increasing the activation of lipogenic enzymes and FA β-oxidation. The favorable effects of *Citrus unshiu* could be attributed to higher levels of anti-inflammatory adiponectin and IL-10, as well as lower levels of pro-inflammatory markers [IL-6, monocyte chemotactic protein 1 (MCP-1), IFN-gamma, and TNF-alpha] in the plasma or liver [138].

6.8. Antidiabetic effect

Naringin slows down the digestion of carbohydrates and reduces glucose absorption in the small intestine, which helps people with diabetes regulate their blood glucose levels. It also inhibit some enzymes to impede digestion [139]. I*n vitro* studies revealed that one of the most efficient strategies of naringin for treating diabetes is to block the digestive enzymes that hydrolyze polysaccharides into small absorbable fragments [140]. The anti-diabetic activity of naringin was shown in a research in which 25 Wistar rats were separated into five groups, with groups III, IV, and V receiving dosages of 125, 250, and 500 mg/kg body weight of sweet orange peel extract. In this study, naringin in citrus fruit peels showed antidiabetic and antihypercholesterolemic actions by antiperoxidative, inhibiting α-amylase enzyme activity, suppressing HMG-CoA reductase, and inhibiting acetyl-coenzyme A acetyltransferase [107]. Researchers showed that naringin (60 mg/kg/day) from red orange extracts (120 mg/kg/day) reduced glucose, cholesterol, and triglyceride levels in the blood in male CD1 mice. According to the findings of the study, naringin demonstrated a notable effect on regulating hyperglycemia and lipid metabolism [108]. The juice of *Citrus clementina* Hort. contains naringin (7.21–12.13 mg/100 mL), which inhibits carbohydrate hydrolyzing enzymes like -amylase and beta-glucosidase while activating c-reactive protein (c-reactive protein). -Jun NH2-terminal kinase [109]. Mandarin fruit extracts (1–3% of the diet) enhanced liver metabolic function and restored antioxidant enzymes in streptozotocin-induced diabetic mice [141]. Another study indicated that taking 1% w/w *Citrus ichangensis* peel extract (CIE) for 8 weeks reduced blood glucose levels and improved glycemic control in female C57BL/6 mice. It is due to naringin, which reduces mRNA expression levels of the peroxisome proliferator-activated receptor (PPAR) and its target genes, as well as the activation of the liver X receptor (LXR), which is important in lipid and glucose metabolism [110]. Additionally, oral treatment of Total Flavonoid Content (TFCB) including naringin ranging from 50 m to 200 mg/kg demonstrated antioxidant and antihyperlipidemic effects in hyperlipemic rats. TFCB had the most significant effects at concentrations ranging from 0.24 to 1.2 mg/mL [100].

6.9. Anti-adipogenic effects

Adipogenesis is characterized as the process by which preadipocytes develop into adipocytes, with processes including the limited expression of the early adipogenic transcription factor, CCAAT element binding protein (C/EBP) alpha, which regulates adipogenesis [113]. *Citrus unshiu* (CU*)* combined with cytolase (CU-C) has anti-adipogenic effect in 3T3-L1 preadipocytes cells at 0.5 mg/mL. Naringin decreased adipocyte differentiation in the CU-C group. It affects adipocyte differentiation and lipid metabolism. CU-C significantly reduced CCAAT/enhancer-binding protein (C/EBP) and peroxisome proliferator-activated receptor gamma (PPAR) protein expression, as well as mRNA levels of CEBP, PPAR, and sterol regulatory element binding protein 1c (SREBP1c) [142]. Lemon extract naringin and hesperidin (4.52 67 and 3.61 g/100 g, respectively) conferred a major role to control adipocyte development and lipid accumulation in 3T3-L1 mouse pre-adipocytes. Their anti-adipogenic properties include suppressing DPPH radicals and reactive oxygen species, as well as displaying high radical scavenger activity [113]. In another study, the researchers discovered that *Citrus aurantium* L. dry extracts at 100 μg/mL concentration improve adipocyte

proliferation of 3T3-L1 Cells Exposed to TNF-α by downregulating miR-155 expression and boosting both C/Ebpβ and Creb mRNA and protein levels [114]. Citrus fruit extract at 1.4 g/d promoted human adipocyte lipolysis, most likely through inhibiting cAMP-phosphodiesterase (cAMP-PDE) or by increasing phosphorylation of cAMP-dependent protein kinase A (PKA) and hormone-sensitive lipase (HSL) in mature 3T3-L1 adipocytes. The lipid-lowering effect of *Citrus sunki* extracts in the diet is mediated by an increase in the phosphorylation levels of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC), both of which are involved in FA β-oxidation [136].

6.10. Anti-obesity effect

Anti-obesity agents are those that aid people in weight loss or maintenance. These drugs affect one of the most basic functions in the body, weight maintenance, by influencing either appetite or calorie absorption. Increased energy expenditure and inhibition of digestive enzymes are also among the factors [143]. Many researches have shown that narirutin has anti-obesity properties. For example, ethanol extracts of citrus peel (300 mg/kg) for 12 weeks lowered body weight increase, mesenteric fat, epididymal fat, and hepatic TG levels in C57BL/6 mice. Upregulation of certain lipolysis enzymes such as HSL and AMPK, as well as downregulation of adipogenesis related genes such as C/EBPα and ACC, are among the processes [115]. Again, *Citrus unshiu* peel extracts with cytolase (CU-C) containing narirutin at different concentrations inhibited lipogenesis and ROS generation during adipogenesis in 3T3-L1 cells by downregulating the lipid metabolism-associated factors and ROS-generating enzymes [116]. Furthermore, flavonoid-rich extracts of *Citrus sinensis* juice at (5 mL/L in fish water) reduced BW and BMI values as well as visceral adipose tissue in zebrafish. Thus, narirutin exhibit anti-obesity and lipolytic activity in both intestine and brain by altering obesity-related genes such as leptin A, orexin, ghrelin, pro-opiomelanocortin (POMC), and neuropeptide Y (NPY) [117]. *Citrus kiyomiponkan* (Jeju Hallabong Tangor) has many physiological properties such as antioxidant, anti-inflammatory, anti-cancer, and anti-obesity effects. In 3T3-L1 adipocytes, it has been shown that Jeju Hallabong Tangor (*Citrus kiyomiponkan*) peel extracts containing

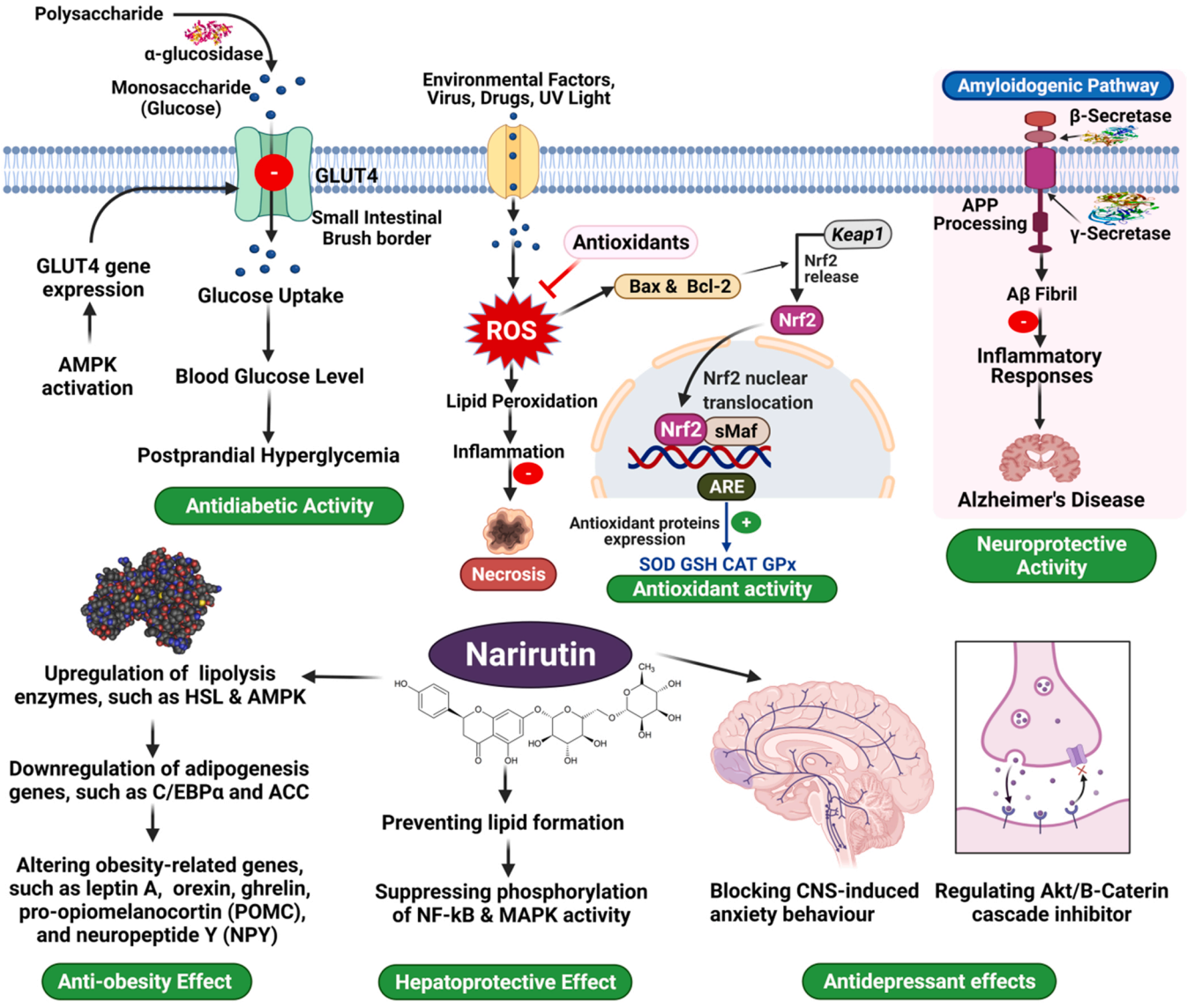

Fig. 5. Pharmacological effects of narirutin. Antidiabetic effect: Narirutin inhibits the glucose uptake; Antioxidant effect: Narirutin increase the expression of antioxidant enzyme; Neuroprotective effect: Narirutin inhibits the amyloidogenic pathway; Anti-obesity effect: Upregulation of lipolysis enzyme and downregulation of adipogenesis; Hepatoprotective effect: suppression of phosphorylation of NF-kB and MAPKs activity; Antidepressant effect: by blocking CNS induced anxiety behavior. Red circle indicates inhibition and Green circle indicates activation.

narirutin impede adipocyte development or induce adipolytic activity. CCAAT/enhancer-binding protein and sterol regulatory element-binding protein 1c (SREBP1c) mRNA levels are reduced in response to insulin [118]. The pharmacological effects of narirutin are shown in Fig. 5.

6.11. Immunomodulatory effect

The bioactive polyphenols narirutin found in citrus fruit juices have intriguing functions in reducing OS and inflammation, as well as boosting intrinsic and adaptive immune responses. Citrus fruit juices are remarkably high in flavonoids (Narirutin), which plays a pivotal role in the proper functioning of immunological barriers and promoting the activity of phagocytes, natural killer cells, T-cells, and B-cells, among other immune cells [133]. These substances promote and increase the body's defenses over OS and assist the organism in the management of cardiovascular illnesses, atherosclerosis, and cancer. Other features include the ability to reduce inflammation as well as the ability to fight against viruses and microorganisms [144]. Total flavonoid concentrations in methanol extracts of Citrus press-cakes (CPCs) were determined to be 477.4 mg/100 g, 463 mg/100 g, and 624 mg/100 g in groups of 11 fish and five food-related pathogenic microorganisms. Strong antibacterial efficacy against harmful bacteria is accomplished by attaching to the surface of bacterial cells, blocking target sites, and altering biochemical processes inside the bacterial cells. In this case, narirutin causes oxidative phosphorylation to be uncoupled, active transport to be inhibited, metabolite reductions, and impairment of protein, nucleic acid, lipid, and polysaccharide formation [119]. Further studies show that narirutin in dried Egyptian Clover and Orange Peels (0.2% ECL+0.4% OP) or (0.2% ECL+0.2% OP) increased egg production, egg quality, and immune response in 36 chickens by inhibiting numerous bacterial strains, destroying pathogenic protozoa, and scavenging free radicals [120]. Antibacterial and immunomodulatory properties of Narirutin, hesperidin extracted from Mentha piperita L. (1.0 g/mL) were observed in twelve rabbits in another study. These include activating macrophages, encouraging secretion, producing nitric oxide, and producing lysosome enzymes and cytokines via the Shikimate pathway, all of which contribute to macrophage phagocytosis [121]. In addition, a phytochemical database called NPACT was used to screen for narirutin, a compound found in citrus fruits, in an in vitro anti-tubercular study. Anti-tuberculosis activity was demonstrated via the Shikimate pathway. *In vitro* testing of the phytochemical's antitubercular activity is conducted. MIC99 against MtbH37Rv is 62.5 μg/mL [123]. We knew from a previous investigation that giving male Wistar rats (100 and 200 mg/kg, p.o.) dosages of narirutin rich fraction (NRF) extracted from grapefruit peel for three days prevented cardiotoxicity. The values of plasma CK-MB, LDH, AST, and ALT have all decreased as a result of the NRF therapy, as have the levels of antioxidative enzymes like CAT and SOD. In male Wistar rats, narirutin rich fraction (NRF) produced from grapefruit peel at 100 and 200 mg/kg (p.o.) for three days is particularly efficient against isoproterenol-induced myocardial infarction. NRF treatment lowered plasma-CK-MB, LDH, AST, and ALT levels, as well as antioxidant enzymes like SOD and CAT, preventing cardiotoxicity [122].

6.12. Anti-allergic activity

Anti-allergic medications are used to avert allergic reactions and to alleviate or regulate allergic symptoms. Narirutin and other flavonoids work as anti-allergic medicines by inhibiting histamine binding to cellular receptors (particularly, the H1-receptors) [145]. Research studies demonstrated that treating rodents with allergic asthma with varying concentrations of the flavonoids chrysin, quercitrin, narirutin, or hesperidin reduces airway hyper responsiveness by decreasing inflammatory cytokines such as histamine and cytokines, as well as cell infiltration. Preventing (IgE) production and mast cell degranulation are also part of the system [124]. An experimental research demonstrated that treating rodents with allergic asthma with varying concentrations of the flavonoids chrysin, quercitrin, narirutin, or hesperidin reduces airway hyper responsiveness by decreasing inflammatory cytokines such as histamine and cytokines, as well as cell infiltration. Preventing IgE production and mast cell degranulation are also part of the system [125]. From further studies, it was found that narirutin from Huoxiangzhengqi oral liquid (a traditional Chinese medicine formula that has antibacterial, anti-inflammation and gastrointestinal motility regulation effects) in concentration of 263.8, 527.6, and 1055 mg/kg/d for 7 days, showed anti-allergic actions in RBL-2H3 cells and in mice, via inhibiting degranulation of mast cells [126].

7. Toxicity

Flavonoids, such as narirutin, may inhibit the function of intestinal CYP3A4, causing more of the medication to reach the bloodstream and remain in the body for a longer period rather than being digested [146]. Cough, dizziness, headaches, flushing sensation, palpitation, angioedema, liver failure, and myositis are common adverse effects of narirutin [147].

Citrus fruit extract also alters medication bioavailability by inhibiting cytochrome enzymes or the drug uptake mechanism in the intestines [148]. There are two organic anion-transporting polypeptides (OATP) in the small intestine that have a role in the absorption of drugs. Grapefruit juice contains naringenin, an organic anion-transporting polypeptide (OATP) 1A2 and OATP2B1 inhibitor, as well as narirutin, a narirutin derivative. In OATP-expressing HEK293 cells, narirutin had IC50 values of 22.6 and 18.2 μM for OATP1A2- and OATP2B1-mediated transport, respectively, and hence inhibits drug absorption [149]. Another in vitro investigation found that Ethanol extracts of IO (immature orange) containing narirutin, naringin, and *Citri unshiu pericarpium* containing narirutin, hesperidin lowered the blood concentration of concurrent medications by upregulating CYP3A4. P-gp, CYP3A4, and PXR expression are all part of the process [150]. As a result, a concentration of 100 μM of grapefruit juice decreased the activity of human liver microsome CYP3A4. There are two ways in which Narirutin works here: reversible inhibition and mechanism-based inhibition (irreversible). A metabolic intermediate that binds permanently to the enzyme and subsequently inactivates it is used in the second method of enzyme inactivation [151]. Although narirutin's anti-inflammatory effects were limited, its aglycone naringenin inhibited the following procedures: nitric oxide production (IC50 = 105 M), nitric oxide synthase induction, Interleukin-6 synthesis (IC50 = 65 M), and inducible soluble epoxide hydrolase activity (IC50 = 267 M) [87]. In comparison to apoRNA, narirutin destabilizes the tertiary structure of pri-miRNA. It is also suggested that narirutin binding to pre-miRNA disrupts pri-RNA structure, resulting in a lack of DICER-pre-miRNA connections via inhibiting pre-miRNA production, hence altering miRNA processing. Further pharmacokinetics and toxicity prediction demonstrated that it is neither carcinogenic, mutagenic, or inhibits the action of the CYPs. Thus, narirutin may be an antagonist of carcinogenic miRNAs, making it effective for miRNA-targeted cancer prevention and treatment [55].

8. Conclusion and future directions

Narirutin is a flavanone that constitutes the major flavonoids found in citrus fruits like oranges, grapefruits, and tangerines. Narirutin has a wide range of therapeutic properties, including anti-adipogenic, anti-inflammatory, anti-allergic, antioxidant, hepatoprotective activities, immunomodulatory effect, anti-obesity effect, anti-adipogenic effects, antidiabetic effect, stress relieve, antidepressant effects, neuroprotective effect, and lastly most effective anticancer and anti-tumor effect. It is an important constituent of all types of citrus and grapefruits and combination therapy with other plant constituents; it can be used for future drug development of cancers and many other diseases. For example,

narirutin exhibited greater binding affinity towards HMG CoA reductase, as compared to atorvastatin via HMG Co-A reductase inhibitory activity and thus can be used for future drug development against dyslipidemia. Narirutin also can be used as a Shikimate kinase inhibitor with anti-tubercular potency and pancreatic lipase inhibitory activity that can be focused for drug development programs. Narirutin in BACE1-targeted therapy for Alzheimer's disease paves the way for future drug development. Future nano-technological analysis of this compound can be effective against different types of diseases including cancers and tumors. Further clinical studies are required to validate the preclinical data and medicinal usage for therapeutic purposes.

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CRediT authorship contribution statement

Saikat Mitra: Conceptualization, Methodology, Investigation, Data curation, Resources, Software, Formal analysis, Writing – original draft. **Mashia Subha Lami:** Methodology, Validation, Visualization. **Tanvir Mahtab Uddin:** Methodology, Validation, Visualization, Writing – original draft. **Rajib Das:** Software, Data curation, Writing – original draft. **Fahadul Islam:** Data curation, Methodology, Investigation, Writing – review & editing. **Juhaer Anjum:** Data curation, Methodology, Investigation, Writing – review & editing. **Md. Jamal Hossain:** Software, Data curation, Writing – review & editing. **Talha Bin Emran:** Funding acquisition, Project administration, Writing – review & editing, Supervision.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets supporting the conclusions of this study are included within the article.

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Conflict of interest statement

The authors declare no conflicts of interest related to this study.

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