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CITRUS-DERIVED BIOFLAVONOIDS: AN ALTERNATIVE APPROACH TOWARDS TREATING DIABETES, NEURODEGENERATIVE DISEASES AND CANCER

Banerjee A[1], Das S[1], Roy K[1], and Maity S[1,2*]

[1]*Department of Zoology, Ramakrishna Mission Vivekananda Centenary College, Rahara, Kolkata 700118, India*

[2]*Department of Zoology, Netaji Mahavidyalaya, Hooghly, WB 712601*

Abstract

Diabetes, neurodegenerative diseases and cancer are some of the major public health issues worldwide. Various synthetic drugs are available for the treatment of these diseases, however, most of them exhibit side-effects. Despite their availability, most of these drugs are unaffordable for a particular sect of population. Also, most of the commercial drugs exhibit critical effects upon long term consumption and sometimes can also be lethal. Flavonoids are bioactive polyphenols that has potent pharmacological properties. In the recent times, apigenin, quercetin and naringenin, derived from citrus plants, are used extensively in the treatment of various diseases and being herbal in nature, these compounds are reported to show no significant side-effects. These said dietary flavonoids do possess high antioxidant, anti-inflammatory, anti-hyperglycemic and anti-apoptotic properties. This review summarises the adverse effects of synthetic drugs available for treatment, suggesting the efficacy of the mentioned flavonoids as possible alternative medicinal approach against the usage of the commercial drugs. In experimental researches like cell culture and animal models, these dietary flavonoids can be used alternatively towards treating those diseases, considering their positive effects. However, further clinical trials are required on humans to check for toxicity.

Keywords: Synthetic drugs, Side-effects, Flavonoids, Citrus, Herbal, Alternative medicine

Introduction

Globally, diabetes is one of the major life-threatening public health issues whose severity may cause damage to various organs including kidneys, eyes, heart, brain, and legs, eventually leading towards mortality. According to the International Diabetes Federation (IDF) Diabetes Atlas 2021, about 537 million adults are diabetic with a mortality rate of 6.7 million deaths. It has been predicted that diabetes may increase up to 643 million by 2030 and up to 783 million by 2045 [1]. Diabetes is majorly classified into three different types: Type-I diabetes mellitus (T1DM), Type-II diabetes mellitus (T2DM) and Gestational diabetes mellitus (GDM)(Webber, 2013).T1DM is an autoimmune disease caused due to insufficient synthesis of pancreatic

*Corresponding Authors' Email: *subho.maity@gmail.com

β-cells, which fails to produce desired amount insulin and leads to hyperglycaemia. It is mostly observed in the adolescent and early adulthood population. Weight loss, fatigue, frequent urination, feeling thirstier and hungrier than usual and blurred vision are some commonly observed symptoms in T1DM patients. If kept untreated, complications may lead to microvascular and macrovascular diseases(Paschou et al.,2018) T2DM is considered to be the most common diabetes amongst all. It is a lifestyle disease and generally affects 35-79 years of age group of population. It is caused mainly due to insulin resistance in the body. Due to increasing obesity, skipping or having unhealthy meals, no physical activity and high blood pressure T2DM is occurs very commonly. Indications to T2DM are almost identical to T1DM. If not properly treated, complexity of T2DM can lead to organ dysfunctioning, hypoglycaemia, hyperglycaemia, diabetic ketoacidosis and even com(Farmaki et al.,2021). GDM is another type of diabetes commonly occurs during pregnancy due to interference of placental hormones in insulin production causing abnormal insulin secretion. However, this insulin resistance is considered a natural part of pregnancy and disappears after childbirth. If insulin resistance becomes too high, it may lead to overweight or obese foetus during pregnancy and the child stays at a greater risk of developing T2DM(Webber,2013).

Most brain related disorders have a crucial role in pathophysiological changes of neurons, that leads to neurodegeneration by the significant loss of neuronal cells. Decreasing trends of tight junction proteins of blood brain barrier (BBB) promotes neurodegeneration, resulting the significant changes in function and expression of receptors (GLUT1, Pgp etc.) and BBB transporters as well as endothelial cells of brain(Knox et al.,2022) Pathological and clinical heterogeneity promotes the diversification of each neurodegenerative disorder with the help of a complicated relationship between genes and environment. Several common neurodegenerative diseases are there, such as Parkinson's disease, the dopaminergic neurons degenerate in substantia nigra pars compacta of midbrain underlies, Alzheimer's Disease, depends on the damage of Cholinergic neurons by decline the level of acetylcholine in affected brain, Huntington's disease, a mutation in a protein gene designated as huntingtin and many more CAG repeats in the huntingtin gene of chromosome-4, Amyotrophic lateral sclerosis, significant decrease of upper and lower motor neuron that promotes the deterioration of muscle action. This huge sphere of neurodegenerative disorders demolishes remarkable number of humans, worldwide 1 billion people affected, and 1.5 million people died every year. In 2019, Worldwide 55 million people had dementia as well as Alzheimer's Disease and by 2050, it is estimated that, 139 million people will be affected. By 2030, statistics manifest that, more than 12 million people will be suffering from neurodegeneration in America(Monroy et al.,2023).

Cancer is a group of diseases caused due to genetic mutations in any part of the body, characterized by rapid and unrestrained cellular division. Hanahan et al. described several hallmarks of cancer cells. These include undergoing chronic proliferation signalling like Epidermal growth factor receptor cell proliferative signaling

which is prevalently upregulated in most types of tumor malignancies, avoiding apoptosis of cells, bearing replicative eternity, inhibiting the tumor growth suppressors like retinoblastoma 1 (RB1), p53 etc. and promoting angiogenesis by upregulating certain angiogenic factors like vascular endothelial growth factor (VEGF), invasive and metastatic properties(Hanahan and Weinberg,2011).There are two types of apoptotic pathway, such as extrinsic pathway which is related to death receptors like tumor necrosis factor receptor 1, fas receptor, TRAMP, TNF-related apoptosis-inducing ligand receptor 1 and 2, death receptor 6 ectodysplasin A receptor and nerve growth factor receptor; another one is intrinsic pathway or Mitochondrial apoptotic pathway that are resisted by cancer cell(Lavrik Golks and Krammer, 2005) According to the global cancer observatory (GLOBOCAN) report in 2020, more than 19 million patients were diagnosed with cancer and approximately 10 million deaths were recorded worldwide due to cancer in 2020(Deo, Sharma and Kumar, 2022).

There are various synthetic drugs available for the treatment of diabetes, neurodegenerative diseases and cancer. Despite their availability, most of the drugs are unaffordable for a particular population due to their high cost. Also, most of the commercial drugs exhibits severe adverse effects upon long term consumption and sometimes can also be lethal. Flavonoids are plant components, which are popular for possessing therapeutic properties against various diseases. In the recent times, applications of citrus bioflavonoids- apigenin, quercetin and naringenin towards treating diabetes, cancer and neurodegenerative diseases is being studied extensively. Based on recent studies, the present review mainly highlights the adverse effects of using commercial drugs against diabetes, neurodegenerative diseases, and cancer, suggesting the efficacy of bioflavonoids- apigenin, quercetin and naringenin, as possible alternatives against administration of synthetic drugs.

Use of synthetic drugs and their side-effects

There are distinct types of synthetic drugs available for the treatment of diabetes which are taken via oral administration either as monotherapy or given in combination. Some of the commonly used classes of antidiabetic drugs includes biguanide, sulfonylureas, sodium glucose co-transporter 2 (SGLT-2) inhibitor, meglitinides, alpha glucosidase inhibitors (AGIs) and thiazolidinediones (TZDs) (**Table 1**) (Tahrani, Barnett and Bailey, 2016; Feingold, 2022). Metformin, the commonly used biguanide, shows various adverse effects, some of which includes abdominal discomfort, decreased appetite, diarrhoea, nausea, lactic acidosis, persuading ovulation, causing unplanned pregnancies, renal complications and also vitamin B-12 deficiency which may lead to anaemia and neuropathy disorders. In T2DM, TZDs (rosiglitazone and pioglitazone) administration causes weight gain with, increase in fluid retention, congestive heart failure (CHF), edema and macular edema, osteoporosis, complications regarding ovulation and bladder cancer. Sulfonylureas are antidiabetic medications mainly used in the treatment of T2DM. Chlorpropamide, tolazamide, tolbutamide and acetohexamide comes under first generation sulfonylureas, while glyburide, glimepiride, glipizide and

gliclazide comes under second generation sulfonylureas. They are also found to exhibit adverse effects that includes hypoglycaemia, weight gain, abnormal secretion of antidiuretic hormone (ADH) that may cause hypernatremia, fluid retention and alcohol flushing. The meglitinides (*repaglinide*and netaglinide) are a class of antidiabetic drugs quite similar to sulfonylureas in functioning. Disorders such as hypoglycaemia is commonly observed in patients having meglitinides along with headache, weight gain, upper respiratory tract infection and cardiovascular ischemia. The next common class of drug used to treat T2DM and T1DM is SGLT-2 inhibitor (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin), delivered orally either as monotherapy or in combination. They cause urinary tract infections, genital mycotic infections, diabetic ketoacidosis, acute kidney injury, hypovolemia and osteoporosis. AGIs (acarbose, miglitol and voglibose) are another class of antidiabetic drugs used to treat T2DM, T1DM and GDM, also shows side effects like flatulence, abdominal pain, diarrhoea, increase in serum transaminase and hyperbilirubinemia are commonly observed. (Tahrani, Barnett and Bailey, 2016; Feingold, 2022).

For diabetes

Table1: Classes, their drugs, respective diabetes type, and their side-effects

Class	**Drugs**	**Diabetes Type**	**Adverse Effects**
Biguanide	metformin	T2DM	abdominal discomfort, decreased appetite, diarrhoea, nausea, lactic acidosis, abnormal ovulation, and pregnancy.
Thiazolidinediones (TZDs)	rosiglitazone and pioglitazone	T2DM	Weight gain, fluid retention, macula edema, bladder cancer, CHF, osteoporosis and abnormal ovulation and pregnancy.

Sulfonylureas			
- **I generation** - **II generation**	chlorpropamide, tolazamide, tolbutamide and acetohexamide glyburide, glimepiride, glipizide and gliclazide	T2DM	hypoglycaemia, hypernatremia, fluid retention and alcohol flushing.
Meglitinides	repaglinide and netaglinide	T2DM	hypoglycaemia, with headache, weight gain, upper respiratory tract infection and cardiovascular ischemia.
Sodium glucose co-transporter 2 (SGLT-2) inhibitor	canagliflozin, dapagliflozin, empagliflozin and ertugliflozin	T1DM & T2DM	urinary tract infections, genital mycotic infections, Diabetic ketoacidosis, acute kidney injury, hypovolemia osteoporosis and fractures.
Alpha glucosidase inhibitors (AGIs)	acarbose, miglitol and voglibose	T2DM, T1DM & GDM	lactose intolerance, flatulence, abdominal pain, diarrhoea, increase in serum transaminase and hyperbilirubinemia.
For neurodegenerative diseases			

Neurodegenerative diseases are treated by using various types of oral or combinational chemical drugs (**Table 2**). In the case of parkinson's disease (PD), levodopa, dopamine agonists, monoamine oxidase type B [MAO B] inhibitors, catechol-o-methyl transferase [COMT] inhibitors, antidyskinetics drug classes are used. Alzheimer's disease is treated by several drug classes, such as, cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonist. Dopamine-depleting agents, antipsychotic medications, psychiatric medications, N-methyl-D-aspartic Acid receptor antagonists are used to treat huntington's disease. Glutamate modulators, muscle relaxants and spasticity medications, saliva-reducing medications, pain management medications, nonsteroidal anti-inflammatory drugs (NSAIDs) are applied to treat amyotrophic lateral sclerosis (ALS) in a combinative way.

Table 2: Classes,their drugs, respective neurodegenerative disease, and their side-effects

Class	Drug	Disease	Adverse effects
Levodopa	madopar, duodopa	Parkinson's Disease	Nervousness, Irregular heartbeat, hallucinations, Vomiting, Diarrhoea, Depression, Twitching, Itching
Cholinesterase inhibitors	aricept, razadyne, exelon	Alzheimer's Disease	Skin rash, Itching, Hives, Nausea, Vomiting, Diarrhoea, Dizziness, Drowsiness, Shakiness
Dopamine-Depleting Agents	reserpine, tetrabenazine, valbenazine	Huntington's Disease	Dizziness, Nasal congestion, Arrhythmias, Bradycardia, Hypotension, Gastric Ulceration, Drowsiness, Drooling, Restlessness
Glutamate Modulators	riluzole	Amyotrophic Lateral Sclerosis (ALS)	Agitation, coma, Drowsiness, Memory loss, Vomiting, Seizures, Sore throat, Rapid heart rate, Blurred vision

Madopar and duodopa are belonging to levodopa class, used for the successful treatment of Parkinson's disease. The drug class has several side effects, those are irregular heartbeat, hallucinations, twitching, itching and vomiting (Diener and Kastrup, 2003). Other drugs, such as mirapex, azilect comtess also have severe life-threatening size effects. In the case of Alzheimer's disease, cholinesterase inhibitors, as first line of treatment, plays a major role in the inhibition of acetylcholine hydrolysis and also promotes several complexities, those includes nausea, vomiting, diarrhoea, dizziness, drowsiness etc (Kroeger *et al.*, 2015). On the other hand, dopamine-depleting agents are effectively used in Huntington's disease (HD) by reducing chorea. Tetrabenazine is used in that case mainly and shows side effects, such as drowsiness, dizziness, restlessness, hypotension, bradycardia, arrhythmias, irregular or stopped periods, blood clot (Landry, Rousseau and Skalli, 2010). In the case of amyotrophic lateral sclerosis (ALS), riluzole is commonly used as novel psychotropic agent mainly, also promotes side effects, such as agitation, seizures, lethargy, coma, vomiting, sore throat, blurred vision, rapid heart rate and memory loss (Cardoos *et al.*, 2013).

For cancer

Chemotherapy is one of the most acknowledged treatments of cancer in which various kinds of cytotoxic drugs are used to decimate the cancer cells. The chemotherapeutic drugs directly promote apoptosis and suppress the overall growth of Cancer cells. At the same time, they also cause some serious side-effects (**Table 2**). 5-fluorouracil, a potent thymidylate synthase inhibitor, which is used to treat breast and colorectal carcinomas, is a cardiotoxic agent that causes various adverse effects like cardiac arrest, irregular heartbeat, hypotension, hypertension etc. (Alter et al., 2006). Trastuzumab administration causes some major heart problems. Left ventricle ejection fraction decreases after treatment with this drug. Gastrointestinal problems like nausea, vomiting, diarrhoea, abdominal pain, bloating are common side effects of trastuzumab. Fatigue and lung problems are also reported (Al-Dasooqi et al., 2009; Huszno et al., 2013). In case of the clinical trial of fulvestrant which is used to treat breast cancer, more than 45% of the total patients faced gastro industrial problems, 21% experienced hot flashes, more than 5% were diagnosed with joint disorders like arthralgia, arthrosis, and arthritis, 3.5% thromboembolic disease, 7.3% patients had infection in the urinary tract (Johnston and Cheung, 2010). Cisplatin, a DNA alkylating drug, has some major adversities on children like hearing loss. Gastrointestinal problems like nausea and vomiting are very common. Patients also suffers from acute renal failure. Neurotoxicological effects like peripheral neuropathy, Sensory ataxia etc. Are very common symptoms after administration of cisplatin (Ciarimboli, 2012).

Table 3: Classes, their drugs, respective cancer type, and their side-effects

Class	Drug	Cancer type	Adverse effects

Enzyme inhibitor	5-fluorouracil	Breast and colorectal cancer	Cardiac arrest, irregular heartbeat, hypotension, hypertension etc.
Antibody drugs	Trastuzumab	Breast cancer	ventricle ejection fraction decrease, gastrointestinal problems like nausea, vomiting, diarrhoea, abdominal pain, bloating etc.
Hormone based drugs	Fulvestrant	Breast cancer	Gastro industrial problems, hot flashes, arthralgia, arthrosis and arthritis, thromboembolic disease, urinary infection etc.
DNA alkylating agent	Cisplatin	Breast cancer, NSCLC, SCLC, stomach cancer, prostate cancer	Deafness in children, nausea and vomiting, acute renal failure, peripheral neuropathy, Sensory ataxia etc.

Flavonoids in brief

Flavonoids are ubiquitous dietary phytomedicinal compounds that are majorly found in fruits, vegetables, leaves, and cereals. Based on structural difference, dietary flavonoids are predominantly classified into three major groups: isoflavonoids (B-ring is anchored to 3rd position of C-ring), neoflavonoids (B-ring is anchored to 4th position of C-ring) and bioflavonoids (B-ring is anchored to 2nd position of C-ring). Isoflavonoids, having high antioxidant and anti-inflammatory properties, are majorly found in soybeans, various vegetables, cereals and leguminous plants while neoflavonoids are polyphenols derived from various plants having high medicinal

values. Bioflavonoids are potent phytochemicals, widely distributed among various citrus fruits and vegetables like berries, grapes, cherries, tomatoes, lemon, etc. They are further sub-divided into six major classes that are flavones, flavonols, flavanones, flavanols (Flavan-3-ols or catechins), anthocyanins and chalcones ***(Figure 1)*** *(Ramesh et al., 2021).*

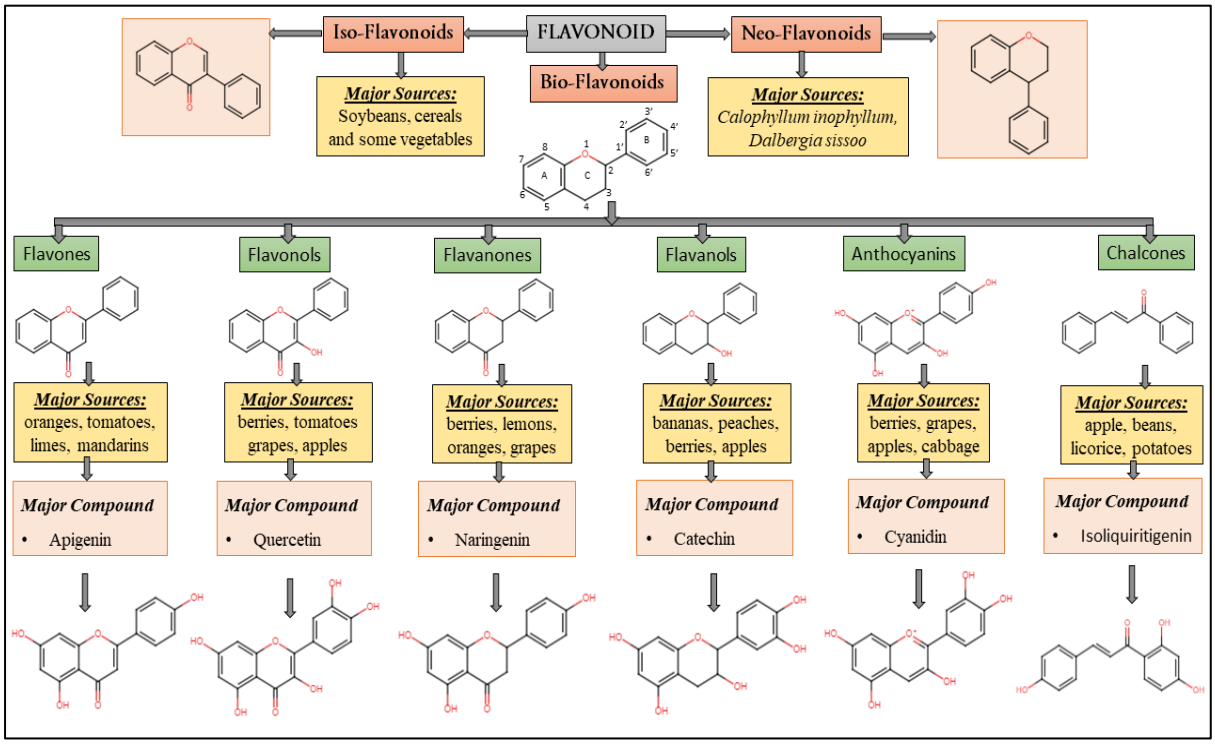

Figure 1: Classification of flavonoids

Bioflavonoids- apigenin, quercetin and naringenin, alternatives towards diabetes, neurodegenerative diseases, and cancer

Flavones are one of the most important and diverse classes of flavonoids, mainly found in citrus fruits and juices. Structurally, flavones carry double bond between C-2 and C-3 and a ketone group at C-4 position of the C-ring. Apigenin and luteolin are considered as the major components of flavones to be present in human diet. Flavonols are a major and widely distributed class of flavonoids, structurally quite similar to flavones. Flavonols contains a hydroxyl group at C-3 position that helps it to differentiate from flavones. They are mainly found in blackberries, strawberries, grapes, apples, broccoli, tomatoes, onions and various other citrus fruits and vegetables along with beverages such as tea and red wine. Among the different flavonols, widespread availability of quercetin is majorly noticed the within citrus plants. Another major class of flavonoids are flavanones that are mostly present in citrus fruits such as berries, lemons, oranges, grapes, persimmon along with some vegetables including onions and cucumbers. Absence of double bond between C-2 and C-3 in the ring makes it saturated and structurally different from other flavonoids. Naringenin and hesperitin are the most abundant compounds, belonging to flavanones, possessing high pharmaceutical properties (Panche, Diwan and Chandra, 2016; Ramesh et al., 2021).

Apigenin

Apigenin (4′, 5, 7,-trihydroxyflavone) is a phytochemical, widely distributed among citrus plants, which includes cherries, grapes, oranges, tomatoes, lemons, limes, and mandarins (**Figure 2**). It is a potent flavone that manifests anti-inflammatory, anti-microbial, anti-obesity, anti-cancer, anti-diabetic, cardio-protective and neuro-protective properties, and functions via various pathways. STZ-induced diabetic rats on treating with apigenin (300 mg kg^{-1} b.w.) for a month enhanced insulin level and lowered serum glucose level along with normalizing cellular lipid profile. Also, apigenin hindered STZ-induced pancreatic β-cell damage. Further, apigenin intake lowered generation of ROS and elevated antioxidant status (upregulation of SOD, CAT, and GSH) during diabetes (Wang et al., 2017). L.C. Miao et al. (Miao et al., 2023) found that high glucose treated insulin-resistant HepG2 cells on apigenin treatment upregulated expression of IRS-1 and IRS-2, two of the key regulatory molecules of the insulin signaling pathway, along with ameliorating the expression of PI3K/Akt and GLUT-4 translocation, which enhanced insulin secretion and cellular glucose uptake and utilization. In diabetic cardiomyopathy, induction of apigenin notably supressed NF-kB/p65-induced expression of pro-inflammatory cytokines (TNF-α, IFN-γ and IL-6) and also inhibited cardiomyocyte apoptosis by lowering Bax and upregulating Bcl2 protein expression (Liu et al., 2017). In diabetic nephropathy, activation of MAPK due to hyperglycaemia triggers the upregulation of NF-kB/TGF-β/Fibronectin pathway that induces inflammation and renal fibrosis, all of which were effectively restored with apigenin. Also, apigenin downregulated serum creatinine, BUN, and urinary albumin (Malik et al., 2017). Hou et al. mentioned that apigenin upregulated the decreased expression of miR-423-5p-USF2 axis during diabetic nephropathy, which supressed inflammation, renal fibrosis and apoptosis along with improving high glucose induced-cell damage (Hou et al., 2021).

Apigenin protects the brain, maintains glia-neuron interactions, and prevents microglial mediated inflammation. It is used to treat several neurodegenerative diseases with minimum side effects. In the case of Parkinson's disease, apigenin ameliorated the concentrations and expressions of TNF-α, TGF-β, IL-10, IL-6 and IL-1β (Yarim et al., 2022). Also, apigenin shows a significant result by exhibiting the effects of superoxide anion scavenging that improved the activity of antioxidative enzyme of superoxide dismutase and the glutathione peroxidase and restored neurotrophic CREB/ERK/ BDNF pathway in cerebral cortex of the brain (Nabavi et al., 2018). Bax and striatal GAPDH were downregulated and also the ERK signaling pathways were modulated in the case of Huntington's disease, another type of Neurodegenerative disease (Gupta et al., 2022). In Amyotrophic Lateral Sclerosis, apigenin inhibited some neuronal apoptotic markers such as Bcl-2,

Bax, caspase-3 etc, that restored the neurotransmitter imbalance, alleviated the oxidative damage, decreased some inflammatory markers and downregulated p38MAPK and c-JNK signaling pathways (Yadav et al., 2022).

Apigenin affects cancer cells by inducing apoptosis or cell death and auto-cannibalism and also by inhibiting the cell cycle progression. Apigenin was also observed to be a potent inhibitor of cell migration and encroachment. Apigenin was able to induce the mitochondrial apoptotic pathway dose-dependently in human breast cancer MDA-MB-453 cells (Choi and Kim, 2009). In human prostate cancer cells like PC-3 and DU145, apigenin triggered apoptosis by decreasing the levels of XIAP, c-IAP1, c-IAP2 and proteins which prevents apoptosis. It also reduced the levels of Bcl-xL and Bcl-2 and activated bax protein. In PC-3 cells, apigenin (10-40 μg) successfully decreased the expression of NF-kB by the suppression of NF-kB- regulated genes like Bcl2, cyclin D1, cyclooxygenase-2, matrix metalloproteinase 9, nitric oxide synthase-2 (NOS-2), and vascular endothelial growth factor. Shukla et al. (Shukla, Fu and Gupta, 2014) showed that apigenin was also able to introduce apoptosis to those cells in TNF-alpha-induced pathway. Apigenin triggered upregulation of pro-apoptotic proteins, and it also downregulated the pro-survival proteins which induced mitochondrial apoptosis pathway in non-small cell lung cancer cell lines. Also, apigenin affected non-small cell lung cancer cells to initiate apoptosis by TRAIL by the upregulation of death receptor (DR4 and DR5) (Chen et al., 2016). In human colorectal cancer cells (SW480 and HCT15), apigenin inhibited the Wnt/β-catenin pathway (Xu et al., 2016). Apigenin also inhibited angiogenesis and growth in gastrointestinal cancers. The application of apigenin in human colon cancer cells caused G2/M cell cycle arrest in human colon cancer cells through the downregulation of cyclin B1, Cdc2 and Cdc25c. It also increased p21CIP1/WAF1 expression, a cyclin dependent kinase (CDK) inhibitor, in dose-dependent manner. Further, apigenin actuated autophagy, acidic vesicular organelle (AVO) was significantly increased after the treatment of apigenin compared to the non-treated ones (Lee et al., 2014).

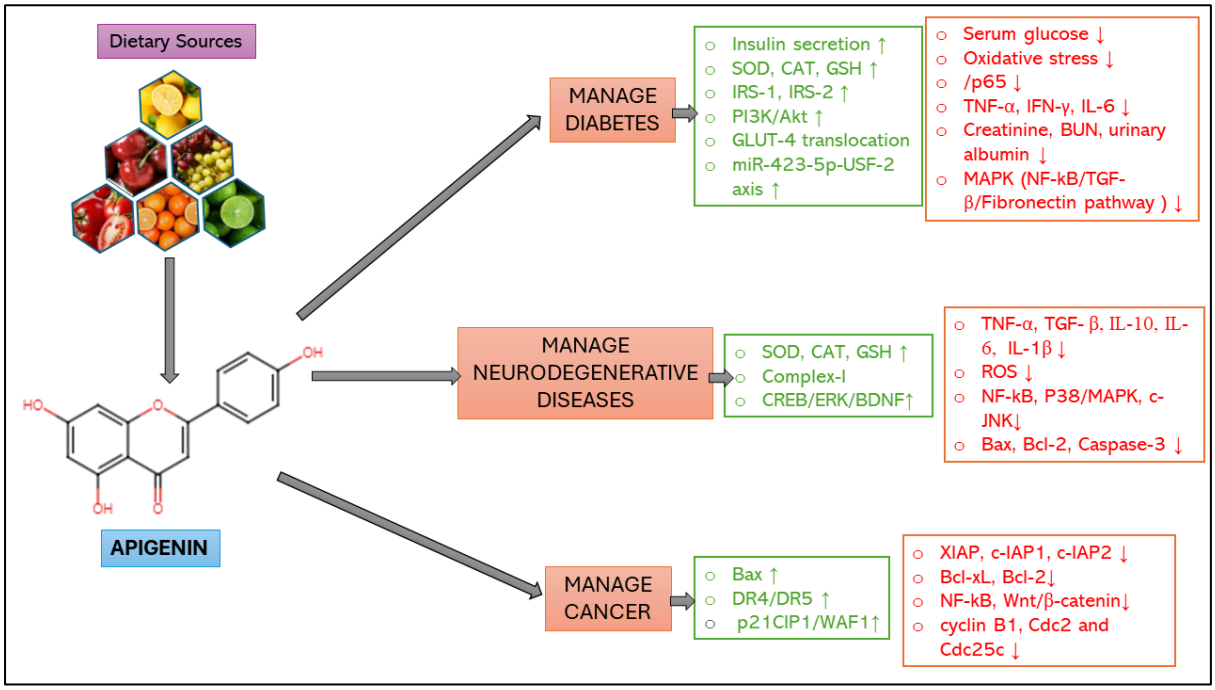

Figure 2: Mechanism of action and the various pathways modulated by apigenin towards treating diabetes, neurodegenerative diseases, and cancer

Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) is one of the commonly used bioactive flavonol in treating metabolic and inflammatory disorders. Several citrus plants like berries, apples, grapes, cherries, tomatoes, broccoli, pepper, and parsley are its rich dietary sources **(Figure 3)**. In a study, quercetin significantly reduced hyperglycaemia, thereby normalizing blood glucose and upregulated antioxidant enzymes (SOD, GPX and CAT) that prevented β-cells against diabetes-induced oxidative damage. Quercetin also enhanced production of Langerhans islets and stimulated insulin production along with normalizing the serum lipid profile (A. Shaikhomar and S. Bahattab, 2021). Quercetin has been found to upregulate AMPK phosphorylation, GLUT-4 translocation, and glycogen synthase in skeletal muscle cells and hepatocytes during T2DM (Eid et al., 2015). In a recent study on folliculogenesis in diabetic mice, it was found that quercetin (30mg kg^{-1} b.w.) reduced hyperglycaemia and increased the number of secondary, antral, and Graafian follicles as well as corpus luteum, whose count were reduced due to diabetes (Bolouki, Zal and Bordbar, 2019). In diabetic nephropathy, quercetin decreased the expression of Bax and caspace-3 via EGFR-signaling pathway that averted diabetes-induced podocyte apoptosis (Liu et al., 2022). In human retinal microvascular endothelial cells (HRMECs), the protein expressions of NLPR3, ASC, caspace-1, inflammatory cytokines (IL-1β and IL-18) and autophagy proteins (LC3-II/I and Beclin-1) were upregulated under high glucose condition. With increase in quercetin concentration, angiogenesis, NLRP3 inflammasome and autophagy signaling pathways were repressed, which alleviated the upregulated protein expressions, thus ameliorating diabetic retinopathy (Li et al., 2021).

Quercetin is a potent herbal component that manifests several neuroprotective effects like decreasing the expression of C/EBP-homologous protein, BiP and, ER stress marker genes with the downregulation of JNK and TNF-α (Chatterjee et al., 2019). In the case of Parkinson's disease, quercetin inhibited the ferroptosis by the activation of the Nrf2 protein that regulated expression of GPX4 and SLC7A11 (Lin et al., 2022). Quercetin ameliorated Alzheimer's Disease by down-regulating the activity of GSK3β and ICAM-1, decreased MDA levels and acetylcholine activity, increased the activity of SOD, CAT, GPX and T-AOC (Yu, Li and Mu, 2020). In Huntington's Disease, quercetin reduced 5-HT turnover and 5-HIAA level, as compared to 3-NP group, clearly inhibiting the effect on the activity of MAO-A and showing heightened inhibitory activity (Liaqat, Parveen and Kim, 2022). Also, quercetin administration ameliorated Amyotrophic Lateral Sclerosis by activating AMPK/SIRT1 signaling pathway that reduced the stress of endoplasmic reticulum, which also alleviated apoptosis and inflammation (Jin et al., 2023).

Quercetin has anti-proliferative properties in different breast cancer cell lines. In MDAMB-231 human breast cancer cell, 20μM of quercetin introduced apoptosis and cell cycle regression via Foxo3a activity through activation of JNK pathway (Nguyen et al., 2017). In human AGS and MKN28 gastric cancer cells, quercetin induced cellular apoptosis and autophagy as the AVO formation was observed to be effectively increased, the Akt-mTOR-and hypoxia-induced factor 1α-mediated signaling was also modulated by quercetin in those cells (Wang et al., 2011). Quercetin was also found to be effective in malignant prostate carcinoma both in vivo and in vitro. It reduced cell proliferation, angiogenesis, tumor growth and promoted apoptosis in various in vivo mice models. In different in vitro models, quercetin decreased the level of ERK-1/2,pAKT, IGF-1, upregulated the DR5 related apoptosis along with increasing the JNK and p53 levels (Yang et al., 2015). In colorectal cancer, quercetin modulates several signaling pathway like Wnt/β-catenin, PI3K/AKT, MAPK/Erk, JNK, and NF-κB. This drug mostly introduces G2/M cell cycle arrest in different colorectal cancer cells (Neamtu et al., 2022)

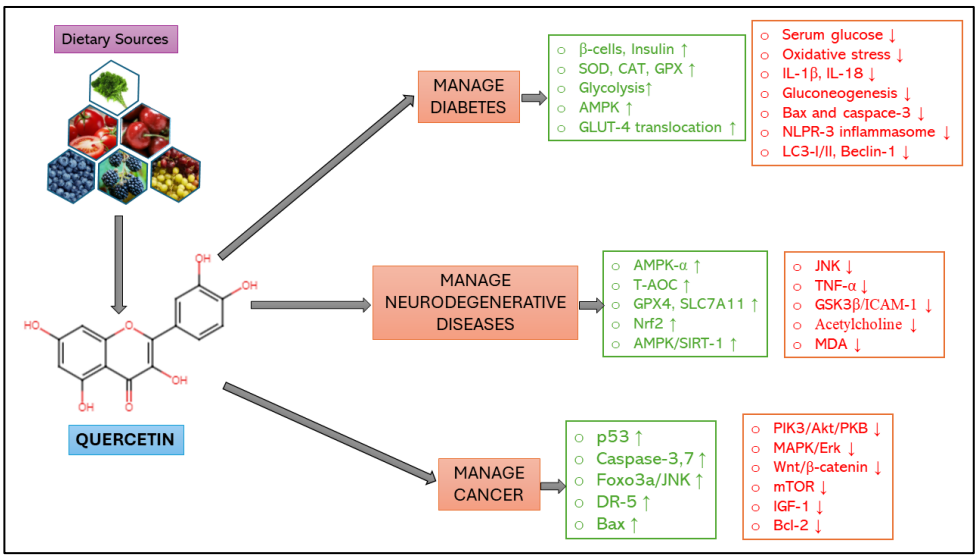

Figure 3: Mechanism of action and the various pathways modulated by quercetin towards treating diabetes, neurodegenerative diseases, and cancer.

Naringenin

Naringenin (4,5,7-trihydroxy-flavanone), a key dietary flavanone, which exhibits potent anti-inflammatory and free radical scavenging properties. It is majorly distributed among various citrus plants such as lemons, grapes, various berries, oranges, tomatoes, bergamots **(Figure 4**). In a study, naringenin normalized blood glucose level along with improving glucose tolerance and upregulated β-cell functioning that enhanced insulin secretion. Further, ingestion of naringenin also regulated lipid homeostasis, reduced oxidative stress and reinstated antioxidant status (Zaidun et al., 2019). Kapoor et al. (Kapoor and Kakkar, 2014) showed that leakage of apoptogenic factors (Cyt-c, AIF, and Endo-G) from mitochondrial pores upregulated caspace-3 and caspace-9 expression, which was inhibited upon naringenin treatment, preventing apoptosis. Also, naringenin inhibited $CD68^{+}$ macrophage infiltration as well as supressed activation of NF-kB and MAPK by inflammatory cytokines (TNF-α and IL-1β), which reduced pancreatic β-cell apoptosis (Mice, 2022). During STZ-induced cardiac hypertrophy, expressions of CYP2J3, serum EET level, and PPARs (PPARα, PPARβ and PPARγ) were downregulated, which were reversed with naringenin (25 and 75 mg kg^{-1}b.w.) treatment (Zhang et al., 2018). Naringenin lowers the expressions of serum creatinine, BUN, and urinary albumin and restores the activities of PPARs that upregulates the expressions of CYP4A protein and serum 20-HETE in NRK-52E cells, all of which were altered during diabetic nephropathy (Ding et al., 2019).

Naringenin exhibits significant neuroprotective effects by targeting inflammatory signals, including suppressor of cytokine signaling 3 (SOCS-3), NF-κB, mitogen-activated protein kinase (MAPK), activator of transcription-1 (STAT-1) and some other signal transducers (Nouri et al., 2019). In case of Parkinson's Disease, TNFα , IL1β and SYN mRNA expressions were downregulated, dopamine transporter (DAT) and tyrosine hydroxylase (TH) protein expressions were upregulated significantly, SOD levels were improved, dopaminergic neuronal loss was alleviated by naringenin (Ahmad et al., 2021). In Alzheimer's Disease, naringenin treatment upregulated cellular antioxidant enzymes and modulating the estrogenic pathway along with upregulating the expression of ERK-CREB pathway (Karim et al., 2020). Also, naringenin ameliorated Huntington's Disease by inducing the expression of HO-1, Nrf2, upregulating Heat Shock Proteins (HSPs) and Atg7 with the help of mTOR–AMPK signaling pathway (Silakari et al., 2024). In the case of Amyotrophic Lateral Sclerosis (ALS), naringenin significantly modulated PI3K/Akt/mTOR pathway resulting in autophagy activation, the activation of Nrf2 signaling pathway and upregulation of HO-1 expression (Bai, Bian and Zhang, 2023).

In triple negative breast cancer cells, naringenin introduced cell cycle arrest at the G0/G1 phase to induce apoptosis (Wang et al., 2019). Naringenin was also found to inhibit the migratory properties of malignant lung

cancer cells. In gelatin zymography assay, matrix metalloproteinases-2 and -9 was observed to be supressed after the treatment of naringenin (Shi et al., 2021). B-catenin signalling pathway was inhibited by naringenin in stomach cancer cells. This natural drug shows its anti-cancerous properties in prostate cancer cells by regulating PI3K/AKT and MAPK signalling pathway, increasing the Bax protein levels and decreasing the Bcl-2 protein levels (Lim et al., 2017). Naringenin also inhibited PI3K/AKT/mTOR signaling pathway and controlled the growth of colorectal cancer cells. It also regulated the expression of Bax and Bcl-2 protein in those cells. Administration of naringenin resulted in downregulation of cyclin D1 in human colorectal cancer cells by phosphorylating at threonine-286 and by introducing a point mutation at threonine-286 which is replaced by alanine (Song et al., 2015).

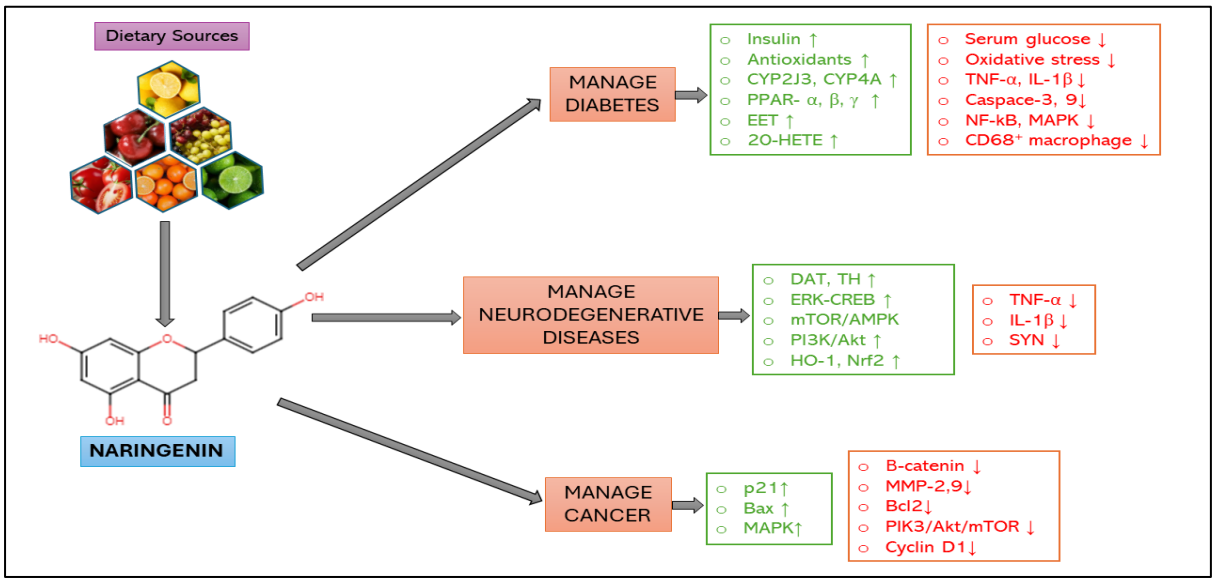

Figure 5: Mechanism of action and the various pathways modulated by naringenin towards treating diabetes, neurodegenerative diseases, and cancer

Conclusion

Apigenin, quercetin and naringenin, derived from citrus fruits and vegetables, possesses high antioxidant and anti-inflammatory properties, and shows no significant side effects against diabetes, neurodegenerative diseases, and cancer in animal models. Considering the positive effects, these dietary flavonoids can be used alternatively towards treating those diseases. However, further clinical trials are required on humans to check for toxicity.

Conflict statement

None

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