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REVIEW

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Health benefits of okra (*Abelmoschus esculentus*) against diabetes mellitus and cognitive dysfunction: a review

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Abstract

Diabetes mellitus (DM), both type 1 and type 2, has been linked to decreased performance across a number of cognitive function categories, with more recent studies emphasizing the contribution of DM mediated dementia. Despite the therapeutic advantages of antidiabetic medications for the management of DM mediated cognitive dysfunction (CD), the majority of these pharmaceuticals are linked to a number of negative side effects, raising questions about their long-term advantages. Botanical medicines, which often have low toxicity and adverse effects, are supported by some latter research. These medicines are attracting increased interest from researchers studying traditional herbal remedies owing to the minimal side effects for prevention and managing DM and CD in developing and developed countries. To emphasize the health benefits of okra (*Abelmoschus esculentus*) against DM and CD. Different databases, including PubMed, Google Scholar, and Scopus, were searched with a combination of keywords. The available research on the health benefits of okra against DM and CD is compiled in this study which indicates that okra has the ability to manage DM and CD. It will serve as a base for further investigation into the okra preparation for its potential commercial production as a therapeutic agent for DM and CD.

Highlights

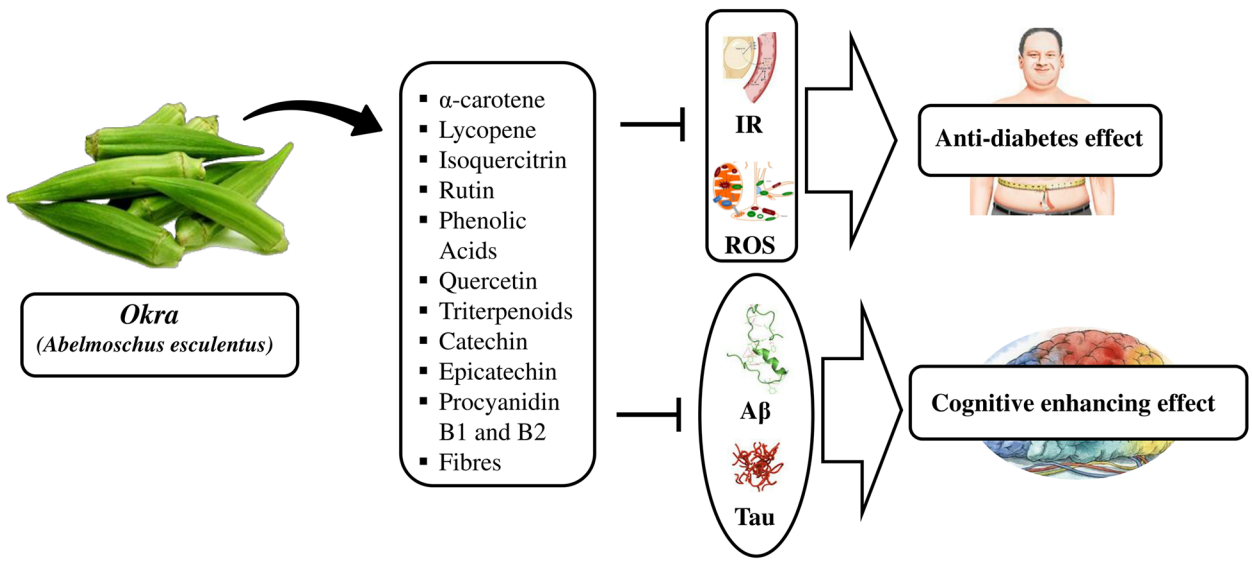
- Diabetes mellitus (DM) is emerging as a serious global health issue.
- Cognitive dysfunction (CD), a neurodegenerative disease, negatively affects memory.
- DM and CD are correlated with each other and have a complex mechanism.
- Disturbed insulin secretion sensitivity in insulin receptors activates oxidative stress.
- Okra polysaccharides reverse DM and CD by regulating insulin signaling.

Keywords Medicinal plants, Metabolic syndrome, Alzheimer's diseases, Insulin resistance, Phytochemical, Animal studies

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Graphical Abstract



Introduction

Diabetes mellitus (DM) is a metabolic syndrome (Dündar & Aklncl, 2022) characterized by hyperglycemia (Kalmar et al., 2022), and the prevalence of DM can be enhanced by multiple factors that include genetic, epigenetic, and environmental factors (Kaimala et al. 2022), autoimmune destruction of β-cells, production of toxins, viral infection, dietary factors (Skyler et al., 2017), insulin resistance, and hyperinsulinemia (Collier & Burke, 2022). Once hyperglycemia occurs, individuals with all types of DM have a higher risk of developing complications, although the progression rate may vary (Skyler et al., 2017). These complications include cognitive dysfunction (CD), obesity, aging, and physical inactivity (Esmaeilzadeh et al., 2020). Since CD and DM are tightly related, diabetic patients have a higher risk of cognitive impairment.

CD is a brain impairment where the attention and working memory are negatively affected (Millan et al., 2012), and CD has a higher probability of development during DM. In most cases, the incidence of DM and CD progresses with age, and because of their severity as chronic diseases, are considered as major causes of mortality and morbidity (Ma et al., 2015). The exact etiology of CD in DM is not completely known, although certain risk factors that produce CD are recognized, including DM, which is considered a major risk factor. Furthermore, comorbid brain diseases, especially CD, can negatively impact DM as well. Several natural therapies such as garlic (*Allium sativum*), *aloe* (*Aloe vera*), *ivy gourd* (*Coccinia indica*), gymnema (*Gymnema sylvestre*), bitter melon (*Momordica charantia*), nopal (*Opuntia streptacantha*), ginseng (*Panex ginseng*), and fenugreek (*Trigonella foenum graecum*) have been confirmed to have health-beneficial effects on DM. Besides herbal therapies, there are some supplements, including alpha-lipoic acid, chromium, coenzyme Q10, magnesium, omega-3 fatty acids, and vanadium ameliorate DM as well (Kodl & Seaquist, 2008; Birdee & Yeh, 2010; Putra et al., 2022, 2023). In similar manner, several natural therapies, namely essential oil (*Polygonum hydropiper*), green tea (*Camellia sinensis*), soybean (*Glycine max*), saffron (*Crocus sativus*), maidenhair tree (*Ginkgo biloba*), and highbush blueberry (*Vaccinium corymbosum*) have been shown to have positive health effects on CD. With the exception of herbal therapies, there are certain supplements, including ascorbic acid and N-3 PUFA also reverse CD (Gupta et al., 2019; Helmi et al., 2020, 2021a, b).

DM and CD have become a burdening issue on global health (Schmidt et al., 2022; Sharma et al., 2021; Tomlin & Sinclair, 2016), and researchers are seeking possible natural treatments that may provide alternatives to chemical medicine and surgery. Currently, natural products are emerging as attractive alternatives to the public instead of synthetic medicines because of the side effects associated with these medicines. Several herbal therapies, including Safflower (*Carthamus tinctorius* L.) and red sage (*Salvia miltiorrhiza*) (Seto et al., 2015),

are the most requested herbal alternatives requested in treating different diseases, including DM and CD (Ajebli et al., 2020; Khodamoradi et al., 2016; Kibiti & Afolayan, 2015; Perng et al., 2018). Okra (*Abelmoschus esculentus*) is one of the most popular botanical sources that is supported by studies that show a positive effect on managing DM and CD (Islam, 2019; Sereno et al., 2022; Tongjaroenbuangam et al., 2011). For instance, okra can decrease glucose absorption, inhibit dipeptidyl peptidase-4 (DPP-4), decrease the expression of peroxisome proliferator-activated receptors, increase the expression of glucose transporter-4, inhibit α-glucosidase, inhibition of α-amylase, reduce insulin-degrading enzyme and tumor necrosis factor-α (TNF-α), and impart antioxidant effects (Esmaeilzadeh et al., 2020; Herowati et al., 2020). Okra is a gluten-free dietary source and contains secondary metabolites ((including α-carotene, lycopene (Khan et al., 2022), quercetin-3-O-gentiobioside, isoquercitrin, rutin, protocatechuic acid and catechin derivatives, catechin, epicatechin procyanidin B1 & B2 (Agregán et al., 2022), quercetin (Anjani et al., 2018), quercetin-3-O-beta-glucopyranosyl-(1→6)-glucoside (Thanakosai and Phuwapraisirisan, 2013)) that can manage DM and CD, respectively (Agregán et al., 2022; Zhu et al., 2020) and consequently have beneficial effects on these diseases.

Intriguingly, the link among DM, CD, and okra has been indicated by many studies published in recent literature. Undoubtedly, individuals living with DM are more liable to initiate CD; however, many studies have shown that okra can simultaneously treat DM and CD. Previously, a review has not been conducted on DM, CD, and their treatment by okra; hence, the present review is aimed at the health benefits of okra in DM and CD therapies.

Methodology

Databases such as PubMed, Google Scholar, and Scopus were searched with the following search strings ("okra" OR "Abelmoschus esculentus" OR "okra extract" OR "okra polysaccharide" OR "okra extract" OR "okra bioactives" "Abelmoschus esculentus" OR "polysaccharide" "Abelmoschus esculentus extract" AND "bioactive compounds" OR "okra" OR "bioactivities", "diabetes mellitus OR type 2 diabetes mellitus" OR "diabetes mellitus" AND "cognitive dysfunction" OR "DM AND CD" OR "okra" AND "diabetes mellitus" OR "okra" AND "cognitive dysfunction"). Almost 230 articles were found without time limitation based on their publication; however, only the most recent articles (143) that had investigated the health-beneficial effects of okra on DM and CD were included. For the inclusion criteria, the authors collected all the published papers which were written in English language only and they took published papers from (2002) to (2023) years only, and For exclusion criteria, they excluded non-English articles, letters, editorials, conference abstracts, practice guidelines, news articles, and conference reports.

Diabetes mellitus

DM is a heterogeneous metabolic (Biessels & Gispen, 2005) and complex noncommunicable disease (Cousin et al., 2022; Kumar et al., 2009) characterized by polydipsia (increased thirst), polyuria (frequent urination), and polyphagia (increased hunger) with consequences of homeostasis disruption because of impaired glucose metabolism. Globally, more than 100 million people are affected by DM, which is considered one of the five leading causes of death (Abbas1 et al., 2021; Deshmukh et al., 2015; Mishra et al., 2017). DM can increase the risk of many complications including cardiovascular diseases, renal failure, blindness, stroke, neuropathy, retinopathy, and amputations (Deshmukh et al., 2015).

DM is the origin of microvascular and macrovascular complications consequently increasing the risk of mortality. Microvascular complications are diseases of the minute blood vessels in the body (Avogaro & Fadini, 2019) and are linked with the progression of nephropathy, neuropathy, and retinopathy (Park et al., 2019) that are highly prevalent in patients with DM. The progression and onset of macrovascular diseases (the diseases of large blood vessels) are obsessed with the combined unwanted effects of various risk factors (Avogaro & Fadini, 2019).

The National Diabetes Data Group (NDDG) proposed a classification for diabetes in 1979 that was mainly based on DM treatment requirements for type 1 diabetes (T1D), insulin-dependent diabetes, type 2 diabetes (T2D), noninsulin-dependent diabetes and gestational diabetes (GD) (Mishra et al., 2017) (Fig. 1). T2D has insulin resistance as its main cause; however, several varieties of atypical diabetes do not fall under the umbrella of these recognized traditional types of diabetes (Bavuma et al., 2019; Sreenivasamurthy & Sreenivasamurthy, 2021) (Fig. 1).

Here, in the figure by 10 to 15% indicates that children with diabetes are diagnosed with "slowly progressing T1D (Rewers, 2012). Worldwide now have diabetes mellitus, 80 to 90% of whom have T2D (Zheng et al., 2018), and GD affects 5 to 10% of pregnant women (Ross, 2006). T2D and GD promotes the production and secretion of more insulin (hyperinsulinemia) to maintain normoglycemia (compensated stage). TD1 usually occurs acutely unless it is a continuation of TD2. It develops suddenly as a result of an autoimmune attack. However, as insulin sensitivity eventually declines and insulin demand rises,

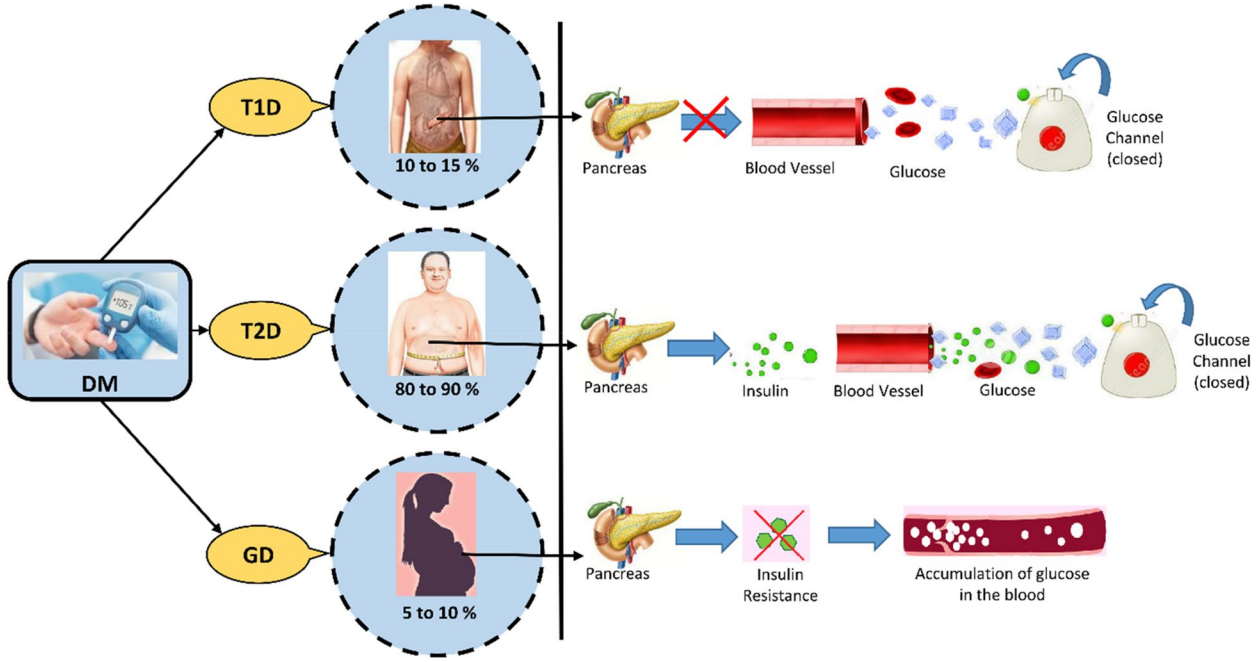


Fig. 1 Diabetes Mellitus (DM), type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes (GD)

β-cells can no longer sustain insulin production, and the patient enters the dysfunctional (decompensated) stage, where hypoinsulinemia, hyperglycemia, and dyslipidemia appear (Hu et al., 2022). GD and pancreatic β-cell dysfunction in women with earlier insulin resistance can progress and increase their risk of developing T2D after pregnancy. GD refers to hyperglycemia with onset during the 2nd or 3rd trimester of pregnancy in women without a previous diagnosis of non-GD (Diaz-Santana et al., 2022).

Contributing factors for T1D pathogenesis, includes genetic factors (HLA, Insulin-VNTR, CTLA-4, PTPN22, AIRE, FoxP3, STAT3, IFIH1, HIP14, ERBB3), epigenetic factors, environmental factors (viruses like rubella and enteroviruses), diet (cereals, cow's milk, vitamin-D, and omega-3 fatty acids), gut microbiota, and immunologic factors (Paschou et al., 2018). Genetic, metabolic and environmental risk factors are interrelated and contribute to the development of T2D (Fletcher et al., 2002).

Cognitive dysfunction

CD or dementia refers to a complex pathological central nervous system disorder (Ritchie, 2022) where memory function declines (Mone et al., 2022) and includes the loss of memory, attention, learning, computation, executive functioning, problem-solving skills, judgmental power, and comprehension (Zhao et al. 2022). These outcomes are linked with dementia and Alzheimer's disease (AD) (a major cause of dementia in older people) (Ahmad et al., 2023a; Ahmad et al., 2023b; Iadecola & Gottesman, 2019). Zheo et al. stated that CD perseveres even in emotional conditions, especially in brain disorders. Consequently, elucidating the pathophysiological mechanisms for CD is of particular emphasis to treat brain disorders (Zhao et al., 2022). The increased human life expectancy has also seen the concomitant increase in the occurrence of brain-related illnesses such as moderate CD (Madhu et al., 2022). The comprehensive pathological process of CD has not yet been clearly addressed (Madhu et al., 2022; Zhao et al., 2022). Saedi and colleagues reported that CD and dementia can be caused by many factors, including AD, degenerative diseases, vascular dementia, certain types of drug abuse, depression, and anxiety, disturbed sleep, hormones, metabolic disorders, DM, alcohol abuse, Lyme disease, hippocampal sclerosis, subdual and epidural hematomas, vitamin B12 deficiency, seizures, human immunodeficiency virus (HIV)-associated neurocognitive disorder, and Hashimoto's encephalopathy (Saedi et al., 2016).

The number of elderly people globally living with CD has significantly risen. In 2017, 962 million individuals with CD were 60 years or older, accounting for 13% of the global population (Sanford, 2017). An AD international report predicted that the dementia population was > 55 million in 2019 and will increase to 78 million in 2030 and 139 million in 2050 (Fig. 2) (Ahmad et al., 2022; Chowdhary et al., 2022). As AD is the possible cause of CD, the increasing prevalence of AD will increase the

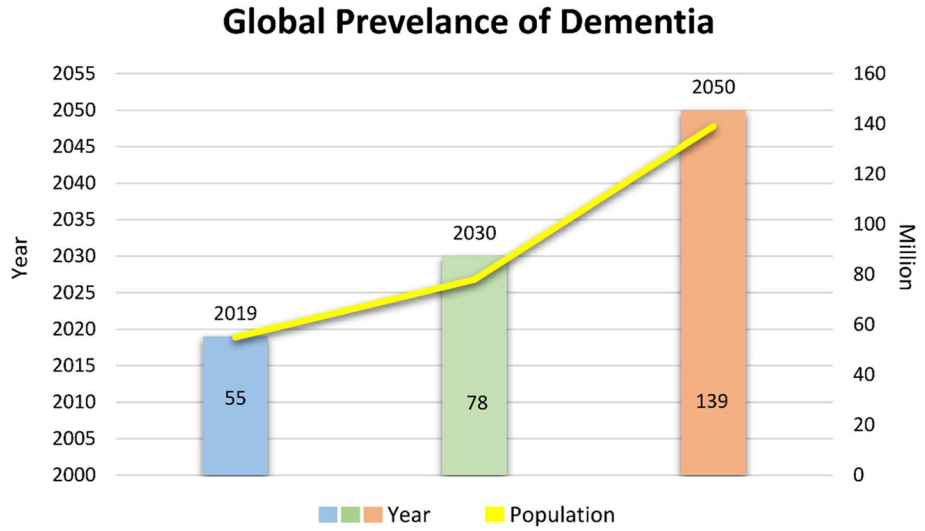


Fig. 2 Estimated growth in the number of people living with dementia from 2019 to 2050 (Chowdhary et al., 2022).

risk of CD. Approximately 75% of the population with dementia is believed to not receive a correct diagnosis (Chowdhary et al., 2022). Additionally, compared with younger age groups, this population is responsible for a higher percentage of overall medical expenses, although CD is a vital contributing factor for that (Sanford, 2017). CD is most common in older adults (≥65 years), and the prevalence is exacerbated with age and has been estimated to be approximately 10% (Mone et al., 2022).

The prevalence and burden of CD remain high because of the lack of understanding of the etiology, medical assessment, and management (Raghunath et al., 2022). In older persons without dementia, CD is characterized as the coexistence of physical dysfunction and cognitive decline (Sanford, 2017) (Fig. 3).

Causes of CD, include Alzheimer's disease, degenerative diseases, vascular dementia, certain types of drug abuse, depression, anxiety, disturbed sleep, hormones, metabolic disorders, diabetes mellitus, alcohol abuse, Lyme disease, hippocampal sclerosis, subdual and epidural hematomas, vitamin B12 deficiency, seizures, HIV-associated neurocognitive disorder, and Hashimoto's encephalopathy.

Competent therapies to control DM and CD are still required that could give enhance the health span to a great extent. The DM and CD were chosen for this review owing to the worldwide public concern. Therefore, this paper discusses the correlation between DM with CD in the next section.

Correlation of T1D, T2D and CD

Over recent decades, CD has become a chronic diabetic complication in clinics (Wang et al., 2022a). Evidence has shown why some diabetic patients have medically relevant neurodegenerative morbidity (Biessels et al., 2008). Wang et al. reported that as the disease progresses, DM increases the risk of CD two-fold, including effects on learning, memory, and spatial cognitive abilities in humans (Wang et al., 2022a). Biessels et al. 2008 and Biessels & Gispen 2005 found that rodent models with long-term DM display correlations with end-organ damage in CD, including that of peripheral nerves, kidneys, eyes, and the brain (Biessels et al., 2008; Biessels & Gispen, 2005). T1D and T2D can lead to CD through different mechanism and collectively these diabetic illnesses can increase the risk of AD and vascular dementia by 50–100% and 100–150%, respectively (Srikanth et al., 2020).

T1D and CD

T1D and CD have a complex mechanism (Shalimova et al., 2019) but share a disturbance in insulin secretion in blood and sensitivity in insulin receptor (IR) to activate oxidative stress (Newsholme et al., 2016) and inflammatory cascade that causes mitochondrial damage, especially in neuronal and dendritic processes in AD (Khan & Hegde, 2020). In neuronal soma and synaptic terminals, the IR participates in the restoration of cognition in the hippocampus (De Felice et al., 2022; Pu et al., 2022). The origin of insulin in the brain is debatable, and it is probable that circulating insulin in the blood can enter across the BBB (Doust et al., 2022; Kamstra & Tups, 2022; Oudbier et al., 2022). Conversely, some literature data indicates that the olfactory bulb and dentate gyrus may produce insulin that regulates the olfactory bulb and hippocampus functions (Fu et al., 2022).

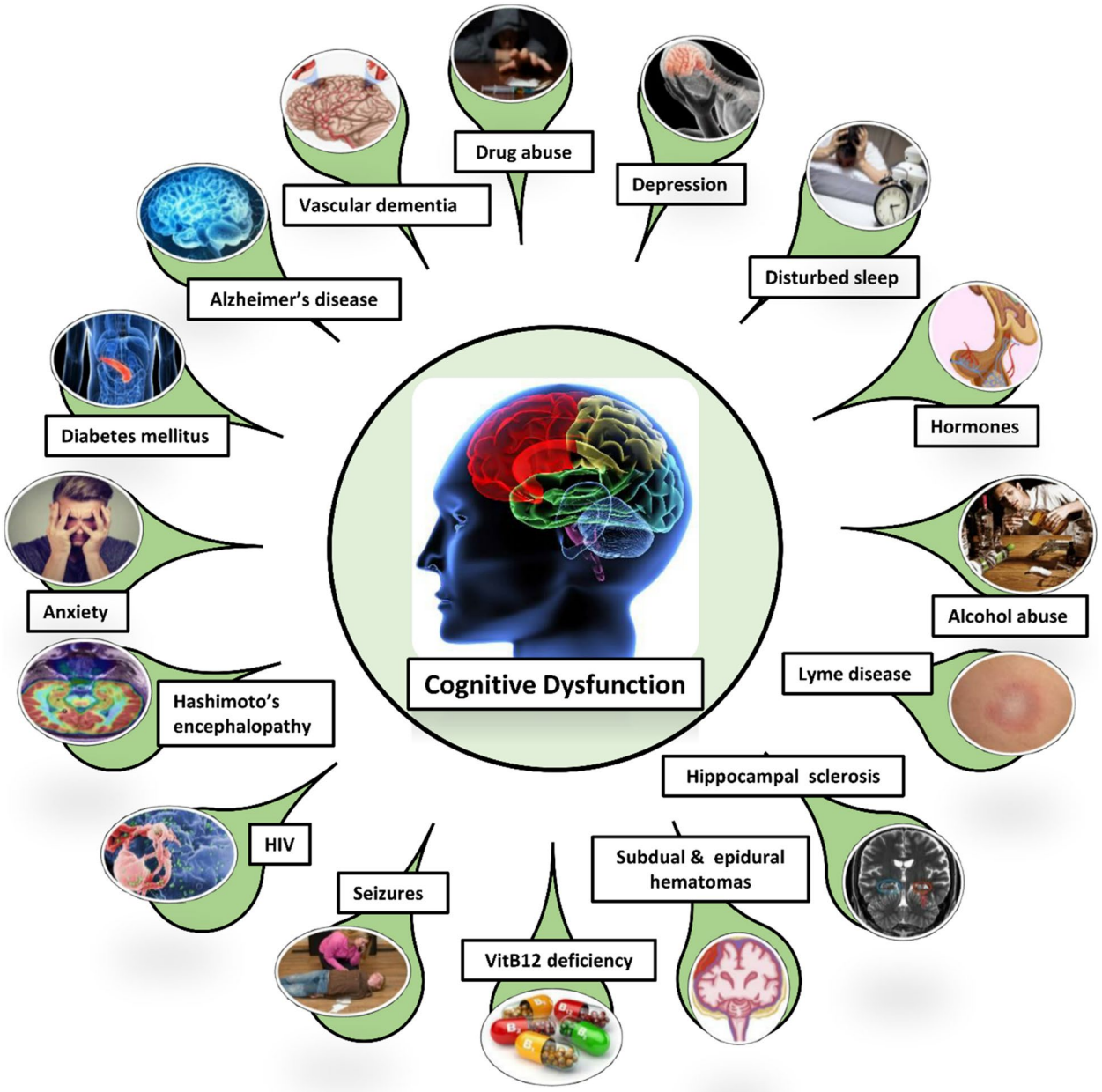


Fig. 3 Possible causes of cognitive dysfunction

In addition, peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) and PTEN-induced putative kinase 1 (PINK1) accelerate ROS synthesis and fatty acid oxidation (Ahuja et al., 2022; Blasiak et al., 2021). Sirtuin 1 (SIRT1) deacetylates nuclear factor kappa-light-chain-enhancer of activated β cells (NF-kB), forkhead box O (FOXO), and PGC-1α and subsequently initiates oxidative metabolism in mitochondria and to suppress ROS production. SIRT1 stimulators decrease the generation of proinflammatory mediators and can have a possible protective effect in AD (Zilliox et al., 2016). Diabetic autonomic neuropathy is another disease linked with low blood pressure and elevated stroke risk, which are both possible aspects of CD (Colombo, 2022); accordingly, orthostatic hypotension is more familiar in CD. Many inflammatory mediators in DM, including NF-kB, TNF-α, interleukin (IL)-1β, and interleukin 6 (IL-6), participate in CD development. In diabetic brains, these cytokines prompt the synthesis of ROS and trigger various cellular pathways such

as advanced glycation end products (AGE), and protein kinase C (PKC) to cause neuroinflammation and neurodegeneration and ultimately CD (Zilliox et al., 2016). Thus, it is assumed that T1D can cause CD by following the described mechanisms of T1D and CD (Fig. 4).

γ-Aminobutyric acid-A (GABA-A), amyloid beta (Aβ), peroxisome proliferator-activated, receptor-gamma coactivator-1α (PGC-1α), PTEN-induced putative kinase 1 (PINK1), reactive oxygen species (ROS), sirtuin 1 (SIRT1), nuclear factor kappa-light-chain-enhancer of activated β cells (NF-kB), forkhead box O (FOXO), diabetic autonomic neuropathy, tumor necrosis factor (TNF), interleukin-1β (IL-1β), interleukin-6 (IL-6), advanced glycation end products (AGE), protein kinase

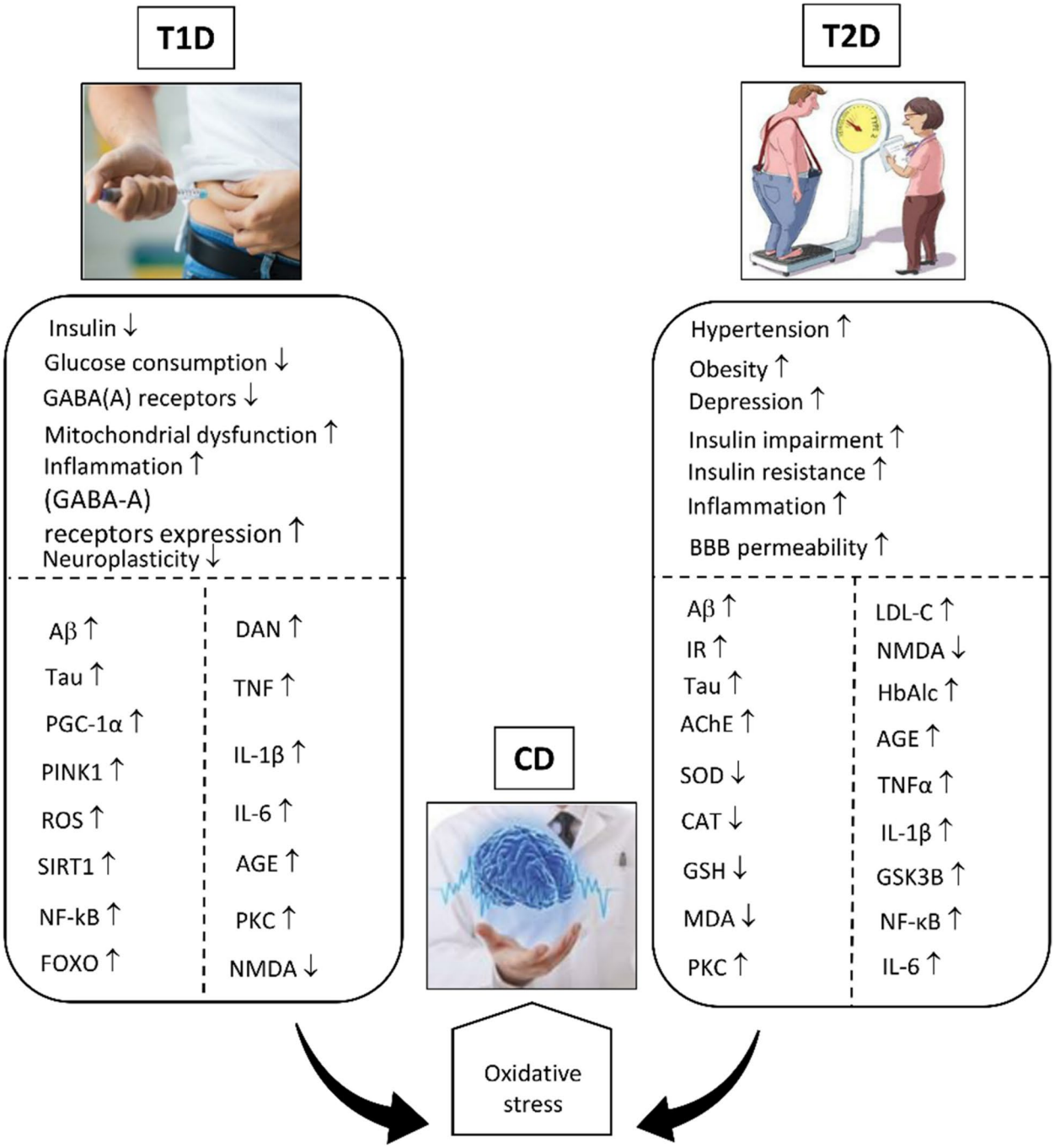


Fig. 4 Correlation of T1D and T2D with CD

C (PKC), N-methyl-D-aspartate (NMDA), blood–brain barrier (BBB), insulin receptor (IR), phosphorylated Tau, acetylcholinesterase (AChE), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), malonaldehyde (MDA), low-density lipoproteins-cholesterol (LDL-C), hemoglobin A1c (HbAlc), and glycogen synthase kinase-3 beta (GSK3B).

T2D and CD

T2D increases the risk of CD similarly to T1D, although T2D possibly causes CD in adults due to hypertension and obesity, both of which are comorbidities. However, clinical studies have shown that hypertension in T2D has no effect on cognition (Srikanth et al., 2020). T2D leads to Aβ accumulation by initiating the mechanism that involves Tau hyperphosphorylation. Phosphorylated Tau is present in the hippocampus of T2D animal models and gives rise to CD (Zilliox et al., 2016). Vascular and neurodegenerative disorders in T2D may involve the same pathways such as hyperglycemia, altered insulin signaling, severe low-grade inflammation, and AGE to cause neurocognitive decline. Furthermore, people with T2D have a higher risk of depression, which causes age-related CD (Srikanth et al., 2020). T2D in combination with obesity increases insulin resistance (a decreased response of body cells to reduce glucose conversion) and/or insulin levels in the blood. The lower proportion of insulin triggers activation of glycogen synthase kinase-3 beta (GSK3B), a multifunctional serine/threonine protein kinase enzyme and ultimately produces hyperphosphorylation of Tau protein and accumulation of neurofibrillary tangles causing CD (Umegaki, 2010). Recent investigations reported that cerebral blood flow is usually increased by insulin, but that this action is blunted by insulin resistance, producing harmful effects such as mitochondrial dysfunction, oxidative stress, and decreased neuronal viability and eventually CD (van Sloten et al., 2020).

Similarly, T2D upregulates the expression of acetylcholinesterase (AChE), and suppresses that of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) while enhancing the expression of TNFα, IL-1β, IL-6, NF-κB, and caspase-3 and production of malonaldehyde (MDA) and subsequent progression of CD. Studies showed that nearly 2000 women participants exhibited CD development 4-fold with hemoglobin A1c (HbAlc) values < 8.0% in T2D; moreover, CD is also associated with the dysregulation of glucose. Insulin resistance, hypercortisolism, Aβ accumulation, and inflammation are components of T2D and linked to AD. Insulin resistance has been observed to hinder cholinergic signaling, and in T2D *in vivo* studies, the synthesis and release of acetylcholine diminished. Inflammatory mediators such as IL-6 and C-reactive protein that increase in T2D and metabolic syndrome are an apparent cause of CD (Chornenkyy et al., 2019). Hyperglycemia in T2D causes toxicity in neurons especially in the brain via oxidative stress and osmotic insults. Perpetuation of severe hyperglycemia increases the production of AGE, which is toxic to neurons (Umegaki, 2010). Analysis of long-term epidemiological data showed that chronic hyperglycemia causes DM-related CD (Kim, 2019). Hence, T2D plays a vital role in CD development (Fig. 4). Many herbal medicines including Okra has been evaluated as a potential agent with health-beneficial properties that might help in the treatment of DM and CD.

Okra

Okra (*A. esculentus* L.), commonly known as bhindi, lady's finger, guino-gombo, guibeiro, and gumbo, belongs to the Malvaceae family or mallow family. Okra is the most popular and economically important edible plant (vegetable) that can be used in soups, salads, and stews. In recent decades, okra has become widely used as medicine with several applications of the flowers, fresh leaves, pods, seeds, buds, and stems, which are cultivated in tropical and sub-tropical regions of the world (De Rosa et al., 2010; Doymaz, 2005; Gemede, 2015; Wu et al., 2022). Okra originated in Ethiopia (Gemede, 2015) and is now cultivated in many countries in Africa (Doymaz, 2005; Wu et al., 2022), such as Egypt and Nigeria (Doymaz, 2005; Liu et al. 2021), Europe, such as Cyprus and Greece (Doymaz, 2005; Gemede, 2015), and Asia, such as India (Doymaz, 2005; Panighel et al., 2022), China (Wu et al, 2022), Iran, Philippines, Japan, Turkey, (Doymaz, 2005), Myanmar, Bangladesh, Pakistan, Afghanistan, Malaysia, and Thailand (Gemede, 2015) and in Brazil and the southern United States (De Rosa et al., 2010; Wu et al., 2022).

Numerous studies have reported that okra is low in calories, and rich in protein, dietary fiber, vitamins, and minerals and therefore possesses notable health benefits (Obomeghei et al., 2022). Okra also contains polysaccharides, fats, carbohydrates, flavonoids and phenolic acids, and minerals such as potassium, sodium, calcium, iron, magnesium, zinc, manganese, and nickel (Doymaz, 2005; Liu et al., 2021; Wu et al., 2022). Okra has attracted research attention because of its various pharmacological benefits that have antihyperglycemic, neuroprotective, antioxidant, anticancer, antihyperlipidemic, antifatigue, antiadhesive, and immunomodulatory properties (Mishra et al., 2017; Obomeghei et al., 2022; Wu et al., 2022) in treating bronchitis, stomach ulcers, dysentery, gastroprotective, and pneumonia (Agregán

Table 1 Composition of different parts (pods, seeds, and leaves) of okra

Okra pods (dry wet basis: g/100g)							
Protein	**Dietary fiber**	**Carbs**	**Fat**	**Ash**	**Moisture**	**Energy (kcal/100 g)**	**Reference**
2.367–3.41	6.781–8.314	7.857–8.261	0.066–0.1	1.514–1.197	84.67–87.65	51.258	(Khan et al., 2022)
2.0	3.2	7	0.1			130	(Elkhalifa et al., 2021)
10.25–26.16	11.97–29.93	36.66–50.97	0.56–2.49	5.37–11.30	9.63–13.33	197.26–245.55	(Liu et al., 2021)
3.55	8.2	4.864	0.066	1.46	81.9	50.57	(Romdhane et al., 2020)
2.68		10.6	0.28	0.85	85.6	55.67	(Petropoulos et al., 2018)
Okra seeds (dry wet basis: g/100g)							
16.45		55.44	12.05	4.96	11.10		(Waiss et al., 2020)
09.69	00.99	18.57	30.86	01.39	38.50		(Ojiako et al., 2013)
41.11	3.45	10.60	31.04	3.42	10.38		(Adelakun et al., 2009)
21.0	29.6	28.3		5.10	7.70		(Aminigo & Akingbala, 2005)
Okra leaves (dry wet basis: g/100g)							
21.55	17.60		4.10	9.10	8.20		(Ilodibia et al., 2017)
09.86	01.00	19.19	29.00	01.59	39.36		(Ojiako et al., 2013)

et al., 2022; Esmaeilzadeh et al., 2020). Okra fruit mucilage contains flavonoids and l-rhamnose, d-galactose, and d-galacturonic acid (Esmaeilzadeh et al., 2020). The nutritional value of okra (pods, seeds, and leaves) is detailed in Table 1.

After cooking, the mucilaginous consistency of okra has properties that have medicinal and nutraceutical applications and are used as a blood volume expander or a plasma replacement for inflammatory and gastric irritative diseases. De Rosa and colleagues reported that okra contains a high amount of dietary fiber (De Rosa et al., 2010) that is beneficial to control diabetes (Sarwar et al., 2022). Moradi and colleagues reported okra can elicit significant hypoglycemic and hypolipidemic effects. An 8-week intake of 10 g of okra flour (100 g of fresh okra fruit) mixed with 150 g of yogurt produced positive effects in modulating fasting plasma glucose levels in a homeostatic model of assessment for insulin resistance in patients with T2D (Moradi et al., 2020). Therefore, okra can be viewed as a beneficial health food that may improve antidiabetic effects (Panighel et al., 2022). Okra polysaccharides can improve memory function, reverse metabolic disorder and cognitive impairment through the insulin signaling pathway (Yan et al., 2020).

Table 2 List of bioactive compounds and their quantities in different parts of okra

Sr. no.	**Compound name**	**Part**	**Quantity**	**Reference**
1.	α-carotene	fruit	0.83 mg/100 g	(Khan et al., 2022)
2.	Lycopene	fruit	0.55 mg/100 g	
3.	Total phenolic content	fruit	288.2 to 3426.2 mg/100 g	
4.	Quercetin-3-O-gentiobioside	fruit	1359.04 µg/g dry weight	(Agregán et al., 2022)
5.	Quercetin-3-O-glucoside (isoquercitrin)	fruit	905.45 µg/g dry weight	
6.	Quercetin-3-O-rutinoside (rutin)	fruit	52.86 µg/g dry weight	
7.	Protocatechuic acid	fruit	114.77 µg/g dry weight	
8.	Catechin derivatives	fruit	284.92 µg/g dry weight	
9.	Quercetin	fresh okra	0.27 mg/g	(Anjani et al., 2018)
10.	Catechin	leaf	9.19 mg/g dry extract	(Agregán et al., 2022)
		seed	56 mg/100 g	
12.	Epicatechin	seed	31.90 mg/100 g	
13.	Procyanidin B1	seed	289.40 mg/100 g	
14.	Procyanidin B2	seed	675.20 mg/100 g	
15.	Quercetin-3-O-beta-glucopyranosyl-(1→6)-glucoside	seed	-	(Thanakosai & Phuwapraisirisan, 2013)

Several bioactive components especially oligomeric catechins and flavonol derivatives (quercetin) that are present in different parts of okra (pod, seed, root, fresh fruits, and leaves) are presented in Table 2. These compounds have the potential to enhance cognition function (Esmaeilzadeh et al., 2020) and control DM (Herowati et al., 2020).

These phyto-compounds have distinct roles in the management of DM and CD. To elaborate on the antidiabetic and memory-enhancing effect of phytochemicals of okra, the outcomes of several studies have been summarized in Table 3.

The glycemic index is a measure of the ability of foods enriched with carbohydrates to enhance the serum glucose level (Koubala et al., 2014). According to the American Diabetes Association, diabetics can freely eat non-starchy vegetables with a low glycemic index. Thus, okra is a good option for individuals with diabetes because it has a very low glycemic index of approximately 20 (Mandal et al., 2021). Although the glycemic load is a dietary measurement of the type and quantity of carbohydrates used as intake (Sieri et al., 2017), the physiologically glycemic load is a predictor of post-prandial glucose levels and

insulin requirements and can be used with foods that are high in carbohydrates and low in fat and protein (Sieri et al., 2017). However, low glycemic-load diets are considered best for patients with DM; therefore, okra is an optimal food choice for them as both the higher dietary glycemic index and load are linked with the progression of T2D (Sahyoun et al., 2008).

Effects of okra on the gut microbiome, DM, and CD

Intestinal flora and a variety of diseases, including type 2 diabetes and neurodegenerative disorders, are being studied more and more these days (Wang et al., 2022b). There are many different kinds of microbes living in an animal's gut. The enteric microorganisms and the gut interact and depend on one another to form a dynamic balance when there are stable bacterial proportions. Because of the occupying impact, nutrition competition, and metabolite and bacteriocin release, the normal microbiota in the microecological balance can build a biological barrier against the exogenetic bacteria. Meanwhile, changes in food content can affect the makeup of gut bacteria (Gao et al., 2018). Diabetes mellitus-related gut dysbiosis is linked to breakdown of the epithelial barrier and a reduction in short-chain fatty acids. Toxins produced by microbes traverse the "leaky gut" and cause insulin resistance and systemic inflammation. Gut dysbiosis in children has been linked to an increased risk of T1D. Transplanting microbiota models allows for the transmission of the obese phenotype. Low-protein plant-based diets and several anti-diabetic medications have been linked to beneficial microbiome effects (Lau et al., 2021). According to studies, gut microbiome dysbiosis contributes to the fast development of insulin resistance in T2D, which causes nearly 90% of all instances of diabetes globally. Dysbiosis of the gut microbiota may alter host metabolic and signaling pathways, as well as intestinal barrier processes, all of which are either directly or indirectly linked to T2D's insulin resistance (Sharma & Tripathi, 2019). The fruits of okra that can be eaten are rich in polysaccharides, pectin, and polyphenolic chemicals. These compounds have a variety of biological actions and may be used as a dietary therapy to reduce metabolic disorders, which are probably caused by alterations in the intricate host-microbiota milieu. By encouraging nutritional supplementation, limiting pathogen colonization, preserving normal mucosal immunity, and controlling fat storage and metabolism, the gut microbiota—also known as the "second genome"—play a critical role in human nutrition and health (Zhang et al., 2020). In a study, the intestinal flora of the STZ-induced diabetic rats was assessed by the okra aqueous extract, which upregulated *Burkholderiaceae*, *Christensenellaceae*, and *Lachnospiraceae* while downregulating Firmicutes and increasing Proteobacteria. It may be possible to use okra aqueous extract as a functional food to control the balance of intestinal microecology in diabetics (Wu et al., 2022). In another investigation, during *in vitro* digestion simulation, a pectic polysaccharide from okra was partially broken down and subsequently used by the human gut bacteria. Furthermore, fecal fermentation led to a notable increase in the number and composition of bacteria, including *Bacteroides*, *Phascolarctobacterium*, *Megasphaera*, and *Desulfovibrio*. These findings from previous study raise the possibility that okra's pectic polysaccharide may have an impact on the composition and abundance of the human gut microbiota (Wu et al., 2021) that may control DM.

The importance of intestinal flora in the brain-gut axis is being increasingly understood as a result of developments in clinical medicine, and this area of study has become increasingly popular. Intestinal flora imbalances in terms of both structure and function could be a major contributor to the global inflammation linked to a number of illnesses. Notable is the possibility that AD is influenced by the brain-gut-microbiome axis. The brain and stomach are interestingly closely and intricately connected. This bidirectional communication between the central nervous system and the intestinal neural system is known as the "brain-gut axis," and the gut microbiome plays a crucial role in it. The remarkable ability of flavonoid chemicals to modulate gut microbiota and function as an immunity booster against illnesses is also

Table 3 *In vivo* investigations of okra against DM and CD.

Extract/ form	Part used	Compound	Dose	Model	*In vitro*	*In vivo*	Induction	Activity	Target	Reference
Powder	Peel and seed	-	100 and 200 mg/kg	Rats	-	✓	STZ	Antidiabetic and antihyperlipidemic	β-cells, insulin secretion and release, insulin sensitivity	(Sabitha et al., 2011)
Methanol	Seed	Isoquercetin and quercetin-3-O-beta-glucopyranosyl-(1→6)-glucoside	1 mg/mL	-	✓	-	-	Antidiabetic	α-Glucosidase, selectively inhibited rat intestinal maltase and sucrase	(Thanakosai & Phuwapraisirisan, 2013)
Aqueous extract	Pods	Rhamnogalacturonan	200 mg/kg b.w/day	Rats	-	✓	STZ	Hypoglycemic effect	-	(Wu et al., 2020)
Powder	Dried okra	Flavonoids, phenolic acids	200 mg/kg/day	Rats	-	✓	STZ	Antihyperglycemic effect	Improve glucose homeostasis, β-cells impairment	(Majd et al., 2018)
Ethanol extract, n-hexane, ethyl acetate, and water	Fruit	Quercetin, triterpenoids	200, 107, 6, and 86 mg/kg b.w	Rats	-	✓	STZ-NA	Antidiabetic Activity	Pancreatic beta cells, inhibition of aldose reductase enzyme	(Herowati et al., 2020)
Aqueous and methanolic	Seed	Phenols, terpenoids	200 mg/kg, p.o.	Mice	-	✓	Scopolamine	Nootropic activities	-	(Doreddula et al., 2014)
Aqueous	Fruits	Polysaccharides	600 mg/kg	Mice	-	✓	$A\beta_{1-42}$	Cognitive function, antidiabetic and antiobesity activity in AD mice	-	(Yan et al., 2020)
60% aqueous ethanol	Fruits	Flavonoids	100 and 300 mg/kg	Kunming mice	-	✓	$A\beta_{1-42}$	Cognitive impairment, AD neuroinflammation.	BDNF	(Yan et al., 2021)
Ethanol	Pod	Catechin epicatechin procyanidin B1 and B2 quercetin and rutin	60 mg/kg/mL by p.o.	Mice	-	✓	Dexamethasone	Neuroprotective, memory function	-	(Tongjaroenbuangam et al., 2011)
Powder	Root	Quercetin	1600 mg/kg b.w	Rats	-	✓	Repeated noise	Cognitive function	-	(Samad et al., 2020)

STZ streptozotocin, *BW* body weight, *STZ-NA* streptozotocin-nicotinamide, *p.o.* per oral, *BDNF* brain-derived neurotrophic factor, *Aβ* amyloid-β, *AD* Alzheimer's disease.

worth mentioning (Wu et al., 2022). In an AD model using APP NL-G-F/NL-G-F mice, the effects of okra polysaccharides-prepared microcapsules with or without *L. plantarum* encapsulation on intestinal microbiota were evaluated using 16S metagenomic analysis and short-chain fatty acids. The results showed that the microbiota improved and AD was reversed through increasing the numbers of *Lactobacillus* in AD mice (Lee et al., 2023). Another experiment showed that polysaccharides could improve cognitive performance in mice by restoring intestinal flora balance caused by D-galactose-induced aging in a mouse model, consequently inhibiting oxidative stress and peripheral inflammation (Gao et al., 2021). The intestinal microorganism composition of the polysaccharide-treated mice was significantly different from that of the control. *Actinobacteria*, *Erysipelotrichia*, and *Bacteroidia* were found in higher concentrations while *Clostridium* was found in lower concentrations. Additionally, the mice treated with polysaccharides showed improved memory and learning capabilities (Su et al., 2018). It was discovered that both exercise and a high-fat diet would have a significant impact on the composition of intestinal microorganisms, including the *Bacteroidetes* and *Firmicutes*, which are the most common in the intestine, and that changes in intestinal flora through exercise could significantly improve cognitive decline brought on by dysbiosis brought on by a high-fat diet. The experiment examined the effects of exercise and a high-fat diet on the intestinal flora of mice as well as the effects of these changes on cognitive function. Furthermore, the researchers discovered that polysaccharides could significantly enhance cognitive function by regulating intestinal flora (Kang et al., 2014). Okra polysaccharides have been found to be effective in regulating gut microbiota, thereby controlling DM and CD.

Molecular mechanism of okra and DM

Polysaccharides have the ability to significantly reduce hyperglycemia, low-grade inflammation, oxidative stress, and improve glucose tolerance in T2D (Ganesan & Xu, 2019; Mishra et al., 2017). The polysaccharides in okra activate the phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT) pathway, improve insulin signaling through insulin receptors, and eventually regulate the extracellular signal-regulated kinase (ERK)/ c-Jun N-terminal kinase (JNK)/mitogen-activated protein kinase (MAPK) pathway. These polysaccharides strongly upregulate insulin promoter factor 1 and B-cell lymphoma 2 (Bcl-2) while significantly down-regulating the mRNA expression of the BCL2 associated X (Bax) protein. Bcl-2 and Bax play role in β-cells survival, however by increasing the ratio of Bcl-2/Bax and enhancing insulin production by restoring insulin promoter factor 1 in DM, okra's polysaccharides play a crucial role in protecting pancreatic islet cells from apoptosis (Ganesan & Xu, 2019).

Treatment with the polysaccharides from okra reduces ROS and MDA while increasing SOD, glutathione peroxidase (GSH-Px), and CAT. Okra polysaccharides alleviated the T2D through the activation of PI3K/AKT/ glycogen synthase kinase 3 beta (GSK3β) pathway, and enhanced the nuclear factor erythroid-2 (Nrf2) expression and promoted Nrf2-medicated heme oxygenase-1(HO-1) and superoxide dismutase expression. Polysaccharides found in okra also reduced mitochondrial dysfunction by preventing NADPH oxidase 2 activation (Liao et al., 2019). Enzymes known as α-amylases catalyses the hydrolysis of internal α-1,4-glycosidic linkages in starch in low molecular weight products including maltose, glucose, and maltotriose units (de Souza & e Magalhães, 2010).

Binding of free insulin to the cell membrane-bound IR results in activation of the intrinsic tyrosine kinase of insulin receptor (IR) then phosphorylates the β-subunit of IR which stimulates activation of the insulin signaling cascade through PI3K and AKT, ultimately leading to translocation of the glucose transporter 4 to the cell membrane of skeletal muscle and adipose cells and uptake of glucose (Styskal et al., 2012). According to reports, increased p38 MAPK activity may eventually cause apoptosis as well as hyperglycemia and diabetes. Okra has the ability to regulate the activity of p38 MAPK. Through AKT, the binding of insulin to its receptor starts a cascade of kinase activity (Ahmed et al., 2014). In a study, the expression levels of peroxisome proliferator-activated receptor-gamma (PPAR-γ) and peroxisome proliferator-activated receptor-alpha (PPAR-α) genes that were elevated in diabetic rats, attenuated in okra-treated rats (Majd et al., 2018). Okra has the capacity to modify the ERK/Nrf2/HO-1 signaling pathway, which is activated during apoptosis (Shopit et al., 2020). Isoquercetin and quercetin-3-O-beta-glucopyranosyl-(1–6)-glucoside, which are present in the methanol extract of okra seeds, inhibit rat intestinal maltase and sucrose (Thanakosai & Phuwapraisirisan, 2013). Okra intake improves glycemic control in patients with pre-diabetes or T2D, according to a comprehensive review and meta-analysis of the clinical data. Okra ameliorated hyperglycemia in pre-diabetic and T2D patients (Mokgalaboni et al., 2023) (Fig. 5).

Molecular mechanism of okra and CD

By lowering NMDA receptor expression, okra extract and its phytochemicals (quercetin and rutin) maintain neuronal function in cornu ammonis-3 hippocampal neurons and alleviate learning and memory deficits in dexamethasone-induced mice (Tongjaroenbuangam et al., 2011). Through the control of PI3K/AKT/GSK3

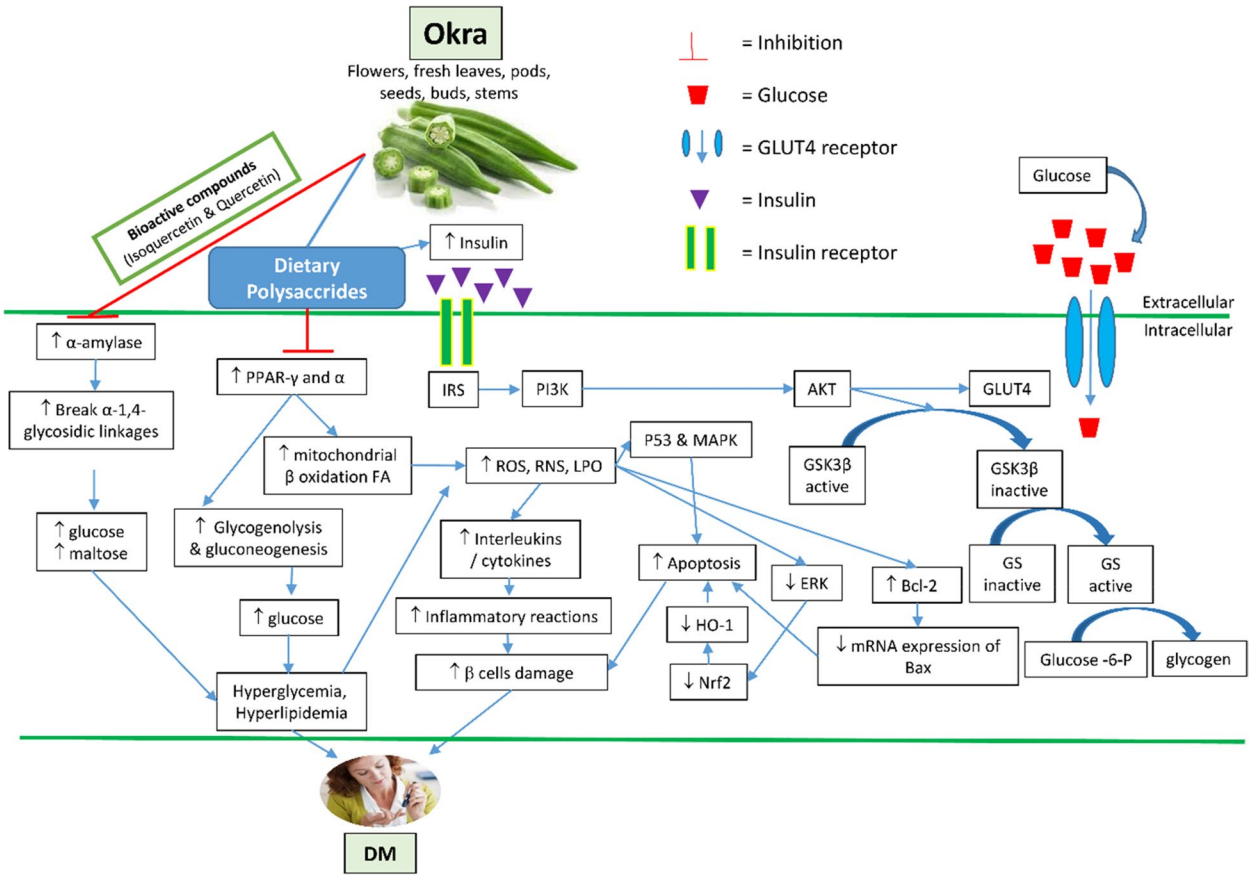


Fig. 5 Depicts the molecular mechanism of okra and DM. Abbreviations: ↑= Increase, ↓=Decrease, DM= Diabetes mellitus, PPAR=Peroxisome proliferator-activated receptor, IRS=Insulin receptor, PI3K=Phosphoinositide 3-kinase, AKT=protein kinase B, MAPK=Mitogen-activated protein kinase, FA=Fatty acids, GS =glycogen synthase, ROS = Reactive Oxygen Species, RNS = Reactive Nitrogen Species, LPO= Lipid peroxidation, GSK3β=Glycogen synthase kinase-3 beta, ERK=Extracellular signal-regulated kinases, HO-1=Heme Oxygenase 1, GLUT4 = Glucose transporter type 4, GSK3β = Glycogen synthase kinase-3 beta, Bcl-2=(B-cell lymphoma 2), Nrf2=nuclear factor erythroid 2–related factor 2, Glucose -6-P=Glucose 6-phosphatase, mRNA =Messenger RNA, MDA=Malondialdehide, NMDA=The N-methyl-D-aspartate, Aβ=Amyloid beta, GSH=Glutathione, SOD=Superoxide dismutase, pGSK3β=Phosphorylated glycogen synthase kinase 3β

signaling proteins, okra polysaccharides alleviate cognitive impairment. By controlling secretases, insulin safeguards against cognitive impairment. The ERK cascade, which converges with a variety of other signaling cascades, including the PI3K/AKT pathway, is crucial for the induction and maintenance of long-term potentiation and memory consolidation in the hippocampus. The activation of PI3K by an IR substrate causes the activation of AKT (Yan et al., 2020). Okra polysaccharides improve the CD in AD-like model mice, which is mediated by the regulation of brain-derived neurotropic factor levels in cortex and hippocampus and up-regulating of cyclic-AMP response element binding (CREB)/ERK and PI3K/AKT/GSK3β pathways. Two free radical scavenging enzymes, GSH-Px and SOD, can scavenge oxidative mediators to lessen oxidative damage in brain tissue. It was the response of the Aβ deposition causes surrounding microglial cell activation. The activation of microglial cells by Aβ deposition promotes the production of proinflammatory and cytotoxic factors, such as TNF-α, IL-1β, IL-6, interferon-gamma (IFN-γ), transforming beta growth factor (TGF-β), chemokines and macrophage inflammatory protein (Yan et al., 2021).

In BV2 microglia cells treated with okra, TNF-α and IL-1 production was also markedly reduced. Okra treatment dramatically reduced the degree of nuclear factor kappa B (NF-kB) p65 phosphorylation caused by lipopolysaccharide. Okra also inhibited Lipopolysaccharide from causing the upstream molecule of NF-kB, AKT phosphorylation (Mairuae et al., 2017). Okra polysaccharides recovers neuron autophagy which are regulated by dipeptidyl peptidase-4 inhibitor, thus preventing the damage to the hippocampus, improving recognition and emotion (Huang et al., 2023). Okra polysaccharides alleviation of oxidative stress and neuroinflammation (Yan et al., 2021) in high-fat-diet (HFD) induced oxidative

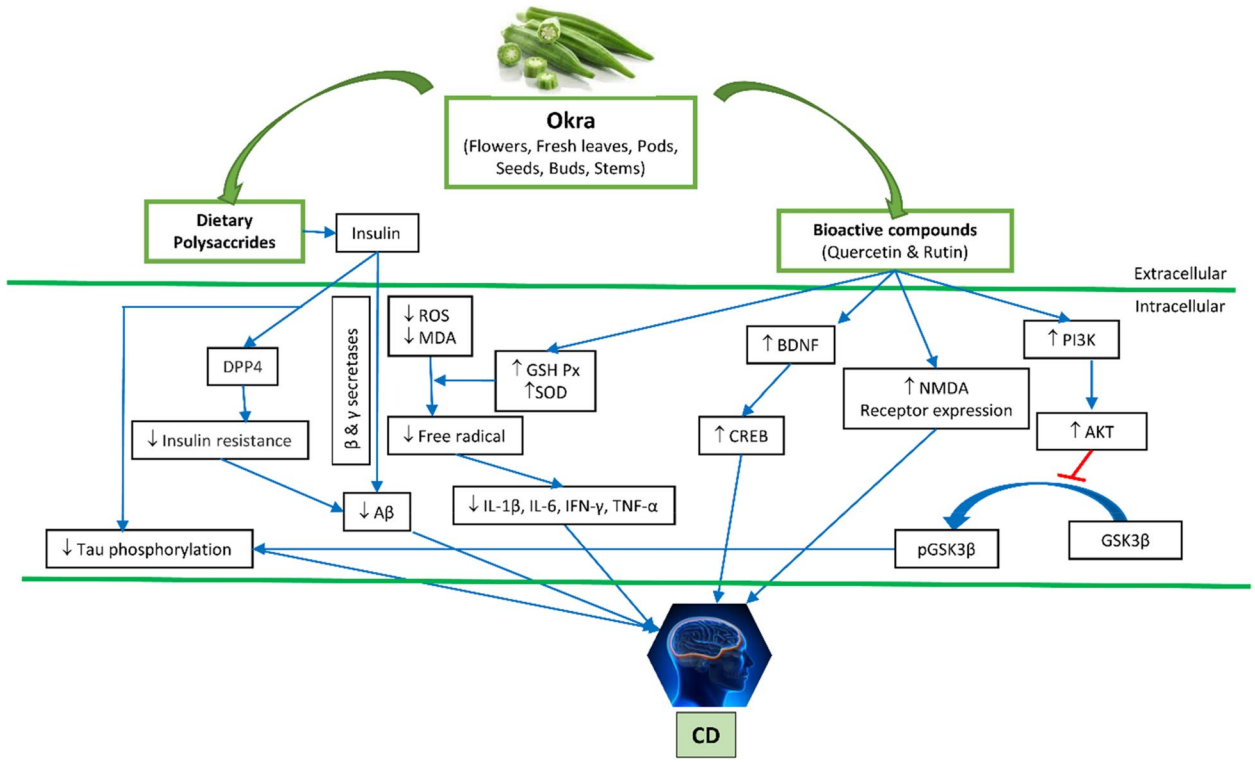


Fig. 6 Exhibits the molecular mechanism of okra and CD. Abbreviations: ↑= Increase, ↓=Decrease, PI3K=Phosphoinositide 3-kinase, AKT=protein kinase B, GS =glycogen synthase, ROS = Reactive Oxygen Species, TNF-α=tumor necrosis factor-α. IL-1β=interleukin-1β, IL-6=interleukin 6, IFN-γ=interferon-gamma, GSK3β=Glycogen synthase kinase-3 beta, pGSK3β = phosphorylated glycogen synthase kinase-3 beta, DPP4=Dipeptidyl peptidase-4 inhibitor, MDA=Malondialdehide, NMDA=The N-methyl-D-aspartate, Aβ=Amyloid beta, GSH=Glutathione peroxidase, SOD=Superoxide dismutase, BDNF= Brain-derived neurotropic factor, CREB=Cyclic-AMP response element binding, pGSK3β=Phosphorylated Glycogen Synthase Kinase 3β, CD=cognitive dysfunction.

stress. HFD causes an excessive production of ROS including MDA, and reduces the antioxidant enzyme levels, leading to increased insulin resistance (Helmi et al., 2021b). An increase in Tau phosphorylation and the expression of pro-apoptotic proteins and a decrease in the expression of anti-apoptotic proteins are caused by decreased insulin activation, which also results in decreased AKT and PI3K activity. This process contributes to neurodegeneration in the hippocampus (Prom-In et al., 2020). Glycogen synthase is activated and produced by liver cells as a result of GSK3 losing its activity after being phosphorylated. As a result of insulin resistance, downstream signal transduction is inhibited, but GSK3 still exists in its active state and hyperphosphorylates a number of substrates, including Tau protein, in nerve cells. The growth of neurofibrillary tangles and microtubule destabilization brought on by hyperphosphorylation of Tau cause AD (Ahmed et al., 2014). Hippocampal neuron survival is restored by okra subfractions, which also reduce insulin resistance and p-tau expression (Huang et al., 2023) (Fig. 6).

Regulatory challenges concerning okra as nutraceuticals, food supplements, and functional foods

Because health care costs are always rising, scientists, medical professionals, and the food business are working hard to develop solutions that will allow problems to be properly controlled. The primary factors driving the growth of the nutraceutical and functional food markets are the increasing prevalence of obesity, diabetes, eye health problems, cardiovascular diseases, changing food consumption patterns in developing markets, growing interest in preventive medicine, and growing demand for multivitamins. Research on nutraceuticals and functional foods has recently shifted to a greater degree in an effort to better comprehend their importance (Hilton, 2017; Aguilar-Pérez et al., 2023) Government agencies, food scientists, and for-profit research facilities are all making significant progress in this direction. In essence, the focus is on identifying various functional foods and their mechanisms that contribute to the prevention or treatment of chronic illnesses, enhance overall health, and eventually lower healthcare expenditures. The process of developing nutraceuticals and functional foods is costly,

time-consuming, and laborious since it is challenging to obtain country legislation, novel food items from food firms that support health claims, and so on. Food corporations have historically provided funding for research into the creation of new and innovative products, but when it comes to functional foods, there are greater dangers involved for both the food industry and consumers. While unique substances can be utilized to create functional and nutraceutical products with patentable rights, most products contain "free" ingredients that can be easily duplicated, giving the inventor company's competitive advantages lessened (Jalgaonkar et al., 2019).

Okra can be registered as food supplements under the food code in addition to being regulated as therapeutic items (Dantas et al., 2021; Negash et al., 2023). Food supplements work to sustain health through physiological and nutritional benefits, whereas pharmacology medicines have qualities related to pharmacology, immunology, or metabolism that are intended to treat or prevent disease. Due to the fact that food supplements often come in forms that are similar to those of medicinal products—such as capsules, tablets, or powder sachets—it can be difficult to distinguish between the two. The nutrients or "other substances" must only have a physiological or nutritional effect in order to meet the definition of a dietary supplement. Products that can potentially impact the human body and metabolism are frequently classified as medicines (Wynendaele et al., 2018). However, a product cannot be classified as a medicinal product for any purpose other than those specified by this portion of the definition. It is also critical to take the active substances' dosage into account. A product is not considered medical if its dose is less than what is now known to be necessary to restore, adjust, or modify a physiological function. The CJEU rulings have clarified and elaborated on this: a product's position as a food supplement persists since the argument that a lower (but sub-therapeutic) amount poses a risk to human health is insufficient to qualify it as a medicine. In addition, consideration of the items' claims and presentation is crucial when it comes to classification problems. Although the term "nutraceuticals" is not legally defined, it is frequently used to refer to goods that resemble both food supplements and pharmaceutical medicines. In addition to food supplements, it should be possible to classify plants that contain secondary metabolites as functional foods because they have been proven to benefit human health and include bioactive components that can lower the chance of disease development. In order for substances to be presented as functional food, they must appear like "regular food" rather than as pills or capsules (Carreño & Vergano, 2012; Siró et al., 2008; Wynendaele et al., 2018). The EU registry on nutrition and health claims does not presently list any plants, although this could change in the future (Wynendaele et al., 2018).

Future perspectives

As okra is inexpensive and easily available, its nutraceutical formulations could be beneficial, and further investigations should be performed using okra components in the design of nutraceuticals or drugs and functional foods (Elkhalifa et al., 2021). A lack of knowledge on the processing and functional aspects of okra remains, and a crucial scientific issue that needs to be resolved is how to fully utilize the health benefits of different parts of okra and to investigate its mechanism and potential risks (Liu et al., 2021). Chronic dexamethasone administration induced a decrease in NMDA receptor subunits in the hippocampal region, and pretreatment with okra extract before dexamethasone treatment prevented these changes from occurring. The precise mechanism of the neuroprotective effect of this plant extract should be further investigated (Tongjaroenbuangam et al., 2011). Future research should investigate the cellular signaling pathways connected to the components present in okra peel to identify which contribute to its effects (Prom-In et al., 2020). The effect of okra against DM and CD may also be caused by the presence of abscisic acid rather than simply okra polysaccharides, but further research into the mechanisms of action is necessary (Zhu et al., 2020). *In vivo*, the gut flora degrades and metabolically processes polysaccharides. Many intestinal flora species are extremely diverse, and each one has a particular predilection for polysaccharides with particular structural traits. Therefore, more research is needed to understand the okra polysaccharides and bacterial dominance following oral treatment (Zhu et al., 2020).

Conclusions

To conclude, improvement in glycemic control was found to be linked with CD prevention. The authors notified the contributing factors of DM and CD, where authors have a much better knowledge of how okra manages T1D, T2D and CD concurrently. The potential health benefits of okra in the treatment and prevention of DM and CD have been re-marked by numerous *in vivo* and *in vitro* investigations. When managing T1D, T2D and CD, okra may be considered as a crucial part of preventive therapy. Quercetin, catechin, procyanidin B1 and B2 are the primary bioactive components of okra, and significant research has been done to examine how it may protect against various DM and CD. Therefore, okra has the potential to be used as a therapeutic agent in the treatment of T1D, T2D and CD, but this process requires preliminary human clinical trials. Even though research in okra has advanced significantly in recent years, gaps remain in the field.

Abbreviations

DM	Diabetes Mellitus
CD	Cognitive Dysfunction
TNF-α	Tumor Necrosis Factor-α
NDDG	The National Diabetes Data Group
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
GD	Gestational Diabetes
HIV	Human Immunodeficiency Virus
BBB	Blood–Brain Barrier
GABA-A	γ-aminobutyric acid-A
IR	Insulin Receptor
PGC-1α	Peroxisome Proliferator-Activated Receptor-Gamma Coactivator-1α
SIRT1	Sirtuin 1
NF-KB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated β cells
FOXO	Forkhead box O
IL-6	Interleukin 6
AGE	Advanced Glycation End Products
Aβ	Amyloid Beta
PINK1	PTEN-induced putative kinase 1
TNF	Tumor necrosis factor
PKC	Protein Kinase C
AChE	Acetylcholinesterase
CAT	Catalase
LDL-C	Low-Density Lipoproteins-Cholesterol
HbAlc	Hemoglobin A1c
GSK3B	Glycogen Synthase Kinase-3 Beta
ApoE-ε4	Apolipoprotein E-ε4 Allele Expression
STZ	Streptozotocin
BW	Body Weight
STZ-NA	Streptozotocin-Nicotinamide
p.o.	Per Oral
BDNF	Brain-Derived Neurotrophic Factor
AD	Alzheimer's Disease
ERK	Extracellular Signal-Regulated Kinase
PPAR-γ	Peroxisome Proliferator-Activated Receptor-Gamma
PPAR-α	Peroxisome Proliferator-Activated Receptor-Alpha
PPAR	Peroxisome proliferator-activated receptor
IRS	Insulin receptor
MAPK	Mitogen-activated protein kinase
FA	Fatty acids
ROS	Reactive Oxygen Species
RNS	Reactive Nitrogen Species
LPO	Lipid peroxidation
HO-1	Heme Oxygenase 1
GLUT4	Glucose transporter type 4
Bcl-2	B-cell lymphoma 2
Nrf2	Nuclear Factor Erythroid 2–Related Factor 2
Glucose-6-P	Glucose 6-phosphatase
mRNA	Messenger RNA
Aβ	Amyloid beta
IFN-γ	Interferon-Gamma
TGF-β	Transforming Beta Growth Factor
HFD	High-Fat-Diet
PI3K	Phosphoinositide 3-kinase
AKT	Protein kinase B
GS	Glycogen synthase
IL-1β	Interleukin-1β
GSK3β	Glycogen synthase kinase-3 beta
DPP4	Dipeptidyl peptidase-4 inhibitor
MDA	Malondialdehide
NMDA	N-methyl-D-aspartate
GSH	Glutathione Peroxidase
SOD	Superoxide dismutase
CREB	Cyclic-AMP response element binding
pGSK3β	Phosphorylated Glycogen Synthase Kinase 3β

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Authors' contributions
Nazir Ahmad and Kaisun Nesa Lesa conceptualized and wrote the initial draft of the manuscript. Nazir Ahmad, Kaisun Nesa Lesa, Zullies Ikawati, and Nanang Fakhrudin participated in data curation and literature search. The review and final editing of the manuscript was carried out by Zullies Ikawati and Nanang Fakhrudin. The supervision of the manuscript writing was performed by Zullies Ikawati and Nanang Fakhrudin. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data used to support the findings of this study are included in the article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors confirm that they have no known financial conflicts of interest or close personal connections that would affect the outcome described in this review study.

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