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REVIEW

The Potential Role of SGLT2 Inhibitors in the Treatment of Depression: Mechanisms and Clinical Prospects

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Abstract: Major depressive disorder (MDD) is a high-burden psychiatric illness characterized by persistent low mood, diminished interest, and cognitive impairment. Its global prevalence continues to rise, accompanied by a significant risk of suicide. Traditional first-line treatments, such as selective serotonin reuptake inhibitors (SSRIs), are limited by delayed onset, limited response rates, and adverse effects, which has spurred the exploration of novel therapeutic strategies. A growing body of research indicates that the pathogenesis of MDD extends beyond the monoamine hypothesis, also involving neuroinflammation, oxidative stress, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and cerebral energy metabolism impairment. Notably, there is a well-established bidirectional association between MDD and type 2 diabetes (T2DM), with the prevalence of depression nearly doubling among diabetic patients. The pathological processes shared by both conditions include insulin resistance, oxidative stress caused by chronic hyperglycemia, accumulation of advanced glycation end products (AGEs), persistent low-grade inflammation, and overactivation of the HPA axis. These mechanisms work synergistically to promote neuronal damage and emotional dysregulation. In recent years, sodium–glucose cotransporter 2 inhibitor (SGLT2i) have emerged as a novel therapeutic direction with dual "metabolic-neural" regulatory potential, as they may intervene in multiple key pathways central to the comorbidity of MDD and T2DM by mitigating neuroinflammation and oxidative stress, inhibiting apoptosis, and enhancing synaptic plasticity. Although evidence for their application in the psychiatric field remains in its early stages, current preclinical and observational studies have already demonstrated significant potential. It is important to emphasize that SGLT2i may still cause adverse effects such as sleep disturbances and anxiety, requiring cautious evaluation in psychiatric applications. Additionally, there is still a significant lack of prospective randomized controlled trials with depression improvement as the primary endpoint, and their true antidepressant efficacy and safety await further validation. This review discusses their therapeutic potential and provides a foundation for developing comprehensive treatment strategies for patients with comorbid MDD and T2DM.

Keywords: SGLT2i, depression, type 2 diabetes mellitus, neuroprotection, oxidative stress

Introduction

Major depressive disorder (MDD) is one of the most common and serious psychiatric illnesses, with a highly complex etiology involving multiple factors.[1,2] Clinically, depression is characterized primarily by persistent low mood, anhedonia, and impairments in cognitive function. Over the long term, the disorder has consistently exhibited high prevalence, substantial disability, and a markedly elevated risk of suicide worldwide, imposing a considerable public health burden.[3] According to the Global Burden of Disease Study 2019, an estimated 290 million individuals worldwide were living with depression as of 2019.[4] Furthermore, the world health organization (WHO)'s 2023 report highlighted that depression has

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become one of the leading contributors to non-fatal health loss globally, underscoring its substantial and persistent impact on public health.[5] In addition, depression shares substantial pathogenic mechanisms with metabolic comorbidities such as type 2 diabetes (T2DM) (see Figure 1). In individuals with T2DM, the comorbidity rate of depressive disorders is markedly elevated. Epidemiological evidence indicates that approximately 25–30% of patients with T2DM experience varying degrees of depressive symptoms or clinically diagnosed depressive disorders[6] A meta-analysis encompassing 26 studies reported that the point prevalence of MDD in individuals with T2DM is approximately 73% higher than that observed in the general population.[7] Meanwhile, several studies have demonstrated that a history of depression also increases the subsequent risk of developing impaired glucose regulation or diabetes.[8,9] These findings suggest that depression is not only a common comorbid condition in individuals with T2DM but also an independent risk factor that drives the onset and progression of diabetes, leading patients with depression to gradually shift from conventional neurological treatment toward interventions targeting metabolic function and cardiovascular risk.

These epidemiological trends underscore the need to re-emphasize metabolic management as an integral component of comprehensive depression care. As highlighted in many national clinical guidelines, depression is commonly managed using a stepped-care approach. The initial step typically involves psychological interventions—such as cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), behavioral activation (BA), and certain forms of brief psychodynamic therapy. Pharmacological treatment follows when necessary, with commonly used agents including

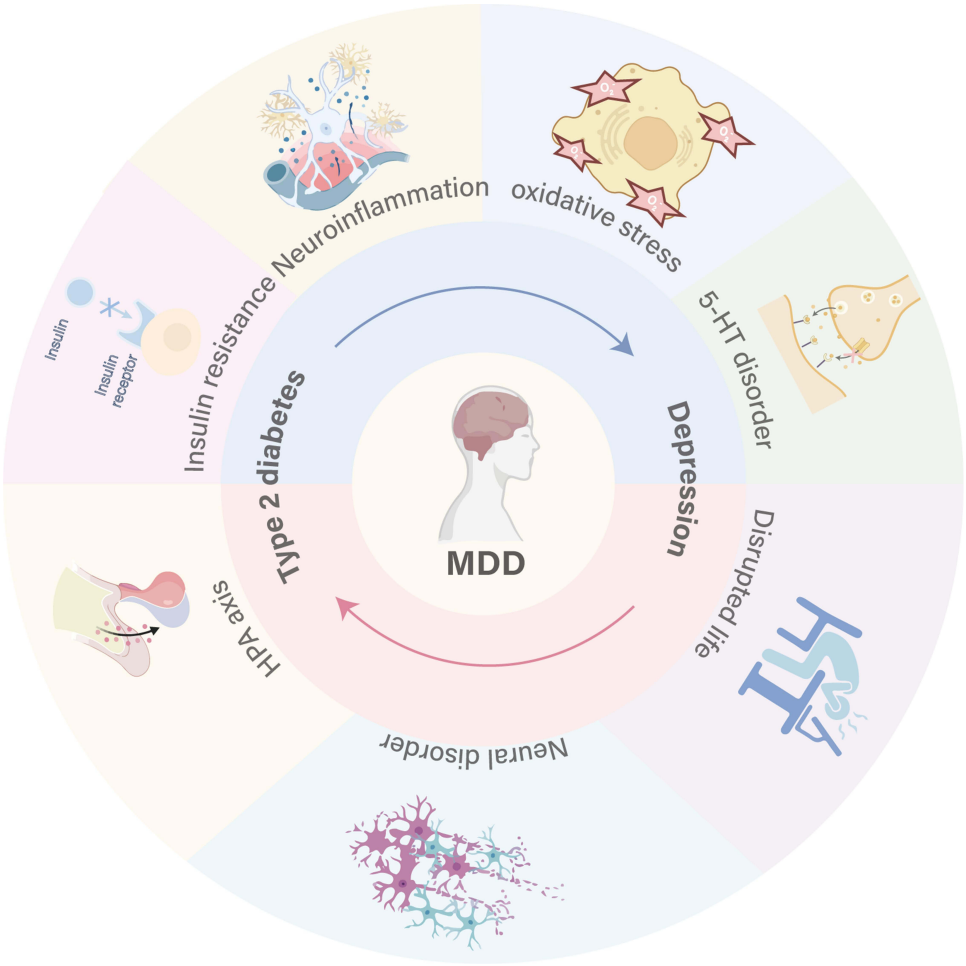

Figure 1 Diabetes-depression comorbidity. Depression and type 2 diabetes mellitus (T2DM) are interconnected through multiple overlapping and mutually reinforcing biological pathways. Chronic neuroinflammation, oxidative stress, hypothalamic–pituitary–adrenal (HPA) axis hyperactivation, insulin resistance, serotonergic (5-HT) dysregulation, and neural circuit dysfunction collectively contribute to the onset and progression of both disorders. Metabolic abnormalities in T2DM exacerbate neurobiological vulnerability to depression, while depressive disorders, in turn, promote impaired glucose metabolism and insulin resistance, forming a self-perpetuating pathological cycle. These shared mechanisms highlight the close integration of metabolic, inflammatory, and neuroendocrine processes underlying the comorbidity between MDD and T2DM.

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selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and several noradrenergic and specific serotonergic antidepressant (NaSSA) antidepressants. However, several limitations of traditional antidepressants such as weight gain,[10] increased cardiovascular risk,[11] and other metabolic adverse effects,[12] combined with their inherently slow onset of action (typically 2–4 weeks) and suboptimal treatment response rates (with only approximately 40–60% of patients achieving clinical benefit after the first medication trial) substantially restrict long-term adherence and overall safety.[11] Therefore, therapeutic strategies that not only confer proven metabolic and cardiovascular benefits but also demonstrate efficacy in treating depression may offer a crucial opportunity to address this unmet need in the comprehensive management of depressive disorders.

Sodium–glucose cotransporter 2 inhibitor (SGLT2i), a novel class of antidiabetic agents, exert their glucose-lowering effects by selectively inhibiting the sodium–glucose cotransporter 2 (SGLT2) in the proximal renal tubules, thereby reducing renal glucose reabsorption and promoting urinary glucose excretion.[13] In recent years, accumulating evidence has shown that SGLT2i are capable of crossing into the central nervous system, where they exert neuroprotective effects. Concurrently, their potential role in managing depression comorbid with T2DM has garnered increasing scientific and clinical interest.[14] A randomized controlled trial further demonstrated this therapeutic potential, showing that patients receiving treatment experienced a marked reduction in hamilton depression rating scale (HAMD) scores from 28.42 ± 3.83 at baseline to 13.42 ± 3.42, a significantly greater improvement than that observed in the placebo group ($p < 0.0001$). Consistently, the Patient Health Questionnaire-9 (PHQ-9) also confirmed more pronounced symptom alleviation in the empagliflozin (EMPA)-treated group ($p < 0.01$).[15] Preclinical studies further demonstrate that SGLT2i exert antidepressant potential through multiple neurobiological mechanisms, including attenuating systemic and neuroinflammatory responses, suppressing oxidative stress and neuronal apoptosis, enhancing ketone body production to ameliorate cerebral energy dysregulation, upregulating brain-derived neurotrophic factor (BDNF), and promoting synaptic plasticity.[16] In light of these findings, SGLT2i represent an appealing multipurpose therapeutic option for patients with depression. In this review, we summarize current evidence supporting their beneficial effects on depression risk, elucidate the underlying biological mechanisms, and discuss their potential role in managing metabolic comorbidities relevant to depressive disorders. Together, these insights provide a conceptual framework for positioning SGLT2i as promising candidates in the treatment of metabolic–psychiatric comorbidities.

Pharmacological Hallmarks of SGLT2i

SGLT2i were originally derived from phlorizin, a natural compound found in apple tree bark.[17] In 1835, French chemists first isolated a flavonoid compound from apple tree bark, namely phlorizin.[18] In 1886, German pharmacologists discovered that rhein caused polyuria, glycosuria, and weight loss in animals, revealing for the first time its relationship with blood sugar regulation. SGLT2i are currently widely used in the treatment of T2DM,[19] heart failure (HFrEF and HFpEF)[20] and chronic kidney disease (CKD).[21] Dapagliflozin (DAPA) is an aryl-C-glucoside containing an aryl ring and a glucose moiety in its chemical structure. This structure prevents DAPA from being hydrolyzed by lactase in the intestine, making it suitable for oral administration.[22] Due to their high efficacy in lowering blood glucose, favorable pharmacokinetic properties, and favorable side effect profile, SGLT2i are considered the preferred treatment for T2DM. In 2013, the first SGLT2i, canagliflozin (CANA), received food and drug administration (FDA) approval for the treatment of T2DM.[23] SGLT2i generally have low water solubility and typically require a longer period to dissolve.[24] After oral administration, they are typically absorbed through the gastrointestinal tract.[25]

Nevertheless, the bioavailability of SGLT2i remains high. Among these, CANA exhibits an absolute oral bioavailability of approximately 60–65% and a plasma protein binding rate of 99%. Following a single oral dose, the terminal half-life of CANA ranges from 10.6 to 13.1 h.[26] Taking egrelin as an example, its primary metabolism involves glucuronidation mediated by UDP-glucuronosyltransferase (UGT). UGT1A9 is the most critical enzyme, responsible for approximately 70%–81% of in vivo clearance. The secondary clearance pathway is CYP-mediated oxidative metabolism, accounting for 12% of total body clearance.[27]

Fortunately, despite the relatively low solubility of SGLT2i, these lipophilic small-molecule drugs possess the potential to cross the blood-brain barrier (BBB).[28] Diabetes and other chronic diseases are often accompanied by inflammation of the central nervous system, which further increases the permeability of the BBB,[29] which enable the

passage of SGLT2i. Wang et al found that luseogliflozin (LUSE) (an SGLT2i) improved cerebral blood flow (CBF) autoregulation, reduced vascular oxidative stress and advanced glycation end-product (AGE) production in the cerebral vasculature of 18-month-old diabetic (DM) rats. They also demonstrated that SGLT2i prevented BBB leakage, impaired functional hyperemia, neurodegeneration, and cognitive impairment in DM rats.[30]

Clinical and Preclinical Evidence

Animal Studies

Animal studies provide an important platform for exploring the potential of SGLT2i in the treatment of depression and elucidating their underlying mechanisms. Currently widely used animal models of depression, such as chronic unpredictable mild stress (CUMS), the forced swim test (FST), and the tail suspension test (TST),[31] effectively mimic core behavioral features of human depression, including persistent low mood, reduced spontaneous activity, loss of interest, and social avoidance.[32] These behavioral changes are often accompanied by pathophysiological alterations such as neuroinflammation, oxidative stress, and metabolic dysfunction, which closely resemble the underlying mechanisms of human depression.[33] As a result, these models have become important tools in preclinical research for antidepressant drugs (see Table 1).

In studies related to EMPA, researchers have utilized the CUMS rat model to observe the effects of the drug on depressive-like behaviors and potential neurobiochemical mechanisms. Research findings indicate that following treatment with EMPA, rats exhibited significantly reduced immobility time in the FST, along with increased struggling and swimming duration, suggesting marked improvement in their despair-like behavior. At the mechanistic level, EMPA exhibits multi-target regulatory effects: It not only significantly inhibits NOD-like receptor protein 3 (NLRP3) inflammasome activation and reduces expression levels of downstream pro-inflammatory factors such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and Nuclear Factor Kappa-B (NF-κB), but also effectively enhances the body's antioxidant defense capacity. This is specifically manifested by increasing levels of endogenous antioxidants like glutathione (GSH) in brain tissue while simultaneously reducing the content of malondialdehyde (MDA), a lipid peroxidation product. Additionally, EMPA has neuroprotective effects. It mitigates neuronal apoptosis by inhibiting key apoptotic factors, such as caspase-3 and cytochrome c.[34] A notable finding was that EMPA exhibited a more rapid onset of action and a more protracted therapeutic effect in animal models when compared to conventional SSRIs. This finding suggests that by regulating multiple pathways—including inflammation, oxidative stress, and apoptosis—EMPA may offer a more comprehensive intervention strategy for alleviating depressive symptoms.[35]

In addition to EMPA, DAPA has also been extensively studied in preclinical models. This drug is commonly used to treat diabetic mouse models induced by long-term high-sugar diets. Research findings indicate that DAPA significantly alleviates anxiety-like and depressive-like behaviors in mice, while also improving cognitive impairments induced by diabetes. DAPA has been shown to reduce oxidative stress markers in the brain,[40] including 8-hydroxy-2′-deoxyguanosine (8-OHdG) and MDA. This reduction in oxidative stress markers has been shown to mitigate depressive symptoms.[36] In the context of neuroinflammation, SGLT2i exert their anti-inflammatory and neuroprotective effects by regulating the levels of key pro-inflammatory cytokines such as tumor necrosis TNF-αand interleukin-6 (IL-6).[37] Building on this, Haneen Amawi et al further elucidated that DAPA, a representative SGLT2i, exhibits clear antidepressant-like effects in a mouse depression model. The underlying mechanism involves the coordinated regulation of multiple pathways. The study found that DAPA significantly inhibits the activation of the NF-κB signaling pathway, thereby reducing the production and release of inflammatory mediators and lowering neuroinflammation levels. Meanwhile, DAPA also downregulates the expression of glutamate transporter 1 (GLT-1) and solute carrier family 7 member 11 (SLC7A11) in the prefrontal cortex, thereby modulating extracellular glutamate homeostasis. This regulation reduces the excessive release and accumulation of glutamate, improving glutamate-mediated excitotoxicity. These effects collectively contribute to the behavioral reversal observed in the lipopolysaccharide (LPS)-induced mouse depression model.[38]

Similarly, CANA, an SGLT2i, has also demonstrated neuroprotective potential. A substantial body of research has demonstrated that the treatment significantly improves symptoms associated with autism, including anxiety, stereotyped

Table 1 Summary of the Effects of SGLT2i in Animal Models of Depression

Drug	Animal Model	Core Symptoms	Main Mechanism	References
EMPA	CUMS in rats	Depressive-like behaviors: reduced locomotor activity, increased latency time, decreased rearing/grooming, increased immobility time (FST), reduced grooming (splash test)	Anti-inflammatory: NLRP3 inflammasome activation↓, IL-1β↓, TNF-α↓, NF-κB↓, caspase-1↓. Antioxidant: GSH↑, decreases MDA↓. Anti-apoptotic: Active caspase-3 ↓and cytochrome c↓. Neuroprotection: Hippocampal histopathology↑, microglial activation (Iba-1) ↓. Improves insulin signaling: Blood glucose↓, serum insulin↓, HOMA-IR↓; GLUT4 expression↑ in hippocampus.	[33]
EMPA	RES-induced depression in rats	Similar to ESCIT: ameliorates depressive-like behavior (reduced immobility in TST & FST), restores locomotor activity (OFT), alleviates hippocampal neurodegeneration.	Activates AMPK, restores autophagy (↑Beclin1, ↑LC3B, ↓mTOR), suppresses neuroinflammation (↓NLRP3, ↓cytokines), enhances neurogenesis via PKCζ/NF-κB/BDNF/CREB pathway.	[34]
DAPA	CUMS in rats	Ameliorate cognitive deficits, spatial memory impairment, hippocampal neurodegeneration	Improves insulin sensitivity, reduces oxidative stress, restores mitochondrial function (↑ATP, ↑cytochrome C oxidase), downregulates p-Akt/p-mTOR, BDNF↑, amyloid↓ and p-tau ↓accumulation	[35]
DAPA	SPS mouse model	Improve depressive-like behavior (FST, TST)	Attenuates HPA axis hyperactivation, reduces neuroinflammation, inhibits apoptosis	[36]
DAPA	LPS-induced depressive-like behavior mouse model	Improve depressive-like behavior (FST, TST)	Modulates GSH homeostasis (↓GLT-1, ↓SLC7A1) and reduces neuroinflammation (↓NF-κB)	[37]
CANA	VPA-induced ASD rat model	High-dose CANA(100 mg/kg) significantly outperformed ARP (3 mg/kg) in reducing repetitive-compulsive behavior in the nestlet-shredding test, with a lower percentage of shredded nestlets observed in the CANA-treated group	Ameliorates oxidative stress (↑GSH, ↑SOD, ↑CAT; ↓MDA), reduces AChE activity	[38]
CANA	CUMS rat model	Despair-like behavior (FST), anhedonia (SPT), anxiety-like behavior (OFT)	Modulates gut-brain axis (↓colonic inflammation, ↑tight junction proteins), reduces neuroinflammation (↓IL-1β, IL-6, TNF-α), inhibits IDO, activates AMPK/mTOR autophagy pathway	[39]

Abbreviations: EMPA, Empagliflozin; CUMS, Chronic Unpredictable Mild Stress; FST, Forced Swim Test; NLRP3, NOD-like Receptor Protein 3; IL-1β, Interleukin-1β; TNF-α,Tumor Necrosis Factor-α; NF-KB, Nuclear Factor Kappa-B; GSH, Glutathione; MDA, Malondialdehyde; Iba-1, Ionized calcium-binding adapter molecule 1; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; GLUT4, Glucose Transporter type 4; ↑, Increase; ↓, Decrease; RES, Reserpine; ESCIT, Escitalopram; TST, the Tail Suspension Test; OFT, Open Field Test; AMPK, Adenosine 5'-Monophosphate (AMP)-Activated Protein Kinase; LC3B, Microtubule-Associated Protein 1A/1B-Light Chain 3 Beta; mTOR, Mechanistic Target of Rapamycin; PKC, Protein Kinase C; BDNF,Brain-Derived Neurotrophic Factor; CREB, cAMP Response Element-Binding Protein; DAPA, Dapagliflozin; ATP, Adenosine Triphosphate; Akt, AKT Serine/Threonine Kinase; LPS, Lipopolysaccharide; GLP-1, Glucagon-Like Peptide-1; SLC1A1, Solute L carrier family 1 member 1; SPS, Single Prolonged Stress; CANA, canagliflozin; HPA, Hypothalamic-Pituitary-Adrenal; VPA, Valproic Acid; ASD, Autism Spectrum Disorder; ARP, Aripiprazole; SOD, Superoxide Dismutase; CAT, Catalase; AChE, Acetyl Cholinesterase; SPT, Sucrose Preference Test; IL-6, Interleukin-6; IDO, Indoleamine 2,3-dioxygenase.

behaviors, and hyperactivity, in a rat model of autism induced by valproic acid (VPA). The findings of this study demonstrate that the administration of the compound in question led to a significant alleviation of oxidative stress in brain regions, as evidenced by a concomitant elevation in GSH, superoxide dismutase (SOD), and catalase (CAT) levels, accompanied by a reduction in MDA and acetyl cholinesterase (AChE) activity.[39] Another study employing the chronic CUMS model found that CANA alleviated depressive-like behaviors, reduced corticosterone levels, and promoted autophagy and neural repair by regulating the intestinal barrier, suppressing inflammatory factors, and activating adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)/inhibiting mechanistic target of rapamycin

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(mTOR) signaling.[41] A collective analysis of two studies has elucidated the multi-target mechanism of CANA in regulating oxidative stress, autophagy, and inflammatory responses, thereby providing experimental evidence for its repurposing in neuropsychiatric disorders.

Clinical Trials

In recent years, SGLT2i, represented by EMPA and DAPA, have gained increasing attention not only for their established role in the management of T2DM but also for their emerging potential in alleviating depressive symptoms. An expanding body of clinical evidence indicates that these agents, beyond improving glycemic control, may exert beneficial effects on mood and psychological well-being through multiple biological pathways (see Table 2).

A 2019 investigation based on the clinical data warehouse of a Japanese university hospital provided preliminary evidence that SGLT2i may substantially reduce the risk of depression, demonstrating a markedly protective association (AOR = 0.09, 95% CI: 0.01–0.63).[55] Building on these findings, Jonathan V. Mui and colleagues conducted a large-scale

Table 2 Human Studies on SGLT2i and Their Impact on Depression and Cognitive Function

Brief Cohort Description	Patients	Results	Side Effects/Study Limitations	References
Randomized, double-blind, placebo-controlled clinical trial. Patients with moderate-to-severe MDD received citalopram 40 mg/d plus either EMPA10 mg/d or placebo for 8 weeks. Outcomes assessed at baseline, week 4, and week 8.	Adults 18–60 years with HAMD ≥17, diagnosed MDD.	HAMD scores decreased more in the empagliflozin group (27.36→7.00) compared with placebo (28.42→13.42). Significant between-group difference (p=0.0001), indicating enhanced antidepressant efficacy.	Small sample size, short follow-up.	[42]
Target trial emulation using OneFlorida+ database (2014–2023). Compared GLP-1RA, SGLT2i, and other antidiabetic drugs. Primary endpoint: ADRD incidence.	396,963 T2DM patients, ≥50years, without baseline ADRD.	GLP-1RA HR=0.67 (95% CI 0.47–0.96), SGLT2i HR=0.57 (95% CI 0.43–0.75) for ADRD risk reduction vs other drugs. No significant difference between GLP-1RA and SGLT2i.	——	[43]
Analysis of NHANES database assessing T2DM, antidiabetic drugs, and depression risk. Depression assessed via PHQ-9.	Analysis of NHANES database assessing T2DM, antidiabetic drugs, and depression risk. Depression assessed via PHQ-9.	T2DM patients had higher depression prevalence. Elderly T2DM reported fewer depressive symptoms. No significant association between SGLT2i use and depression risk.	Cross-sectional, cannot infer causality.	[44]
A population-based, active comparator, new-user cohort study using Taiwan's National Health Insurance Database.	551,917 patients with T2DM who initiated SGLT2i or DPP4i between 2016–2018. After propensity score matching, the final cohort comprised 267,522 patients (133,761 in each group).	Compared to DPP4i users, SGLT2i users had a significantly lower incidence of depression (7.18 vs 10.12 per 1000 person-years). The adjusted HR was 0.77 (95% CI: 0.73–0.80), with a dose-dependent protective effect. Results remained consistent across sensitivity and subgroup analyses.	Observational design, unable to establish causality; lacks data on medication adherence, lifestyle factors, depression severity, and socioeconomic status; relatively short follow-up period (3 years).	[45]

(*Continued*)

Table 2 (Continued).

Brief Cohort Description	Patients	Results	Side Effects/Study Limitations	References
Retrospective cohort study using TriNetX, comparing associations of four glucose-lowering monotherapies with depression risk and all-cause mortality.	359,787 patients with T2DM on monotherapy (Met, GLP-1RA, DPP4i, SGLT2i).	Compared to DPP-4i, SGLT2i significantly reduced depression risk (HR 0.62–0.70) and all-cause mortality risk (HR 0.54–0.65). Compared to Met, GLP-1RA and DPP4i were associated with higher risks of depression and mortality, with DPP4i showing the highest risk.	Observational design with potential for unmeasured confounding; lacks data on dosage, socioeconomic, and lifestyle factors; pairwise comparisons only	[46]
Japanese case report of a patient with comorbid T2DM and depression.	A 55-year-old female with a 5-year history of depression and a 3-year history of T2DM. She was previously on Met+ VIL (DPP-4i) and antidepressants (DUL, MIR).	After unexplained worsening of glycemic control (HbA1c 7.9%), ipragliflozin (SGLT2i) 25mg/day was added. HbA1c improved to 6.4%, and depressive symptoms (including suicidal ideation) resolved. This suggests a potential dual metabolic and psychiatric benefit of SGLT2i.	Single case report; cannot establish causality; improvement may be coincidental or due to other factors; no quantitative assessment of depression severity was performed.	[47]
A retrospective cohort study using the Japanese Nihon University CDW.	40,214 Japanese adult patients with T2DM, divided into a case group (with depression, n=1,979) and a control group (without depression, n=38,235).	After adjustment for confounders, the use of DPP4i was significantly associated with a lower risk of depression (AOR: 0.31, 95% CI: 0.24–0.42). SGLT2i also showed a significant association (AOR: 0.09, 95% CI: 0.01–0.63), but only 1 depression case was observed in SGLT2i users. No significant association was found for other OHA classes.	Retrospective design with potential for selection bias and unmeasured confounding; very small number of depression events in the SGLT2i group (n=1), limiting the reliability of this specific finding; the study could not assess the effect of GLP-1RA.	[48]
Hong Kong retrospective cohort (2015–2019) of T2DM patients comparing SGLT2i vs DPP4i. Propensity score matched (1:1) for demographics, comorbidities, medications.	58,506 T2DM patients (19,381 SGLT2I, 39,125 DPP4I). After matching: 38,762 (19,381 each). No prior depression/psychiatric history.	SGLT2i linked to lower depression risk vs DPP4i (HR: 0.52, 95% CI: 0.35–0.77, P=0.001). Consistent in sensitivity analyses.	Observational design, indirect adherence assessment, residual confounding, exposure duration not controlled.	[49]
Retrospective cohort study using TriNetX network. T2DM with bipolar disorder initiating SGLT2i vs DPP4i, matched 1:1, followed ~800–900 days.	3,422 patients (1,711 SGLT2i, 1,711 DPP4i).	Suicidal events: 5.1% (SGLT2i) vs 7.3% (DPP4i); HR=0.66 (95% CI 0.47–0.92, p=0.0145). All-cause mortality also lower with SGLT2i (HR=0.59, p<0.001). No increased DKA/infection risk.	Observational design, mechanism unclear.	[50]

(*Continued*)

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Table 2 (Continued).

Brief Cohort Description	Patients	Results	Side Effects/Study Limitations	References
Case-control study comparing SGLT2i and sulfonylurea users with healthy controls. Biomarkers of inflammation measured; cognition, depression, and QoL assessed.	166 subjects (55 controls, 57 SGLT2i, 54 SU).	SGLT2i group showed lower inflammation biomarkers, higher MoCA (22.5±4.2 vs 20.0±2.0 in SU), and lower PHQ-9 scores (6.5±3.8 vs 8.2 ±1.7 in SU).	Small sample, short-term effects only.	[51]
Randomized controlled clinical trial. T2DM elderly patients on metformin randomized to incretin therapy vs SGLT2i for 12 months. Cognitive tests and metabolic parameters assessed.	39 elderly T2DM patients (mean age 77).	No significant cognitive decline in either group after 12 months. SGLT2i group showed metabolic benefits: weight loss (−1.95 kg), BMI reduction (−0.69), HDL increase (+5.73 mg/dl).	Very small sample size.	[52]
Retrospective chart review (10 months) at a VA Diabetes Clinic, comparing depression scores (PHQ-9) across T2DM regimens in overweight/obese veterans with depression (PHQ-9 ≥5).	88 veterans with T2DM and depression (mean age 64.2, mean BMI 32.3). Regimens: insulin alone (n=35), Met ±insulin (n=23), GLP-1RA ±insulin (n=17), SGLT2i ±insulin (n=13).	GLP-1RA (PHQ-9: 8.82) and SGLT2i (PHQ-9: 8.08) groups had significantly lower depression scores vs Met group (12.04) (p=0.0486, p=0.0311). Insulin-only group score: 11.03. No BMI or A1c differences between groups.	Small sample, single-center retrospective design, PHQ-9 collected clinically (not research-structured), no control for depression treatment or medication adherence.	[53]
Prospective cohort study with follow-up up to 6.4 years. Cognitive function assessed by RBANS in relation to SGLT2i use.	476 T2DM patients (mean age 60.6); 138 long-term SGLT2i users, 54 with ≥3 years of use.	Long-term SGLT2i use (≥3 years) associated with improved overall cognition, language, and executive function (β=0.54–1.12, p=0.01).	Needs larger sample size for validation.	[54]

Abbreviations: EMPA, empagliflozin; MDD, Major Depressive Disorder; HAMD, Hamilton Depression Rating Scale; HR, Hazard Ratio; GLP-1RA, Glucagon-like peptide-1 receptor agonist; SGLT2i, Sodium–Glucose Cotransporter 2 Inhibitor; T2DM, Type 2 Diabetes Mellitus; ADRD, Alzheimer's Disease and Related Dementias; NHANES, National Health and Nutrition Examination Survey; PHQ-9, Patient Health Questionnaire-9; DPP4i, Dipeptidyl Peptidase-4 Inhibitor; Met, Metformin; VIL, vildagliptin; DUL, Duloxetine; MIR, Mirtazapine; HbA1C, Glycated Hemoglobin; CDW, Clinical Data Warehouse; ADR, Adjusted Odds Ratio; CI, Confidence Interval; OHA, Oral Hypoglycemic Agent; DKA, Diabetic Ketoacidosis; QoL, Quality of Life; SU, Sulfonylurea; MoCA, Montreal Cognitive Assessment; BMI, Body Mass Index; HDL, High-Density Lipoprotein; VA, Department of Veterans Affairs; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; →, changed to.

retrospective cohort study using territory-wide clinical data from Hong Kong to further compare the risk of incident depression between users of SGLT2i and DPP-4 inhibitors. The study included more than 58,000 patients, employed 1:1 propensity score matching to balance baseline characteristics, and validated the results through multivariable Cox regression and extensive sensitivity analyses. The investigators reported that patients treated with SGLT2i had a significantly lower risk of developing depression compared with those receiving dipeptidyl peptidase-4 inhibitors (DPP-4i) (HR = 0.52), with consistent protective trends observed across different SGLT2i subclasses.[56]

Following the accumulating evidence from Japan and Hong Kong, even larger population-based analyses have been conducted to validate this association at a broader epidemiological level. A recent large-scale cohort study from Taiwan, involving more than 550,000 individuals with T2DM, demonstrated that new users of SGLT2i had a significantly lower risk of developing depression compared with those initiating DPP-4i (adjusted HR = 0.77). Notably, this protective association appeared to follow a dose-dependent pattern.[57] This association was further corroborated by a large retrospective cohort analysis utilizing the global TriNetX research network. The study directly compared four commonly prescribed antidiabetic monotherapies—metformin(Met), GLP-1 receptor agonists (GLP-1RA), DPP-4i, and SGLT2i—in

relation to depression risk and all-cause mortality. The findings revealed that SGLT2i users exhibited a substantially lower risk of developing depression compared with those receiving DPP-4i (HR 0.62–0.70), along with markedly reduced all-cause mortality (HR 0.54–0.65). Notably, SGLT2i also conferred lower mortality risk relative to Met, whereas DPP-4i users demonstrated significantly higher risks of both depression and mortality when compared with EMPA and SGLT2i users.[58] Collectively, these findings suggest that among commonly used modern antidiabetic therapies, SGLT2i may offer a relative advantage in reducing the risk of depression and improving long-term clinical outcomes.

Beyond symptomatic improvement, another clinically relevant outcome concerns suicidality, a critical risk in patients with comorbid psychiatric and metabolic disorders. A real-world cohort study revealed that patients diagnosed with bipolar disorder and T2DM who utilized SGLT2i exhibited a substantially reduced incidence of suicide-related events when compared to those who used DPP-4i. The findings indicate that the incidence of suicide-related events in the SGLT2i group was 5.1% lower than the 7.3% observed in the DPP-4i group (hazard ratio [HR]: 0.660, 95% confidence interval [CI]: 0.473–0.921, $p = 0.0145$), along with lower all-cause mortality (HR: 0.594, 95% CI: 0.451–0.783, $p < 0.001$). These findings suggest that SGLT2i may offer new therapeutic directions by reducing suicide risk and all-cause mortality through improvements in patients' metabolic and mental health.[59] A real-world study conducted among veterans also showed that, compared with the use of EMPA or insulin monotherapy, patients with T2DM who were treated with SGLT2i or GLP-1RA had significantly lower PHQ-9 depression scores. Moreover, this effect was independent of body mass index and glycemic control, further supporting the potential of these agents to improve mental health in patients with diabetes.[42]

In particular, research has increasingly focused on the combined use of SGLT2i and SSRIs in the treatment of depression. SSRIs exert their antidepressant effects primarily by inhibiting serotonin reuptake and enhancing synaptic 5-hydroxytryptamine (5-HT) availability;[43] However, their therapeutic effectiveness remains limited by the suboptimal improvement of depressive symptoms in some patients with diabetes, which may undermine treatment adherence and negatively affect overall clinical outcomes. Clinical evidence suggests that SGLT2i can complement these shortcomings. In a randomized, double-blind, placebo-controlled trial including 200 patients with T2DM and MDD, adjunctive EMPA on top of citalopram (20–40 mg/day) for 12 weeks led to a significant reduction in depressive symptoms: HAMD scores decreased from 28.42±3.83 at baseline to 13.42±3.42, compared with 20.20±3.82 in the placebo group ($p < 0.0001$). Similarly, PHQ-9 scores confirmed greater improvements in the EMPA group ($P < 0.01$). Notably, this combination appears to exert synergistic benefits through multiple pathways, including attenuation of neuroinflammation, optimization of cerebral energy metabolism, and enhancement of neurotrophic signaling, thereby addressing the complex pathophysiology of depression more comprehensively. Future studies should further evaluate combination strategies of SGLT2i with agents of different mechanisms, optimize dosing regimens, assess long-term safety, and determine their therapeutic potential in non-diabetic populations.[15] Meanwhile, in a case study from Japan, a 55-year-old woman with a 5-year history of depression and a 3-year history of T2DM experienced unexplained deterioration in glycemic control while receiving EMPA plus vildagliptin (VILDA) for diabetes and duloxetine plus mirtazapine for depression, with her hemoglobin a1c (HbA1c) rising to 7.9%. After adding the SGLT2i ipragliflozin (IPRA) (25 mg/day), her HbA1c decreased to 6.4%, and her depressive symptoms—including suicidal ideation—also improved markedly.[44] Furthermore, the evaluation employing the PHQ-9 revealed that depression scores in the EMPA treatment group exhibited a substantial decrease compared to pre-treatment levels and the placebo group ($P < 0.01$), indicating that this pharmaceutical agent can effectively ameliorate depressive symptoms in diabetic patients.[45,46] Future research should further evaluate combination strategies involving SGLT2i and agents with complementary mechanisms, optimize dosing regimens, assess long-term safety, and explore their therapeutic potential in non-diabetic populations.

Studies have shown that, among individuals with diabetes, improvement in depressive symptoms is often accompanied by enhanced cognitive function, and depression itself is an important precursor to cognitive decline. Multiple prospective cohort studies have found that depression in both midlife and late life significantly increases the risk of future all-cause dementia, with the association being particularly pronounced for late-life depression, suggesting that it may represent an early clinical stage of neurodegenerative pathology.[47] Against this backdrop, the close coupling between mood and cognitive function not only reinforces the mechanistic basis for their bidirectional interaction but also provides

a theoretical rationale for pharmacological interventions. It is noteworthy that existing research has indicated that SGLT2i may not only alleviate depressive symptoms but also exert a positive impact on cognitive function.[48,49] A recent double-blind randomized controlled trial also provides preliminary evidence: in patients with early-stage Alzheimer's disease, although DAPA did not significantly improve the primary cerebral metabolic endpoint, it demonstrated good tolerability and was accompanied by improvements in systemic metabolism and elevated cerebral glutathione levels, while also showing certain enhancement in executive function tests.[50] Haya Majid and colleagues conducted a case-control study to evaluate the comparative efficacy of SGLT2i versus sulfonylureas (SU) in patients with T2DM. The findings of this study suggest that SGLT2i demonstrate superior efficacy in reducing neuroinflammatory markers, including high-mobility group box 1 (HMGB1), a disintegrin and metalloproteinase 10 (ADAM-10), TNF-α, IL-1β, and IL-6, as well as metabolic markers, such as mTOR and Klotho, when compared with sulfonylureas. The SGLT2i group had significantly better cognitive function (MoCA: 22.51 ± 4.2) and lower depressive symptoms (PHQ-9: 6.5 ± 3.8) than the sulfonylurea group (MoCA: 20.03 ± 2.04, PHQ-9: 8.2 ± 1.67) ($p < 0.001$). These findings suggest that SGLT2i may offer an effective therapeutic strategy for managing cognitive health in diabetic patients by improving both metabolic and cognitive functions.[51]

Certainly, it is normal for divergent perspectives to exist within scientific discourse. Ashurova Nodirahon et al (2024) reported in their observational study that type 2 diabetes patients treated with SGLT2i exhibited a significantly higher incidence of depressive symptoms (as indicated by elevated PHQ-9 scores) and cognitive impairment (reflected by lower MoCA scores) compared to a healthy control group, alongside an elevation in thyroid-stimulating hormone levels.[60] We speculate that the discrepancy in these findings may stem from the observed elevation of thyroid-stimulating hormone (TSH) in the medication group, as thyroid dysfunction itself can directly lead to emotional and cognitive issues. Therefore, it remains unclear whether this is due to the influence of SGLT2i on thyroid function or whether these patients already had underlying thyroid disorders, which the study failed to differentiate.

The Potential Mechanism of SGLT2i in Combating Depression

Depression is a complex neuropsychiatric disorder, traditionally attributed primarily to dysfunctions of monoamine neurotransmitters. However, a growing body of evidence in recent years indicates that its pathophysiological mechanisms extend far beyond this, involving multiple abnormalities such as neuroinflammation, metabolic dysregulation, increased oxidative stress, and impaired neuroplasticity. Initially developed for the treatment of T2DM, SGLT2i have demonstrated broad neuroprotective effects beyond glycemic control. A growing body of preclinical and clinical evidence suggests that SGLT2i can modulate several key pathological pathways closely associated with the onset of depression, offering a novel multi-target intervention strategy for the disorder. This section will systematically review the potential mechanisms through which SGLT2i may exert antidepressant effects, focusing on five key aspects: inhibition of neuroinflammation, improvement of cerebral energy metabolism, promotion of neurotrophic factor signaling and plasticity, modulation of the stress response system, and enhancement of antioxidant and anti-apoptotic capacity (see Figure 2).

Inhibit Neuroinflammation

In the pathogenesis of depression, neuroinflammation is considered one of the core pathological mechanisms. Chronic low-grade inflammation can lead to neuronal dysfunction and emotional dysregulation. SGLT2i (such as EMPA and DAPA) significantly reduce neuroinflammation by inhibiting the activation of the NLRP3 inflammasome, thereby decreasing the activation of NF-κB and the release of pro-inflammatory cytokines (such as IL-1β, IL-18, and TNF-α). This helps to mitigate neuroinflammation and its associated effects.[61] In a CUMS-induced depression model, EMPA effectively alleviated depressive-like behaviors, which was associated with a reduction in inflammatory cytokines.[52] Compared to traditional antidepressants (such as SSRIs), which primarily regulate inflammation indirectly by increasing synaptic serotonin (5-HT) levels, SGLT2i demonstrate a more direct anti-inflammatory mechanism. They not only inhibit inflammasome activation but also enhance antioxidant functions, improve oxidative stress, and provide more comprehensive neuroprotection.[53]

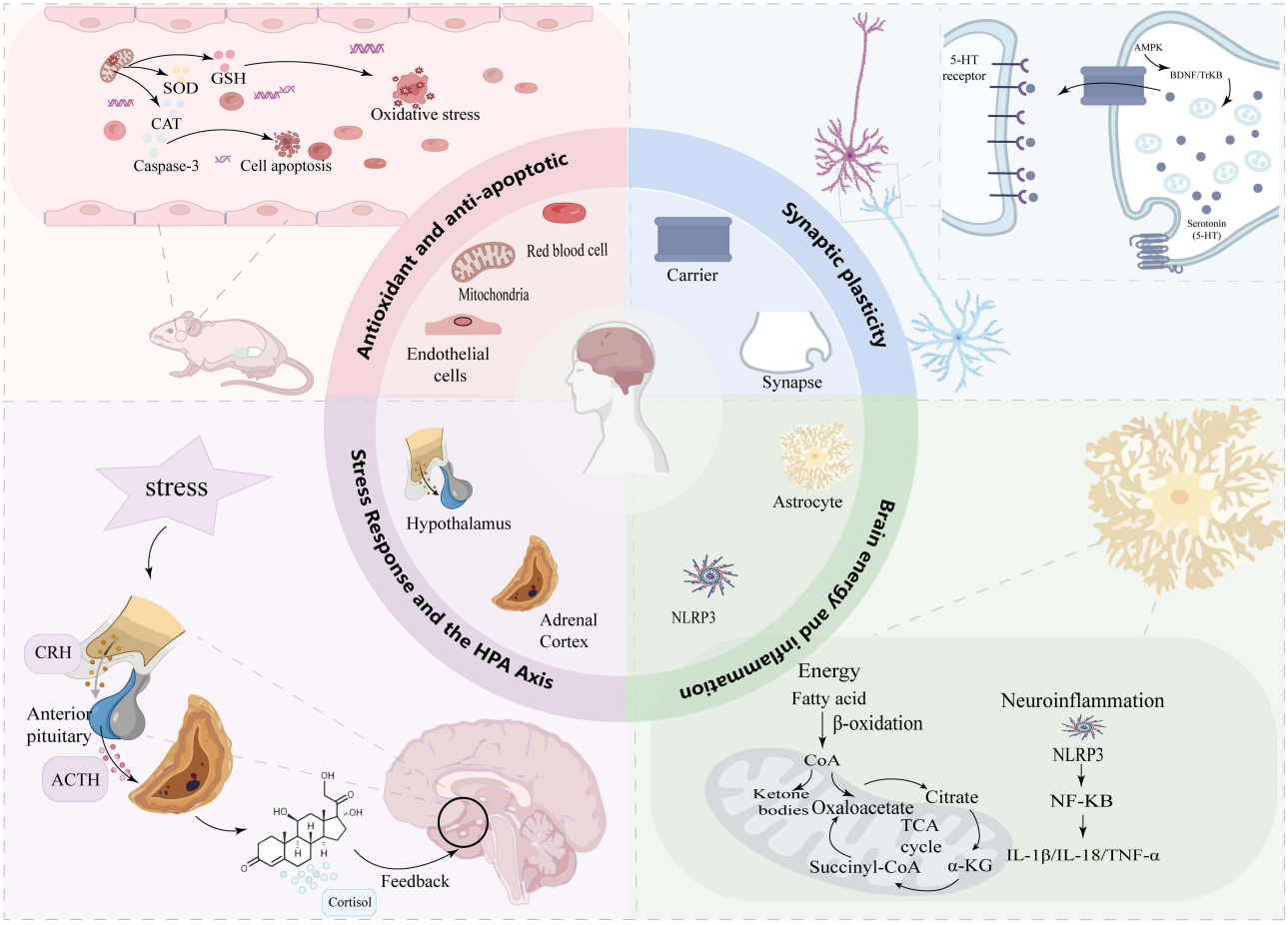

Figure 2 Proposed mechanisms of SGLT2i in alleviating depression. The diagram illustrates the neuroprotective role of sodium-glucose transporter 2 inhibitors (SGLT2i). SGLT2i can influence various pathways to exert its protective effects on neurons. It can inhibit the activation of nuclear factor kappa-B (NF-κB), which is a transcription factor that, when activated, can lead to the production of inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-18 (IL-18), and tumor necrosis factor-α (TNF-α), contributing to neuroinflammation. By blocking this pathway, SGLT2i may reduce inflammation. Additionally, SGLT2i can promote the production of ketone bodies, which serve as an alternative energy source for neurons, potentially improving energy metabolism. It also affects the endoplasmic reticulum (ER) stress pathway by modulating the AMP-activated protein kinase (AMPK) and Brain-Derived Neurotrophic Factor/Tropomyosin receptor kinase B (BDNF/TrkB) signaling, which can enhance synaptic plasticity and neurotrophic support. Furthermore, SGLT2i can mitigate oxidative stress by reducing the production of reactive oxygen species (ROS) and activating antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT), which can prevent apoptosis (programmed cell death) of neurons. Overall, these mechanisms converge to support the neuroprotective effects of SGLT2i.

Improve Brain Energy Metabolism

Brain energy metabolism dysfunction is closely associated with the onset and progression of depression. Mitochondrial dysfunction and insufficient energy supply, in particular, significantly impact neuronal circuit function and emotional stability.[54] SGLT2i, particularly EMPA, can promote ketone body production, mimicking the metabolic state of a ketogenic diet. This provides an alternative energy source for the brain, which can help alleviate energy metabolism dysfunction often observed in depression.[62,63] Several clinical studies have suggested that ketogenic diet (KD) holds potential therapeutic effects in various psychiatric disorders, including depression, anxiety, and bipolar disorder.[64] A case analysis by Laurent et al on a patient with bipolar disorder demonstrated that, under conditions of high adherence, the KD significantly improved metabolic markers and resulted in sustained relief of mood and stress symptoms, as reflected by multiple assessment scales.[65] Similarly, a 10–12 week adjunctive intervention study for college students with major depressive disorder (MDD) conducted by Dr. Decker in 2025 found that the KD significantly reduced depression severity, with reductions of 69% on the PHQ-9 and 71% on the hamilton rating scale for depression (HRSD). The study also observed weight and body fat reduction, a 52% decrease in serum leptin levels, a 32% increase in BDNF levels, and improvements in several cognitive functions.[66] Further studies have found that SGLT2i also have a significant positive effect on mitochondrial function. They help repair mitochondrial DNA, restore ATP production, and enhance

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neuronal energy metabolism and protective mechanisms.[67] These effects help alleviate neuronal damage caused by energy metabolism dysfunction, providing a new metabolic modulation strategy for the treatment of depression,[68] becoming potential new direction for the treatment of depression. These findings provide new scientific evidence for the application of SGLT2i in neuroprotection and the treatment of depression.

Promote Neuronutrition and Highlight Plasticity

A deficiency in neurotrophic factors and a decline in synaptic plasticity are common neurobiological alterations in depression.[69] Directly affecting the adaptability of neural circuits and their ability to recover function.[70] Unlike SSRIs, which primarily rely on neurotransmitter modulation,[71] SGLT2i exert neuroprotective effects through multiple mechanisms, including improving neural metabolism, reducing oxidative stress, and increasing BDNF levels.[72] Studies suggest that they can activate the AMPK signaling pathway, which in turn enhances BDNF/Tropomyosin receptor kinase B (TrkB) signaling, promoting synaptic plasticity and neurogenesis.[73] In animal models, EMPA has been shown to restore BDNF expression and improve behavioral deficits. DAPA, on the other hand, upregulates neurogenesis and synaptic markers such as doublecortin (DCX) and synaptophysin in the hippocampus, demonstrating its potential in neuronal repair.[74]

Regulating Stress Responses and the HPA Axis

Chronic and excessive stress-induced dysregulation of the HPA axis is a key endocrine foundation of depression.[75] Its abnormal activation can lead to sustained elevation of cortisol levels, further exacerbating neuronal damage. SGLT2i, such as DAPA, have demonstrated the ability to regulate the HPA axis in studies. They can reverse the overactivation of the axis induced by stress, reducing levels of cortisol and other stress hormones.[76,77] In animal models of post-traumatic stress disorder (PTSD) and depression comorbidity, the drug significantly improved behavioral phenotypes and restored neuroendocrine balance,[78] indicating that it provides a new therapeutic avenue for stress-related psychiatric disorders by modulating the stress response system.

Antioxidation and Anti-Apoptosis

Oxidative stress and the process of cell apoptosis are commonly observed in depression,[79,80] not only exacerbating neuroinflammation but also directly leading to neuronal damage and functional loss.[81] Notably, the endogenous antioxidant defense system, particularly the selenoprotein family (such as GPx and SEPP), is recognized as playing a core role in maintaining redox balance and regulating cellular stress responses in diabetes, a condition frequently comorbid with depression.[82] This intersection highlights a potential shared mechanistic pathway between metabolic and mood disorders, a pathway that is also targeted by neuroprotective natural compounds such as chinonin.[83] SGLT2i, such as EMPA and DAPA, have been shown to significantly reduce oxidative stress markers (such as 8-oxodG and MDA), enhance the activity of antioxidant enzymes (such as SOD and CAT), and inhibit the excessive generation of reactive oxygen species (ROS).[84,85] At the same time, these inhibitors reduce apoptosis by inhibiting Caspase-3 activity and decrease the expression of inflammatory factors such as IL-6 and TNF-α in inflammation models. This multi-level mitigation of biological damage in depression expands their potential clinical applications.[86,87]

The Potential Protective Effect of SGLT2i on Comorbidities

Depression does not exist as an isolated mental illness but is often highly comorbid with metabolic disorders such as obesity and diabetes. While traditional antidepressant medications exert therapeutic effects, they are frequently accompanied by adverse reactions such as arrhythmia, weight gain, and aggravated insulin resistance, which further worsen pre-existing metabolic risks. It is noteworthy that, in addition to potentially directly reducing the risk of depression, the significant advantages of SGLT2i in improving cardiovascular and metabolic outcomes have been confirmed by multiple large-scale randomized controlled trials. This suggests that for cardiovascular events—such as arrhythmia[88] and cardiovascular death,[89,90] which may occur during the treatment of depression with traditional antidepressant medications, SGLT2i can provide substantial cardiovascular protection, thereby achieving "killing two birds with one stone" in terms of long-term benefits.[91,92] In the management of metabolic diseases such as obesity, SGLT2i have demonstrated

robust preclinical and clinical evidence.[93] Therefore, for patients with depression comorbid with metabolic disorders, SGLT2i may hold significant therapeutic potential and could represent a promising direction for future clinical intervention.

In summary, integrating SGLT2i into the comprehensive management strategy for patients with depression extends their role beyond that of conventional glucose-lowering agents. For individuals with complex depression, particularly those comorbid with T2DM, heart failure, or metabolic disorders, SGLT2i undoubtedly offer an effective treatment option for managing such multifaceted and comorbid conditions.

Future Challenges

Currently, the evidence for the efficacy of SGLT2i primarily stems from populations with diabetes, and their antidepressant potential in non-diabetic individuals has not yet been fully investigated. Although the core mechanism of these drugs is to lower blood glucose by inhibiting renal glucose reabsorption,[94] a growing body of evidence suggests that they may also positively regulate mood and psychological states through multiple pathways, including anti-inflammatory, antioxidant, and neuroprotective effects.[49,95] Particularly in diabetic patients comorbid with depression, SGLT2i have demonstrated additional benefits in alleviating depressive symptoms.[84] However, current research on the antidepressant effects of SGLT2i still faces several limitations. Firstly, there is a lack of direct, systematic head-to-head comparisons with other commonly used antidiabetic agents such as metformin and DPP-4 inhibitors in clinical study design, making it difficult to clarify their relative advantages. Existing studies are generally limited by small sample sizes, and most consist of subgroup analyses or retrospective observations in diabetic populations, with a scarcity of prospective randomized controlled trials specifically targeting antidepressant efficacy. Secondly, study populations are often confounded by factors such as varying durations of diabetes, complications, concomitant medications, and baseline depression severity, which may obscure or confound the true effect of the drugs on mood. Furthermore, most trials have relatively short follow-up periods, making it challenging to evaluate the sustained effectiveness and safety of long-term treatment on depression risk. In terms of mechanistic exploration, current research has not sufficiently integrated multi-omics analyses, neuroimaging, and emotion-related biomarkers, leaving the unique pathways underlying their antidepressant effects poorly understood.

It is important to note that, in addition to the evidence gap regarding population applicability, another significant challenge lies in the unclear long-term impact of SGLT2i on brain emotional circuits. While short-term data suggest that they may improve mood through mechanisms such as regulating neuroinflammation, optimizing brain energy metabolism, and modulating neurotransmitter function,[96] it remains to be seen whether long-term use could lead to structural and functional adaptive changes in the brain's emotional circuits, which requires further investigation. In addition to the known physical side effects of long-term SGLT2i use, such as genitourinary infections,[97,98] diabetic ketoacidosis,[99,100] and mild reductions in bone density leading to clinical fractures,[101,102] further exploration of their impact on long-term brain function and emotional regulation is necessary. A cross-sectional study in patients with type 2 diabetes, using standardized scales (PHQ-9, GAD-7, PSQI), found that the use of SGLT2i was significantly associated with poorer sleep quality (OR = 2.076, P = 0.045).[103] Recent genetic evidence from Mendelian randomization studies offers new perspectives on the neuropsychiatric safety of SGLT2i. A study utilizing causal inference methods indicated that genetic inhibition of SGLT2 is significantly associated with an increased risk of certain psychiatric disorders, particularly anxiety disorders, obsessive-compulsive disorder, and bipolar disorder. Notably, this effect appears to be independent of its blood glucose-lowering action.[104] These findings underscore the necessity of monitoring long-term neuropsychiatric outcomes in patients receiving SGLT2 inhibitor treatment.

Despite the emergence of these new concerns, the overall clinical evidence continues to indicate a favorable benefit-risk profile for SGLT2i. Large-scale clinical trial data across multiple domains, including type 2 diabetes, chronic kidney disease, and heart failure, consistently demonstrate that SGLT2i have an overall good and manageable safety profile.[105,106] This provides a preliminary safety foundation for their long-term application in neuropsychiatric areas. Moreover, a case report even documented a 32-year-old female who, after a suicide attempt involving an overdose of an SGLT2 inhibitor (ipragliflozin, up to 1500 mg) and an ARB/CCB combination, did not experience severe hypoglycemia despite an extremely high plasma drug concentration (9516.3 ng/mL). The observed toxic reactions primarily consisted of

transient renal impairment (eGFR dropped to 42.3) and hypotension, with renal function recovering rapidly as the drug concentration decreased.[107] In this context, future research should particularly focus on systematically evaluating the neurobiological mechanisms underlying the effects of SGLT2i. Utilizing neuroimaging technologies such as functional magnetic resonance imaging (fMRI) will enable the assessment of the long-term impact of these drugs on the activity and connectivity patterns of key emotion-related brain regions, including the default mode network and the prefrontal-limbic system.[108,109] This approach not only helps elucidate the drug's mechanism of action but also lays a solid foundation for its long-term safety profile.

Conclusion

SGLT2i demonstrate therapeutic potential for depression by targeting multiple pathological mechanisms, particularly in patients with metabolic abnormalities and depressive symptoms. However, their clinical application faces several challenges. First, the evidence for their antidepressant effects is primarily derived from retrospective cohort analyses in diabetic patients, small-scale clinical trials, and inferences based on improvements in metabolic and neuroinflammatory pathways. There is a notable lack of large-scale, prospective, randomized controlled trials with improvement in depressive symptoms as the primary endpoint. Second, given that individuals with T2DM are themselves at high risk for depression, their psychiatric history should be considered a valuable factor when selecting second-line glucose-lowering agents such as SGLT2i. Given comparable treatment conditions, for diabetic patients with comorbid depression, the potential antidepressant effects of SGLT2i undoubtedly provide an additional compelling rationale for their therapeutic selection. Future research should validate the current findings in multicenter, multiethnic, and non-diabetic depressed populations. Furthermore, systematic evaluations are needed to assess the impact of different SGLT2i types and treatment durations on efficacy, while clarifying the combined effects and optimal treatment strategies with traditional antidepressants. Additionally, although SGLT2i demonstrate significant therapeutic potential in suppressing neuroinflammation, improving brain energy metabolism, enhancing synaptic plasticity, and modulating stress responses, attention must also be paid to their potential adverse effects, such as decreased sleep quality, worsening anxiety symptoms, and the emergence of obsessive-compulsive symptoms. In summary, SGLT2i represent a novel therapeutic approach with dual "metabolic-neural" regulatory functions. Through in-depth mechanistic studies and rigorous clinical trials, they hold promise for providing more comprehensive and effective treatment strategies for depression, particularly in patients with comorbid metabolic conditions.

Abbreviations

MDD, Major Depressive Disorder; WHO, World Health Organization; SGLT2i, Sodium–Glucose Cotransporter 2 Inhibitor; SGLT2, Sodium–Glucose Cotransporter 2; T2DM, Type 2 diabetes mellitus; HPA, Hypothalamic-Pituitary-Adrenal; NaSSA, Specific Serotonergic Antidepressant; SNRIs, Serotonin–Norepinephrine Reuptake Inhibitors; CBT, Cognitive Behavioral Therapy; IPT, Interpersonal Psychotherapy; BA, Behavioral Activation; AGEs, Advanced Glycation End Products; CKD, Chronic Kidney Disease; KD, Ketogenic Diet; FDA, Food and Drug Administration; DAPA, Dapagliflozin; CANA, Canagliflozin; GLP-1,Glucagon-Like Peptide-1; HFrEF and HFpEF, heart failure; UGT, UDP-glucuronosyltransferase; BBB, Blood-Brain Barrier; GLP-1, Glutamate Transporter 1; CBF, Cerebral Blood Flow; TrkB, Tropomyosin Receptor Kinase B; LUSE, luseogliflozin; DM, diabetic; Met, Metformin BDNF,Brain-Derived Neurotrophic Factor; EMPA, Empagliflozin NLRP3, NOD-like Receptor Protein 3; GLP-1RA, GLP-1 Receptor Agonists; AMPK, Adenosine 5′-Monophosphate (AMP)-Activated Protein Kinase; LPS, Lipopolysaccharide; TSH, Thyroid-Stimulating Hormone; HRSD, Hamilton Rating Scale for Depression; VPA, Valproic Acid;; NF-KB, Nuclear Factor Kappa-B; SLC7A11, Solute Carrier Family 7 Member 11; CUMS, Chronic Unpredictable Mild Stress; FST, Forced Swim Test; TST, the Tail Suspension Test; GSH, Glutathione; VILDA, Vildagliptin; HbA1c, Hemoglobin A1c; IPRA, Ipragliflozin; HMGB1, High-Mobility Group Box 1; ADAM-10, a disintegrin and metalloproteinase 10; MDA, Malondialdehyde; SSRIs, Selective Serotonin Reuptake Inhibitors; 8-OHdG, 8-Hydroxy-2′-Deoxyguanosine; VPA, Valproic Acid; SOD, Superoxide Dismutase; EuDKA, Euglycemic Diabetic Ketoacidosis; HAMD, Hamilton Depression Rating Scale; PHQ-9, Patient Health Questionnaire; DPP-4i, dipeptidyl peptidase-4 inhibitors; CAT, Catalase; SU, Sulfonylureas; ADAM-10, A Disintegrin and Metalloproteinase Domain-10; AChE, Acetyl

Cholinesterase; TNF-α,Tumor Necrosis Factor-α; IL-1β, Interleukin-1β; IL-18, Interleukin-18; IL-6, Interleukin-6; HMGB1, High-Mobility Group Box 1;BMI, Body Mass Index; HDL, High-Density Lipoprotein; 5-HT, 5-Hydroxytryptamine; DCX,Doublecortin; PTSD, Post-Traumatic Stress Disorder; ROS, Reactive Oxygen Species; fMRI,Functional Magnetic Resonance Imaging; HDRS, Hamilton Depression Rating Scale; mTOR, Mechanistic Target of Rapamycin.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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