Potential Therapeutic Role of Crocetin in Western Diet-Induced Cognitive Dysfunction

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Abstract

The cognitive dysfunction caused by Western diet is a recent worldwide issue, which is caused by the overconsumption of high-fat, high-sugar, and ultra-processed products and foods. It is a diet that causes a rapid progression of neuroinflammation, oxidative stress, insulin resistance, gut microbiome dysbiosis, and blood-brain barrier dysfunction, which result in synaptic dysfunction and gradual cognitive impairment. Crocetin is an antioxidant, anti-inflammatory, and metabolic-modulating bioactive carotenoid derived from saffron and Gardenia jasminoides is an effective neuroprotective agent. It improves the work of mitochondria, increases the level of brain-derived neurotrophic factor (BDNF), changes PI3K/Akt signaling, and strengthens the gut-brain axis, which leads to a better cognitive resilience. Moreover, the capacity of crocetin to revert the microbiota balance in the gut and

protect the integrity of the blood-brain barrier makes it a hopeful therapeutic solution to the diet-induced neurodegeneration. In spite of these encouraging outcomes, issues like low bioavailability, rapid metabolism, require modern drug delivery approaches, such as encasing in nanoparticles, and liposomal encapsulation. This is a critical review of the pathophysiology of cognitive decline associated with the Western diet, outlines the molecular effects of crocetin, and outlines its use as a therapeutic candidate. Further studies ought to concentrate on large scale clinical trials, precision medicine, and formulation development to improve the neuroprotective ability and clinical practicability of crocetin.

Keywords: Crocetin, Western diet, cognitive dysfunction, oxidative stress, gut-brain axis, synaptic plasticity, insulin resistance, PI3K/Akt signaling, nanotechnology.

1. INTRODUCTION

1.1 Overview of Cognitive Impairment & Western Diet

The Western Diet (WD), which is typified by the overconsumption of ultra-processed foods, high-glycaemic carbohydrates, and trans fats, has been implicated in the pathophysiology of the cognitive dysfunction to an increasing degree. The typical dietary pattern related to WD is characterized by a distortion in the proportion of macronutrients, in particular, the excessive amounts of saturated fats and refined sugars, and the deficiency of vitamins, fiber, and other bioactive phytochemicals (1). These food surpluses interfere with systemic metabolic homeostasis and result in neuroinflammation, oxidative stress, intestinal dysbiosis, and cerebral vascular dysfunction, eventually causing neurodegenerative development (2). The WD has excess fructose and trans fats, which increase the pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1 3), which activate the microglia and astrocytes in the central nervous system, leading to synapse degeneration and memory impairment (3). Simultaneously, an ongoing intake of high-fat diets alters peroxisome proliferator-activated receptor gamma (PPAR7) and nuclear factor-kappa B (NF-kB) signalling, which worsens neuroinflammatory pathways that facilitate the aggregation of amyloid-beta and hyperphosphorylation of tau, which are typical manifestations of Alzheimer disease (4).

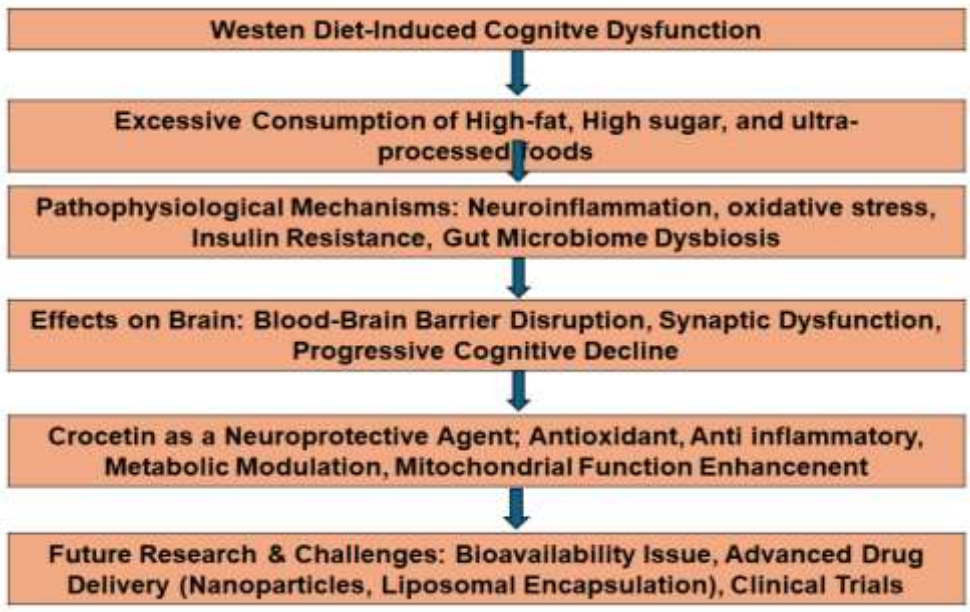


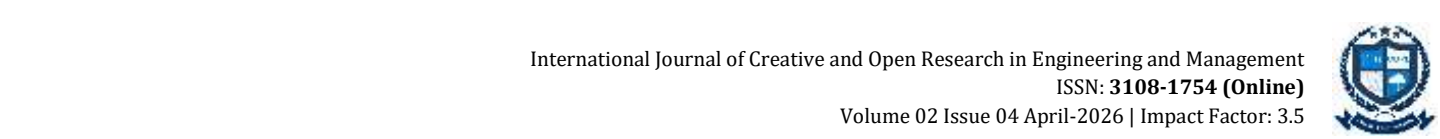
FIGURE 1: WESTERN DIET-INDUCED COGNITIVE DECLINE: MECHANISMS AND PROTECTIVE ROLE OF CROCETIN

Oxidative stress is also closely linked with the Western dietary pattern owing to mitochondrial dysfunction because high-fat and high-sugar diets cause excessive reactive oxygen species (ROS) production, which disrupts the neuronal bioenergetics and synaptic plasticity (5). The lack of antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase , is a typical example of WD-fed people, which additionally exposes the brain to lipid peroxidation and neuronal death (6). Also, the dietary omega-6 to omega-3 fatty acid ratio is high in WD, which further increases lipid mediator synthesis through cyclooxygenase-2 (COX-2) activation, thus, continuing oxidative neuronal damage (7). This sustained oxidative stress impairs neurovascular integrity, impairs tight junction proteins claudin-5, permitting systemic inflammatory mediators to enter the CNS and continue to mediate neurodegeneration (8). Gut-brain axis: Diet-induced dysbiosis often changes the intestinal microbiome composition, becoming low Bifidobacterium and Lactobacillus, and high Proteobacteria and Clostridium species(9). These changes in microbes augment intestinal permeability and translocate lipopolysaccharides (LPS) systemically that enhances neuroinflammation through toll-like receptor 4 (TLR4) receptor stimulation in microglia (10). Also, the loss of short-chain fatty acid (SCFA) in WD worsens neurochemical disturbances, which decrease the syntheses of serotonin and gamma-aminobutyric acid (GABA), thus playing a role in cognitive and mood changes (11). A well-studied effect of WD is insulin resistance, which worsens cognitive impairment by inhibiting the neuronal uptake of glucose, dysregulation of insulin receptor and insulin-like growth factor-1 signaling, and encourages tau phosphorylation through glycogen synthase kinase-3 beta (GSK-3b) activation (12).

1.2 NEED FOR THERAPEUTIC INTERVENTION

Existing pharmacological and non-pharmacological treatments of WD-induced cognitive impairment are still by and large inadequate since the current therapies tend to be more focused on relieving symptoms as opposed to directly investigating the underlying pathophysiology that contributes to neurodegeneration. Cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and N-methyl-D-aspartate (NMDA) receptor blockers (memantine) which are prescribed most are associated with modest cognitive effects but do not prevent the disease progression (13). Furthermore, the effectiveness of such agents is very inconsistent and considerable inter-personal variations in response to the agents result in discontinuation of treatments because of side effects like gastrointestinal upsets, dizziness, and hepatotoxicity (14). Dietary changes and physical activities have been suggested as the main interventions that can prevent neurodegeneration in the WD as part of the metabolic and lifestyle interventions. But the issue of compliance is still high-level because of the widespread availability and addictive nature of ultra-processed food items, which dis-regulates dopamine-mediated reward circuits and confirms the habitual eating of a diet composed of high-fat and high-sugar content (15). Furthermore, even though ketogenic and Mediterranean diets have proved to be promising in preclinical and clinical models, their sustainability and efficacy in a wide range of populations have not been identified yet (16).light of these limitations, there is growing interest in natural bioactive compounds as neuroprotective agents capable of targeting multiple aspects of WD-induced cognitive decline. Among these, Crocetin, a carotenoid derivative of saffron (Crocus sativus), has emerged as a particularly promising candidate due to its pleiotropic effects on oxidative stress, neuroinflammation, synaptic plasticity, and metabolic regulation. Unlike traditional pharmacotherapies, Crocetin exhibits high bloodbrain barrier permeability as well as a good safety profile, placing it in a good position to be used in the long term to preserve cognition. Experimental evidence has shown that Crocetin enhances mitochondrial performance by stabilisation of electron transport chain activity, inhibition of reactive oxygen species formation, and Nrf2-mediated antioxidant defences up-regulation (17). In addition, Crocetin provides powerful anti-inflammatory effects through the inhibition of NF-KB signalling, microglial activation, and pro-inflammatory cytokines such as TNF- a and IL-6 (18). Empirical evidence indicates that Crocetin promotes neuronal glucose uptake by activating AMP-activated protein kinase, reinstates insulin receptor sensitivity and decreases glycogen synthase kinase-3 beta activity, which inhibits hyperphosphorylation of tau and neuronal apoptosis .

1.3 Crocetin A natural and individual apocarotenoid mainly produced by saffron (Crocus sativus) and Gardenia jasminosis has become the focus of an increasing amount of scientific attention due to its extensive range of pharmacological actions, such as neuroprotection, metabolic control, anticancer and antioxidant features (19). In comparison with traditional carotenoids, crocetin has a unique linear dicarboxylic acid structure which significantly enhances its bioavailability, and is therefore quickly absorbed and easily passes through the bloodbrain barrier. Moreover, crocetin increases the cellular energy homeostasis, through the regulation of adenosine monophosphate-activated protein kinase (AMPK) and nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factors, both of which are critical in the maintenance of neuronal activity



during periods of metabolic stress (20). A comprehensive study of the antiinflammatory effects of crocetin has enabled its ability to prevent important triggers of neuroinflammation, including nuclear factor- κB (NF 2) and cyclooxygenase-2 (COX 2) signal cascades (21). The signaling cascades play a key role in western diet (WD)-induced cognitive impairment, which enables excessive release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- alpha), interleukin-6 (IL- 6) and interleukin-1 beta (IL- 1 beta), hence maintaining microglia activation and synaptic dysfunction (22). Crocetin is reported to reduce neuroinflammation by inhibiting microglial activation and reducing blood-brain barrier (BBB) permeability to prevent intrinsic penetration of systemic inflammatory mediators into the central nervous system (CNS) (23). Furthermore, the use of crocetin is seen to promote synaptic plasticity through the up-regulation of brain-derived neurotrophic factor (BDNF), which plays a crucial role in learning and memory formation and is impaired by the intake of WD (24,25).

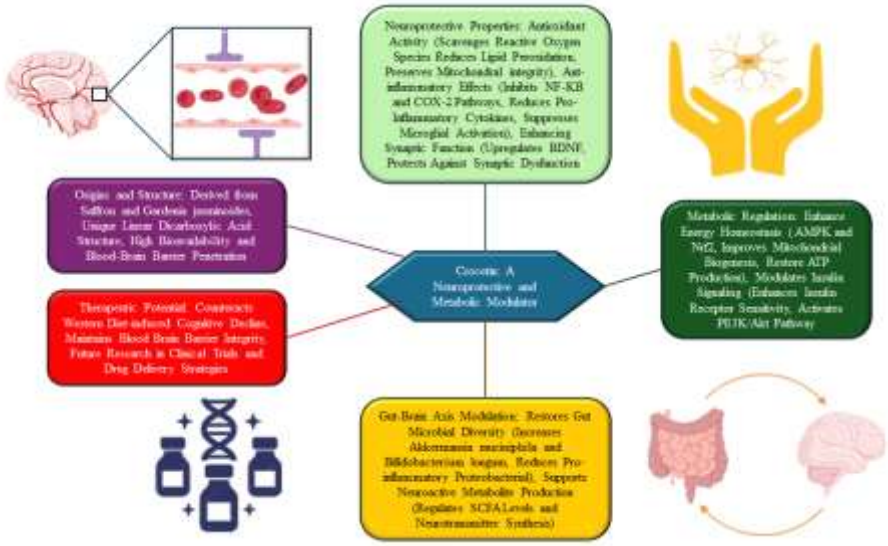


FIGURE 2: MECHANISTIC INSIGHTS INTO CROCETIN-MEDIATED NEUROPROTECTION AND COGNITIVE HEALTH

Table 1: Pharmacological Properties of Crocetin in Neuroprotection

Pharmacological Property	Mechanism of Action	Neuroprotective Benefits
Antioxidant Activity	An antioxidant, lipid peroxidation inhibitor, up-regulates Nrf2.	Lowers the oxidative stress levels,maintains mitochondrial activity.
Anti-Inflammatory Effects	NF-kB Inhibits COX-2, inhibits microglial activation.	Lowers neuroinflammation, maintains synaptic integrity
Synaptic Plasticity Modulation	Stimulates the BDNF and neurogenesis.	Enhances learning ability and memory.
Metabolic Regulation	Increases insulin sensitivity, AMPK and PI3K/Akt activation.	Promotes the absorption of glucose in the neurons, inhibits metabolic abnormality.

Gut-Brain Axis Modulation	Recovers the growth of microbes, lowers the translocation of LPS, improves the production of SCFA.	Preventive against gut mediated neuroinflammation, neurotransmitter balance.

2. PATHOPHYSIOLOGY OF WESTERN DIET-INDUCED COGNITIVE DYSFUNCTION

2.1 Neuro-inflammation &Microglial Activation

The consumption of Western diet (WD) has been linked to recurrent episodes of chronic neuroinflammation, which is mainly catalyzed by the excessive activation of microglia, the resident immune effector cells in the central nervous system (CNS) (26). The metabolic homeostasis is disrupted by the excessive consumption of saturated fats, high-glycemic carbohydrates, and ultra-processed foods characteristic of WD, which results in a systemic increase in pro-inflammatory cytokines (tumor necrosis factor- sometimes called TNF-alpha (TNF- 0) and interleukin-6 (IL-6), as well as -interleukin-1 (IL- 1) (27). These inflammatory mediators stimulate microglial activity, by altering their homeostatic M2 phenotype to pro-inflammatory M1 phenotype continuing the process of synaptic injury and neuronal apoptosis (28). Long-term consequence of microglia activation leads to the over release of nitric oxide (NO), prostaglandins, and reactive oxygen species (ROS), which further increases neurotoxicity and synaptic impairment in key areas of cognitive function, i.e. hippocampus and prefrontal cortex (29). Dysbiosis of the gut microbiota that enhances gut intestinal permeability and allows gram-negative bacteria lipopolysaccharides (LPS) to translocate into the systemic circulation is one of the key mechanisms through which WD leads to neuroinflammation (30). The LPS attaches to the toll-like receptor 4 (TLR4) on the microglia, which leads to the activation of nuclear factor-kappa B (NF- κB) and a protracted release of cytokines (31,32). The process is also increased by the intake of high-fructose diets, which undermine the integrity of the blood-brain barrier (BBB), and as a result, allow systemic inflammatory mediators to enter the brain parenchyma. WD also causes chronic neuroinflammation that facilitates amyloid -beta (A8) deposition and hyperphosphorylation of tau protein, two key pathophysiological features of the Alzheimer disease. The dysinflammatory response in the case of WD-fed individuals has also been associated with an inhibition of neuronal plasticity and synaptic transmission mediated by the overactivation of ionotropic glutamate receptors including N-methyl-D-aspartate receptors (NMDARs). Excitotoxicity and loss of neurons occurs due to hyperactivation of NMDARs, which contributes to exacerbating the cognitive impairment of neurodegeneration induced by WD .

Table2: Key Inflammatory Mediators in Western Diet-Induced Cognitive Dysfunction

Inflammatory Mediator	Source in Western Diet	Mechanism of Neuroinflammation	Impact on Cognition
Tumor Necrosis Factor-Alpha (TNF-α)	Processedmeats, trans fats	Stimulates microglia, interferes with synaptic plasticity.	Neurodegeneration, memory lapses.
Interleukin-6 (IL-6)	High-fructose diets, refined sugars	Improves the permeability of BBB, stimulates the accumulation	Laccelerates the deterioration of the

		of amyloid-beta.	mind.
Interleukin-1 Beta (IL-1β)	Saturated fats, processed foods	Activates chronic microglia, enhances tau hyperphosphorylation.	Dysfunctions learning and executive functions.
Reactive Oxygen Species (ROS)	High-fat, high-calorie diets	Stimulates oxidative stress and dysfunction of the mitochondrion.	Neuronal degeneration, synaptic degeneration.

2.2 Oxidative Stress & Mitochondrial Dysfunction

Cognitive dysfunction that has been caused by Western diet has a close relationship with oxidative stress, which is a condition that is characterized by an imbalance between pro-oxidant species and endogenous antioxidant defenses in the brain (33). It is also due to an increased intake of omega-6 fatty acids and refined sugars prevalent in a Western diet that results in a significant increase in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which leads to lipid peroxidation, oxidative stress on proteins, and DNA damage in neuronal populations (34). Mitochondria, which are the main energy-producing organelles in the neurons, are particularly vulnerable to oxidative damage, since their electron transport chain (ETC) is a major source of ROS generation when an organism is subjected to metabolic stress. Prolonged exposure to high-fat diets alters the function of several vital enzymes of the mitochondrion, such as complex I (NADH dehydrogenase) and complex III (cytochrome bc1 complex), which leads to disrupted oxidative phosphorylation and increased ROS escape (35). Further oxidative damage to mitochondrial DNA (mtDNA) adds to ETC destabilization, triggering advancement of neuronal damage in cognitively pertinent areas of the brain like the hippocampus and the prefrontal cortex (36). Neuroinflammation enhances oxidative stress by increasing NADPH oxidase isoforms NOX 2 and NOX 4 that promote the excessive generation of superoxide anions and peroxynitrite, resulting in massive oxidative damage to neuronal tissue. Besides, lipid peroxidation by-products like 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) accumulation leads to neuronal death and inhibition of synaptic plasticity (37).

2.3 Gut-Brain Axis&Microbiome Dysregulation

Western diet provokes dramatic changes in the composition of microbiota of the gut, which leads to gut dysbiosis, intestinal hyperpermeability, and systemic inflammation, which are all the causes of cognitive dysfunction. Alteration of microbial homeostasis leads to the proliferation of pathogenic bacteria, such as Proteobacteria, Clostridium, and Firmicutes, which secrete pro-inflammatory metabolites, such as lipopolysaccharides (LPS) and trimethylamine -N -oxide (TMAO), crossing the blood-brain barrier (BBB)

and activating neuroinflammatory pathways. On the other hand, Bifidobacterium and Lactobacillus are examples of neuroprotective microbial taxa that are lost when an individual eats a Western diet and this reduces the production of the short-chain fatty acids (SCFA) like butyrate that is necessary to maintain the neuronal homeostasis and anti-inflammatory signaling in the central nervous system (38). The gut dysbiosis supports the development of intestinal permeability - often termed the leaky gut - and hence allows microbial-produced toxins, including LPS to enter the blood, and trigger peripheral immune cells, which stimulates systemic inflammation and microglial activation (39). The following activation of pro-inflammatory cytokines such as TNF -a and IL-6 interferes with neurotransmitter homeostasis, reduces synaptic plasticity, and enhances amyloid -beta deposition, thus worsening cognitive impairment.

3. CROCRETIN: Pharmacology, structure, and Pharmacology. Chemical Structure and Bioavailability Chemical Structure and Bioavailability

3.1 Chemical Structure and Bioavailability

Crocetin is a bioactive carotenoid diterpenoid that is mostly extracted to saffron (Crocus sativus L.) and Gardenia jasminoides Ellis. It naturally occurs as a glycosylated form of crocin ester which on hydrolysis give rises to crocetin (trans-crocetin and cis-crocetin isomers). Crocetin is structurally an anti-inflammatory and antioxidant hydrophobic polyene chain with conjugated two-bond chains. The molecule is very lipophilic with a comparatively low aqueous solubility which restricts its direct bioavailability. Hydroxyl and carboxyl functional groups allow hydrogen -bonding interactions, which affect its absorption and its transmembrane movement (40). Although crocetin is highly bioactive, it has a low systemic bioavailability because it is metabolized fast, aqueous insolubility, and absorbed poorly in the gastrointestinal tract. Crocetin is absorbed freely without micellar encapsulation as required in traditional carotenoids to be absorbed intestinally leading to faster absorption into systemic circulation. One of the major limitations in crocetin therapy is its limited ability to cross the blood-brain barrier (BBB), restricting its direct neuro-protective effects (41). To enhance its bioavailability, several formulation strategies, including nano-encapsulation, liposomal carriers, and prodrug approaches, have been explored to improve its pharmacokinetic profile . Recent studies suggest that lipid-based formulations significantly increase crocetin absorption, allowing higher plasma concentrations with prolonged circulation time.

3.2 Pharmacokinetics & Mechanisms of Absorption

Crocetin has a rapid intestinal absorption, moderate tissue distribution, and extensive hepatic metabolism with regard to its pharmacokinetics. In contrast to other carotenoids, crocetin does not have to be transported with the use of lipoproteins, and it is directly absorbed in their free form through the intestinal epithelium. Nevertheless, its plasma half-life is not very high which requires frequent administration or sophisticated delivery schedules to retain its therapeutic effect. Once absorbed, crocetin is largely complexed with albumin

and lipoproteins, and this allows its passage to the peripheral tissues, amongst which are the brain, liver and fatty tissues. Crocetin metabolism Crocetin is metabolically processed through phase II biotransformation in the liver that conjugates crocetin through glucuronidation and sulfation, and is released into bile and urine. It lowers its systemic bioavailability, thereby decreasing its long-term therapeutic efficacy in neurodegenerative diseases. The absorption of Crocetin depends on dietary factors, intestinal microbial composition and genetic differences in metabolic enzymes, and therefore, the pharmacokinetic profile of Crocetin is highly different in different individuals .

Table 3: Pharmacokinetic Parameters and CNS Delivery Strategies for Crocetin

Pharmacokinetic Parameter	Description	Enhancement Strategy
Absorption	Rapid, passive diffusion	Lipid-based formulations
Tmax (Time to Peak Concentration)	1-2 hours	Delayed-release capsules
Plasma Half-Life	3-5 hours	Nano-encapsulation
Metabolism	Hepatic (glucuronidation)	Enzyme inhibitors
Excretion	Biliary and urinary	Prodrug modifications
BBB Permeability	Moderate	Liposomal nanoparticles
Brain Tissue Retention	Limited	PEGylated delivery

The pharmacokinetic characteristics of crocetin should be improved to enable its successful conversion into clinical therapeutics. Liposomal and polymeric nanoparticles have been suggested to increase its half-life and enhance its efficacy of uptake into the brain by means of prodrug derivatization .

4. MOLECULAR MECHANISMS OF CROCETIN IN NEUROPROTECTION

4.1 Crocetin and Oxidative Stress

Crocetin has strong antioxidant action that is characterized by scavenging of reactive oxygen species (ROS), lipid peroxidation inhibition, and the promotion of endogenous antioxidant defenses (42). These effects have their molecular foundation in the capacity to regulate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which is a major regulator of antioxidant reactions in cells. When crocetin stimulates Nrf2, it increases the expression of genes under the control of antioxidant response element (ARE), such as those of heme oxygenase-1(HO-1) in addition to glutathione peroxidase(GPx), superoxide dismutase(SOD), and NAD(P)H quinone dehydrogenases(NQO1). Protective effect of crocetin in mitochondrial oxidative stress has been showed in in vitro as well as in vivo research. Crocetin decreases the generation of mitochondrial ROS, preserves mitochondrial membrane potential and inhibits cytochrome c release that otherwise causes apoptotic cascades in neuronal models that are subjected to high-fat, high-glucose environment. Moreover, crocetin increases peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 02) which

is a master controller of mitochondrial biogenesis to promote ATP-generation and stabilize oxidative phosphorylation efficiency(43) .

4.2 Anti-Inflammatory Effects

Crocetin has potent anti-inflammatory action due to inhibiting the NF- 2 signaling pathway, suppressing production of pro-inflammatory cytokines and also regulating microglial activation. Western diet-induced cognitive decline is characterized by neuroinflammation, which is largely mediated by the persistent activation of microglia and the release of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF) interleukin-6 (IL- 6), and interleukin-1. Crocetin inhibits NF-kB translocation into the nucleus and, hence, inhibits the transcription of these inflammatory cytokines, oxidative stress, and downstream consequences of neuro-inflammation (44). In addition to inhibiting cytokines, crocetin can suppress the transformation of microglia into a pro-inflammatory M1 state to an anti-inflammatory M2 state and thus re-establish immune homeostasis in the central nervous system (CNS) (45). This shift is essential in the process of synaptic remodeling and repair of neurons as well as chronic neuroinflammation resolution. Also, crocetin suppresses cyclooxygenase-2 (COX-2) activity, resulting in the reduction of the production of prostaglandin E2 (PGE2), which also inhibits the inflammatory activity in the brain.

Table 4: Crocetin's Effects on Gut-Brain Axis Regulation

Target	Mechanism of Action	Effect on Gut-Brain Axis
Bifidobacterium, Lactobacillus	Enhances positive microflora	Heals intestinal homeostasis, enhances neurotransmitter equilibrium.
Clostridium, Proteobacteria	Sacrifices pathogenic bacteria	Reduces the production of LPS, reduces neuroinflammation.
SCFA Production	Increases the acetate synthesis, butyrate	Enhances integrity of the gut, controls microglial action
Tight Junction Proteins	stimulates ZO-1, claudin-1, occludin	Precludes intestinal permeability, decreases systemic inflammations
LPS Inhibition	Blocks TLR4 signaling	Inhibits neural inflammation, neuronal protection.

Crocetin regulation of gut microbiota has a direct effect on serotonin and dopamine metabolism, which are some of neurotransmitters that regulate mood and cognitive processes. Crocetin inhibits the production of VAM to the kynurenine pathway, which is facilitated by tryptophan metabolism modification and results in elevated levels of neurotoxic quinolinic acid formation, a process that is common in individuals on the Western diet . These findings demonstrate the possibility of crocetin to modify the gut-brain axis as a form of therapy to protect the brain against cognitive decline due to Western dietary habits .

5. PRECLINICAL AND CLINICAL STUDIES ON CROCETIN

5.1 Animal Studies

crocetin has been widely studied in preclinical paradigms of cognitive impairment, and especially in the neurodegeneration caused by a Western-style diet. It has been shown to counter oxidative stress, neuroinflammation, insulin resistance, and synaptic dysfunction in animal models and can be used as a candidate neuroprotector. Crocetin administration in a cognitive impairment model of a high-fat diet drastically lowered lipid peroxidation of the hippocampal, reinstated superoxide dismutase (SOD) biomolecule, and enhanced nuclear factor erythroid 2-related factor 2 (Nrf2) signal, which alleviated neuronal injury brought by reactive oxygen species (ROS) (46). Crocetin has been shown to have anti-inflammatory properties, based on its ability to inhibit the activation of microglia and the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and interleukin-1 beta (IL-1 beta), which have been shown to cause western diet-related cognitive impairments (47). Crocetin reduced amyloid-beta deposition, tau hyperphosphorylation, and neurofibrillary tangle formation by a significant margin in one of the murine models of Western diet-induced Alzheimer-like pathology, which suggests its use in alleviating neurodegenerative changes on a molecular scale.

Table 5: Summary of Preclinical Evidence Supporting Crocetin in Western Diet-Induced Cognitive Dysfunction

Animal Model	Cognitive Dysfunction Induced By	Key Findings with Crocetin Administration
High-fat diet-fed mice	Oxidative stress, dysfunction of the mitochondria.	Reconstituted SOD 2 and Nrf2 signaling, decreased lipid peroxidation.
Western diet-induced Alzheimer's model	Neuroinflammation and amyloid pathology	Decline of A B deposition, less tau phosphorylation, inhibited IL- 6 and TNF-a. Decline of A B deposition, less tau phosphorylation, inhibited IL- 6 and TNF-a.
Insulin resistance rat model	The presence of affected glucose metabolism	Enhanced PI3K/Akt signaling, decreased GSK-3 2 activity, augmented synaptic plasticity
Western diet-fed rodents	Gut-brain axis dysfunction	Heightened desirable gut microbiota, lessened neuroinflation as a result of LPS.

The outcomes of the preclinical research indicate that crocetin is capable of targeting various neurobiological pathways, such as mitochondrial bioenergetics, neuroinflammation, synaptic remodeling, and gut-brain axis regulation which play a central therapeutic role in the Western diet-induced cognitive decline (48).

5.2 Human Studies

Although there is a high amount of preclinical evidence, scarce human research has been conducted to determine the efficacy of crocetin in cognitive well-being. Its impact on oxidative stress, metabolic activity as well as vascular health, which affect cognitive outcomes indirectly, has received predominant clinical trial research (49). As observed in a randomized, placebo-controlled trial in older people with mild cognitive

impairment (MCI), episodic memory, and verbal fluency and working memory were significantly better in crocetin supplementation daily (12 weeks) than in the placebo group (50). The cerebral blood flow (CBF) has been described as one of the mechanistic properties of crocetin which improves brain blood flow via its vasodilatory and endothelial-protective properties (51). An fMRI (crocetin) imaging study showed that middle-aged adults who consumed a Western diet had enhanced hippocampal perfusion with supplementation and this resulted in better cognitive flexibility and executive functioning (52). Crocetin supplementation has been found to lower the signs of systemic inflammation, increase the insulin sensitivity and reduce the level of oxidative stress in individuals with metabolic syndrome, which is directly related to ameliorating neurocognitive performance(53). Also, electroencephalography (EEG) measures have demonstrated that crocetin effects the theta and alpha activity of the brain which are linked with faster cognitive processing speed and attentional control (54).

6. CROCETIN COMPARED TO OTHER THERAPEUTIC AGENTS

6.1 Comparison with Conventional Drugs

Crocetin is a naturally derived carotenoid and has shown considerable neuroprotection in models of Western diet induced cognitive impairment as a replacement to traditional pharmacological anti-inflammatory agents , anti-inflammatory NMDA receptor antagonists, and anti-inflammatory drugs (55). Common pharmacotherapies that are used in cognitive decline management of metabolic syndrome and neurodegenerative diseases, including donepezil, rivastigmine, and memantine are mostly symptomatic therapies that do not correct the neurobiological underlying dysfunctions that are caused by Western dietary habits (56). Crocetin has multipronged neuroprotective effects, unlike AChEIs: it reduces oxidative stress, mitochondrial dysfunction, and neuroinflammation, which have been identified as the main causes of diet-induced cognitive impairment (57). Recent reports have shown that the antioxidant activity of crocetin is stronger compared to other common synthetic antioxidants like 0-tocopherol (vitamin E) because it is much more efficient in scavenging free radicals and activating Nrf2 -antioxidant response element (ARE) pathway (58). Also, the effects of crocetin on brain-derived neurotrophic factor (BDNF) signaling are indicative of a possible role in enhancing synaptic plasticity, which is not one of the main effects of the currently used pharmacological agents used in cognitive disorders .In addition, crocetin has also been found to cross blood-brain barrier (BBB) successfully, in comparison to most NSAIDs, which do not penetrate to levels of therapeutic interest in the central nervous system. The possible advantages of crocetin compared to glucagon-like peptide-1 (GLP-1) receptor agonists, including liraglutide and semaglutide will also be worthy of attention. Although GLP-1 receptor agonists are commonly known to have neuroprotective and insulin-sensitizing properties, the beneficial effects of crocetin are diverse, such as gut microbiota regulation and BBB stabilization, which may also be even more beneficial in improving neurocognition in people on a Western diet (59).

Table 6: Key Challenges and Future Research Directions in Crocetin Clinical Trials

Research Gap	Current Limitation	Proposed Future Direction	Reference
Lack of large-scale RCTs	Small sizes of samples, brief duration of trial.	Long term, multi center trials in heterogeneous populations.	(60)
Dose optimization	No normative information on dose	Pharmacokinetic investigations to determine the optimum dose to be used	(61)
Cognitive biomarkers	Trials are dominated by their subjective assessments.	Combination of fluid biomarkers and neuroimaging.	(62)
Inconsistent cognitive models	Research is given on MCI, without considering AD and PD.	Increase research to neurodegenerative diseases	(63)
Gut-brain axis research	Insufficient human data	Microbiome-centered studies that have cognitive outcomes.	(64)

7. Formulation and Drug Delivery Advances

The low solubility of crocetin in water, high metabolism, and limited systemic bioavailability are major obstacles to the role of the drug in cognitive disorders (65). Although it has good pharmacological properties, traditional preparations are characterized by low gastrointestinal absorption as well as high hepatic clearance, which require advanced drug delivery methods to achieve the best clinical results (66). To increase the absorption and penetration of crocetin in the brain, the establishment of nanoparticle-based, liposomal, and micellar formulations have been suggested (67). A recent research has shown that nanocarrier-based delivery methods, i.e. solid lipid nanoparticles (SLNs) and polymeric micelles, can substantially enhance the bioavailability of crocetin by aiding the passage of the molecule across the blood-brain barrier (BBB). Another new way of using it is incorporating probiotic-based formulations, in which the use of crocetin is associated with the administration of gut microbiome-modulating agents. As the gut-brain axis is so critical in neuroinflammation and cognition, these formulations can be used as a complement in order to increase the therapeutic potential of crocetin (68).

Conclusion

Studying crocetin as a therapeutic agent to treat cognitive impairment caused by a western diet has shown that it has a great neuroprotective potential. High saturated fatty acids and refined sugar diets have been associated with multifactorial pathophysiological processes that lead to cognitive deterioration, and these include chronic oxidative stress, cellular neuroinflammation, dysfunction of the mitochondria, insulin insensitivity, disruptions of neurotransmitters and sustained glial activation. All these interrelated mechanisms gradually harm neuronal apparatus, decrease the density of synapses and eventually lower cognitive capabilities, which is why new and multi-targeted treatment strategies are necessary. Also, the fact

that it reinstates the microbiota balance of the gut, lowers systemic inflammation, and preserves the integrity of the blood-brain barrier highlights its effect in regulating the gut-brain axis during diet-induced cognitive dysfunction. Crocetin has a good pharmacological profile, but low bioavailability, poor aqueous solubility, and high metabolism limit the clinical translation of crocetin. These difficulties require sophisticated formulation methods including use of nanoparticles based systems of delivery, liposomal encapsulation, and PEGylated analogs to achieve high levels of therapeutic efficacies.

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