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PHARMACOLOGICAL IMPACT OF RUTIN IN COGNITIVE IMPAIRMENT: A STORY OF JEWEL OF GARDEN FROM MARKED BENEFITS, MECHANISMS, AND MOLECULAR TARGETS TO ITS NOVEL FORMULATION DEVELOPMENT

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ABSTRACT

Quercetin-3-rutinoside hydrate is a plant pigment (flavonoid) widely distributed in many fruits and vegetables known as rutin. Its therapeutic properties are mainly attributed to its potent antioxidant and anti-inflammatory activities. Its effect is well known as an antimicrobial, antifungal, and anti-allergic agent while extensive research has shown its multi-spectrum pharmacological benefits in cancer, diabetes, hypertension, hypercholesterolemic conditions, and neurodegenerative conditions. Currently, no clear-cut remedies available to prevent the progression of Cognitive impairment (CI) along with that one major pharmaceutical constraint associated with rutin is bioavailability, aqueous solubility, and stability. CI are a state which includes loss in comprehension with perception, logic, planning, attention, judgment, and memory. It is associated with Alzheimer's, Parkinson's, dementia, head injury, schizophrenia, cerebrovascular impairment, and depressive disorder. The present review emphasizes the current knowledge available for rutin in the treatment of CI, its mechanism of action, and molecular targets based on preclinical research. Clinical trials, toxicity profiles, and formulation development are also mentioned in this report. Rutin is a treasure of the garden have diversified health benefits due to its restoration of PARP activity, P-95, reversal of the levels of BACE 1 and p-STAT3, ameliorated synaptophysin protein expression in the hippocampus, and partly reversed the level of dopamine and decreased expression of Bcl-xL and Bcl-2. Novel formulation of rutin is overcoming the pharmaceutical challenges and bring this to the forefront as an alternative therapy in CI and other diseases.

Keywords: Neurodegeneration; Rutin; Cognitive impairment; Novel formulation; Pharmaceutical challenge

1. INTRODUCTION

Cognitive neurosciences were acknowledged by George Miller and Michael Gazzaniga in the 1970s **[1]** and cognition implicates the proper processing of the brain which involves proper transformation, reduction, storage, recovery, and utilization of sensory input **[2]**. Cognition indicates intuition, comprehension, perception of the individual with their logic, execution of planning with attentivity, judgment, and finally their memory. Cognitive impairment (CI) is a barrier to these neurological responses which is associated with the function of the brain. Hence CI results in, deficits of intelligence, learning, working, memory and attention. Such deficits can bring about a decrease in quality of life, and can not only affect the individual but their family, and society as a whole. Broadly cognition can be social and neurocognition. Social cognition includes interaction with the social environment while neurocognition is an association of distinct brain area and neuron system **[3]**. The incidence of this defect is rapidly increasing in Americans at the age of 65 and older and it is estimated that 88.5 million people will be suffering from this disease in 2050 **[4]**. 75-90% of cases of traumatic brain injury are due to neuronal cell loss in the hippocampus and impairment in verbal memory **[5]**. One of the studies comprising 10 countries demonstrated that about 30% of ischemic stroke patients are diagnosed with CI. Even the incidence of schizophrenia in the Indian population is approximately 4 per 10,000 and the worldwide point fact is approximately 4.6 per 1000 population **[6, 7]**. CI in the Indian population > 60 years will increase from 7.7% in 2001 to 12.30% by 2025. In India, the CI incidence rate was reported to differ from Himachal Pradesh 3.5%, Uttar Pradesh 5.1%, and Kashmir 6.5%. The CI prevalence was found to be 11.5% in South India at a place called Kerala aged group greater than 65 years old **[8]**. Hence, CI is a major health problem to the world as it can further lead to neuropsychiatric and neurodegenerative disorders such as Alzheimer's **[9]**, Parkinson's **[10]**, dementia, head injury, schizophrenia, cerebrovascular impairment, and depressive disorder occurs. Type II diabetes mellitus **[11]**, hormonal imbalance, genetic predisposition, deficiency of proper nutrients, and aging also affect cognition. Cognitive deficits in any participant along with other diseases or disorders are not only the concern of affective medication or symptomatology but also imitate premorbid developmental abnormalities. Some of the pharmacological agents including Donepezil, rivastigmine, tranquilizers, nicotine, galantamine, chlorpromazine, memantine helps to treat the symptoms of impaired cognitive

behaviors, and discontinuation of drugs may produce some side effects. A natural component is known to possess fewer side effects and minimal toxicity **[12]**. Therefore, this work is trying to collect the strength of rutin to control various disorders with a special impact on CI. The present review will highlights current updates of CI and its types with the mechanism as well as potential benefits of rutin with their mechanisms molecular targets, clinical impact and toxicity studies.

1.1. Versions of Cognitive impairment (CI)

CI can be identified as a 6D phenomenon that includes dyslexia, dysgraphia, dyscalculia, dyspraxia, dysphasia, and dysthymia. Dysthymia involves a kind of complication in which a person feels difficulty in decoding and not able to convince someone as they are finding it difficult to select specific words while listening and reading capacity is more perfect. The fundamental reason for this is due to abnormal activation of the left inferior frontal gyrus and decreased gray matter **[13]**. On the other hand difficulties in written expression, spelling, and bad handwriting is characterized as dysgraphia. This neurological defect is due to motor and memory dysfunction. Such a person also used to face difficulty in sound analysis and revitalizing letters **[14]**.

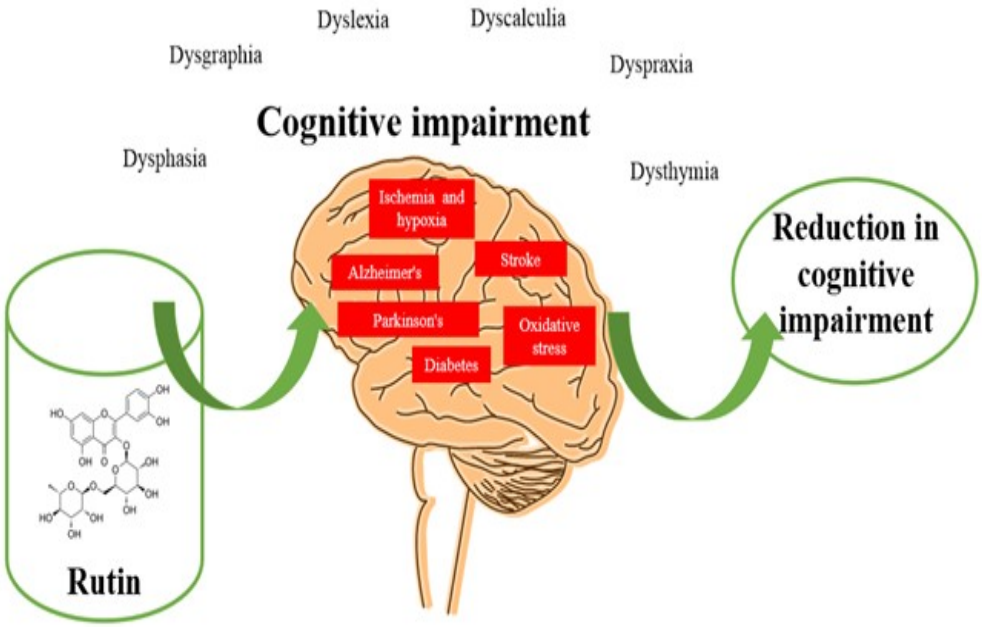

Figure 1: Causes, types, and treatment of CI

Impairment in understanding mathematical numbers, their calculation is due to the reduction of anatomical-physiological action in brain parts which is called dyscalculia **[15]**. Dyspraxia is impairment in gross motor skills and fine motor skills or both. So that the children are unable to judge about finger movement and they may have poor eye-hand coordination **[16]**. Dysphasia is a language or communication disorder. It is also a neurological disorder that is due to strokes, infection, head injury, and trauma affecting normal responses of the brain **[17]**. If a person used to report/diagnosed as having depression, loss of hope, feeling of guilt, always in sorrow and sad situation, extensive sleeping with fatigueness and as a result of this distraction from work is called dysthymia **(Figure 1) [18]**.

1.2. Causes of CI

It can occur from the time of fetal development, at birth, shortly after birth, or at a point of life, sometimes it is difficult to determine due to multiple factors. In this case, changes occur in the brain and its function resulting in CI. These are the following candidates that can be an important concern in the deployment of CI which is explained below:

1. Genes: Zinc finger protein 41(ZNF41) is responsible for X- linked mental retardation. The absence or stoppage of ZNF41 transcripts contributes to mental disorder i.e. intellectual disability **[19]**.

2. Brain injury: It is used for inducing memory dysfunction which increases the release of NO production in rats' brains, which causes impairment of cognitive function **[20]**. In brain injury,blood-brain barrier strongly damage in the hippocampus and ipsilateral cortex and lead to extravasation of serum protein might form due to neuronal necrosis that results into vasogenic edema, that is the inability to bring out metabolic by-product and nutrient, and inflammatory reaction which produces cell lysis **[5, 21, 22]**.

3. Diseases and infection: Its best example is Alzheimer's, Parkinson and brain tumors ease that affect the structure of brain network like lead to cognitive impairment. Any generation of neurofibrillary tangle and distraction in nigrostriatal track causes Alzheimer's, Parkinson's respectively **[9, 10, 23]**. Bacterial and viral infection usually attack the vessel wall and that leads to the release of cytokine which increases the risk of vascular disease. E.g. Chronic hepatitis c infection can result in cerebral dysfunction and lead to cognitive deficits **[24, 25]**.

4. Stroke: It occurs due to any developed lesions on neuroanatomy like rupture of cerebral vessels or due to decrease blood flow to the brain which contribute to cognitive dysfunction **[26]**.

5. Hormones: Melanin-concentrating hormone (MCH) activates the $MCHR_1$ receptor which regulates several symptoms of CI like behavior, motor activity, food intake, learning, and memory. So inactivation of $MCHR_1$ in the CA_1 region of the hippocampus lowers the NMDA response **[27]**. Estrogen which is also essential for memory function enhances the level of choline acetyltransferase important for the synthesis of acetylcholine in the CA_1 region in the hippocampus, frontal cortex, and basal forebrain **[28]**.

6. Age: With the increase in age brain size reduces and it starts affecting **[29]** both gray and white matter regions. Gray matter areas decline due to neuronal loss which leads to impairment in cognitive function **[30]**. Disease like Alzheimer's, hypertension, sleep disturbance which increases with the age is usually associated with neuronal collagen creation in the cortex as well as hippocampus region **[31]**.

1.3. Consequences of CI

CI occurs in various disorders and it can be multifactorial. It can appear along with schizophrenia, Compulsive disorders, Mood disorders, Personality disorder, Borderline Somatoform disorder, Substance abuse, Alzheimer and Parkinson's. It is important to note that in these disorders person used to give various responses of CI which can range from verbal memory impairment to working impairment and visuoperceptual and visuospatial deficits **[32-34]**. Working memory, executive function, vocabulary, old learning, visual perceptual skills kind of the problems that were recorded in schizophrenia. One of the common problems of CI like Executive function was majorly observed in Compulsive disorders, Mood disorders, Personality disorders **[32]**. In the case of Alzheimer's disease patients used to face abnormalities in episodic memory, executive function, semantic memory, and attention while visuoperceptual and visuospatial deficits with functional and memory defects were investigated in Parkinson's **[33, 34]**.

1.4. Molecular mechanism of CI

There are various clinical states in which CI appears but induction of this disease can take place using alcohol, scopolamine, ketamine **[35]**, phencyclidine **[36]**, isoflurane **[37]**, etc. Alterations in neuronal cell energy metabolism due to several reasons are the key mechanisms affecting normal brain development and contributing to cognitive disorders. CI due to traumatic brain injury usually depends upon the degree or extent of damage to the brain. Direct impact on the brain due to any injury results in mechanical damage to the neuronal and glial cells and vasculature and strains axons and this lead to systemic complication which further arises to edema, increased intracranial pressure (ICP), and

hemorrhage, leading to declining in cerebral blood flow (CBF) and impaired metabolism causing ischemia **(Figure 1)**. Ischemia due to these systemic impairments leads to the potentiation of biochemical and cellular cycles comprising glutamate excitotoxicity, calcium overload, free radical generation, mitochondrial dysfunction, inflammatory events, and pro-apoptotic gene activation and this contributes to neuronal loss. Neuronal cell loss, axonal degeneration, and impaired synaptic plasticity all result to cognitive dysfunction in mild to moderate cases of TBI **[38]**.

Nitric oxide (NO), a free gas radical presents its modulatory effects in both the central and peripheral nervous system acting as an intracellular messenger. NO which is usually produced in response to the activation of N-Methyl-D-aspartate receptors through a cluster of enzymes called nitric oxide synthase (NOS). NO contributes to numerous neurobiological properties of the brain like learning and memory **[39]**. The couple with superoxide anions to produce peroxynitrite, a highly reactive species, later contributes to nitration of proteins, lipid peroxidation, and formation of carbonylation of proteins and finally causing neuronal death **[40]**. A recent report gives an ample suggestion of NOS with the neurobiology of memory functions and its association with pathologic mechanisms of the disease **[41]**.

Synaptogenesis has two essential molecule synaptophysin and growth-associated protein 43 (GAP-43), which is very important for different forms of learning and memory **[42]**. Elevation in the expression of synaptophysin and GAP-43 is strongly associated with the cognitive-enhancing property of several factors, such as environmental enrichment, mildronate treatment **[43]**. So the loss of synaptophysin and GAP-43 in the brain are marked as neurodegenerative disorders, such as Alzheimer's disease **[44]**. Expressions of extracellular neurotransmitters in the brain are closely correlated to cognitive function. This relation is especially reflected that dopamine (DA) plays an important part in the regulation of learning and memory **[45]**. DA leads to hippocampal-dependent one-trial or episodic memories by inducing protein synthesis in hippocampal neurons. However, the role of synaptophysin and GAP-43 in TMT-induced memory loss and learning impairment in vivo is still unclear. Likewise, whether the dopaminergic system is involved in the protective role of rutin remains unknown **[46]**.

Aging is the primary risk factor for CI. It is stated that cerebral blood flow (CBF) or regulation of cerebral circulation is reduced in the elderly, or it can be expected that

aging-lead to cognitive impairment which is affected by a decrease in CBF as a result of brain ischemia and energy depletion. CBF regulation is related to cerebral metabolism so it plays a significant role in the preservation of cognitive function. Like hypertension contributes to vascular hypertrophy and remodeling and stimulates atherosclerosis in large cerebral arteries and lipohyalinosis in penetrating arterioles. These alterations at the structural and vascular level facilitate vascular occlusions and cerebral perfusion as well as the function of cerebral blood vessels, which induce impairments in endothelium-dependent relaxation **[47]** and cerebrovascular autoregulation. Abnormal vasculature along with resting CBF, metabolism, and cognitive function are decreased in patients with hypertension **[48]**. So it can be stated that variation in vascular risk factor-induced weakening of CBF or dysfunction of CBF regulation is related to cognitive function **[49]**.

Chronic pain has a marked impact on the daily lifestyle of a person, both physical and mental health is affected. From the previous data it is stated that chronic pain disturbs mood, productivity, social life, participation in leisure activities, and sleep and from the literature point of view it is reported that for chronic pain, cognitive impairment is a comorbid condition. Acetylcholine regulates the responses of pain in the spinal cord **[50]**. Cholinergic receptors present in the spinal cord in the superficial and deep dorsal horn, are used for the transmission and regulation of pain. So decline of cholinergic neurons in the brain and the loss of neurotransmission is the major factor for the decline in cognitive function in patients with AD. The progressive synthesis and aggregation of β-amyloid (Aβ), a proteolytic fragment derived from amyloid precursor protein (APP), are additional critical factors involved in AD pathogenesis and that is involved in cognitive impairment **[51, 52]**.

1.5. CI in Alzheimer's disease, Sleep deprivation, and Parkinson disease

1.5.1. Alzheimer's disease

It is a general age-related neurodegenerative disorder first explained by Dr. Alois Alzheimer. The gene for amyloid-beta precursor protein (APP), the gene for presenilin-1(PS1), and a gene for presenilin -2(PS2) are answerable for the growth of Alzheimer's disease. Amyloid plaque density and escalation in accumulation and generation of the neurofibrillary tangle and any damage to the brain and hippocampal volume is key feature of Alzheimer's disease **[53]**. The person who would develop Alzheimer's disease presented a baseline deficit of cognition. Some studies also reported that CI can manifest in the preclinical phase of Alzheimer's disease dementia **[54]**.

1.5.2. Sleep deprivation

To maintain the health and well-being of workers a total sleep of 7-8 hours is important. Sleep is essential for the body as it leads to energy conservation, thermoregulation, and tissue recovery as well as for cognitive performance and memory consolidation **[55]**. Sleep deprivation results in activation of the sympathetic nervous system that can lead to an elevation in blood pressure and cortisol secretion, impaired immune response, and metabolic changes. A decline in cognitive performance, motor performance, and mood alterations are observed for those people who are exposed to sleep deprivation. Those people who are having sleep loss usually affected by alertness and attention, the selective effect on certain brain structure and function **[56, 57]**.

1.5.3. Parkinson disease

It a chronic neurodegenerative disorder affecting 4.6 million in 2005 globally **[58]**. Parkinson's disease is due to nonmotor symptoms and comprises REM sleep disorder, cognitive deficits, olfactory dysfunction, neuropsychiatric disturbances. Cognitive deficits related to Parkinson's disease in the frontal lobe, lead to impairment in planning, attention, working memory, and concept formation as well as a deficit in visual perception and object recognition. Cognitive symptoms are dependent on the death of dopaminergic neurons in the substantia nigra, brain region includes the amygdala, hippocampus, and prefrontal cortex. This effect has supported the examination of the clinical Parkinson model **[59]**. A large no. of the population received different types of the drug for alteration in cognitive deficits like donepezil, fluoxetine, rivastigmine, nicotine, as their respective doses. These treatments are not only merely to treat cognitive deficits, but it is also given in improving diseases like Alzheimer's disease, schizophrenia, and Parkinson disease

2. Rutin: A bioflavonoid

Rutin (quercetin-3-rutinoside hydrate) is a dietary flavonoid widely distributed in vegetables and fruits which has many therapeutic properties, mainly attributed to its potent antioxidant and anti-inflammatory activities. Rutin (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside), also known as vitamin P or rutoside and its common sources are apple peels, black tea, asparagus, buckwheat, onions, green tea, figs, and most citrus fruit. Rutin is a rutinoside that is quercetin with the hydroxy group at position C-3 substituted with glucose and rhamnose sugar groups. It has a role as a metabolite and an antioxidant. It is a disaccharide derivative, a quercetin O-glucoside, a tetrahydroxy-flavone and a rutinoside. Many studies

have demonstrated its beneficial health properties, which prevent neuro-degenerative disorders, cardiovascular diseases, and skin cancer, among others. However, the health benefits of rutin can be influenced by its quantity and its bioavailability for absorption. Rutin from different sources can be also incorporated into functional foods such as bakery products and different strategies have been applied to overcome its low solubility in water. Therefore, rutin is a phytochemical dietary flavonoid, abundantly distributed in food plants with functional properties and enormous health benefits, that can be consumed as part of our diet **[60]**.

2.1. Structure activity relationship (SAR) of rutin

All the positions of functional groups, substitutions, availability of chains, and glycosylation provide a shred of evidence for its diversified functions **[61] (Figure 2)**. Polyhydroxylated substitutions on rings A and B, a 2,3-double bond, a free 3-hydroxyl substitution, and a 4-keto moiety responsible to give antiperoxidative effect, Glycosylation decreases AChE inhibitory activities of flavonoids and affinities for AChE (1–5 times) **[62-69]**.

2.2. Pharmacokinetics of rutin

Evidence regarding the absorption, metabolism, and excretion of flavonoids in humans is contradictory. Some studies reported that the most intensely studied dietary flavonoid, quercetin, is absorbed in significant amounts. However, naturally occurring flavones present largely in a glycosylated form rather than in their aglycone form and this form of the flavonoid seems to influence the rate of absorption and rutin being quercetin glycoside don't get absorbed in its native form, but after its hydrolysis in caecal microflora in the large intestine, it gets absorbed **[70]**. That's the reason rutin has poor solubility in aqueous media **[71]**. Flavonoids (catechins) initiate the conjugation of a glucuronide moiety in intestinal cells which is then bonded to albumin and transported to the liver and here it can further conjugate by adding a sulfate group, a methyl group, or both. Usually, the concentrations of any flavonoids and their biologically active conjugates are not high enough after occasional intake but their half-lives are longer so accumulation can occur when taken regularly which will result in required concentrations **[72]**.

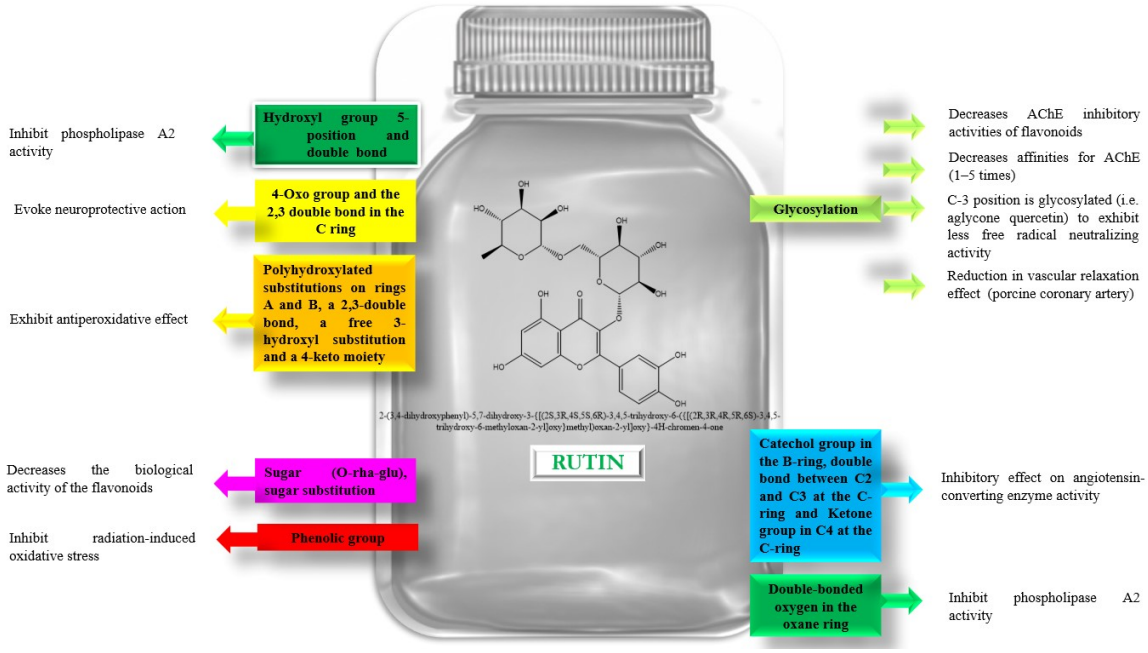

Figure 2: Actions of rutin on the basis of structure activity relationship

2.3. Pharmacological effects of rutin in CI

Rutin or vitamin P was given to male Wistar rats (450 –500 g) to evaluate its effect on CI and oxidative damage in the intracerebroventricular-streptozotocin (ICV-STZ)–infused rats. Pre-treatment with rutin at a dose of 25mg/kg was given which improved the learning performance of rats on the Morris water maze task and increase the path length of the rats, even it attenuated thiobarbituric acid reactive substances (TBARS) levels significantly from 110.83±5.55 to 72.96±5.63, the GSH content in the hippocampus was also depleted after the treatment, activities of antioxidant enzymes like GPx, GR, and catalase were also decreased in the treated group, nitrite level and PARP activity were increased after the treatment indicating that rutin offered significant neuroprotection to the rats by improving its cognitive impairment **[73]**. S.-w. Wang *et al*., 2012 presented a study on where rutin is capable to inhibit amyloid-ß aggregation and cytotoxicity. As soluble amyloid-ß plaque is the hallmark of AD and aggregation of amyloid-ß aggregation leads to neurotoxicity, inflammatory reactions, oxidative stress, and nitric oxide (NO) generation. So from the study, it was concluded that rutin can reduce the generation of reactive oxygen species (ROS), NO, glutathione disulfide (GSSG), and malondialdehyde (MDA), decreases inducible nitric oxide synthase (iNOS)

activity, even attenuated mitochondrial damage, elevates the glutathione (GSH)/GSSG ratio, enhances the activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) stating that rutin is potent constituents for treatment of AD, although further investigation is needed **[74] (Table 1)**. A study was performed to examine the efficacy of rutin as a neuroprotective agent and its antioxidant mechanism in 6-hydroxydopamine (6-OHDA)- induced toxicity in PC-12 neuronal cells. 100Mm of rutin was administered to PC-12 neuronal cells which resulted in a decrease in oxidative stress, glutathione, MDA, and increased glutathione peroxidase GPx, and superoxide dismutase increased SOD. Rutin presented its neuroprotective effect as it protected PC-12 neuronal cells against 6-OHDA-induced neurotoxicity and also came as a potent therapeutic agent for neurodegeneration related to free radical generation in the central nervous system **[75]**. Park *et al*., 2014, demonstrated that rutin obtained from *Dendropanax morbifera* Leveille had to protect effect on human dopaminergic cells against rotenone-induced cell injury by inhibiting JNK and p38 MAPK signaling pathway. Cheng, J., *et al*., (2016) designed a study on diet-induced obese mice for the evaluation of treadmill exercise and rutin intervention (100mg) for the improvement of cognitive function. Male mice 6J/C57BL were taken who were given treadmill exercise and rutin intervention for 16 weeks and after that, it was observed that it improved the cognitive function in the diet-induced mice from the morris water maze task reduced escape latency and increased time spent in the target quadrant and the number of crossing, Beta- secretase(BACE1) an enzyme involved for Aß production was reduced in the hippocampus along with that transducer signal transducer and activator of transcription (STAT3) level which is important for cognition ad are usually inactivated in hippocampal neurons of AD, this was also restored to normal level after treatment. Another protein that is post-synaptic density protein 95 (PSD-95) is a synaptic plasticity-related protein that plays an important role in cognitive function was also restored to a normal level after the treatment. Hence after the treatment, it was concluded that treadmill running and rutin improved cognitive impairment, and p-STAT3, BACE1, PSD-95 are the potent mediators that are usually involved in the protective effect **[76]**.

Table 1: Impact of rutin on CI

Animal model	Animal used	Dose of rutin	Remarks	Ref
Intracerebroventricular-streptozotocin (ICV-STZ)–induced CI	Male Wistar rats	25mg/kg	In the Morris water maze task improved the learning performance, TBARS significantly decreased from 110.83±5.55 to 72.96±5.63. GSH also reduced to 1.44±0.11, activities of antioxidant enzymes, GPx, GR, and catalase were improved 354.213±7.37, 700.384 ±4.17, and 50.64±2.77; PARP activity was restored 262.74±24.95).	[73]
High fat diet (HFD)	Mice 6J/C57BL male	100mg dissolved in 100g of HFD	Exercise and rutin improved cognitive function reduced escape latency and increased time spent in the target quadrant and number of crossing; even reversed the levels of BACE 1; p-STAT3 levels and P-95 were restored to normal level in the cortex	[76]
Phenytoin	Swiss albino mice 30 to 45g	125, 250, and 500 mg/kg	Chronic studies of Spontaneous Alternation Behavior has positive result with 79.6;whole-brain AChE activity was 127.8	[77]
Bilateral common carotid artery occlusion (BCCAO) model of chronic cerebral hypoperfusion.	Adult male Sprague-Dawley rats ,(380 ± 30 g)	50mg/kg	Rutin improved spatial learning and memory impairments spent more time in the target quadrant(9.631); T-maze apparatus alleviates cortex-dependent memory deficits (16.531); alleviated the decrease of ACh level and ChAT activity; prevents neuronal damage; even inhibits glial activation and oxidative damage	[78]
Sevoflurane and propofol	C57BL/6 pregnant mice	25 to 50mg/kg	Morris Water Maze test reduced the escape latency, in cued trial mice reach the platform much quickly	[79]
Traumatic head injury	Adult male Wistar rats (250-300 g)	20,40,80mg/kg	Lowered transfer latency in head-injured rats i.e improvement in learning and memory; shortened the escape latency improved memory performance; from water maze task shortened the path length, improvement in learning and memory; attenuated the oxidative stress markers and increased AChE activity	[41]
Scopolamine-induced short-term episodic memory deficits	12-week-old, healthy female Wistar rats (150–200 g)	50 to 100mg	Familiarization trial reduced short-term episodic memory deficits, discriminative and recognition indices were also improved	[80]
Chronic unpredictable stress (CUS) induced	Adult Swiss albino mice (25 to 35g)	100mg/kg	Locomotor and muscle coordination with open field test was 35 and from beam walk test was 70, elevated plus maze and open field gave anxiety as1.16; novel object recognition test was 25.16; Integrity of the hippocampal neurons was 3.53	[81]
Trimethyltin-induced	male BALB/c mice of 25 to 30g	20mg/kg	Reduction in escape latency in Morris water maze test; ameliorated synaptophysin protein expression in the hippocampus and partly reversed the level of dopamine	[46]
Passive avoidance induced	Male Wistar rats (200–250 g)	5, 10, and 100 mg/kg	Before training-induced a significant increase in memory retrieval and passive avoidance in the second and third test	[82],
Old age	old male WAG rat(400-500g)	100 , 200mg/kg	Total escape latency reduced during learning phase from training phase, swimming speed also reduced, no changes in the crossing over the area, increased level of dopamine and its metabolite	[83]
Isoflurane-induced	Pregnant female Sprague-Dawley rats	10,20, 40mg/kg	Expression of apoptotic proteins modulated, decreased expression of Bcl-xL and Bcl-2; Decrease the escape latency, improving learning and memory	[84]
Cadmium chloride	Male Wistar rats (170–200 g)	100mg/kg	Morris water maze (MWM) test enhanced memory function as it shortened the escape latencies, improved the spatial memory function by enhancing acetylcholine availability, heightening endogenous antioxidant property, more effective when conjugated with a-tocopherol	[85]
Cadmium	male Wistar albino rats (150–180 g)	25 and 50mg/kg	Reduction in cadmium bioavailability, decreased cholinesterase activities, improved spatial working memory and learning processes through Morris water maze and Y-maze tasks	[86]

Cadmium-	**Male Wistar albino rats (150-180 g)**	**25 and 50mg/kg**	**Reduced ectonucleotidase, ADA, and MAO activities, cadmium level, an increased level of the anti-oxidant enzyme**	**[87]**
entylenetetrazol (PTZ)- induced	**Male Wistar rats (200–250 g)**	**50 and 100mg/kg**	**Increased memory retrieval, reduced kindling development**	**[88]**
Intracerebroventricular (icv) injection of Ab_{1-42}	**(ICR) male mice**	**100 µg/mL**	**Promoted Aß disaggregation, prevented the H_2O_2-mediated inhibition of BDNF production, inhibition of the EGFR/GRK2 phosphorylation**	**[89]**
Mouse model of AD	**APP/PS1 (APPswe/PSEN1 dE9) double-transgenic mice,**	**18-25mg/kg**	**Morris water maze improved spatial learning and memory deficits, reduced escape latency time, improved crossing number, improved synaptic plasticity, a decrease of Aβ deposition, inhibited astrocytic activation, reduced Iba1 protein level, (IL-1β), IL-6, and (TNF-α) finally decreases chronic neuroinflammation.**	**[90]**
Phenylenetetrazole	**zebrafish**	**50mg/kg**	**Behavioral Scores of height (index of anxiety), locomotion response to different colors (red and yellow) was all normalized and time spent in the light area increased**	**[91]**
Scopolamine	**C57BL/6J male mice(17–19 g)**	**50-150mg/kg**	**Confirmed restoration of spatial learning and memory function, improved cognitive performance, improved BDNF gene expression, Nuclear levels of Nrf2, protein expression of PSD-95**	**[92]**

A study was designed to evaluate the effect of the co-administration of phenytoin (PHT) and rutin on CI in swiss albino mice of 30 to 45g. after the treatment it was reported that rutin along with PHT, significantly reversed PHT-induced decrease in spontaneous alternation without changing the efficacy of PHT against Increasing current electroshock seizure (ICES), in both acute and chronic experiment. Further, it also normalized PHT-induced increase in AChE activity **[77] (Table 1)**. Qu, Jie, *et al.*, (2014) designed a study in a rat model with permanent bilateral common carotid artery occlusion (BCCAO) a model of chronic cerebral hypoperfusion to evaluate the efficacy of the rutin on cognitive impairment through behavioral tests, biochemical and histopathological analyses. Rutin at a dose of 50mg/kg was administered to adult male Sprague-Dawley rat for 12 weeks where rutin with multitargeted therapeutically potential like improvement in hippocampus-dependent spatial learning and memory impairments, alleviates cortex-dependent memory, alleviates central cholinergic dysfunction, inhibits glial activation, reduces the levels of proinflammatory cytokines even prevents neuronal damage which cognitive deficits. So it's a promising new candidate for the treatment of cognitive impairment **[78]**. To investigate the influence of rutin on memory and cognition a dose of 25 to 50 mg/kg was given to neonatal rodent model C57BL/6). After the treatment, it was reported that it reduces the intensive apoptotic neurodegeneration, from the Y maze task it improved the working memory of mice. From the Morris Water Maze (MWM) which measures hippocampus-

dependent spatial navigation and reference memory it reduced escape latency and in the cued trial that evaluate swimming and visual abilities, here also mice reached the platform more quickly. In so current study Rutin exhibited potential neuroprotective effects and cognitive impairment **[79]**. Wistar rats were exposed to head trauma and treated with rutin at a dose of 20, 40, and 80 mg/kg for 2 weeks. Rutin was able to significantly attenuate these behavioral, biochemical, and molecular alterations associated with head trauma that is it lowered retention transfer latency in head-injured rats it leads to the improvement in learning and memory; shortened the escape latency time improved memory performance; from water maze task shortened the path length, improvement in learning and memory; attenuated the oxidative stress markers and increased AChE activity. So from this, it was concluded that rutin gave its protective aspects neurodegeneration of hippocampal and cerebral cortex neurons and cognitive loss in a rat model of traumatic head injury **[41]**. Rutin alleviates episodic memory deficits in two differentially challenged object recognition tasks **[80] (Table 1)**. Efficacy of rutin was on chronic unpredictable stress (CUS) mouse mode was investigated **[81] (Table 1)**. Many other protective effects of rutin in CI is summarized in **Table 1**.

3. Clinical trials of rutin

A randomized single-blind placebo-controlled trial was conducted for 6 weeks to investigate the antioxidant effect of rutin on 18 healthy non-obese normo-cholesterolaemic female volunteers. Supplementation of rutin into the subjects significantly raised the levels of three plasma flavonoids (quercetin, kaempferol, and isorhamnetin) with no significant changes in plasma antioxidant expression. Indicators of liver function were observed normally in the required range, and there was a decline in the expression of endogenous base oxidation in lymphocyte DNA and levels of urinary MDA or on the level of urinary 8-iso-PGF2a [93]. In another trial, at Rajah Muthiah Medical College Hospital, Annamalai University, Annamalainagar with 30 diabetic subjects. All these 30 subjects were given 500 mg caplets rutin supplementation for 120 days. After the completion of the study, it was observed that rutin reduced the fasting blood glucose, body mass index, both systolic and diastolic blood pressure. However, with these positive impacts also still more experimental and clinical studies are required to prescribe rutin as a supplement for the treatment of diabetes **[94]**.

4. Recent pharmaceutical approach: A novel formulation

4.1. Marketed of rutin

Solgar, UK, KAL, USA, Carlson labs, USA marketing rutin in the form of a tablet, its capsules are marketed by Cardiovascular research, Ltd., USA, Now Foods, the United States as Bioflavonoid caps, Now Foods, USA, Natural factors, USA and H &H, Pharmaceuticals, India. Its soft gel, gel, and V-capsules are marketed by Cipla, India, Novartis, the USA, and Horphag Research, Switzerland respectively **[71]**.

4.2. Challenges of formulation development of rutin

The oral bioavailability of rutin is 20%. This is because of poor aqueous solubility and it is available to absorb after hydrolysis into quercetin **[95]**. In one of the finding, it was observed that AUC (39.20 ± 12.10 mg·h/L), MRT (0.726 ± 0.13 h), Eli $T_{1/2}$ (5.413 ± 0.57 h), and Cl (0.424 ± 0.071 $L \cdot h \cdot kg^{-1}$) when rutin was given to the in normal rats. When 300 mg/kg of rutin was administered to rats then in plasma AUC, $T_{1/2}$, Cmax and MRT was 150 ± 22 (min μg/ml), 67 ± 8 (min), 1.35 ± 0.37 (μg/ml), and 206 ± 20 min respectively. On the other hand in Lymph AUC, $T_{1/2}$, Cmax and MRT were 395 ± 41 (min μg/ml), 89 ± 20 min, 0.86 ± 0.13 (μg/ml), and 318 ± 43 (min) respectively. Absorption and transportation of quercetin and rutin take place via blood circulation. The investigation explored that the AUC of both drugs in lymph fluid appeared higher than their respective AUC in plasma **[93, 96, 97]**. Hence it is now clear that the major pharmaceutical challenge of rutin is its poor oral bioavailability and it is due to its low aqueous solubility **[98, 99]**.

4.3. Approaches to improve pharmaceutical challenges

The disadvantage of rutin is concerned with its formulation and development due to its poor aqueous solubility and decreased bioavailability. Hence, scientists and health care professionals proposed different approaches to increase rutin solubility, in the aqueous and lipid phase.

4.3.1. For aqueous phase

The nanoparticulate system provides an improvement in aqueous solubility as it causes complete redispersion of substance in water and enhances dissolution velocity. Hence, Nanocrystal, nanocapsules, nanoemulsion, nanostructured lipid carriers (NLC), self-emulsifying drug delivery systems (SEDDS), and solid self-emulsifying drug delivery systems (SSEDDS) of rutin were developed and investigated for the enhancement of its aqueous solubility **[100]**. The results of these developed formulations showed improvement in physiochemical properties as well as its protection against abrupt conditions **[101-103]**. Derivatization of phenolic groups can also help to increase their solubility. It includes hydroxylation, carboxylation, and sulfonation reaction which brings more solubility and stability

to the product (eg. Venoruton®, Paroven®, Relvene® or Varemoid®) **[104-107]**. In the structure-activity relationship, we have seen the enhancement of pharmacological responses with the functional group addition and deletion. Carboxylate and sulfonated groups' introduction in rutin sugar moiety causes a 110-fold increase in aqueous solubility **[108, 109]**. Similarly, enzymatic oligomerization provides a shred of evidence for enhancement of aqueous solubility up to 4200 fold with an increase in biological activities. Laccase has been used to obtain oligorutin. Oligorutin fractions exhibited potent inhibition of the mutagenicity against 2-aminoanthracene and methyl-methanesulphonate. It was also observed that oligorutin reduces the genotoxicity induced by hydrogen in comparison to monomeric rutin **[110-112]**.

4.3.2. For lipid phase

Nanoparticulate systems offer an improvement in the photostability, chemical as well as functional stability of rutin. This can be achieved with rutin-loaded gelatin nanoparticles. When this developed formulation subsequently associated with chemical filters causes an increase in the SPF by 48% **[113, 114]**. It is important to note that in this formulation gelation and rutin both have antioxidant properties hence, produces improvement in free radical scavenging activity by 74% compared with respect to the free form of rutin. An increase in solubility was also recorded when rutin was provided in the phospholipid complex. It not only maintains the biological response but also improves lipophilicity and also hydrophilicity **[114-117]**.

Acylation increases its antioxidant effect as it causes derivation of the phenolic hydroxyl group is taking place **[118]**. On the other hand Lipases, subtilisin, and esterases like enzymes causes known to cause enzymatic acylation and bring about acyl donation from C2 to C16 **[114, 119, 120]**. In order to enhance the stability and solubility of rutin acylation of flavonoids are also an important and successful step as it makes them more hydrophobic by fatty acid linkage. It is an important point to note that enzymatic acylation is more regioselective while chemical acylation is not regioselective **[121]**.

5. Safety profile

Rutin-rich dough obtained from the Tartary buckwheat to conduct acute (10,000mg/kg) and subacute (5000mg/kg) toxicity studies on rats. No toxic symptoms on the acute toxicity test were recorded even not a single rat died after the test and a similar observation was reported for subacute toxicity with few symptoms like an increase in urine protein and serum albumin which was due to other factors like transient changes. So a dose of 10000 to 5000mg/kg was not considered toxic **[122]**.

Subchronic toxicity of enzymatically decomposed rutin i.e. isoquercitrin was conducted at different concentrations of 0, 0.2, 1, and 5% for 13 weeks to male and female rats. There was no mortality or any toxic, unusual, or abnormal symptoms wee observed from any of the groups. In the group of rats who received a 5% concentration of rutin, there was a decrease in weight at the 10^{th} week, and few observations like reduced RBC count, hemoglobin concentration was observed but that was also negligible. Based on the study observation rutin gave no-observed-adverse-effect levels (NOAELs) for both male and female rats **[123]**. Roy, Souvik, *et al*., (2015) demonstrated in their study regarding the oral acute toxicity and repeated oral subacute toxicity study of vanadium–rutin complex in balb/c mice. These mice were administered a dose range of 90, 45, and 20 ppm for 28 days. It was reported that at lower dose there was no toxicity and at 90 ppm dose there was an increase in WBC count, bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP) and there were little alterations in liver, kidney, and stomach at this high dose. However, there was no alteration after the administration of 20ppm to the mice **[124]**. One of the research articles also reported the toxicity assessment of polyherbal combination (PHC)i.e (Curcumin, quercetin, and rutin) on female Swiss albino mice and reported that this polyherbal combination had no toxicity or abnormal or unusual symptoms, along with that there was no alteration in the bodyweight of the mice or their lipid profile, or biochemical parameters even there was no mortality in any of the groups **[125]**.

Conclusion and future perspective

This review aimed to summarize the molecular mechanism of rutin based on preclinical studies and clinical trials. Numerous health benefits are provided by rutin due to its diverse mechanism of action. Investigation suggests that it is a potent molecule in the effective treatment of CI and has no toxic effect. Now, efforts should be made to focus on finding a reliable formulation, co-administration with the exact mechanism that can justify the health benefits of rutin. It can be possible if we can enhance the bioavailability of rutin using novel drug delivery methods with lesser side effects. The fundamental problem of the food industry is to translate basic-applied research and technology innovations into safe products which can provide benefits to society.

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Conflicts of interest

Declared none.

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