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# SYNERGISTIC NEUROPROTECTIVE EFFECTS OF FLAVONOIDS AND MICRONUTRIENTS ON OXIDATIVE STRESS AND NEUROINFLAMMATION

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***Abstract***

*Neurodegenerative diseases are also being perceived as one of the major health challenges in the world, where the degeneration of neurons, their cognitive abilities and their dysfunctional nervous systems are associated with the disease. Oxidative stress and chronic neuroinflammation are two key processes that cause these disorders, and are both involved in interrupting cellular homeostasis and increasing neuronal death rate. Recent studies have begun pointing to the possibility of moderating these pathological processes through the action of nutritional compounds, flavonoids and micronutrients to some extent. Flavonoids are polyphenols of diverse chemical structure but originally found in plants and were associated with potent antioxidant and anti-inflammatory actions contributing to the regulation of cellular signal transduction of neuronal defense. Micronutrients such as essential vitamins and trace minerals have major roles in the preservation of neuronal metabolism and antioxidant defense systems as well as in the preservation of mitochondrial functions. The combined effect of different flavonoids and micronutrients is beginning to be investigated as a potential synergistic approach to stimulating neuroprotective effects and improving their ability to mitigate oxidative free radicals as well as adjust inflammatory processes in the central nervous system. These synergistic responses have the potential to enhance neuronal capacity and quality in aging and provide cognitive health. This review investigates the biological pathways of the oxidative stress and neuroinflammation in neurodegenerative disorders and attempts to analyze the complementary effects of flavonoids and micronutrients in neuroprotection. The knowledge of these interactions can be useful in devising dietary ways and nutraceutical interventions that could prevent or delay the onset of the neurodegenerative diseases.*

## 1. INTRODUCTION

The importance of neurodegenerative diseases has been on the rise in the world because of the aging population and rising life expectancy. The progression of neuronal deterioration and the decrease of neurological functionality are the main

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characteristics of such disorders as Alzheimer's disease, Parkinson's disease, and other types of cognitive impairments. These disorders have severe disadvantages of memory, motor coordination and cognitive performance which in the end leads to diminished quality of life and added burden to the healthcare systems across the globe. The epidemiologic data show that the incidence of neurodegenerative diseases has been steadily increasing over the last few decades, which also reveals the fact that there is an acute necessity to develop effective prevention and treatment approaches aimed at modifying biological processes that result in neuronal destruction (Prince et al., 2015). Even with the improved medical science, most of the present treatments are simply aimed at management of symptoms but not the cause of the neuron destruction.

Oxidative stress and neuroinflammation became one of the most acceptable pathological processes among the main biological processes leading to neurodegeneration. Oxidative stress is a condition when the generation of reactive oxygen species surpasses that of antioxidant defense mechanisms of the body. Neurons are highly susceptible to oxidative damage because of the high level of metabolic rate, significant intake of oxygen, and comparatively low regenerative potential. Over-reactive oxygen species may destroy cellular constituents e.g. lipids, proteins and nucleic acids, which ultimately disturbs the structure and functioning of the neurons. Studies have indicated that oxidative stress can contribute to the development of neurodegenerative diseases through the facilitation of the mitochondrial dysfunction and the inhibition of neuronal signaling pathways that are fundamental to cell survival (Uttara et al., 2009).

Along with oxidative stress, neuroinflammation has proven itself to be another factor of utmost importance in causing neurological disorders. Neuroinflammation is the expression of immune functions within the central nervous system especially via microglia and astrostrocytes. Although acute inflammatory reactions might early have a protective effect through the removal of cellular debris and the elimination of injured neurons, chronic neuroinflammation can result in sustained release of pro-inflammatory cytokines and neurotoxic mediators. The result of such inflammatory processes is neuronal damage, synaptic impairment and neurodegeneration. There is an increasing amount of evidence indicating that neuroinflammation and oxidative stress are tightly linked, forming a pathologically looping mechanism that quickens the rate of neuronal involvement and sickness development (Heneka et al., 2015).

Over the last few years, interest in natural dietary compounds with potential neuroprotective effects through an ability to regulate oxidative and inflammatory mechanisms has increased. Nutritional neuroscience has been developing a growing interest in the importance of bioactive chemicals and beneficial micronutrients found in plants to keep the brain healthy. In contrast to traditional pharmacological methods, dietary compounds have rather a range of biological effects and may at once have a number of different pathological mechanisms of action leading to neurodegeneration. Consequently, supplementary measures against or delaying neurological deterioration have elicited influence through dietary interventions (Vauzour et al., 2010).

Flavonoids are also another name group of Natural compounds in the large group polyphenolic compounds that are broadly distributed in fruits, vegetable foods, tea, among other plant foods. The compounds have been characterized as being strong antioxidants, and they alter cellular state signaling pathways implicated with inflammation, oxidative stress, and cell survival. It has been demonstrated that experimental studies have determined that flavonoids can also be employed to alter the brain functionality through the augmentation of neuronal interaction, elimination of oxidative damage on neurons and the minimization of the levels of inflammatory reactions within the central nervous system (Spencer, 2009). There are other micronutrients such as vitamins and trace minerals that are essential in the maintenance of neurological integrity besides flavonoids. Other nutrients that contribute to antioxidant defense mechanism, mitochondrial activity and immune

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processes in the brain are vitamin E, vitamin C and zinc, selenium and magnesium.

A new area of study is emerging which examines the disparities in the interactions of flavonoids with the micronutrients; whether they are synergistic or otherwise. Synergy: This application can be understood as two or more compounds are interacting and hence producing an overall biological impact that does not equate to that of a single impact only. Alternatively, flavonoids and micronutrients may be coexist with that of neuroprotection to enhance the antioxidant levels, cell membrane stability, and inflammatory signal transduction. According to the empirical evidence of nutritional studies and biomedical studies, the following interactions may facilitate neuron resistance to oxidation and inflammatory damage, which subsequently improve brain physiology and mental performance (Bastianetto and Quirion, 2002).

The concept of this review is to investigate the synergies between flavonoids and micronutrients in relation to their neuroprotective action against oxidative stress and inflammation of the brain. The review examines the problem of interactions among these compounds to regulate the main biological pathways related to neurodegeneration by combining the results obtained in recent empirical research. The comprehension of these integrated mechanisms can be used in formulating effective nutrition programs and treatment measures in minimizing the risk and pathogenesis of the neurodegenerative diseases.

**2. Oxidative Stress in Neurodegeneration**

Oxidative stress has long been known to play an important role in neuronal damage and the development of neurodegenerative diseases. It arises when a relative balance between the generation of reactive oxygen species and the antioxidant protective system of cells is disturbed. In normal physiological conditions, reactive oxygen species are produced as natural products of cellular metabolism and they have functions in signaling pathways, which control cellular activities. Nonetheless, when these reactive molecules overpower, they may destroy the biological macromolecules, and therefore the survival of neurons. The brain is prone to oxidative damage because it has a higher intake of oxygen and has a huge number of lipid structures (Dias et al., 2013).

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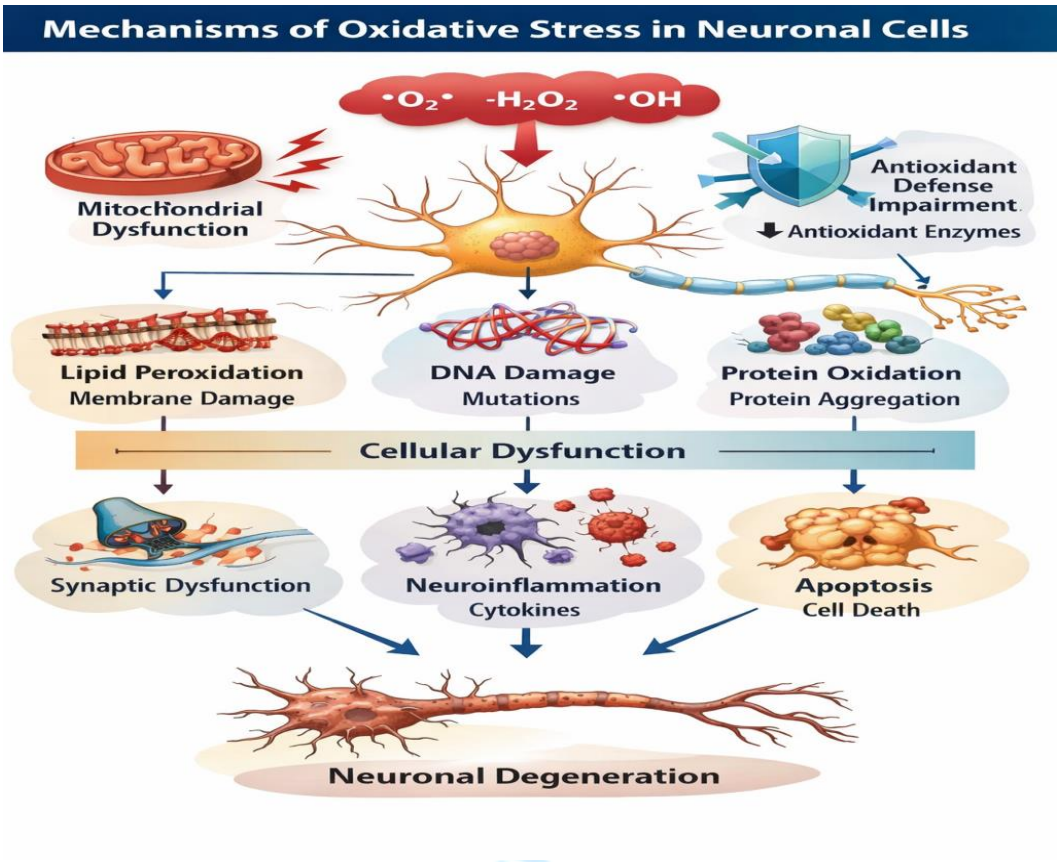



**Figure 1: Mechanisms of Oxidative Stress in Neuronal Cells**

On a biochemical scale, oxidative stress can be caused by reactive oxygen species, namely, superoxide anions, hydroxyl radicals, hydrogen peroxide, etc. These are molecules formed as a part of the metabolic activity in mitochondria and other cell structures. The neurons engage in extensive production of reactive oxygen species, which in turn leads to continuous high metabolic activity, therefore, strict regulation is necessary to ensure the integrity of the cells. Oxidative reactions initiated by the inability of the antioxidant system to take good care of these molecules target cellular components such as membranes, proteins, and genetic material. The resulting imbalance triggers a series of cellular maladaptation that may eventually result in neuronal necrosis or apoptosis (Cobley et al., 2018).

Reactive oxygen species have a key role in the damaging of neurons by a variety of mechanisms. Among the main consequences there is distortion of cellular membranes by oxidative interactions with lipid molecules. Polyunsaturated fatty acids are very sensitive to oxidation, and found in large concentrations in the neuronal membranes. The interaction of reactive oxygen species with these lipids leads to chain reaction that disrupts the structure of the membranes and also weakens cellular signaling events. This type of damage impacts on ion channels, receptor activity, and synaptic signaling and disrupts neuronal transmission and brain activity (Angelova & Abramov, 2016).

Another significant way in which oxidative stress plays a role in neurodegeneration is mitochondrial dysfunction. Mitochondria are key structures that assist in the generation of energy in cells during the process of oxidative phosphorylation. Mitochondrial function is very important in the neurons as they are energy consuming. In case of the damage of mitochondria under the impact of oxidative stress, their power to generate adenosine

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triphosphate reduces thus causing a shortage of energy in neuronal cells. Moreover, malfunctioning mitochondria produce even more reactive oxygen species and develop a chain of oxidative injury which, by itself, amplifies itself. This loop of action speeds up the process of degeneration of neurons and also leads to the development of neurological conditions (Gandhi & Abramov, 2012).

Lipid peroxidation that is also among the most harmful processes affecting the neuronal cells is also caused by oxidative stress. Lipid peroxidation The oxidative process uses reactive oxygen species to activate oxidative reactions in lipids of the membrane and this causes the production of toxic aldehyde products. The compounds interfere with normal cell metabolism by disrupting the stability of membranes. Products of lipid peroxidation may also react with proteins and nucleic acids, further increasing the cell damage. It has been shown that elevated concentrations of lipid peroxidation markers are often observed in the brains of persons with neurodegenerative conditions and therefore the pathological importance of this process to the diseases (Sayre et al., 2008).

Besides the damage to lipids, oxidative stress may also result in major harm to DNA molecules. Oxidative DNA Trading in both nuclear and mitochondrial DNA can cause mutations and harm the cell repair mechanisms. DNA damages have long-term effects on neuronal survival due to the limited ability of the neurons to generate more cells, which are long-lasting cells. Oxidative DNA damage would be able to interfere with gene expression patterns necessary in cellular maintenance and synaptic plasticity and eventually lead to functional deterioration of the nervous system (Madabhushi et al., 2014).

Another significant effect of oxidative stress when it comes to neurodegenerative conditions is protein oxidation. Reactive oxygen species have the ability to adjust the structure and biological activity of proteins by modifying the amino acid residues in them. The Oxidized proteins usually lose their functioning ability and they may be aggregated to cause interference to the cellular processes. Aggregation of proteins is known to be a characteristic of a number of neurodegenerative disorders. As an illustration, pathological alterations which take place in Alzheimer disease and Parkinson disease are associated with abnormal protein accumulation, and this poses that oxidative damage of proteins is a very critical factor in the development of diseases (Grimm & Eckert, 2017).

Oxidative stress has a specific contribution especially in significant neurodegenerative diseases. Oxidative damage has been linked to accumulation of amyloid-beta and abnormalities in tau protein in the disease Alzheimer, they affect neuronal communication leading to synaptic degeneration. Oxidative stress is also involved in the destruction of dopaminergic neurons in the substantia nigra, which is a motor control area in Parkinson disease. Equally, in amyotrophic lateral sclerosis, oxidative injury has been attributed to motor neuron loss and the eventual muscle weakness. These findings point to the ubiquitous presence of an oxidative stress in any one of a variety of neurology diseases (Barnham et al., 2004).

The brain is prone to oxidative damage and therefore antioxidant defense system is essential as a protective factor in neuronal retention. The body possesses multiple enzymatic and non-enzymatic antioxidant systems that are directed to responding to reactive oxygen species. Such enzymes include superoxide dismutase, catalase and glutathione peroxidase that help in converting the reactive molecules into less toxic forms. Besides this, the cells are defended against oxidative damage by endogenous antioxidant molecules such as glutathione. The effective working of these systems is vital in avoiding the excessive level of oxidative stress and neuronal integrity. Under conditions of impairment or overload of antioxidant defenses, neuronal damage is more probable, which adds to the genesis and pathogenesis of neurodegenerative diseases (Dringen, 2000).

The science on how oxidative stress plays a role in neurodegeneration is crucial in determining ways of distributing the protective effect to the functioning of neurons. Studies are still underway to determine how nutrition-related compounds and any other intervention can improve

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antioxidant defenses and minimize oxidative harm in the brain. These methods can offer some promising leads to prevent or delay the development of neurological diseases.

### 3. Neuroinflammation and Its Role in Neurological Disorders

Neuroinflammation is the immune reaction that takes place in the central nervous system towards injury, infection, or toxic agents. The immune environment in the brain is filled with specialized immunological structures controlled by resident immune cells and immune barriers, which is unlike that of peripheral tissues. In the physiological condition, immune reactions in the brain have protective functions, which are important in ensuring that there is no homeostasis which helps in repairing mechanisms after cellular damage takes place. But in cases when the inflammatory responses are sustained or maladjusted, they are capable of playing a role in neuronal impairment and neurodegeneration. There is growing experimental and clinical data that neuroinflammation represents a primary aspect of numerous neurological conditions, such as Alzheimer disease, Parkinson disease and multiple sclerosis (Glass et al., 2010).

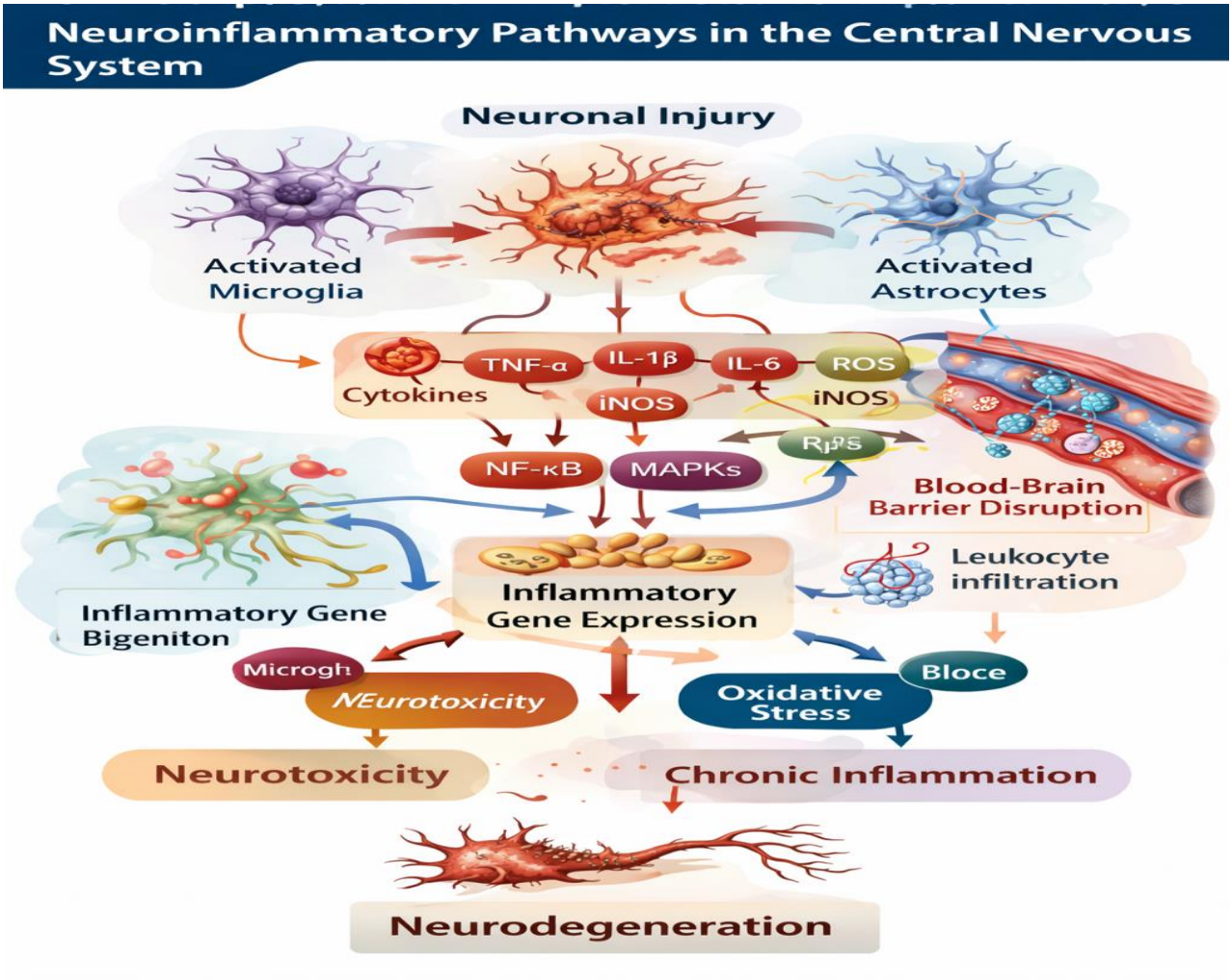



**Figure 2: Neuroinflammatory Pathways in the Central Nervous System**

It is the responsibility of the microglia and astrocytes to mediate the immune defense system of the central nervous system, which has a distinct system of its own. Microglia are regarded as the

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most important immune cells of the brain that are the initial base of protection against pathogens and cell damage. In the resting state, the microglia persistently cytotoxic the environment of the neurons in dynamic processes that sense some sort of neural tissue abnormality. Microglia are activated in response to neuronal injury or pathological stimuli and this is characterized by morphological alterations, movement of the microglia to the damage location and the release of inflammatory mediators. This activation has earlier useful purposes like destroying the damaged cells and debris by phagocytosis and hence maintaining neuronal survival and repair of the tissues (Block et al., 2007).

Another way in which the astrocytes are instrumental is in the control of the immune reactions in the brain. These glial cells are starlike and support metabolism of neurons, keep the blood-brain barrier and also balance neurotransmitters. Astrocytes become inflamed due to beginning to respond to injury or a disease, a process referred to as reactive astrogliosis. In the process, the astrocytes grow and synthesize a number of inflammatory molecules, which could affect the functionality of neurons and immune cells. Whereas reactive astrocytes can enhance protection of the tissue by inhibiting the extent of harm, over-activation is equally capable of promoting heightened inflammation and neuronal toxicity (Sofroniew, 2015).

Production of inflammatory cytokines and mediators is one of the most significant characteristics of neuroinflammation and it affects the survivability and communication among neurons. Tumor necrosis factor alpha, interleukin-1 beta, and interleukin-6 are the released cytokines that control immunological signals in the brain produced by the activated microglia and astrocytes. These cytokines are able to modify the work of synapses, interfere with the equilibrium of neurotransmitters, and disrupt the functioning of the neuron as a signaler. The production of other inflammatory molecules that increase the level of inflammatory responses may also occur through the effects of inflammatory mediators. The continued discharge of these aspects might slowly cause harm to the neurons and the eventual development of a downward trend in the neurons (Lucas et al., 2006).

Neurodegenerative diseases have been closely linked to the existence of chronic neuroinflammation. Inflammatory responses that accompany the build-up of amyloid plaques and neurofibrillary tangles are strongly related in Alzheimer disease, which causes the activation of micro-glia and astrocyte. On the same note, in Parkinson disease, inflammatory signaling plays a role in depleting the dolominergic precursors in the substantia nigra. Having the immune cells continuously active in the brain leads to the prolonged secretion of inflammatory mediators, which are capable of interfering with the work of neurons and accelerating the disease process. Such a long-lasting inflammatory condition not only causes neuron injury but also disrupts processes that maintain neuronal repair and regeneration (Ransohoff, 2016).

There is also a close interrelation between neuroinflammation and oxidative stress, and a complex network of pathological processes strengthening each other exists. The process of immune reactions includes the formation of reactive oxygen species by the activated immune cells. Even though these molecules are useful in the removal of harmful agents, the overproduction causes oxidative destruction to the adjacent neural tissue. The oxidative stress in its turn can trigger the other inflammatory signaling cascades that further trigger immune responses. The combination of these two processes makes oxidative stress and inflammation develop into a vicious cycle that increases neuronal damage and leads to the development of neurological disease (Wilkins and Swerdlow, 2017).

The molecular mechanisms of neuroinflammatory reactions include the presence of various important signaling systems that control the activation of the immune system in the brain. Two of these pathways include nuclear factor kappa B and mitogen-activated protein kinase signaling that have a role to play in regulating the expression of inflammatory genes. The stimulation of these signaling transductions results in elevated levels of cytokines, chemokines and other inflammatory mediators which affect neuronal survival and

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immune cell recruitment. These pathways have been found to be dysregulated in other neurological diseases and thus, the importance of these pathways in neurodegenerative pathology development is evident (Tansey and Goldberg, 2010).

Considering the increasing evidence suggesting the interconnection between neuroinflammation and neurological conditions, the modulation of inflammatory mechanisms has attracted significant interest as the method of therapeutic interventions development. Mechanisms to limit the inflammatory signal or constrain the work of the immune cells could assist in constraining the harm to the neurons and to delay the progression of the disease. The studies in the search of anti-inflammatory compounds, dietary compounds and lifestyle interventions hint at the potential of neuroinflammation by altering it as a promising solution to brain health protection. Specifically, natural extracts containing antioxidants and anti-inflammatory can be observed receiving more and more attention as potential agents that can potentially prevent or inhibit neurodegenerative damage (Cherry et al., 2014).

It is inevitable to comprehend the multifaceted processes governing neuroinflammation, and only under these circumstances, the effective strategies of preventing and treating the neurological diseases will be found. Current studies are ongoing to explore the possibility of addressing the immune behaviour in the brain by producing modes of immune regulation to aid neuronal survival and integrity of the immune system. This knowledge can be used to design new initiatives that would help in the maintenance of cognitive ability and the minimization of the global burden of neurodegenerative disorders.

**4. Flavonoids as Neuroprotective Compounds**

The Flavonoids are a versatile family of naturally occurring polyphenols that are common in plants and are also frequently found in fruits, vegetables, grains, and beverages (tea, cocoa, etc.). These compounds have gained much scientific interest in their potential health-promoting effects, especially, the capability to prevent oxidative and inflammatory damages of neuronal cells. Flavonoids are structurally similar to have a common phenolic backbone building of two aromatic rings that are linked together by a three carbon bridge. Differences in chemicals that cause a number of subclasses of flavonoids; flavonols, flavones, flavanones, flavanols, anthocyanins and isoflavones. All the subclasses also have distinct biochemical properties and biological activities that make them have neuroprotective potential. Improving findings on nutritional neuroscience indicate that flavonoids are important agents in overall maintenance of cognitive performance and prevention of neurodegenerative diseases (Williams and Spencer, 2012).

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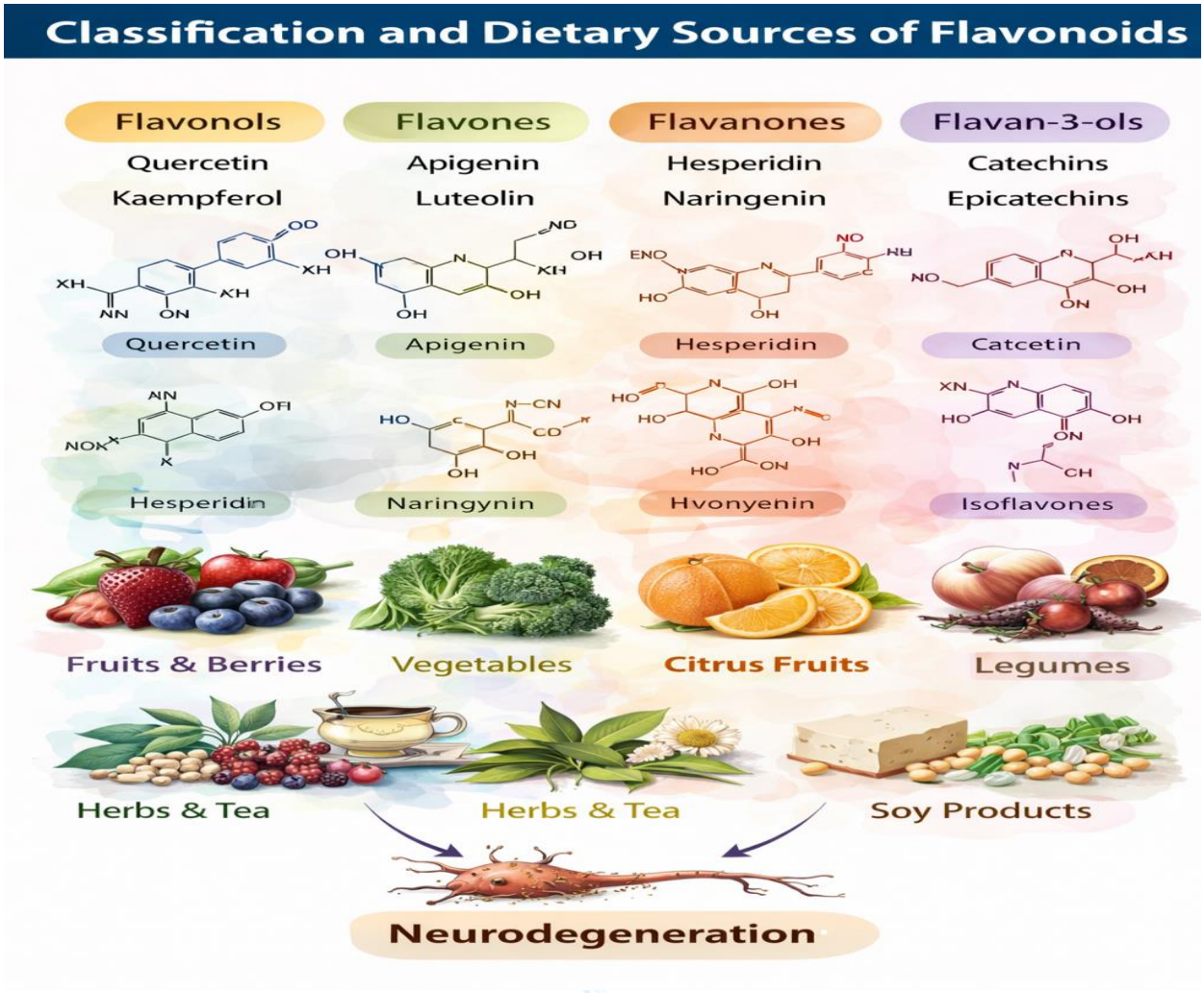



**Figure 3: Classification and Dietary Sources of Flavonoids**

Flavonoids are found in many sources of plant-based foods that constitute a balanced diet. Other significant sources of diet are these berries, citrus fruits, apples, and onion, kale, spinach, soy, as well as drinks like green tea, black tea, and red wine. Dark chocolate and cocoa products are also known to contain high-flavanol. The variety of foods rich in flavonoid would enable people to access the bioactive compounds with normal dieting. Epidemiological research has implicated that groups who are on high fruit and vegetable diets have reduced incidences of cognitive failures and neurodegenerative diseases. These facts have prompted investigators to study the exact ways in which flavonoids could serve as an effector of brain health and neurological activity (Joseph et al., 2009).

The high antioxidant ability of flavonoids is one of the most significant qualities of flavonoids that allow it to cancel the effect of reactive oxygen species leading to neuronal damage. Oxidative stress is especially sensitive to the brain because it consumes oxygen rapidly and has lipid-rich neuronal membranes in large quantities. Flavonoids have direct scavenging abilities of reactive oxygen species and therefore oxidation reactions consequently cause damage to cell constituents. Besides direct antioxidant effects, flavonoids have also been shown to increase the action of other endogenous antioxidant enzymes, further upgrading the brain defenses against

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oxidative stresses. In such ways, flavonoids prevent the oxidative damage of neurons and enhance the survival of cells (Rice-Evans, 2001).

In addition to acting as antioxidants, flavonoids can also control the oxidative stress by the means of regulating intracellular signal pathways. Studies have shown that these compounds affect the molecular responses to cellular stress such as those that relate to nuclear transcription factors and gene expression of antioxidants. Flavonoids are able to stimulate endogenous antioxidant protein synthesis which neutralizes oxidative damage by triggering protective signaling pathways. These regulatory implications enhance the protective action of flavonoids in addition to the radical scavenging effect and provide long-term protection to cells in the neuronal tissues (Surh, 2003).

The role of Flavonoids also involves a major role in regulating inflammatory signalling pathways in the brain. Neuroinflammation has been a central facilitator in the pathogenesis of a variety of neurodegenerative conditions and hyperactivation of the inflammatory pathways may result in neuronal dysfunction. Flavonoids have been demonstrated to suppress the stimulation of inflammatory mediators through the control of cellular signaling molecules in question in relation to immune responses. As an illustration, various flavonoids lower the aggressiveness of transcriptional factors that cause inflammation as well as inhibit the formation of pro-inflammatory cytokines discharged by stimulated microglia and astrocytes. Flavonoid helps to reduce damage to inflammatory responses caused by it as well as preserving neurons against the devastating effects of chronic neuroinflammation through these mechanisms (Calderón-Montaño et al., 2011).

Besides alleviating oxidative stress and inflammation, the flavonoids also affect neuronal communication and synaptic plasticity which play critical roles in the learning and memory processes. Some flavonoid compounds have been reported to stimulate the signal transduction that deals with neuronal development and synaptic activity. An increase in new synaptic connections and enhanced neuron-neuron communication might occur owing to these effects. It is also experimentally evaluated that even in the aging process of animal model diets rich in flavonoids can lead to improved cognitive functioning and memory operating, which can confirm their potential in preserving brain functions in old age (Williams et al., 2008). The neuroprotective potentials of flavonoids based on the laboratory experiments are also demonstrated. Flavonoids in cell studies have also been found to inhibit apoptosis and inflammatory degeneration of neurons caused by oxidative stress in cell research. These studies show that flavonoids can stabilize the activities of the mitochondrial system, inhibit cellular toxicity and improve the survival of neurons in stressful conditions. Neuronal damage and an improvement in behaviour have also been shown by animal studies to be enhanced through flavonoid supplementation in neurodegenerative disease models. The results of such designs are useful in providing an insight into the mechanisms of action of flavonoids in the generation of protective effects on the nervous system (Schroeter et al., 2007).

Clinical studies also have promising results which investigated the consumption of flavonoids by human population. Diets rich in flavonoids have been shown to be associated with other benefits of dietary flavonoids to larger cognitive-performance and reduced incidences of cognitive-decline in older individuals as observed in observational studies. In one study, the influences on memory and executive functioning as well as cerebral blood flow have been reported to improve upon the consumption of food containing flavonoid that contains berries and chocolate. These findings suggest that the regular intake of flavonoids might be beneficial to the brain and contribute to the overall neurological well-being. However, additional clinical trials are required to determine the optimal dose, bioavailability and prolonged effects of the best practice on different populations (Letenneur et al., 2007).

The scientific data of the neuroprotective properties of flavonoids is rapidly accruing, but even nowadays, there are still several obstacles to the application of these studies into practice in clinical therapeutic practice. Such aspects as bioavailability, metabolism, and individual variation in the absorption of diet flavonoids

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determine the biological effects of flavonoids on the human body. In addition, the interactions occurring between flavonoids and other food components may occur to affect their potential in protecting the operation of neurons. The ongoing researches continue to identify the ways of how these compounds can be efficiently applied in dietary supplements and treatment regimens to deter neurodegenerative conditions.

Overall, flavonoid is an interesting group of natural compounds with neuroprotective potency of high level. Their combinational antioxidant, anti-inflammatory, and signaling regulatory activities contribute to maintenance of the neuronal integrity and support of cognitive functioning. The awareness of the biological activity of flavonoids may bring significant positive data on the dietary practices that might be employed in the prevention and management of neurological conditions.

**5. Micronutrients and Brain Health**

Micronutrients are important as they help to keep the normal functioning of the neurological system as well as in general brain maintenance. These vital nutrients, such as vitamins and trace minerals, are needed in modest amounts but possess basic biochemical functions which maintain neuronal integrity, neurotransmitter production and cellular metabolic rate. The human brain is an extremely metabolically active organ that requires the continuous intake of micronutrients to ensure structural integrity and functional prowess. These nutrients are especially required in adequate quantity since the lack thereof may cause disruptions in the neurochemical communication between neurons, cognitive dysfunction, and the formation of neurological diseases. Growing amounts of evidence in nutritional neuroscience are pointing to the fact that micronutrient status plays an important role in brain development, cognitive functioning, and cognitive neurodegenerative disorders (Benton, 2010). Various vitamins are highly crucial in various metabolic activities aiding the well-being of neurons. Of them, the B-complex vitamins are especially known to serve the neurological purpose. One-carbon metabolism that involves vitamins B6, B9, and B12 controls the processes of DNA synthesis in the brain, neurotransmitter generation, and methylation. These biochemical activities play a critical role in ensuring the neuronal communication and synaptic plasticity. The impairments of these pathways might cause cognitive impairments and become more susceptible to neurodegeneration. Clinical studies have demonstrated that B vitamin deficiencies are correlated with high concentration of homocysteine, a metabolic substance that is, according to the studies, correlated with high risk of cognitive impairment and neurogenic disease (Smith and Refsum, 2016).

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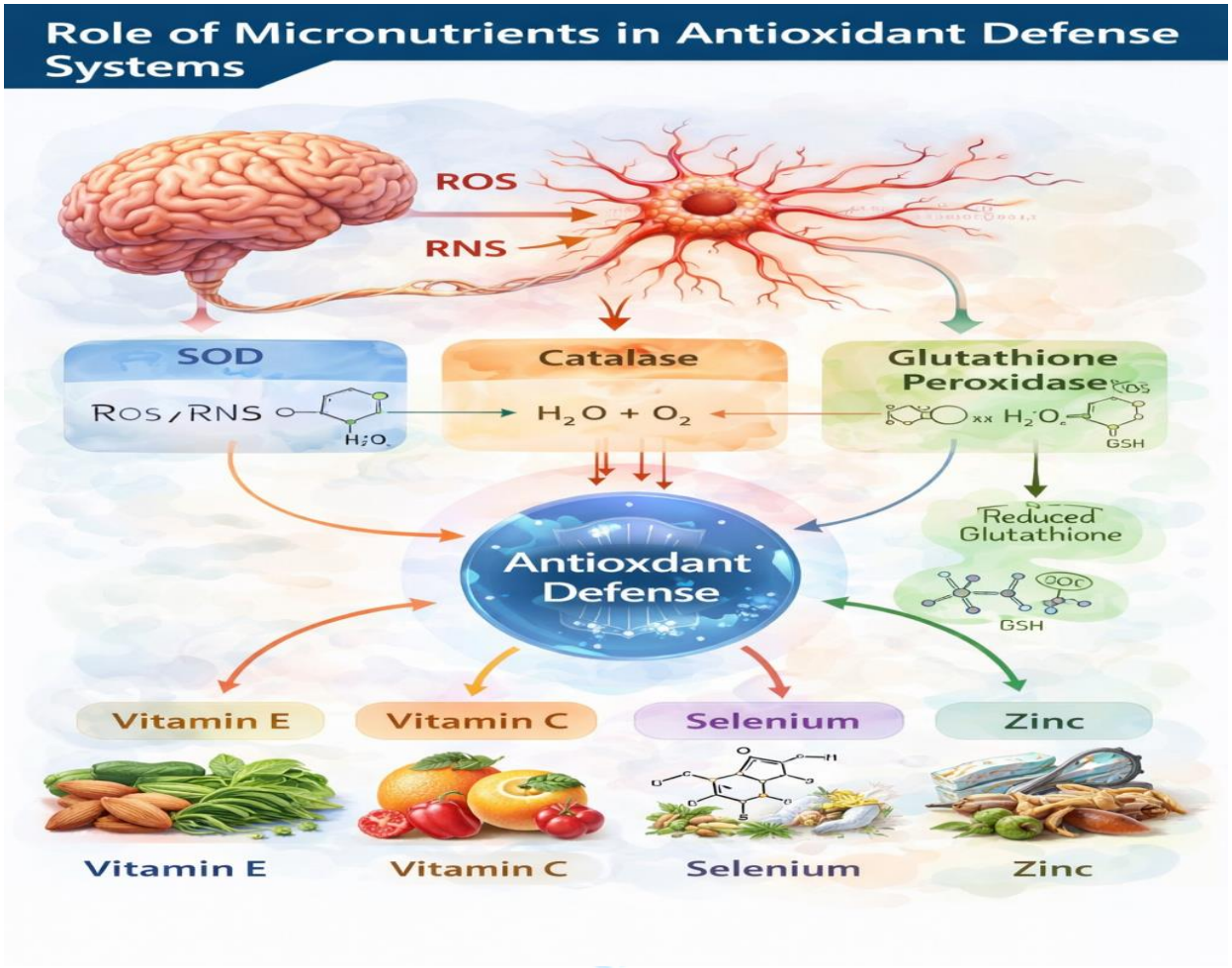



**Figure 4: Role of Micronutrients in Antioxidant Defense Systems**

The fat soluble vitamins are also noted to be important in ensuring that neuronal cells are not damaged. An example of this is vitamin D that has been reported to have an effect on the development of the brain, the differentiation of neurons and neurotrophic signal transduction. The fact that vitamin D receptors are located in several parts of the brain indicates that the nutrient can help in controlling the brain and neural traffic. Studies have shown that poor vitamin D levels correlate with the higher the chances of impairment of the mind and neurodegenerative disorders. It is possible that the neuroprotective properties of vitamin D can be explained by the possibility to regulate the inflammatory processes and calcium levels in neuronal cells (Annweiler et al., 2013).

Minerals also play a significant role in ensuring that the neurons are healthy and that the brain is functioning well. Zinc, magnesium, and iron are trace elements, which are involved in diverse activities of the enzymes that affect the neurotransmission and metabolism of neurons. An example of such is Zinc, which is linked to synaptic signaling and has a regulatory role in neuronal communication in the hippocampus, a brain region that is linked with memory formation. With the aid of magnesium, ion channels, and neuronal excitability are regulated, whereas iron helps to transport oxygen and produce energy in the mitochondria. All these minerals are necessary in a balanced level to ensure appropriate neurons work properly and avoid metabolic imbalances in the brain (Takeda, 2001).

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The role of micronutrients in the antioxidant defense systems, which prevents oxidative damage to the neurons, is also important. Some vitamins and minerals also serve as cofactors to enzymes that combat antioxidant reactive oxygen species. As a case in point, selenium is an essential constituent of glutathione peroxidase; an enzyme that is involved in clearing harmful oxidants in cells. Other enzymes that are essential in alleviating oxidative stress are superoxide dismutase which are cofactors of copper and zinc. Micronutrients in these way repair the oxidative damage that may be brought about to the neuron structure due to disbalances in their redox (Rayman, 2012).

Malabsorption of micronutrients may produce enormous impacts on the nervous system. The lack of adequate consumption or absorption of the necessary vitamins and minerals can result in a greater oxidative stress and inflammatory activity occurring in the brain. As an illustration, a low amount of the vitamin E has been linked to elevated oxidative harm done to neuronal membranes owing to a subsequent decrease in the capacity to protect lipid peroxidation. On the same note, zinc or magnesium deficiencies can disrupt neurotransmission and predispose an individual to neurotoxicity. These nutritional changes can eventually hamper cognitive capacity and in the development of the neurodegenerative disorders (Mocchegiani et al., 2005).

The micronutrient deficiencies are mostly of concern when the brain is developing at rapid rates and when it is aging. During the early years, poor nutrition can disrupt the maturation of the neurons and the development of synapses which may result in permanent cognitive impairment. The reduction in the absorption of nutrients and diet in the elderly can be a contributing factor to progressive nervous degradation. It has been observed that in epidemiological research, people with poor status of micronutrients tend to develop a high risk of cognitive deterioration and memory loss. These discoveries underscore the need to ensure that there is proper nutritional consumption at various stages of life in order to enhance the best brain performance (Prasad, 2013).

Clinical and experimental studies have shown that micronutrient supplementation continues to offer positive results regarding the neurological functionality. Some intervention studies have reported the upgradation of cognitive and memory after supplementing certain vitamins and minerals. Indicatively, B vitamin supplements have been found to decrease the level of homocysteine and delay the pace of brain atrophy in people with a mild form of cognitive impairment. Likewise, experimental studies have demonstrated magnesium supplementation to be linked to improved synaptic plasticity, and improved memory performance. There is an implication of these results that cocaine micronutrient supplementation can serve to protect the brain and maintain a person in cognitive calmness (Slutsky et al., 2010).

Though micronutrient supplementation has been promising as evidenced by the latest studies, one should bear in mind that the optimal health of the brain requires a balance of various nutrients, but not the use of a single compound. Vitamins, minerals, and other bioactive compounds may have a nutritional interaction that affects their biological action. Hence, dietary interventions such as the variety of the foods of the nutrients type can provide the most effective dietary approach to the maintenance of the neurological condition and prevention of neurodegenerative disorders.

In conclusion, micronutrients play vital roles in the integrity of neurons, regulation of antioxidant systems and cognition. Some vitamins and minerals should be consumed in ample quantities in order to maintain the health of the brain and reduce the risk of the neurological disease. The future research of the impact of micronutrients and other neuroprotective nutrient interactions may provide helpful information on how effective nutritional programs can be designed to improve the long-term neurological health.

**6. Synergistic Interactions between Flavonoids and Micronutrients**

Synergistic bioactivity is an emerging concept in the area of nutritional neuroscience wherein scientists are attempting to comprehend the

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impact of blend of dietary substances on the well-being of the brain. Synergy refers to interaction between two or more biological agents having a resultant effect which is greater than the product of the individual effects. Since the current trend has been the synergistic effect in flavonoid and micronutrients, such co-administrations can be considered to offer cells higher potential to deal with oxidative stress, regulate inflammation, and maintain neuronal integrity. Such compounds might work together in a complementary biochemistry rather than working alone and fortifying protective pathways at the central nervous system. Such interactions can play a significant role in determining nutritional strategies that can have more favorable impact in providing an efficient protective barrier to neurodegenerative processes. (Liu, 2004).

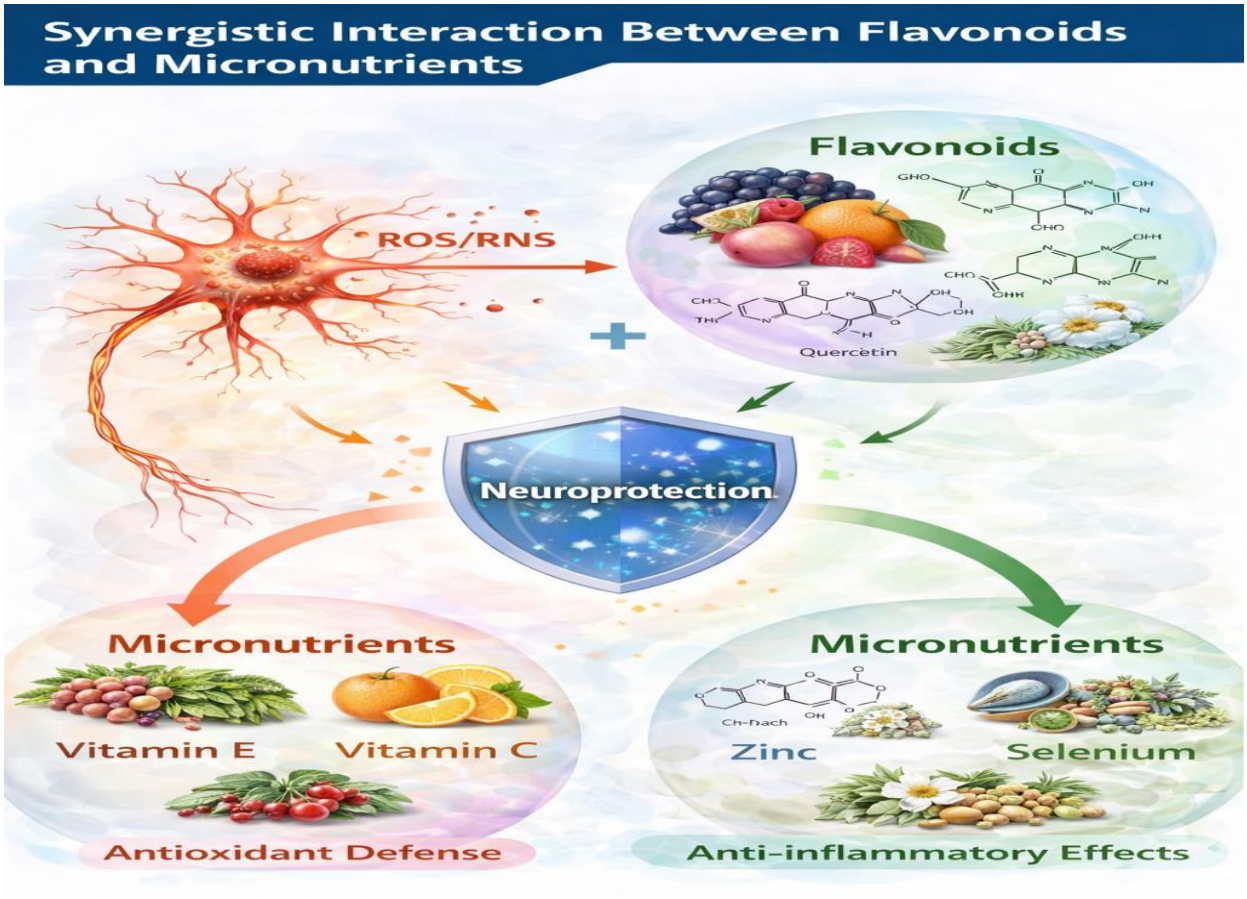



**Figure 5: Synergistic Interaction Between Flavonoids and Micronutrients**

There are several overlapping biological functions that flavonoids and micronutrients share and this is likely to contribute to their synergistic ability. The antioxidant effect of flavonoids is not a novel finding, and most of the micronutrients have been reported as cofactors of antioxidant enzymes, which neutralise reactive oxygen species. When combined with these compounds, they possibly increase the protective effect of each other when they occur together. As an example flavonoids have the potential to scavenge reactive oxygen species directly and reduce oxidative load on neurons whereas micronutrients such as zinc, copper and selenium facilitate the activity of endogenous antioxidant enzymes like superoxide dismutase and glutathione peroxidase. Interaction between flavonoids and micronutrients, through these complementary processes could be highly effective in increasing the antioxidant ability of the cell and preventing oxidative damage to the neuronal structures (Scalbert et al., 2005).

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The other way the flavonoids and micronutrients interact can take place in the process of regulating intracellular signaling pathways that can be related to the response of oxidative stress. Some flavonoids are reported to regulate cellular defense mechanisms leading to increased expression of antioxidants proteins. Simultaneously, micronutrients can act as necessary cofactors needed by these protective enzymes to be active. This communication enables the cells to have a better redox balance even during metabolic stress. One experimental finding has indicated that these types of cooperative effects can enhance the protection of cells against oxidative damage, which subsequently mitigates the susceptibility of neurons under conditions of high levels of oxidative stress (Dajas, 2012).

Flavonoids and micronutrients can be combined to control inflammatory action in the brain in addition to improving antioxidant defenses. Neuroinflammation is also extremely important in the process of neurodegenerative diseases development, and an over-response to the activation of inflammatory pathways may result in neuronal damage. Flavonoids have been found to suppress inflammatory signaling inhibiting the transcription factors controlling cytokine production. In the meantime, there are some micronutrients that assist in the regulation of immune responses and the appropriate functionality of immune cells. As an example, magnesium and zinc are also reported to have an effect on inflammatory signaling and release of cytokines. These micronutrients combined with flavonoids might result in a more moderate immune response to suppress overinflammation without impairment of protective immune responses (Holt et al., 2005).

Integrated response of inflammatory processes includes also the adherent intricate cell signaling systems shaping the survival of neurons. A number of inflammation and oxidative cohesion related molecular effectors meet at signaling systems governing the expression of genes in neuronal cells. Flavonoids have the ability to affect these signaling cascades through interfering with the activity of kinases and transcription factors that regulate the expression of inflammatory genes. Micronutrients could also be involved in stabilizing cellular metabolism and preserving enzymatic activity necessary to do so. Combined with regulated control over the signaling pathway, the compounds can potentially inhibit extended inflammatory reactions in the onset of neuronal loss (Spencer et al., 2008).

The other effect that flavonoids and micronutrients have is in mitochondrial functioning. Mitochondria play a role in the generation of energy needed by the neurons, and their impairment is strongly linked to neurodegenerative dysfunctions. Oxidative stress and inflammation might affect mitochondrial performance resulting in decreased energy production and reactive oxygen species increments. Flavonols have been known to facilitate the stability of the mitochondria in reducing oxidative stress and balancing mitochondrial signaling pathways. Meanwhile, micronutrients, including magnesium and coenzyme related nutrients, are important in energy metabolism and enzyme functioning in the mitochondria. The combination of these compounds can potentially stabilize, keep the mitochondria intact, and support an efficient generation of energy in neuronal cells (Garcia-Salguero et al., 2018).

The synergistic effect of flavonoids and micronutrients to systems that control neuronal survival and synaptic activity is also extended. Neurons survive on complex signaling pathways which assist cellular growth, synaptic plasticity and adaptive responses to environmental stimuli. Some flavonoids also have the ability to activate neurotrophic signaling pathways which facilitate neuronal resilience and improvement of synaptic communication. There is a potential role of micronutrients in strengthening these effects, as they are needed to keep the metabolic conditions necessary to support neuronal signaling. Consequently, joint dosage of percentages of these substances may lead to enhanced neuron survival and maintenance of cognitive functioning (Mandel et al., 2008).

Evidence has been observed in various experimental studies, of synergistic neuroprotective effects of flavonoids and

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micronutrients. The laboratory experiments with the cultures of the client neuronal cells have demonstrated that interaction between antioxidant compounds is more effective than individual compounds to minimize the oxidative injury. These studies suggest that there is a potential of flavonoids to enhance the activity of micronutrient-dependent antioxidant systems that result in the amplified protection of cellular stress. Research results of animals have also revealed that, nutritional diet rich in not only flavonoid, but essential micronutrients can also be used to boost cognitive skills and reduce measurements of oxidative tissue damage in the brain. These findings indicate the importance of food composition with regard to maximization of neuroprotective effects. (Joseph et al., 2009).

The clinical observations also indicate the possible positive effects of combined intake of nutrients on the brain. Epidemiological literature suggests that patterns of diet based on high intake of fruits, vegetables, whole grains and foods with high density of nutrients are related to reduced incidences of cognitive alterations and neurodegenerative diseases. Complexes of flavonoid and micronutrient are the characteristic components of these foods that can or can be synthesized to defend neuronal structures. These dietary plans supply an extensive supply of bioactive substances instead of depending on independent nutrients and influence each other in biological pathways to assist cognitive functions and neural resilience (Devore et al., 2012).

Along with the identification of the synergistic effects of flavonoids with micronutrients, there has been a significant implication of this relationship on dietary interventions and micronutrient therapeutic development. The nutritional strategies in which the maintenance of the balance between the body and the several bioactive compounds is recognized might be the most protective measures than the disjointed support of the individual nutrients. Research and development in the field is taking a more promising direction in considering the possibility of combined nutraceutical products that combine flavonoids with vital micronutrients as ways to address several pathways during the process of neurodegeneration. These approaches can contribute to the complicated biological processes of the development of the neurological disorder and complementary care in addition to the traditional curative measures (Lamport et al., 2016).

Nutritional neuroscience studies are likely to continue in the future to clarify how flavonoids and micronutrients can interact to affect the functions of the brain. More data on how dietary compounds can influence neuronal signaling networks and metabolic processes might be provided by the application of molecular biology and metabolomics. This information on such interactions might be useful in the context of developing the evidence-based dietary and treatment strategies aimed at the prevention of the threat of neurodegenerative diseases.

In conclusion, the combination of flavonoids and micronutrients can be a nice area to study in the neuro-protective field. The compounds can be mutually healthy to the wellbeing of the brain and act on its cognition by complementary actions on antioxidant defense mechanisms, action pathways of inflammation, mitochondrial dynamics, and survival programs of the brain. These interactions can also be studied further in the formulation of more efficient nutritional treatment to avoid the impairment of the brain by oxidative and inflammatory processes.

## 7. Therapeutic Implications and Future Research Directions

The growing understanding of the biological processes between flavonoids and the micronutrients has devastating implications on the prevention and treatment of neurodegenerative diseases. Neurodegeneration is a complicated process which involves oxidative stress, chronic inflammations, malfunctioning of the mitochondria, and breakdown of neuronal communication. The concurrent nature of these pathological processes implies that treatment which activates multiple pathways will be more effective as compared to one which just activates single mechanisms. The use of multimedia dietary interventions which contain flavonoids and micronutrients has therefore come to the limelight

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of being a promising neuroprotective agent. Evidence suggests that experimental and epidemiological studies indicate that a high score in the intake of polyphenols and essential micronutrients of plant origin are also associated with improved cognitive performance and preventive effects against an incidence of neurodegenerative diseases. (Solfrizzi et al., 2011).

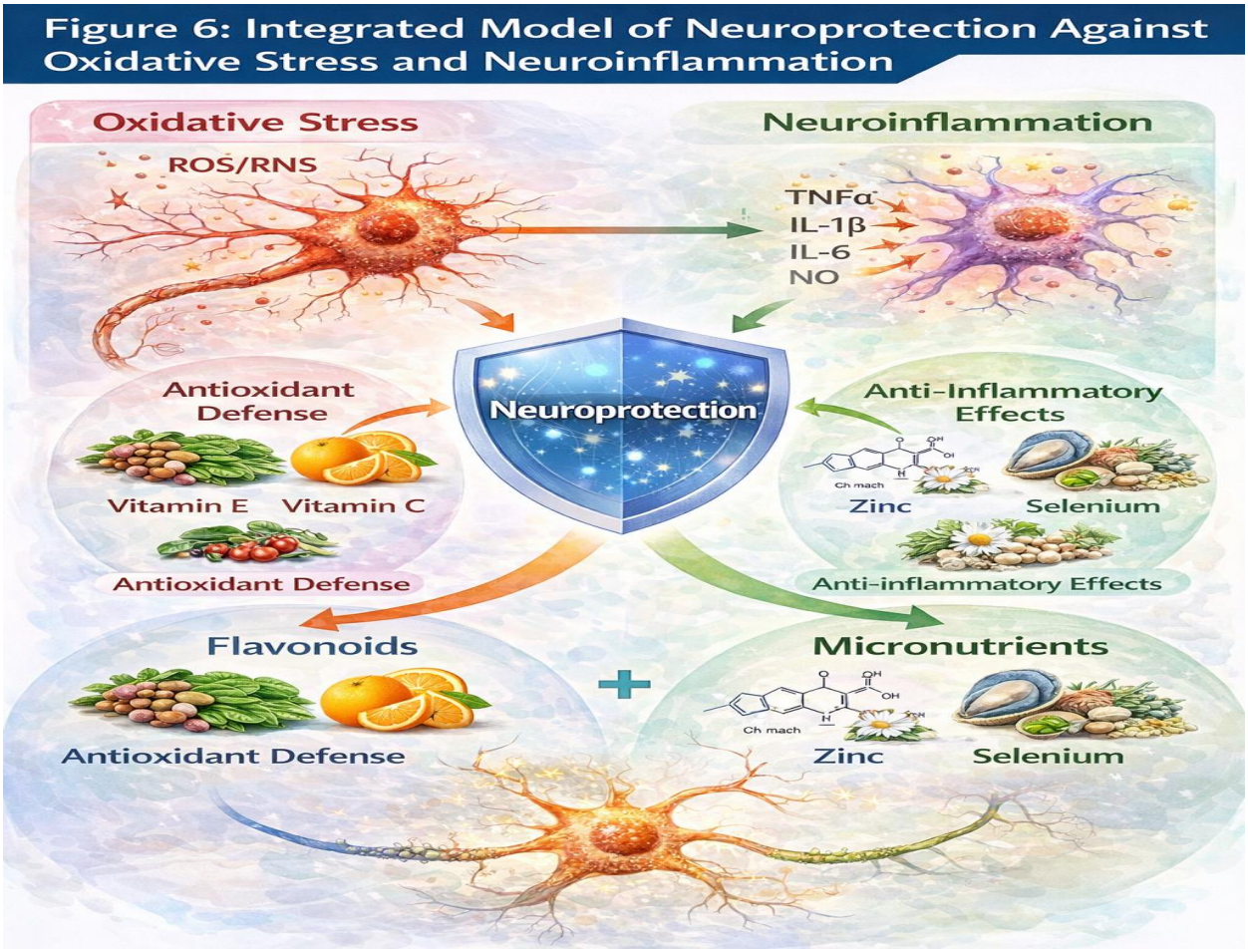



**Figure 6: Integrated Model of Neuroprotection Against Oxidative Stress and Neuroinflammation**

Flavonoids and micronutrients may have synergistic activities to enhance the antioxidant capacity of the body, regulated inflammatory responses, and energy production of the mitochondria. The combined effects of flavonoids may be beneficial in protecting the neurons from the build-up of cellular injuries that occur when one grows old. Dietary interventions using these substances can thus help in the long term preservation of cognitive and neuronal structure. Eating habits, like the Mediterranean diet, which highlights fruits, vegetables, nuts, and whole grains, offer natural sources of combinations of flavonoids and micronutrients which when combined help in maintaining the brain. According to observational research, the following diets have a relationship with a decrease in cognitive decline cases and better neurological results in aging populations (Psaltopoulou et al., 2013).

Even with these positive results, there are a number of limitations in the ability to reduce laboratory findings into therapeutic techniques. Among the biggest obstacles, there is the

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bioavailability of flavonoids and parts of the micronutrients. Most flavonoids are subjected to a very high level of metabolic changes to the digestive system and liver after consumption and may change their biologic actions. Also, there are variations in the absorption and distribution of micronutrients based on the contents of diets, gastrointestinal awareness, and individual metabolic parameters. Such complications complicate the process of establishing the best levels of intakes needed in order to bring about neuroprotective effects to humans (Manach et al., 2005).

The other notable challenge is how to establish the right dosage and formulation of combined nutritional intervention. The interplay between the various bioactive compounds may affect their efficacies and over-consumption of specific micronutrients may have a negative outcome. Thus, the dosage ranges and nutrient interactions should be considered carefully to be safe and effective. There is still little clinical research done on the use of combined nutraceutical preparations, indicating that well-designed human trials are necessary to look into the long-term neurological effects (D'Archivio et al., 2010).

The notion of individual nutrition is also significant in the further evolution of the nutritional interventions on brain health. Genetic variations, metabolism, lifestyle, and intestinal microbiomes of individuals could have an impact on the absorption and use of nutrients in the body. Consequently, one diet plan has been shown to be more effective in a certain person, yet it might fail to do the same thing in another. The use of nutritional genomics and metabolomics is just getting started and starting to offer information on how individualized nutritional methods can be personalized to improve neurological wellbeing and prevent disease (Ordovas et al., 2018).

The future of this area of research would tend to concentrate more in synergistic nutraceutical parameters, which entail the combination of several bioactive elements which aim at addressing complementary biological pathways. Further research involving the combination of molecular biology, clinical nutritional, and neuroimaging approaches could help to gain a deeper insight on the effects of flavonoids and micronutrients on the structure and functionality of the brain. The clinical trials that are vital in this case are long-term trials that will involve the effectiveness of the combined dietary interventions in averting neurodegenerative diseases. Such studies can eventually lead to evidence-based nutritional guidelines that can be used for supporting cognitive health and reducing the worldwide incidence of neurological diseases.

## 8. Conclusion

Neurodegenerative diseases are a significant form of health problems in the world, and they manifest the effects of depression and cognitive abilities in neurons, causing progressive degeneration. Neuroinflammation and oxidative stress are considered significant contributors to neurodegenerative diseases because they impair the homeostasis of neurons and favor their destruction. There is a growing body of scientific research on the role of nutritional factors in controlling neuroinflammation and oxidative stress. Flavonoids and micronutrients are some of these nutritional factors that have been shown to facilitate the control of neuroinflammation and oxidative stress in neurons. These are bioactive compounds that facilitate the control of neuroinflammation and oxidative stress in neurons. Flavonoids have direct and indirect antioxidant effects and influence cellular signaling for controlling neuroinflammation and oxidative stress. Vitamins and minerals are essential micronutrients that facilitate metabolic processes for controlling neuroinflammation and oxidative stress. Combination The biological effects of these compounds are considered to be synergistic when they are taken in combination and are considered to be superior to the effects of the compounds taken individually.

Combined flavonoid and micronutrient strategies have a potential. The development of nutritional strategies to prevent neurodegenerative diseases and maintain cognitive health should be a promising area. However, it requires further research to solve the problems associated with the bioavailability of nutrients, the dose of the

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nutrients, and the individual variability of the metabolisms of the nutrients. Further research into the field of synergistic nutraceutical interventions may provide useful information regarding the proper diets interventions to maintain neurological health.

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