The Role of Antioxidants as Immunity Booster and in the Prevention and Treatment of Cancer, Signs of Aging, Covid-19 & Autism: Review

By

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study does not involve any kind of animal and human trial.

Abstract

The excessive synthesis of reactive oxygen species in the body contributes to the development of a variety of chronic diseases, including lung diseases, cancer, neurological diseases, and age-related diseases. Several studies showed the effective effects of antioxidants to combat these chronic conditions. Recent research has demonstrated a beneficial enzymatic effect in combating the severity of Covid-19. The use of antioxidants as an adjuvant therapy alongside chemotherapy has been shown in some studies to improve therapeutic efficacy while reducing side effects. In addition, ROS overproduction in mitochondria is linked to several neurological illnesses, which can be treated with a variety of metabolic antioxidants. For the successful application of antioxidants in the prevention and treatment of chronic diseases, additional understanding is required. The purpose of this article is to provide an overview of the antioxidants' potential benefits in managing and treating five distinct chronic diseases.

Keywords: Antioxidants; Oxidative stress; chronic diseases; Covid-19; Autism Spectrum Disorder (ASD).

Dedication

Dedicated to my parents.

Acknowledgement

To begin, I want to express my gratitude to Almighty Allah for keeping me safe and sound during this pandemic. I would not be able to complete my thesis project without his blessings.

I am indebted to my respected supervisor, Dr. Sharmind Neelotpol (Associate Professor, School of Pharmacy, Brac University) for allowing me to work on this topic. It would be impossible for me to complete this project successfully without her ongoing assistance, guidance, encouragement, and support. I consider myself fortunate to have been able to complete my thesis project under her supervision. Additionally, I owe gratitude to all faculty members in the School of Pharmacy for increasing my knowledge and enabling me to apply it while conducting my thesis project. I shall forever be grateful to them for their continuous encouragement and technical assistance.

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ROS Reactive Oxygen Species

ASD Autism Spectrum Disorder

SCCP Single Cell Chemical proteomics

SOD Superoxide dismutase

Chapter 1

Introduction

The cells present in the human body are constantly exposed to numerous risks ranging from malnutrition to viral disease. Besides these, a serious risk is also caused by a group of chemicals that can exploit cellular components and genetic materials. These chemicals are unavoidable by-products of the body to generate energy from consumed food. Sunlight, exercise, tobacco smoke and environmental pollution create Free radicals. There are numerous types of free radicals. Each of them has a strong desire for electrons, snatching them from neighboring materials. The function of the substance that loses electrons is altered by this loss of electrons. It can dame damage both the structure and genetic information of that substance. This can increase the probability of flowing low-density lipoprotein (LDL) which is also known as bad cholesterol, getting stuck in the wall of the artery.

Moreover, this can also affect the cell membrane and alter its permeability. Chronically high levels of free radicals induce oxidative stress inside the body that affects tissue and is responsible for different chronic illnesses. Fortunately, to fight against this threat, the body produces several more compounds which smother free radicals. These protectors are called "antioxidants". They continuously donate electrons to free radicals but they do not become electron drawing materials. They help in repairing damaged DNA and keep cells healthy (*Antioxidants | The Nutrition Source | Harvard T.H. Chan School of Public Health*, 2022). Therefore, antioxidants can help the body combat the negative effects of free radicals that accelerate cell damage. Besides, Antioxidants can be found in both natural and synthetic sources. Red meats, egg yolks, and some other animal products have been found to contain high levels of antioxidants (*Antioxidants - Better Health Channel*, 2021). Antioxidants produced by plants are known as phytonutrients. Moreover, some antioxidants are also made

by the body, known as endogenously generated antioxidants. Exogenous antioxidants are also known as those found outside the body (*Antioxidants: Health Benefits and Nutritional Information,* 2018). Moreover, chronic inflammation induced by oxidative stress is considered to contribute to the majority of chronic diseases, including cancer, cardiovascular, neurological, and pulmonary diseases (Reuter et al., 2010). As a result, antioxidants are being considered as a potential weapon against cancer and autism, and numerous studies have been conducted recently to determine the effects of antioxidants in the treatment of Covid-19. Additionally, antioxidants boost immunity and are widely used in skincare.

This study aims to evaluate the enhancing and anti-aging properties of some types of antioxidants and their effects in the prevention and treatment of some high-risk diseases such as Cancer, Covid19 and Autism

The objectives of this study are as follows:

1) To gain a better understanding of the relationship between the reactive oxygen spices and antioxidants balance in the body and how this imbalance contributes to the development of chronic diseases and disorders.

2) To determine the efficacy of antioxidants in the prevention and treatment of cancer, as well as the reduction of chemotherapy-related side effects.

3) To find the correlation between reactive oxygen species (ROS) and anti-aging characteristics and to identify antioxidants' positive anti-aging effects.

4) To assess the efficacy of enzymatic antioxidant therapy in treating Covid-19.

5) To gain a better understanding of the association between excessive ROS generation in the brain and various neurological illnesses, particularly autism, and how antioxidants may aid in autism management.

Chapter 2

Materials and Methods

Comprehensive assessment of the literature on the role of antioxidants in the prevention and treatment of various diseases and ailments, utilizing secondary sources such as research articles, news items, academic publications, and government websites. This study analysed articles from prestigious journals such as Nature, Elsevier, PubMed and MDPI. The data was gathered from many publications and their findings, which aided in the identification of variable clinical data that may play a vital role in the future aspects of the treatment of various diseases using antioxidant therapy.

Chapter 3

Discussion

3.1 Antioxidant as Immunity Booster:

Free radicals are considered to produce lipid bilayer, enzymatic, and DNA damage. Antioxidants aim to safeguard the structural stability of tissues and cells by neutralizing free radicals. Consumption of antioxidants provides a major impact on various immune processes. In this particular instance, increasing the activity of immune cells was facilitated by the use of vitamins C, E, and A or beta-carotene. Vitamin intake helped protect people from the free radical-laden environment by offering a supply of antioxidants to the immune system. Consumption of vitamin A, a weaker antioxidant, reduces the number of people who die and suffer complications from measles infections in children (Bendich, 1993). The body's immune system needs to have a working cell-to-cell information exchange for the process to work effectively. Impairment to the system will therefore impede immune response. Excess free radicals damage the immune system because phagocytic cells produced free radicals to fight infection. Destruction of the cells associated with the immune system occurs as a result of inadequate levels of antioxidants that protect the cells from harm. Antioxidants such as ascorbic acid, α-tocopherol, carotenoids, and polyphenolic flavonoids can be easily obtained from the diet, or they need other micronutrients as necessary elements. It has been observed in several epidemiological findings that there is a strong connection between foods having antioxidant properties and a lessened occurrence of cancer. Immunity boosting properties of antioxidants are thought to be the reason behind it. Even though there is a clear indication that antioxidants have a larger impact on the immune system function in older adults, several studies have shown that the same nutrients can affect cellular immunity in younger people as well (Hughes, 1999).

3.2 Antioxidant in the prevention & treatment of Cancer:

For decades, study has demonstrated that ongoing oxidative stress leads to chronic inflammation, which in turn mediate chronic illness like cancer, pulmonary diseases, diabetes, cardiovascular diseases and neurological diseases. In addition to activating various transcription factors including NF-κB, AP-1, p53, HIF-1α, PPAR-γ, β-catenin/Wnt, and Nrf2, oxidative stress may also activate these transcription factors through the process of oxidative stress activation. The expression of more than 500 different genes, including several growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules, and anti-inflammatory molecules, is possible through the activation of these transcription factors. So far, findings to date point to the connection between oxidative stress, chronic inflammation, and cancer. While an elevated level of reactive oxygen species (ROS) is crucial for regulating healthy cellular processes, uncontrolled ROS progression can result in disease, such as cancer, in humans. Besides, multiple studies have shown to be highly correlated with an enhanced generation of Ros, which promotes tumorigenesis, improves cell growth, and promotes cell proliferation, with DNA damage and genetic instability also being observed.

Moreover, it has been shown that increasing levels of reactive oxygen species (ROS) results in promoting an anti-tumorigenic signalling pathway, in which ROS induces tumour cell death. A tumour's cells can modify their susceptibility to oxidative stress by boosting antioxidant levels, while preserving the signalling that helps the tumour grow and resisting apoptotic cell death. Because cancer cells possess a modified redox balance in comparing to their conventional counterparts, ROS manipulation may be a good therapeutic target for cancers (Reuter et al., 2010). In the context of the body, oxidative stress causes numerous negative modifications, such as mutations, lipid peroxidation, and DNA damage. Chemotherapy uses free radicals (ROS) to kill cancer cells. Ionizing radiation damages tumour cells, which is why

radiation therapy is performed. Direct molecular lesions, such as DNA lesions, are caused by radiation therapy.

Free radicals released during oncology treatment can cause a wide range of adverse effects (Arfin et al., 2021). A wide range of different cancers has been linked to the relationship between free radicals and DNA, resulting in both dangerous cell cycle effects and even death threats. In a way, antioxidants serve as evidence that they help treat the tumors and allow them to be more sensitive to chemotherapy and radiation treatment. Without interfering with normal cells, tumor growth can be suppressed. Antioxidants can help prevent cell expansion due to chemotherapy-induced toxicity by inhibiting the activity of free radicals. Furthermore, it has been revealed that antioxidants can reduce oxidative stress, thus helping to alleviate the harm that can be caused by it, as well as limiting the development of neurodegenerative disease (Fuchs-Tarlovsky, 2013). Furthermore, oxidative stress is thought to play a role in the killing of cancer cells by chemotherapy drugs that cause high levels of this stress. Chemotherapy may be less effective if oxidative stress is present.

Oxidative stress slows cell replication, but chemotherapy kills cancer cells during cell replication, so chemotherapy may be less effective if cell replication is slowed by oxidative stress. Antioxidants can be added to chemotherapy in order to reduce oxidative stress and thus increase the effectiveness of the treatment. Chemotherapy and antioxidants interact in a more complex way than simply promoting or preventing oxidative stress. Chemotherapy and antioxidants each have their own unique mechanisms of action that can be explored further. Even the dosage of an antioxidant can have an impact on how it interacts with chemotherapy (Akanji et al., 2020). Moreover,it has been found that some antioxidants can help restore the body's natural antioxidants after chemotherapy, resulting in less side effects and a longer survival time for cancer patients. Antioxidants and their precursors can be used to reduce the

toxic effects of medications, thus enhancing therapeutic efficacy through targeted nutrient therapies (Gummadi, 2016)

3.2.1 Chemotherapy with antioxidants

Antioxidants' role in cancer therapy is a fiercely debated topic because of two critical aspects. There are two types of antioxidant doses used to categorize data on the role of antioxidants in cancer therapy: a low dose and a high dose. The data shows that the preventive dose protects both normal and cancerous cells. The data shows that the therapeutic dose inhibits cancer cell growth, but not normal cell growth. When looking at data for preventive doses, it's a little strange to see (Singh et al., 2018).Several original research publications have examined the question of whether supplementary antioxidants supplied during chemotherapy can protect normal tissue without affecting tumor control. When it comes to determining whether supplemental antioxidants during chemotherapy can lead to decreased tumor control due to variation in study design, intervention protocol, cancer type, the timing of observation, inclusive criteria, and statistical analysis of chemotherapy regimens, there is no clear answer. According to a recent review, antioxidants do not interfere with chemotherapy, boost the cytotoxic effect of chemotherapy, protect normal tissue and increase patient survival and therapeutic response when taken concurrently with chemotherapy (Yasueda et al., 2016), (Simone et al., 2007) .

3.3 Anti-aging properties of Antioxidants

Free radicals are unstable molecules with unpaired electrons. This causes a chain reaction that damages healthy cells in an attempt to gain stability. Free radicals are produced normally in our bodies, but they can also be caused by exposure to environmental factors such as Ultraviolet

radiation, environmental degradation, tobacco smoke, as well as other contaminants. When our system is overloaded with free radicals, it leads to oxidative stress, or a disparit between the generation of free radicals and the body's ability to neutralise or detoxify their negative impacts (Lobo et al., 2010). Furthermore, ROS-induced oxidative stress is a key aspect in skin transformations, particularly those caused by Ultraviolet exposure and aging, according to the study. Oxidative stress is eliminated by several endogenous mechanisms in the human body. It should be possible to increase protection against oxidative stress and enhance skin aging prevention by using some anti-oxidants, such as vitamin C, tocopherols & polyphenol (Rinnerthaler et al., 2015).

Both intrinsic and extrinsic aging occur in the skin. Commonly occurring free radicals contribute to intrinsic aging as a consequence of natural metabolism. A decrease in cellular efficiency causes fine wrinkles and a more relaxed appearance. Attributable to extrinsic aging, the skin is subjected to excessive damage by free radicals due to exogenous factors including such Ultraviolet rays and tobacco smoking. Not only do these environmental stressors speed up skin aging, but they are also subject to possible damage-causing fine lines and wrinkles and hyperpigmentation as well as chronic inflammation and abnormal elastin formation (Poljšak & Dahmane, 2012). Besides, Antioxidants are known to reverse the visible signs of aging. Antioxidants can help protect one’s skin from sun damage. Vitamins C and E facilitate brightening Anti-oxidants help the skin safeguard itself by reducing the production of reactive oxygen species, which may lead to skin damage. Lentigines (sunspots) can be reduced with regular use, as well as countering the noticeable aging signs and soothing irritated skin. Multiple antioxidants give the skin hydrating properties and assist in retaining moisture, making it appear and feel revived. So undoubtedly, antioxidants act as anti-aging protectors, helping to protect skin from aging (Antioxidants in Skin Care: How Do They Work and Which

Ones Are the Best? 2021). Since oxidants have their physiological functions, antioxidants help to return oxygen homeostasis, not just get rid of all the oxidants (Zhang & Duan, 2018).

3.3.1 The role of oxidative stress/reactive oxygen species (ROS) in the skin.

Inflammation of the skin

UVB radiation causes erythema in the skin, commonly referred to as a sunburn. The NOS inhibitor NG-monomethyl-L-arginine and the COX inhibitor indomethacin both decrease UVB-induced erythema. Through prostaglandin E2 production, ROS, including NO, produce cutaneous erythema. COX-2 expression, a critical enzyme in prostaglandin E2 synthesis, is increased in response to ROS, which stimulates the inflammatory process (Rhodes et al., 2001).

Skin surface oxidation

Oxidized lipids and proteins affect the state of the skin. When applied topically to the skin, oxidized squalene (squalene Mono hydroperoxide) impairs the skin barrier function acutely and promotes skin roughness chronically. Alkyl aldehydes further oxidize lipid hydroperoxides and proteins in the stratum corneum, resulting in carbonylated proteins (SCCP). SCCP concentrations increase in response to UV exposure. Additionally, patients with atopic dermatitis had greater SCCP levels than normal persons. SCCP levels appear to correlate with the degree of oxidative stress caused by the environment in the skin. Thus, oxidative stress caused by reactive oxygen species (ROS) affects skin conditions (Kostyuk et al., 2012).

Enhancement of Sebaceous gland function

UV-induced oxidative stress increases sebaceous gland function, resulting in increased sebum output as a result of higher levels of oxidized lipids, triglyceride hydroperoxides, and

cholesterol hydroperoxides [. Propionibacterium acnes (P. acnes), a Gram-positive anaerobic bacterium, manufactures coproporphyrin under UVA exposure and hence plays a vital role in the development of acne's inflammatory lesions. O_2-produced by P. acnes-infected keratinocytes further stimulates the inflammatory response (Picardo et al., 2009).

Melanocytic pigmentation

ROS has a contradictory effect on melanocytes, as it increases both depigmentation and pigmentation in the skin. Vitiligo is a condition that results in confined depigmented macules in the skin as a result of oxidative stress. The skin of people with vitiligo vulgaris contains a high concentration of superoxide dismutase and a low concentration of catalase. When the ROS scavenging mechanism is out of equilibrium, H_2O_2 accumulates in the skin. Keratinocytes are a source of the reactive oxygen species (H_2O_2) that affects melanocytes. H_2O_2 quickly penetrates the cell membrane and is thus readily transported from keratinocytes to melanocytes. The transfer of H_2O_2 is believed to be one of the vitiligo pathogenetic processes. Additionally, ROS can expedite the process of skin pigmentation. Keratinocytes in close proximity to melanocytes have a significant role in UV-induced skin pigmentation. NO produced by keratinocytes induces melanogenesis by raising the levels of the melanogenic factors tyrosinase and tyrosinase-related protein. 1. Moreover, the role of reactive oxygen species (ROS) in melanogenesis has been demonstrated in research utilizing antioxidants. UVB-induced elevations in a-Melanocyte stimulating hormone are reversed by the administration of N-acetyl cysteine, a precursor of GSH. Additionally, activation of melanocytes with an endogenous antioxidant, metallothionein, decreases melanogenesis (Masaki, 2010a).

Matrix dermal

ROS has been implicated in UV-induced skin aging, which manifests as wrinkles. In general, wrinkles are caused by modifications to the dermal matrix, which result in lower collagen levels due to faster breakdown and decreased collagen production (Masaki, 2010).

3.3.1 Ascorbic acid as anti-aging agent

To counteract and remove oxidants such those found in pollution and after exposure to UV radiation, vitamin C is a powerful antioxidant. The epidermis, which has a high concentration of vitamin C, appears to be particularly important for this function. As a result, vitamin C is merely one of many enzymatic and non-enzymatic antioxidant defences in the arsenal. Antioxidants have been found to be effective in preventing oxidative damage to skin in most intervention trials. When combined with vitamin E, vitamin C is particularly efficient at reducing skin oxidative damage. Since it is an excellent regenerator of vitamin E that has been deoxidized, this is in line with its previously reported role in reducing the amount of oxidative damage that can be done to cell membranes (Pullar et al., 2017).

In vitro and in vivo studies have indicated that vitamin C derivatives, such as the magnesium phosphate ascorbyl derivative, reduce melanin synthesis. The rate-limiting enzyme in melanogenesis, tyrosinase, is thought to be the reason for this activity. Tyrosinase is involved in the oxidation of DOPA to ortho-quinone, and the hydroxylation of tyrosine to dihydroxyphenylalanine (DOPA). Vitamin C is expected to suppress the synthesis of melanin by reducing the ortho-quinones formed by tyrosinase, but additional processes are also feasible. Skin hyperpigmentation problems including melisma and age spots are treated with melanogenesis-decreasing agents (Gillbro & Olsson, 2011).

Despite the lack of particular research on vitamin C and skin aging, several studies have looked at the role of nutrition in general. Twenty-seven interventions or reported dietary intakes were

found in a recent comprehensive evaluation of research on nutrition and appearance. Research on vitamin supplements or general foods was linked to better skin elasticity, wrinkles, roughness, and color in the most reliable trials (15 studies total). Nutritional interventions that demonstrated a positive effect included high consumption of fruits and vegetables, which provide a considerable amount of vitamin C to the diet

Furthermore, the effects of UV radiation on the skin are similar to the gradual aging process, although one important distinction is the earlier beginning. Vitamin C has been shown to reduce the effects of UV exposure. A radical-generating mechanism is directly responsible for this form of damage, and the primary means of prevention is the antioxidant activity of the affected cell. Both topical and dietary vitamin C intake have been used to demonstrate this with cells both in vitro and in vivo. Vitamin C level in the epidermis appears to be depleted by UV light, suggesting that oxidants produced by this exposure are the likely culprits. Following UV exposure, vitamin C protects cultured keratinocytes from apoptosis and enhances cell survival by preventing lipid peroxidation (Brenner & Hearing, 2008).Moreover, improved and objective imaging methods like ultrasound have lately been utilized to measure the thickness of the various skin layers. A person's vitamin C status may influence the effectiveness of topical vitamin C creams for wrinkled skin. The detected changes in wound repair and collagen synthesis in smokers, abstinent smokers, and non-smokers with related variations in plasma vitamin C status indicate that increased vitamin C level could safeguard against wrinkle formation through improved collagen synthesis. Smokers' vitamin C levels were lower than those of non-smokers' and quitting smoking increased wound healing and collagen production (Pullar et al., 2017).

3.4 Role of Antioxidant in Covid-19

Covid-19, which is caused by the SARS coronavirus 2 (SARS-CoV-2), has many accompanying symptoms including severe pneumonia, pulmonary alveolar collapses, and inadequate oxygen exchange. To disseminate across a host's cells, the virus must detect receptors on the host's cells, then cut open the host's membrane, and finally combine. SARS-CoV-2 specifically binds to the angiotensin-converting enzyme 2 receptors (Astuti & Ysrafil, 2020). Besides, phagocytic white blood cells such as neutrophils, monocytes, macrophages, and eosinophils, all of which are present in the blood, use reactive oxygen species to oxidize tissues in their tissues of interest. Free radicals contribute to promoting cell death. The thing about NFkB and cytokine manufacturing genes is that they also activate the process of inflammation by participating in NFkB activation and inducing the transcription of cytokine production genes. Cytokines are released when cytokines are released, and this serves to worsen the inflammation.

During serious conditions, oxidative stress is increased, which results in organ dysfunction. In the COVID-19 example, a cytokine storm results from an intense inflammatory response that is thought to be driven by oxidative stress. Antioxidant therapy in COVID-19 is under study and not fully established, but the possible benefits and risks of antioxidant therapy in sepsis, ARDS, and acute lung injury are understood. Increased oxygenation and glutathione levels, along with a strengthened immune response are all gained from consuming it. This lowers the duration patients need to be mechanically ventilated, the period they spend in the intensive care unit, multi-organ failure, and the duration of hospitalization and increase survival chances (Soto et al., 2020). Moreover, this COVID-19 disease is associated with acute and infectious lung disease and ARDS. SARS-CoV-2 is responsible for the disease because it relates to the Coronaviridae family alongside MERS-CoV and SARS-CoV-1. For the virus to survive, replicate, and propagate in the host, the virus has the positive-sense RNA as its genome that

codes for the proteins mentioned above. This disease can be transmitted when people who are infected cough or sneeze, spreading infected aerosol droplets. While there are multiple contributing factors, COVID-19's pathogenesis is intricate and it encompasses inhibition of the patient's antiviral and innate immune system as well as induction of oxidative stress and subsequent hyperinflammation, which causes the cytokine storm, tissue fibrosis, and pneumonia. There are numerous drugs and vaccines currently being tested to see if they work, if they are safe, and to find out the right dose for COVID-19. Because of this, studying the natural substances' recyclability may provide new options to combat COVID-19.

Several nutraceuticals have demonstrated the ability to increase immune function, reduce viral load, protect the body from oxidative stress, and alleviate inflammation. There are various nutrient components included, including zinc, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, selenium, lactoferrin, quercetin, etc. Experimentally grouping some of these phytonutrients in the right combination can assist to stimulate the immune system, prevent the spread of viruses, impede the onset of clinical complications, and inhibit hyperinflammation, offering both preventive and therapeutic measures to help keep the levels of COVID-19 under control(Mrityunjaya et al., 2020a).

3.4.1. Covid-19 Treatment with Antioxidant Enzyme

Accumulating data suggest that a subset of individuals with severe COVID-19 may have cytokine storm syndrome, a major immunological deregulation caused by cytokine overproduction. It happens frequently during virus infection, organ transplantation, immunotherapy, and autoimmune illnesses, and if left untreated, can lead to mortality. Considering the results that high amounts of reactive oxygen species (ROS) are linked to inflammation, oxidative damage, and viral infection and replication. It is possible that lowering the level of reactive oxygen species (ROS) in COVID-19 patients could help with hyper

inflammation, tissue protection from oxidative harm, and viral replication suppression. After infection with SARS-CoV-2, leukocytes are attracted to infected areas, producing cytokines and reactive oxygen species (ROS), as shown in Scheme 1A. Through DNA damage, lipid peroxidation, and protein oxidation, and increased ROS level increases viral propagation,

produces oxidative injury, and induces cell apoptosis, exacerbating the immunological response. As a result, more leukocytes are attracted, generating more ROS and cytokines, leading to hyper inflammation and cytokine storm syndrome (Lange et al., 2021)

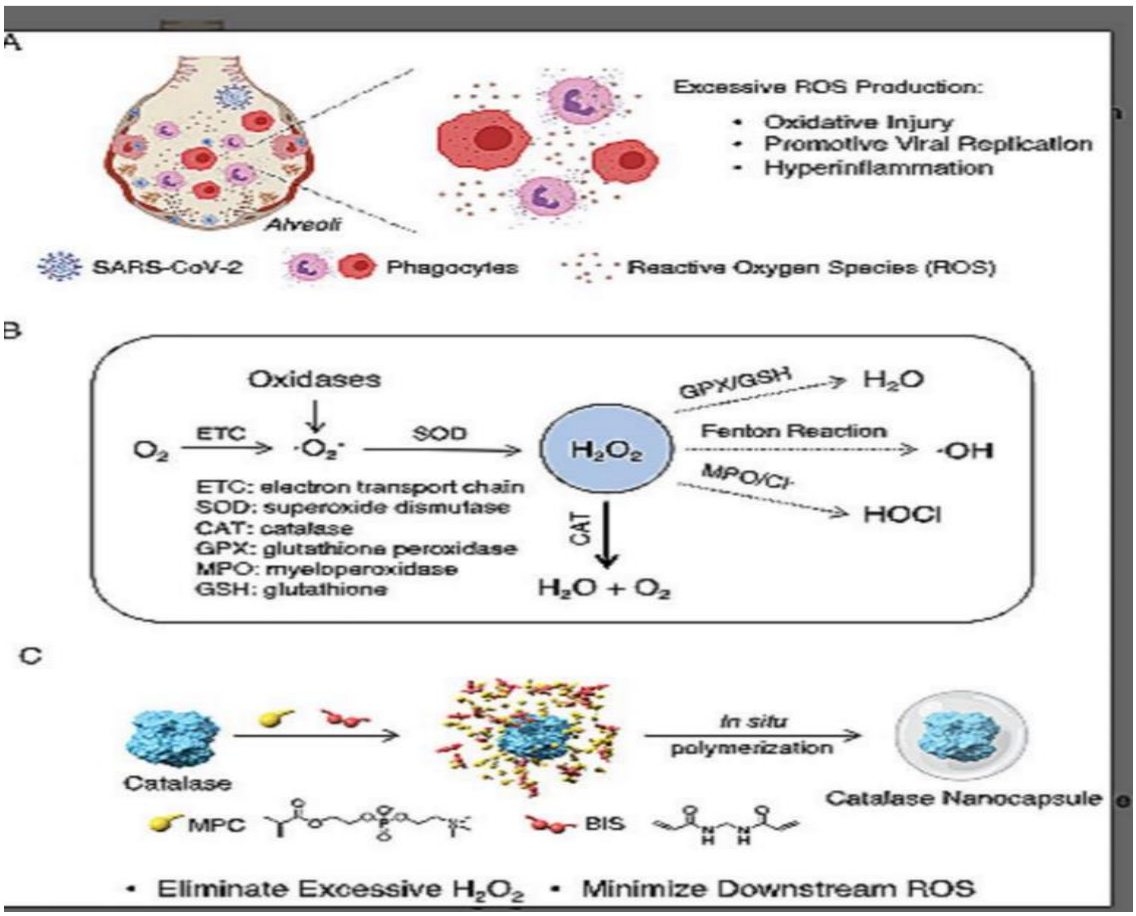

Figure 1: Catalase nano capsules: proposed mechanism of action and synthesis (Qin et al., 2020).

A) A diagram represents how oxidative damage, viral replication, and the cytokine storm

syndrome are all triggered in COVID-19 patients when ROS levels are increased. B) ROS reaction pathways show that removing H_2O_2 is essential for lowering Ros formation farther down the line (B). (C) Catalase nanocapsules with improved stability and propagation half-life were produced by in situ polymerization of MPC and BIS over single catalase molecules (Qin et al., 2020).

As by-products of cell metabolism, ROS are moderately decreased oxygen metabolit es that have a high oxidizing potential and are formed in mitochondria and cytochrome P450. NAPDH oxidase (e.g., in phagocytes and endothelial cells) is another significant source of oxidation.

Hydrogen peroxide is generated by converting superoxide anions (•O2) to hydrogen peroxide by the superoxide dismutase enzyme, as shown in Scheme 1B. (SOD). As a result of the Fenton reaction, HOCl and myeloperoxidase can interact with H_2O_2 to produce hydroxyls (OH• and OH-). MPO, H_2O via glutathione/glutathione peroxidase (GSH/GPX), and H2O / O_2 via GSH/GPX, and H_2O / O_2 via Catalase (CAT). (Qin et al., 2020).

Among the most potent H_2O_2 decomposition catalysts, catalase is highly abundant in the hepatocytes, erythrocytes, and polyphenols of the alveolar epithelial cells: The anti-inflammatory, anticarcinogenic, antimicrobial, fungicidal, and antiviral effects of polyphenolic compounds from plants have been studied in certain depth in the recent research literature. A number of phytochemicals, including luteolin, daidzein, apigenin, amentoflavone, quercetin, epigallocatechin and gallocatechin gallate, inhibit the proteolytic activity of SARS-CoV 3C type protease, which is critical for viral replication. These compounds have been shown to have antiviral activity. Thymoquinone and epigallocatechin-3-gallate (EGCG) are now on the market and offered as dietary supplements for their antiviral and Nrf2 activating properties (Ben-Shabat et al., 2020).

Each catalase molecule can degrade 107 H_2O_2 molecules in a second, yet catalase is unstable and has a short plasma half-life despite its high turnover number of 107 s1. The plasma half-life of Catalase, unfortunately, is brief. Catalase is encased in a thin polymer shell and tested for its medicinal efficacy using in situ polymerization. APM, N,N'-methylenebisacrylamide, and N-(3-aminopropyl) methacrylamide hydrochloride are all demonstrated in the following Figure 1C as the monomers and crosslinkers (BIS). When these molecules are brought together by noncovalent interactions and then polymerized, a single - layered shell develops around the cataldehyde molecules, resulting in Nano capsules with the prefix "n." (CAT). The thinner shell surrounds the enzyme whilst letting H_2O_2 to flow across rapidly, offering n (CAT) enhanced enzymatic activity, integrity, and plasma half-life (Qin et al., 2020)

Curcumin

Patients having COVID-19 may benefit from curcumin, a polyphenolic compound. Recently, an in silico study utilizing molecular docking involving specific receptors like SARS-CoV-2 protease as well as the receptor binding domain (RBD) of spike glycoprotein found that curcumin interacts to the SARS-CoV-2 target receptor. According to these collected data, curcumin can be used as a preventative or prophylactic medication for viral infection. Interferon production and inflammatory response are also stimulated by the conjunction of vitamin C, curcumin, and glyceryl stearate. SARS-CoV-2 infections could benefit from the combination of vitamin C, curcumin, and glycyrrhizic acid, which boosts interferon production and reduces inflammation, according to a new study. Iron chelation can be achieved both *in vivo* and *in vitro* by the curcumin compound. It is believed to play a double role in controlling iron levels, in particular, As an iron chelator, it is actually rather effective. As shown by decreased ferritin levels, elevated TfR1 levels, and stimulation of iron-regulatory proteins, curcumin also depletes liver cells of iron (Rattis et al., 2021).

Hydroxytyrosol

Olive oil's minor ingredient, hydroxytyrosol, contains a phenolic compound called hydroxytyrosol. Antioxidant, anti-inflammatory, anti-atherogenic, and antiviral activities stand out among the many studies that have examined its biological features. Hydroxytyrosol can also be used to treat influenza and other viral illnesses. Furthermore, hydroxytyrosol has been shown to minimize oxidative stress in neutrophil respiratory burst and suppress pulmonary fibrosis in rats. COVID-19 prevention and treatment might benefit from all of these positive effects on health (Quiles et al., 2020).

When lipid peroxides and singlet oxygen are present in the cell membrane, carotenoids have been shown to quench ROS such as these two molecules. As an example, women with low levels of lutein/zeaxanthin and total carotenoids were more likely to have greater IL-6 levels. Several studies have examined the antiviral activities of carotenoids like lutein and zeaxanthin as well as carotene plasma concentrations. An increased risk of death has been associated to low plasma carotenoid levels. Vitamin A precursors include numerous carotenoids, which suggests that their immune-modulating properties are not dependent on vitamin A. Among its many functions, vitamin D contains anti-inflammatory and immunomodulatory characteristics. Vitamin D also has an effect on the activity of nuclear factor kB (NF-kB), increasing the NF-B inhibitory protein's expression (IB). It has been shown that NF-kB enhances the synthesis of numerous pro-inflammatory cytokines (such as IL-6 and IL1-), as well as the creation of some inflammatory enzymes. A number of proinflammatory cytokines and enzymes are modulated or inhibited by NF-kB, including iNOS, COX-2 and PLA2. In addition, it damages tissue by releasing free radicals. Study results show that the immune system is bolstered by vitamin D, which reduces the chance of infection and favorably regulates the inflammatory response (Martens et al., 2020).

Besides,A meta-analysis of 25 randomized controlled studies found that taking vitamin D supplements reduced the chance of getting an acute respiratory tract infection. Vitamin D supplementation has also been linked to a decreased risk of influenza and COVID-19 infection. Vitamin D deficiency in individuals with COVID-19 may necessitate therapy with 25-hydroxyvitamin D, according to these data. Damage to tissue and cellular macromolecules in COVID-19 patients is a result of oxidative stress and pro-inflammatory activity. As a result of oxidative stress and initiation of pro-inflammatory cytokines, COVID-19 patients experience tissue damage. Oxidative stress and degradation to cellular macromolecules can arise from elevated angiotensin II levels and activity, which may add to the complexity of COVID-19, (Mrityunjaya et al., 2020b).

Moreover, Antioxidants can prevent ROS production and aid disease treatment across a number of ways. Inactive forms of ROS are readily available for disposal. Hydrogen peroxide is converted to water by enzyme catalase and glutathione-dependent peroxidases. As the name suggests, this enzyme reduces the highly reactive superoxide anion to hydrogen peroxide. Antioxidants, including glutathione and thioredoxin, shift hydrogen to free radicals to scavenge them. Another way to reduce ROS is by using antioxidants like as ferritin and transferrin that bind metal complexes like Fe2+ while simultaneously producing superoxide anion and the hydroxyl radical when combined with molecular oxygen or hydrogen peroxide. To modulate ROS levels in the context of oxidative stress and disease states linked with ROS, anti-oxidants are essential. Antioxidants may not be as efficient as initially thought in treating certain ailments, according to a number of studies. Using too much antioxidants may really be detrimental, according to some studies. Reactive oxygen species have a variety of functions in the etiology of numerous diseases, and some researchers have questioned the efficacy of dietary supplementation with antioxidants because of these factors. Because of an imbalance between ROS and ROS oxidation products when ROS are inadequate, adverse effects on homeostasis

might occur (ROS-ROS). Cell stress can be caused when the body's homeostatic ratio between free radical and antioxidant levels is interrupted. antioxidant phenols such as quercetin can also assist stabilizing free radicals by delocalizing an unpaired electron to form stable resonance hybrids when proton donation occurs to free radicals. By weakening the new link and decreasing the rate of abstraction, electron delocalization reduces the ability of free radical scavenging (Mrityunjaya et al., 2020b).

Antioxidants have been used to treat COVID-19. Because of its antioxidant and immune-stimulating properties, ascorbic acid or ascorbate (for example) has gained a lot of interest. In COVID-19 patients, vitamin C levels were found to be considerably lower, and this has been connected to the progression of the disease. COVID-19 patients may benefit from taking vitamin C along with antiviral and anti-inflammatory medications. In a randomized clinical trial, patients with COVID-19 who took vitamin C showed no improvement in their treatment outcomes. Studies are presently underway to examine the effects of intravenous high-dose vitamin C on cytokine levels, lung function, and hospitalization length in COVID-19 patients Click here to enter text. (Carr & Rowe, 2020).

1,25-Dihydroxyvitamin D is the most potent form of vitamin D as an anti-inflammatory and immune-modulating steroid. Vitamin D's inflammatory and immune-suppressive qualities make it a potential treatment for COVID-19, according to researchers. COVID-19 individuals have been discovered to have insufficiency in vitamin D, which may have an effect on the course of the disease. Additionally, 25(OH) D levels were found to be decreased in patients with PCR positive SARS CoV-2 (Charoenngam & Holick, 2020).

3.5. Antioxidant in the treatment of Autism:

The collection of neurodevelopmental disorders, known as autism spectrum disorder (ASD), has a wide range of symptoms and is classified solely on the basis of behavioral observations. Oxidative stress and decreased antioxidant capability have been linked to this illness. This stress has been examined at the membrane stage as well as by evaluating products of lipid peroxidation, detoxifying agents such as glutathione, and antioxidants involved in the defense mechanism against reactive oxygen species (ROS). As many as a dozen studies have linked autism to variations in the activity of antioxidant enzymes, such as glutathione peroxidation and catalase. Additionally, autism has been linked to alterations in glutathione levels, homocysteine/methionine metabolism, inflammation, excitotoxicity, and mitochondrial and immunological dysfunction. Autism's oxidative stress sensitivity may be exacerbated by additional interaction between genetic and environmental factors. All of these findings point to an elevated level of oxidative stress in autism as a factor in its pathophysiology and manifestation of symptoms. A reduction in autistic behaviors and severity has been linked to the use of antioxidants or methods to ameliorate the metabolite levels in the interrelated transmethylation and trans-sulfuration pathways.

ASD is a debilitating neurodevelopmental illness that is often diagnosed before to the age of three. Communication and social skills are impaired, as well as the ability to form long-term habits. In addition to behavioral problems, ASD is linked to a high incidence of autoimmune diseases, GI diseases, dysbiosis, and mental retardation. Autism has increased in prevalence during the past few decades. In 2008, one in every 88 children in the United States was diagnosed with ASD. In light of the public health ramifications of the growing occurrence, there has been a great deal of inquiry into possible causal factors. Despite the fact that the cause and pathogenesis of autism remain a mystery, numerous theories have been put up as to how it

might be caused. It's common to find evidence of oxidative stress and other pathological conditions in autistic people, as well as immune system issues. Several neurological diseases, including Alzheimer's, Mental retardation, Parkinson's disease, psychosis, bipolar disorder, and autism, have been linked to oxidative stress. (Hodges et al., 2020).

Oxidative stress occurs when the number of reactive oxygen species (ROS) in a cell exceeds its antioxidant capacity. Brain injury, strokes, and neurodegenerative illnesses all have a part in its mediation. As a result, regulating ROS production is critical for normal cell function. A number of antioxidative defense systems, such as SOD, catalase, and glutathione peroxidase (GSH-Px), help to reduce reactive oxygen species (ROS). Increased production of ROS in the brain and plasma may lead to a reduction in brain cell counts, resulting in autistic pathogenesis and programmed cell death. This could be due to increased ROS production in the brain and plasma. Studies reveal that certain antioxidant supplements and certain dietary managements can reduce irritation in children with autism and diminish their repetitive behaviors, according to some researchers. A larger study is needed before supplementation for children with autism may be recommended, according to the researchers (Zorov et al., 2014).

Illnesses such as autism spectrum disorder (ASD) are complex neurodevelopmental disorders that are characterised by social and communication deficits, as well as difficulty with verbal and nonverbal expression. In its most severe form, autism is often referred to as an autistic disorder or a classical autism spectrum disorder (ASD). Pervasive developmental disorder, Asperger syndrome, and childhood disintegrative disorder are also other possible diagnoses. If a child is mildly impacted by ASD, it may go undiagnosed, especially if it is disguised by more severe disabilities. Experts estimate that by the age of eight, one in every 88 children will be

diagnosed with an autism spectrum disorder (ASD). Parents are typically the ones to make the early-stage diagnosis based on the presence of certain symptoms (Ecker, 2014).

According to expert evolutions ,by the time a child reaches the age of 1, he or she should be babbling or pointing, and he or she should be able to respond to his or her name, as well as make eye contact or two-word phrases. Autism's usual triad of symptoms has long been thought to have a strong genetic, cognitive, and neurological basis. On the other hand, there is growing evidence that autism is a multifactorial disorder with multiple etiologies that commonly manifests. Even though autism has a major genetic base, it is not clear if the complicated genetics of autism are explained by uncommon multigame fusions of genetic variations or rare mutations having major impacts. This complexity is the result of multiple interconnections between many genes, epigenetic factors, and the environment. They do not change the DNA sequences, although they are heritable and could even influence gene expression. Autism syndrome, by definition, cannot be linked to a single chromosome malfunction or a Mendelian mutation, in which fixed and indecomposable features controlled wholly or overwhelmingly by a single genetic locus are passed down over many generations. While none of the genetic diseases associated to ASDs have been demonstrated to generate ASDs preferentially. Several genes have been found, with only little impact assigned to any one of them. The spontaneous duplication or deletion of genetic material during meiosis can cause a wide range of autistic people with normal family relatives. No reliable studies have substantiated other claims about environmental causes. Infectious diseases, solvents, phthalates, and polychlorinated biphenyls (PCBs) in diesel exhaust are all examples of environmental factors (*Autism Spectrum Disorder Fact Sheet | National Institute of Neurological Disorders and Stroke*, 2021).

Supplement to the diet:

Numerous nutritional supplements have also been demonstrated to help with autism treatment. Amyloidosis and beta-amyloid (A) formation in cells has been demonstrated to be inhibited by omega-3 polyunsaturated fatty acids. Omega-3 supplements have antioxidant qualities and have been linked to lower levels of A in the brain in people with early-onset autism. Furthermore, there is significant in vitro evidence that an omega-3 supplement is a promising therapeutic in the treatment or prevention of autism. It is anti-inflammatory, antioxidant, and anti-amyloid pathology. Other factors, in addition to the supplements, have been proven to interact with antioxidants in attenuating autistic neuropathology. Nonetheless, critical information about its bioavailability, tolerance, and safety is lacking. Most of the micronutrients routinely supplied as multivitamins are not required by most children with ASD. This frequently results in overconsumption, putting youngsters at risk of ill effects. When taking supplements, it is important to pay close attention to the amount of vitamin D and calcium consumed (Mahmood et al., 2018).

3.5.1 Enzymes and antioxidants with mitochondrial targeting

In addition to SOD enzymes and metal chelators that help protect cells from free radical damage, there are other antioxidants that help mitochondria thrive, like GSH-Px, and cytoplasmic antioxidant enzymes like copper-zinc SOD. Autism's cognitive - behavioral symptoms can be treated with any of these, which have been shown to be helpful in protecting the brain's neurons from various oxidative damages. Other antioxidants, such as CoQ10, NADH, -lipoic acid (LA), glutathione, and Mito Q, Szeto Schiller peptide, may be useful in the therapy of various neurodegenerative diseases by catabolizing H_2O_2. Because many neurodegenerative diseases, including autism, are linked to mitochondrial dysfunction,

establishing novel therapeutic approaches that target mitochondria could provide new insights into autism treatment. Even some of the medications targeting mitochondria which have been studied or are in investigation are metabolic antioxidants since ROS increased concentration by mitochondria is regarded to be one of the primary reasons leading to autism. In addition to R—LA and CoQ10, these antioxidants have the ability to penetrate both mitochondria and cells, offering the best defense (Mahmood et al., 2018).

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Estrogen

Estrogen has been found to protect neurons from a damage by acting as an antioxidant. In autism patients, estrogen appears to have neuro protective effects, but it does not appear to enhance cognitive or functional difficulties. X chromosome (one of two sex chromosome in humans) has been linked to autism and the incidence of autism in turner syndrome has been studied in a study. In the final phase of growth hormone therapy, estrogen therapy can be started at the same time as the normal onset of puberty, around the age of 12. Unfortunately, there is no evidence to suggest or support the use of estrogen as an antioxidant to lower the incidence of autism or delay the advancement of already-existing autistic disorder. As a result, further research is needed to determine whether estrogen ‘medication might prevent or postpone the onset of autism or lower its severity (Crider & Pillai, 2017).

Carotenoids, vitamins, and other nutrients

When it comes to antioxidants, there are two types: those that penetrate the Blood Brain Barrier (BBB) (i.e. Vitamin A and E) and others that don't. As exogenous antioxidants that disrupt harmful chain reactions in neurons, vitamins C, E (-tocopherol), and -carotene have been shown to suppress dementia development in mammalian cells and reduce free-radical-mediated damage ("Oxidative Stress and Free Radical Damage in Neurology," 2011). As a potent lipid-soluble chain-breaking antioxidant present in both lipid membranes and lipoproteins and low-density lipoprotein particles, -tocopherol is an essential lipid-phase antioxidant. Vitamin E has been proven to reduce the toxic effects of -amyloid and improve cognitive function in people with fairly severe neurological impairment in experimental investigations (Mahmood et al., 2018). Studies show that -tocopherol, which has been shown to slow the advancement of neurodegenerative disorders such as autism, may help autistic people avoid clinically significant declines in their ability to communicate and interact with the world around them (Lord et al., 2018).In addition, vitamins decrease brain lipid peroxidation and considerably reduce the Aβ levels. However, despite a decrease in brain oxidative stress, no influence on the amyloid tic phenotype is shown if Vitamin E treatment is initiated after amyloid plaques have already formed (Gugliandolo et al., 2017). The beneficial use of high-dose B complex vitamins must be accommodated in any mechanistic theory for autism. Multiple clinical research have shown that supplementing autistic youngsters with Vitamin B6 and magnesium can improve their behaviour. The excite-toxic threshold can be lowered by taking B complex vitamins. Even though these vitamins are particularly susceptible to oxidative species (i.e., hydroxyl and singlet oxygen), treatment with these vitamins can disrupt the numerous enzymes and neurotransmitters in autism if there is a deficit of B complex vitamins. (Ford et al., 2018)

Furthermore, zinc deficiency in autism has been shown to increase oxidative stress. Lipid peroxidation and free radicals in cellular membranes, mitochondria, and other organs are

exacerbated when zinc is deficient. Glutathione, glutathione-S-transferase, Vitamin E, and SOD levels are all reduced as a result. Autism, on the other hand, is associated with copper overload. Autistic children have greater amounts of total serum copper, higher levels of unbound serum copper, and lower levels of ceruloplasmin. Unbound copper is extremely pro-oxidant, although supplementary copper is rarely necessary in autism. Copper has been shown to cause harmful behavioral consequences, even in modest levels. Zinc may be necessary to copper-zinc SOD, a critical antioxidant enzyme, based on the theory that oxidative stress reduces clinical zinc retention (Mahmood et al., 2018).

A number of studies have shown that autism is associated with metabolic anomalies that are linked to the metabolism of folate, methionine, and glutathione when these pathways are altered, the cellular redox homeostasis, methylation potential, and the production of DNA are all compromised leading to abnormal glutathione redox state. Most typically, oxidative stress is caused by a malfunction in one or more metabolic pathways

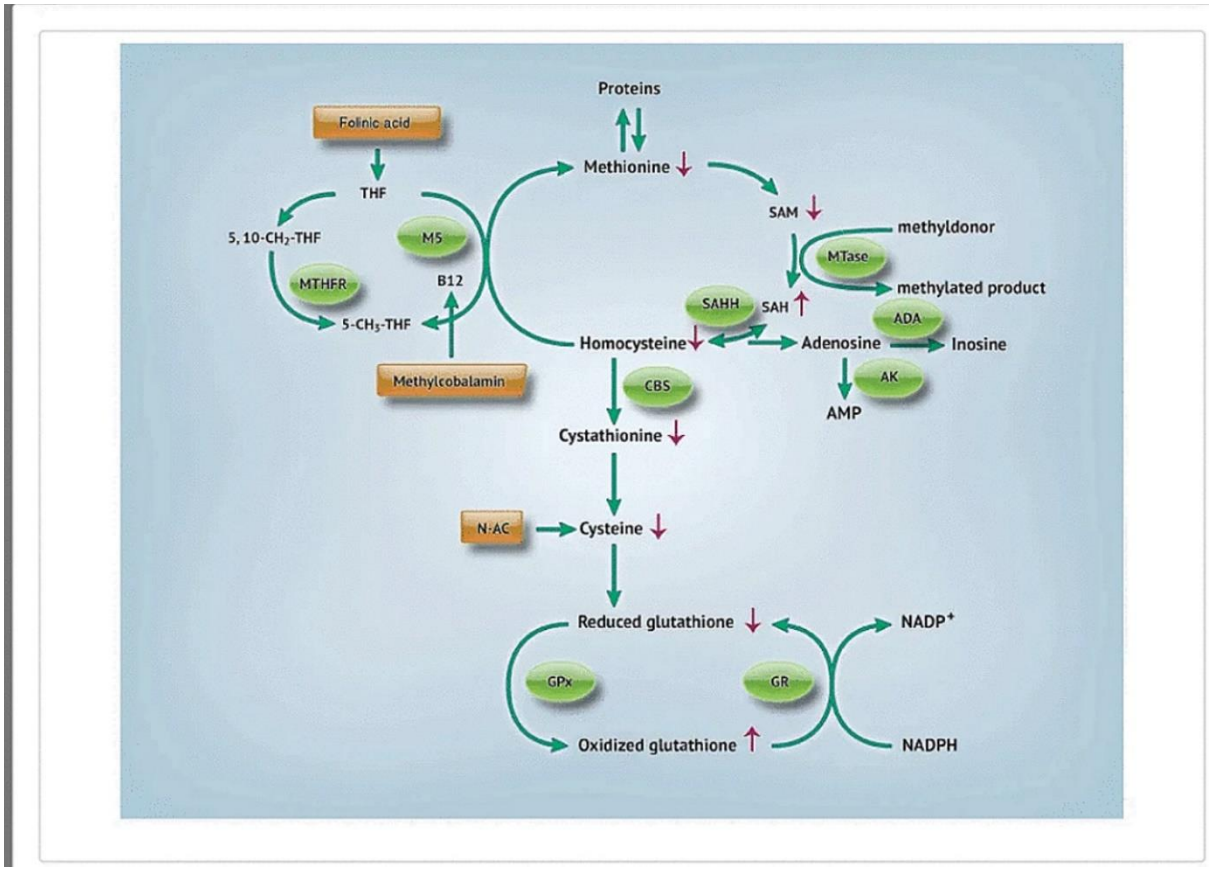

Figure 0-2: Trans methylation reaction (Castejon & Spaw, 2021)

Figure 2: depicts the transmethylation and transsulfuration processes. Methionine synthase transfers a methyl group from methylcobalamin to homocysteine in the transmethylation pathway Methyltransferase activity and 5–methyltetrahydrofolic acid provide the methyl group needed by methylcobalamin for this methionine regeneration. Using S–adenosylmethionine (SAM), an additional methyl donor, methionine can rebuild homocysteine. There are two ways that homocysteine can be used: either as part of the transmethylation cycle or as cysteine, which is permanently eliminated by cystathione–B synthase (CBS). Glutathione production cannot take place without cysteine.

A Trans methylation reaction (Fig. 2)

Autistic individuals have abnormalities in the routes of methylation and sulfur translocation, as seen in Figure 1. Levels are being raised, as shown by the arrows () levels have dropped as indicated by the arrows. Circles denote enzymes that are involved in the reaction. Intervening methods are depicted in rectangles. Abbreviations: It's important to remember that the acronyms ADA, AMP, AK, and CBS all stand for different things. For example, the acronym 5,10–CH2–THF stands for 5,10–methyl tetrahydrofolate, while 5–CH3–THF stands for 5,10–methylenetetrahydrofolate. Methionine Synthase, Methyltransferase, and NADPH are all examples of enzymes that convert glutathione to glutathione peroxidase. Metabolic tetrahydrofolate reductase (MTHFR): It is important to know the acronyms for the following terms and abbreviations: SAH, SAHH, S–Adenosylhomocysteine, S–Adenosylmethionine, and THF (Castejon & Spaw, 2021).

3.5.2. Autism spectrum disorder in children

Adenosine deaminase (ADA) is reduced in children with autism, resulting in an increase in adenosine or homocysteine levels. Because of the increased s–adenosylhomocysteine (SAH) and resulting in the inactivation of methyltransferase due to the inactivation of SAHH, this buildup occurs. Autism has a negative impact on methylation. Due to a lack of methionine, protein synthesis is also reduced. This has major downstream effects. Reduced cysteine levels are the root cause of low glutathione levels in this condition (Castejon & Spaw, 2021).Glutathione is an important endogenous antioxidant and detoxifier that is made of cysteine, glycine, and glutamate. Reduced GSH and oxidized GSH are two different forms of GSH that can neutralize harmful free radicals present in the body. It is important to know the glutathione redox ratio (GSH: GSSG) as an indicator of glutathione status and intracellular reducing conditions. Redox–sensitive enzyme activity, detoxification and membrane signaling

all play a role in the regular functioning of the immune system. Pools of glutathione can be found in mitochondria, as well as in the cytoplasm. Neuronal oxidative stress vulnerability has been linked to reduced mitochondrial glutathione levels (Alanazi et al., 2015).

In children with autism, glutathione deficiency increases oxidative stress vulnerability. Deficiencies in antioxidants and antioxidant enzymes can lead to mitochondrial malfunction, which has been associated to autism. Heart disease, cancer, autoimmune disease, and neurodegenerative disorders have all been researched for possible approaches to improve the anomalies in the trans methylation and trans sulphuration pathways and their consequences. These situations necessitate increased antioxidant support, which could be a potential pharmacological treatment for autism (Castejon & Spaw, 2021).

Chapter 4

Conclusion

4.1. Discussion

This study focuses on the beneficial effects of antioxidants in combating some serious illness by increasing immunity and by preventing and treating conditions like cancer, autism, aging, COVID 19. Several studies have established the concept of dietary antioxidants improving immunity in adults, and other studies have demonstrated improved cellular immunity in younger persons as well. Some researches proved that, Antioxidants not only help prevent cancer, but when combined with chemotherapeutic medications, they increase the efficacy of the treatment, and some antioxidants help restore the body's natural antioxidants following chemotherapy. As we know the Covid 19 is the global health crisis and the greatest challenge of our time. Fortunately, recent researches revealed that antioxidants may have a crucial role in the treatment of Covid-19. According to the findings, in SARS-CoV-2 infections, treatment with catalase enzyme has shown potential effects in reducing oxidative stress by degrading excess H_2O_2 and so reducing cytokine storm and inflammation in the lungs' alveoli. This can open a new door to provide an effective treatment option in this pandemic situation. Besides, many antioxidants, such as zinc, vitamin C, vitamin D, curcumin, and selenium, have been shown to boost immune function, decrease viral load, inflammation, and viral reproduction, and protect against oxidative stress. Aging is a physiological change that led to the decline of the biological functions which every living being must go through. Aging brings some noticeable changes in the skin. Several researches demonstrated that Vitamin C and E brighten the skin, while antioxidants protect against sunspots, soothe sensitive skin, and hydrate the skin. Also, Vitamin E and Vitamin C in combination have been shown to be beneficial at preventing oxidative damage. Some findings indicated that Polyphenols have the capacity to

directly scavenge ROS and have a preventative effect on certain diseases due to their ability to decrease cellular senescence. Moreover, numerous studies have established that oxidative stress has a role in the pathogenesis of a variety of neurological disorders, including Alzheimer's disease, Down syndrome, Parkinson's disease, schizophrenia, and autism. According to the findings of several studies on neurological disorders, omega-3 fatty acids have been related to a reduction in beta amyloid production in the brain of children with early onset autism. Moreover, overproduction of reactive oxygen species (ROS) by mitochondria is suggested to be a significant factor in autism. Numerous metabolic antioxidants, including estrogen, carotenoids, vitamins, and zinc, act specifically on mitochondria, offering the best protection against the excessive ROS produced by mitochondria. So, adding these antioxidants in the diet would be a great treatment option for autistic patients.

4.2 Limitations of the study

As it is a review study, a lot of relevant articles are required but many paid articles are locked. I could not access to those articles. Some articles are written in different languages other than English. So I could not extract information from those articles.

4.3 Future research opportunities

According to this review study, antioxidants derived from phytonutrients may be used to treat SARS-CoV-2. Additional pre-clinical and clinical trials are needed to repurpose these nutrients into ready-to-eat food supplements that may be used prophylactically and adjuvant against COVID-19. Additionally, this review discusses a treatment strategy for the COVID 19 pandemic using the enzymatic antioxidant Catalase, which assists in regulating cytokine production, protecting against oxidative injury, and repressing SARS-CoV-2 replication in

human leukocytes and alveolar epithelial cells, as well as rhesus macaques, without causing noticeable toxicity. As a potential treatment for COVID-19, such a therapeutic can be readily manufactured at a low cost. Likewise, this review sheds light on neurodegenerative diseases such as autism disorder that are associated with mitochondrial dysfunction; therefore, developing new therapeutic strategies that target the mitochondria may put a spotlight on autism treatment. Future research on dietary intervention in cases of altered state of consciousness (ASCs) may benefit from examining the structural and biochemical changes in the brain following dietary intervention. Along with elevated levels of oxidative stress and pro-inflammatory molecules, individuals with ASD frequently have nutritional deficiencies, making a nutritional assessment of each patient critical. This allows for rapid selection of an effective strategy for addressing ASD-like behaviours. Finally, this study discusses the use of antioxidants as adjuvant therapy in combination with chemotherapy to increase treatment efficacy and minimize side effects. Continuous research and the involvement of multidisciplinary teams including oncologists and nutritionists in monitoring additional clinical trials would aid in broadening treatment options for cancer using antioxidants and reducing drawbacks at a reasonable cost

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