A Synthesis Review of Vitamins Involved in the Fight against Covid-19

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Abstract

Although literature studies on earlier viruses such as the Severe Acute Respiratory Syndrome (SARS), the Middle East Respiratory Syndrome (MERS), and other similar viruses, in terms of treatment of coronavirus suggested the repurposing of some antiviral drugs, some Covid-19 specific treatments, general forms of treatments, the use of convalescent plasma, as well as nutritional interventions in the form of vitamins, it is imperative to interrogate the nutritional status, age, and comorbidities of each infected patient before receiving any form of treatment. In the absence of any conclusive treatment so far, the study encourages the use of all likely interventions that could help arrest the spread of the disease. In addition, the current study has a particular interest in the syntheses and applications of vitamins and their derivatives which have been touted to play a significant role in the fight against Covid-19, namely, vitamins A–E. It must, however, be mentioned that literature is not comprehensive.

Keywords: Coronavirus, Covid-19, Nutritional interventions, SARS-CoV-2, Vitamin syntheses

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1 Introduction

The sudden emergence of a novel coronavirus ascribed as Covid-19 has sent shock waves around the world. Covid-19 which took just a few months to reach a pandemic of intercontinental proportions threatened both life and the economy worldwide as a result in the absence of any treatment when the pandemic started, alternative means of treatment had to be employed to try and curb the spread of the disease.

The emergence of a series of unknown pneumonia cases in December 2019 in the city of Wuhan, Hubei Province, China, signalled the start of the outbreak of the 2019 novel coronavirus (2019-nCoV) referred to as the SARS-CoV-2 [1–3]. The International Committee on Taxonomy of Viruses (ICTV) Nidovirales Study Group (NSG) carefully named the virus as 'severe acute respiratory syndrome 2' (SARS-CoV-2) and classified the virus as follows:
Category: *Coronaviruses*
Realm: *Riboviria*
Order: *Nidovirales*
Sub-order: *Cornidovirineae*
Family: *Coronaviridae*
Sub-family: *Orthocoronaviridae*
Genus: *Betacoronavirus*
Sub-genus: *Sarbecovirus*
Species: Severe acute respiratory syndrome-related coronavirus
Individuum: *SARS-CoV-2* [4].

The World Health Organisation (WHO) initially ascribed the name 2019-nCOV for the novel virus, a name which was then changed to coronavirus disease 2019 (COVID-19) on February 11, 2020 [5]. It took just a span of three months for the WHO to declare the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a pandemic of global proportions, that is, since its identification on January 08, 2020, it took about two weeks to reach most provinces in China and by March 16, 2020 there were already more than 170 000 confirmed cases which were accompanied by more than 6500 deaths already [6].

The last few decades from 1940 has seen a steady rise in the number of emerging infectious diseases which are as a result of zoonotic diseases, vector-borne pathogens, as well as drug-resistant pathogens such as the human immunodeficiency virus (HIV), ebola, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and of late the severe acute respiratory syndrome-2 (COVID 19) which is believed to be an enzoonotic virus that emanates from bats that now switched its host to humans through an intermediate host [7].

The novel COVID-19 was found to belong to the β-coronaviruses that had been seen in the last two decades, namely, the SARS β-coronavirus and the MERS β-coronavirus. Eighteen years ago, a novel virus presenting with the cause of peculiar

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form of pneumonia which also originated from southeast China in Guangdong province named SARS-CoV suddenly surfaced [8]. The SARS epidemic was responsible for 774 fatalities out of a total of greater than 8000 confirmed infections, and thus a fatality rate of 7 % [9]. A decade later, another pathogenic β-coronavirus named Middle East respiratory syndrome (MERS-CoV) emerged and was responsible for an endemic in the Middle East [10].

It took a period of seven months to completely control SARS, whereas, with MERS which does not transmit from person to person and only transmit via a primary host such as a camel resulted in 858 (34.4 %) deaths out of a total of 2494 confirmed cases worldwide, that is, a case-fatality rate of 34.4 % [11].

Coronaviruses are positive single-stranded RNA viruses that due to the embedded spike glycoproteins on the envelope display a crown-like appearance [12, 13]. Coronaviruses can be classified into four major genera: α-coronavirus, β-coronavirus, γ-virus, and δ-virus [14]. SARS-CoV-2 is a member of the β-coronavirus [15]. It is an enveloped and pleomorphic spherical virus which resembles a solar corona when examined under transmission electron microscopy imaging with the diameter of the virus particles around 60 to 140 nm that display distinctive spike glycoproteins of about 8 to 12 nm in length [16, 17]. In fact, these distinguishing spike glycoproteins are mechanistically exploited by the SARS-CoV-2 as but a means to attach to the membrane of the host cell and, thereafter, structural interchanges between SARS-CoV-2 and the human alveolar cells II occur where the SARS-CoV-2 displays remarkable affinity for the angiotension-converting enzyme 2 (ACE2), a key ingredient which is richly deposited on the surface of the alveolar cells [18].

It is noteworthy to posit that such a mechanism that involves the host-receptor angiotensin-converting enzyme 2 (ACE2) as a key ingredient is not only confined to humans but transcends to all other species that bear human-like ACE2 receptors and as such rendering the species susceptible to SARS-CoV-2 [19]. SARS-CoV-2 is a positive-sense single-stranded RNA genome that contains 29 891 nucleotides in size which encodes 9860 amino acids and it is characterized by having 89 % nucleotide identity with bat SARS-like CoVXCZ21 as well as that of human SARS-CoV [20, 21].

There are currently no registered treatment drugs or vaccine or monoclonal antibodies that have been approved to treat human infections due to SARS-CoV-2 [22]. In fact, the antiviral drugs that are currently used have so far displayed limited effects [23]. In the race against time, due to shortage of active drug compounds against COVID-19 as well as its accompanying variants, employing different strategies, research scientists all over the world are working hard to find active drug analogues to mitigate and help fight the risk posed by SARS-CoV-2, that is, strategies that involve repurposing of antimalarial, antiviral, and rheumatoid drugs such as chloroquine and its derivative hydroxychloroquine, lopinavir/ritonavir, ribavirin, redemsivir, favipiravir, ivermectin, and tocilizumab [18].

Strategies that employ natural product compounds where compounds belonging to the phenolic family, were recently found to be the most promising inhibitors against SARS-CoV-2 [24]. To date, in the quest for active drug analogues against COVID-19, much work and effort has been placed on repurposing of existing drug compounds as well as on the use of natural-based active compounds, and studies are scanty that look at the laboratory-based synthetic drug analogues. Therefore, the aim of this current review is to explore syntheses of potential drug targets and nutritional interventions that are purported to have an effect on SARS-CoV-2.

2 Vitamin A

In its natural form, vitamin A **1** (Fig. 1) is encountered as an ester that is extremely soluble in organic solvents and insoluble in aqueous media. The precursor to vitamin A is a major provitamin carotenoid referred to as β-carotene which displays similar solvent properties [25]. Retinoid is the scientific name ascribed to vitamin A derivatives as well as other synthetic compounds that share the same biological activity as vitamin A. These include the three physiologically active forms of vitamin A, namely, retinol (alcohol) **1**, retinal (aldehyde) **2**, and retinoic acid (acid) **3** (all in Fig. 1) [26, 27].

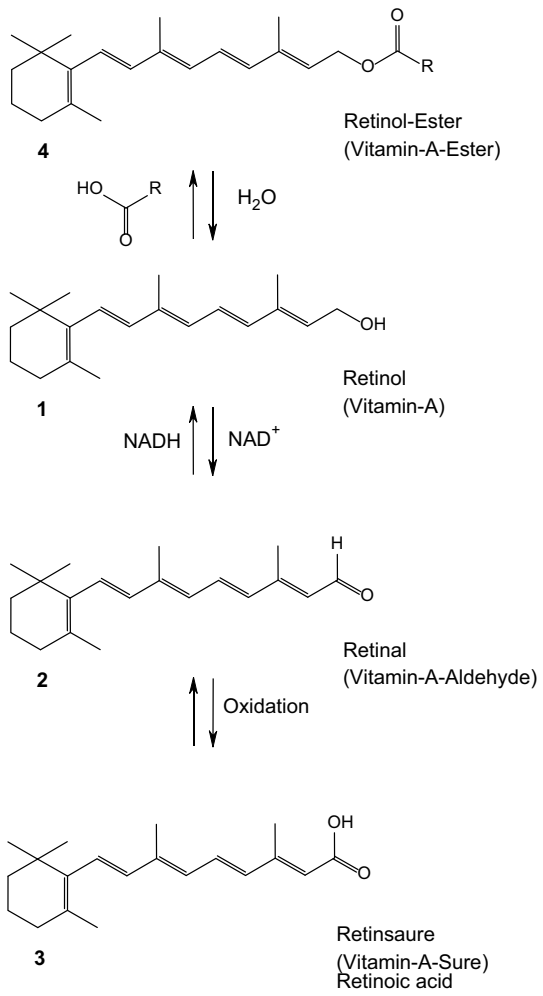


Figure 1. Vitamin A and its derivatives.

Although vitamin A **1** has been accepted as the "anti-infective" in the last 100 years, it is only in the past few decades that it has undergone onerous experimental and clinical trials where it has been made known to strengthen immunity and thereby help curb childhood morbidity and mortality that result from communicable diseases [28]. Vitamin A deficiency (VAD) as defined by the World Health Organization (WHO) refers to the low levels of serum retinol ($< 20\ \mu g\ dL^{-1}$) which affects nearly a third of children in low- and middle-income countries in the world [29]. Measles which are responsible for case-fatality rates of about 30 % in developing countries are attributed to poor nutrition with respect to vitamin A [30].

Vitamin A supplementation was also shown to yield positive results in preventing respiratory and diarrheal disease morbidity [31]. Direct supplementation with large doses of vitamin A **1** to HIV-positive children led to decreased episodes of diarrhea, improved CD 4-cell count, and suppressed all-cause mortality [32]. The need for the exploration of the synthesis of vitamin A and its derivatives is worth visiting and thus cannot be over-emphasized. The administration of vitamin A has been demonstrated to yield without any side effects due to protracted vitamin A supplementation, remarkable remission of oral leukoplakia which are basically precancerous cells [33].

Vitamin A plays a crucial role in the optimal functioning of the immune system and not only that, but also potentiates cell proliferation and differentiation [34]. Vitamin A and its related retinoids have been shown to be responsible for the modulation of a number of immune responses such as expression of keratins and mucins, natural killer cells, T lymphocytes and B lymphocytes, cytokine production, apoptosis, function of neutrophils, lymphopoiesis, and production of immunoglobulin [35]. Although a controversy exists with respect to vitamin A and acute lower respiratory tract infections (ALRIs), low-dose vitamin A contributes to the reduction of recurrence of bronchopneumonia while moderate-dose vitamin A is responsible for decreasing the time to remission of signs in children having the normal serum levels of retinol [36].

Vitamin A **1** which is currently used as a nutritional food supplement and which plays a significant role in the immune system has been found to possess very strong and beneficial pharmacological activity against SARS-CoV-2 via associated antiviral and anti-inflammatory effects, immunoregulation, and cytoprotection. The new and emerging network pharmacology strategy reveals an association between the molecular mechanism of vitamin A and the corresponding anti-SARS-CoV-2 targets and thus suggests that indeed vitamin A could be employed as an additional treatment against COVID-19 [37].

SARS-CoV-2 is said to employ angiotensin-converting enzyme 2 (ACE2) as a way to attach to the host cell receptors, thus leading to downregulation of the renin-angiotensin system. Once SARS-CoV-2 is inside the host cell, the SARS-CoV-2 viral DNA sparks off the production of CD_4^+ T-helper type 1 cells as well as the cytokine storm that entails TNF-α, IL-1, IL-6, and IL-18. In the lung tissue, SARS-CoV-2 results in severe respiratory syndrome as a direct result of increased pulmonary fibrosis which is invariably increased by lipofibroblast-myofibroblast transition. Librofibroblasts, on the other hand, depend on retinoids to kick-start, synchronize, organize as well as regulate alveolar septal eruption and alveologenesis. Thus, the impending loss of vitamin A due to its catabolism during the virus-induced lipofibroblast-myofibroblast transition could decrease the ability of the lung tissue to restore damaged epithelial surfaces, thus, resulting in long-lasting scarring, fibrosis of the lung, and as such decreased lung capacity, which later would result in a phenomenon referred to as long COVID.

Treatment of COVID-19 with glucocorticosteroid dexamethasone results in local and systemic vitamin A deficiency due to the decrease of retinoid-binding proteins and receptors. On the other hand, SARS-CoV-2 could also bring about increased systemic vitamin A deficiency through increased urinary losses, reduced intake and absorption, and increased utilization. The effects of local and systemic vitamin A deficiency lead to decreased regulatory as well as protective immunity. Thus, this vicious cycle of increased vitamin A deficiency, decreased regulatory and protective immunity impairs recovery and as such is likely to lead to increased morbidity and mortality. Increased vitamin A supplementation reverses the effects of SARS-CoV-2, particularly on the angiotensin system.

A schematic representation of the mechanism of action of vitamin A against SARS-CoV-2 is illustrated in Fig. 2 [38]. The stability of vitamin A has by a great number of studies been pointed out to be of immense concern [39]. Factors such as minerals, temperature, nature, and degree of diluents have all been shown to yield adverse effects on the stability of vitamin A in feeds [40]. In addition to temperature, other factors such as humidity, presence of oxygen, light, pH, oxidizing and reducing agents, presence of metal ions and other ingredients have also been shown to lead to losses of vitamin A activity given that vitamin A (retinoids and caretenoids), being a group of unsaturated hydrocarbons, follows the same degradation pathway as other hydrocarbons [41]. It has also been shown that techniques such as encapsulation of vitamin A can help enhance stability of vitamin A [42].

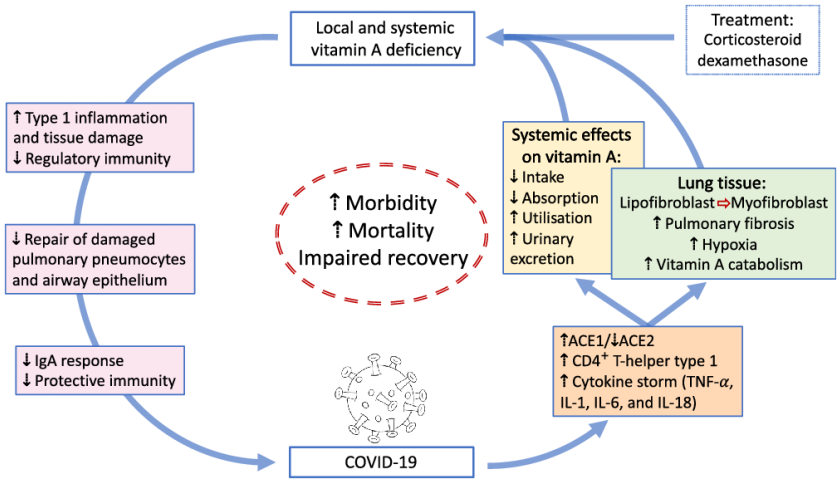
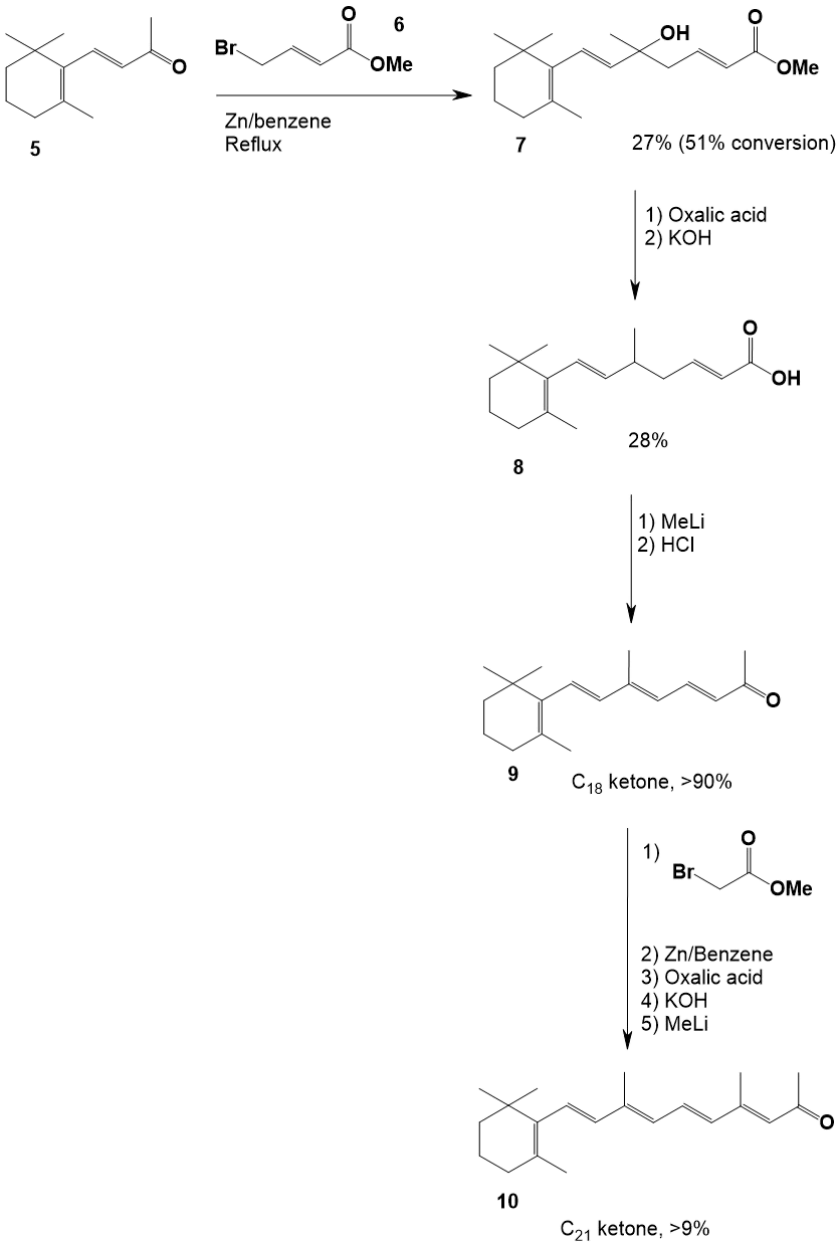


Figure 2. Overview of possible interactions between vitamin A and SARS-CoV-2.

2.1 Synthesis of Vitamin A

In the quest to synthesize vitamin A, Arens and van Dorp [43] sought to develop a linear multistep synthesis that aimed at generating a carboxylic acid **8** starting from a β-ionone **5** which was treated with methyl γ-bromocrotonate **6** in the presence of zinc under benzene reflux in a reaction known as the Reformatsky reaction to furnish the corresponding hydroxyl-ester **7**. The hydroxyl-ester **7** was then dehydrated by employing anhydrous oxalic acid in the presence of potassium hydroxide to generate the desired ester which yielded three crystalline acids upon saponification forming the desired ionylidine crotonic acid **8** being the major product. The resulting crotonic acid **8** was then methylated using methyllithium in the presence of hydrochloric acid to form a thick yellow oil C_{18} ketone **9** in excellent yield of 90 % which is the key intermediate in the synthesis of vitamin A **1**. The four reaction steps above were then repeated: Reformatsky reaction using methyl γ-bromocrotonate, dehydration with the use of anhydrous oxalic acid, hydrolysis of the ester using potassium hydroxide, and lastly, addition of methyllithium in the presence of hydrochloric acid yielded the corresponding C_{21} ketone **10** as demonstrated in Scheme 1.



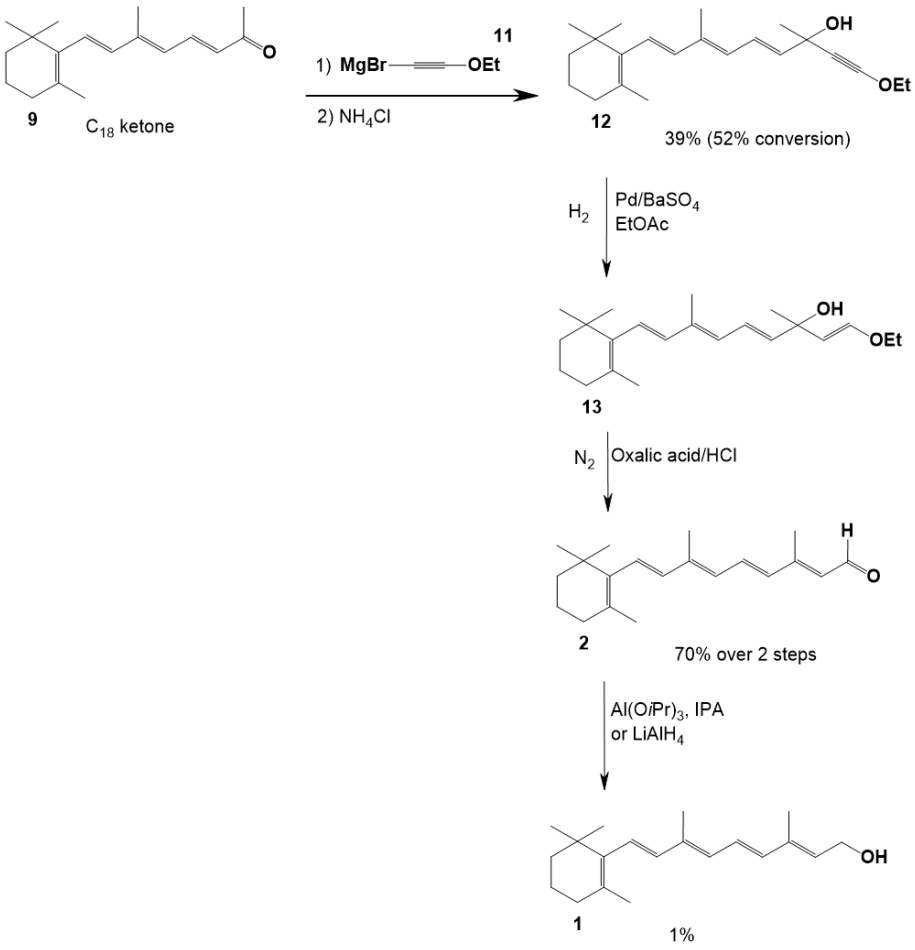
Scheme 1. The synthesis of C_{21} intermediate.

The key intermediate **9** in the synthesis of vitamin A **1** formed in Scheme 1 was now used as the starting material in the synthesis of the desired vitamin A **1** in Scheme 2. The C_{18} ketone **9** underwent a Grignard reaction with ethoxyacetylene derivative **11** in the presence of ammonium chloride to form the corresponding Grignard product **12**, in which under a poisoned palladium catalyst the triple bond was reduced to yield the desired product **13** [43]. The following hydrolysis of the enol ether **13** using oxalic acid followed by aqueous hydrochloric acid leads to the removal of the hydroxyl group to form the corresponding vitamin A aldehyde **2**. Retinal **2** is then reduced over two steps with the use of aluminum isopropoxide and isopropyl alcohol in a reaction known as a Meerwein-Ponndorf-Verley reduction to yield the desired vitamin A **1**.

3 Vitamin B

B vitamins are a group of eight water-soluble vitamins that play a significant role in cellular functioning, behaving as coenzymes in vast series of cell metabolism reactions [44]. Vitamin B_2 **14**, generally referred to as riboflavin **14a** (Fig. 3), occurs as the precursor of flavin adenine dinucleotide (FAD) **14b** as well as the monophosphorylated form, flavin mononucleotide (FMN) **14c** as shown in Fig. 3.

FAD **14b** and FMN **14c** occur in a non-covalently bonded form to yield enzymes that are responsible for the structure and functioning of flavoproteins. In other words, riboflavin **14a** is crucial for ATP-dependent phosphorylation that occurs in cells [45–47]. Riboflavin deficiency leads to a spectrum of clinical abnormalities that extend to include haemolytic anemia, growth retardation as well as neurologic dysfunctions [48]. It has been shown that moderate deficiency of riboflavin **14a**, which occurs at the level of mitochondrial β-oxidation, is in fact a result of damage of enzymatic activity of the acyl-CoA dehydrogenases (ACDHs) where it has actually been estab-



Scheme 2. The synthesis of retinol via Arens-van Dorp method.

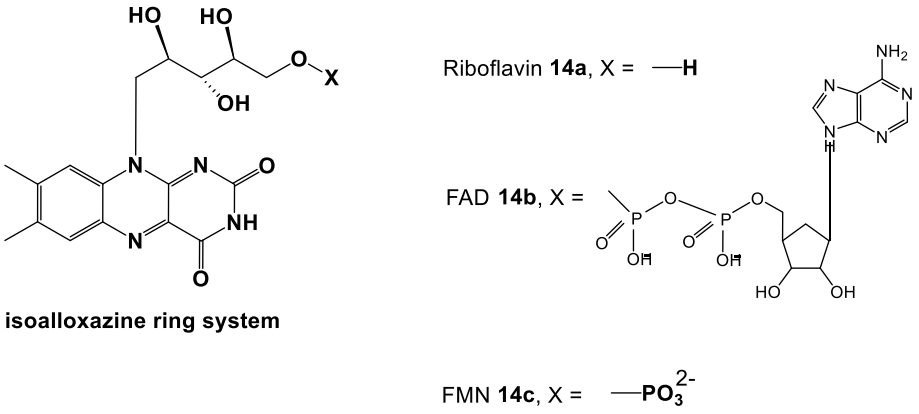


Figure 3. Structures of riboflavin, FAD, and FMN.

lished that some ACDHs are found to be very sensitive, more especially the short-chain acyl-CoA dehydrogenase (SCAD) and isovalery-CoA dehydrogenase which are short chains that are mainly responsible for amino acid metabolism.

In liver cells, deficiency of riboflavin **14a** results in oxidative stress and cell damage [49]. Studies in countries such as the United Kingdom and the United States of America reveal that insufficiency in riboflavin **14a** is seen in 10–41 % of the elderly population and is linked to conditions such as depression and cognitive function changes, thus, supplementation of riboflavin **14a** in the elderly group could help as a neuroprotective barrier against conditions such as Alzheimer's disease, dementia, and Parkinson's disease [50].

The characteristic feature, which mitochondria possesses, is its crucial role it takes part in which is that of generation of energy in the cells in the presence of oxygen via oxidative phosphorylation (OXPHOS). In fact, the OXPHOS system is basically a 5-enzyme complex which includes the mitochondrial respiratory chain (complexes I–IV), complex V, as well as two mobile electron shuttles which are coenzyme Q10 and cytochrome c. Electrons that come from oxidation of pyruvate and fatty acids are channelled via NADH to complex I which consists of FMN-dependent NADH-ubiquinone oxidoreductase, whereas electrons that are derived from succinate in the Krebs cycle are channelled to complex II which consists of FAD-dependent succinate-ubiquinone (coenzyme Q10) and then complex III (reduced CoQ-cytochrome c reductase), and via a series of cytochrome oxidate (COX) (complex IV), then to the terminal oxidase of respiratory chain just before converting molecular oxygen to water [51].

Riboflavin transporter deficiency (RTD), once known as Brown-Vialetto-Van Laere syndrome, is an example of a neurodegenerative disorder in children that is characterized by motor neuron degeneration and sensori-neural deafness that occurs as a result of energy metabolism pathways which involve affected flavoproteins [52].

Glutathione in its reduced form, GSH, is responsible for maintaining the cell membrane intact and thereby protect the cell from oxidative stress or rather protect it from antioxidants in the form of reactive oxygen species as well as other free radicals. Glutathione does this by behaving as a substrate for the reduction of peroxides to alcohols which are less damaging and the enzyme responsible for this reaction is glutathione peroxi-

dase. Glutathione generates the corresponding disulfide (GSSG) when exposed to free radicals or reactive oxygen species and to maintain sufficient amounts of GSH in the cell, the disulfide (GSSG) is then converted back to GSH with the help of glutathione reductase. Glutathione reductase activity, on the other hand, is FDA-dependent and hence in individuals with insufficient riboflavin **14a** glutathione reductase activity is suboptimal [53].

The Mirasol pathogen reduction technology (PRT) system for platelets and plasma employs a combination of riboflavin **14a** and ultraviolet light (UV light) to selectively bring about damage to nucleic acid-containing agents. The PRT system is effective against certain pathogens where it inactivates leukocytes without damaging the efficacy of the blood product of perhaps losing the blood product [54, 55]. It has been shown that the use of riboflavin **14a** together with UV effectively dropped the strength of SARS-CoV-2 in both human blood and whole blood [56]. Vitamin B is tasked with the responsibility of activating not only innate immunity but also adaptive immunity, in other words, vitamin B downregulates pro-inflammatory cytokine levels, thus, by so doing ameliorates respiratory function, maintains the integrity of the epithelial tissue, and helps prevent hypercoagulation. Therefore, vitamin B can certainly be used as a non-pharmaceutical supplement.

A summary of the different actions of vitamin B against SARS-CoV-2 is shown in Fig. 4 [57]. Physical and chemical factors such as light, heat, moisture, oxidizing and reducing agents, acids and bases all impact the stability of vitamin B negatively [58]. A study on fortification of freeze-dried meals demonstrated that this method would be a significantly fruitful means of improving the quality of military pack meals that addresses shortfalls in vitamin B levels [59].

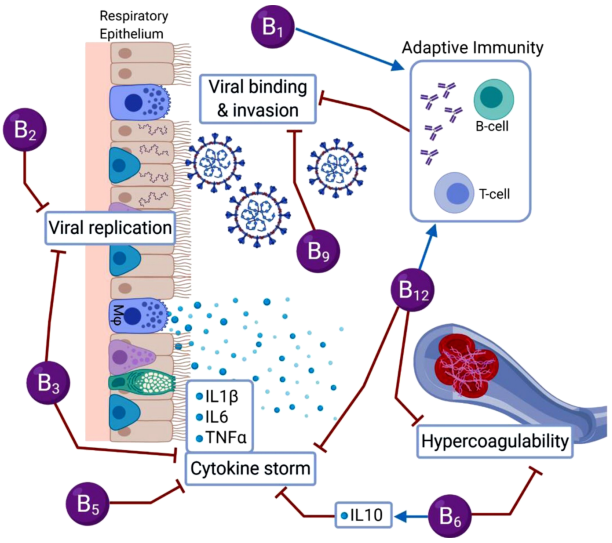


Figure 4. The different roles played by vitamin V against Covid-19.

3.1 Synthesis of Vitamin B_2 14a

Yoneda and co-workers [60], in 1972, extended the synthesis of isoalloxazines **25–27** to the desired riboflavin **14a**. The synthesis began with treatment of 6-chlorouracil **15** with *N*-methyl-3,4-xylidine at 180 °C for 10 min to generate the corresponding 6-(*N*-methyl)-3,4-xylidino)uracil **17** in quantitative yield. Similarly, the condensation of 6-choloro-3-methyluracil **16** with *N*-methylaniline and *N*-methyl-3,4-xylidine furnished 6-(*N*-methylanilino)uracil **18** in 90 % yield and 3-methyl-6-(*N*-methyl-3,4-xylidino)uracil **19** in 95 % yield. Treatment of **17**, **18**, and **19** with sodium nitrite in acetic acid gave rise to luminflavin-5-oxide **21** in 75 % yield, 3,10-dimethylisoalloxazine-5-oxide **22** in 72 % yield, and 3-methylluminflavin-5-oxide **23** in 70 % yield. The resulting *N*-oxides **21**, **22**, and **23** were then subsequently deoxygenated using sodium dithionite in water to give the corresponding lumiflavin **25**, 3,10-dimethylisoalloxazine **26**, and 3-methyllumiflavin **27** in quantitative yields.

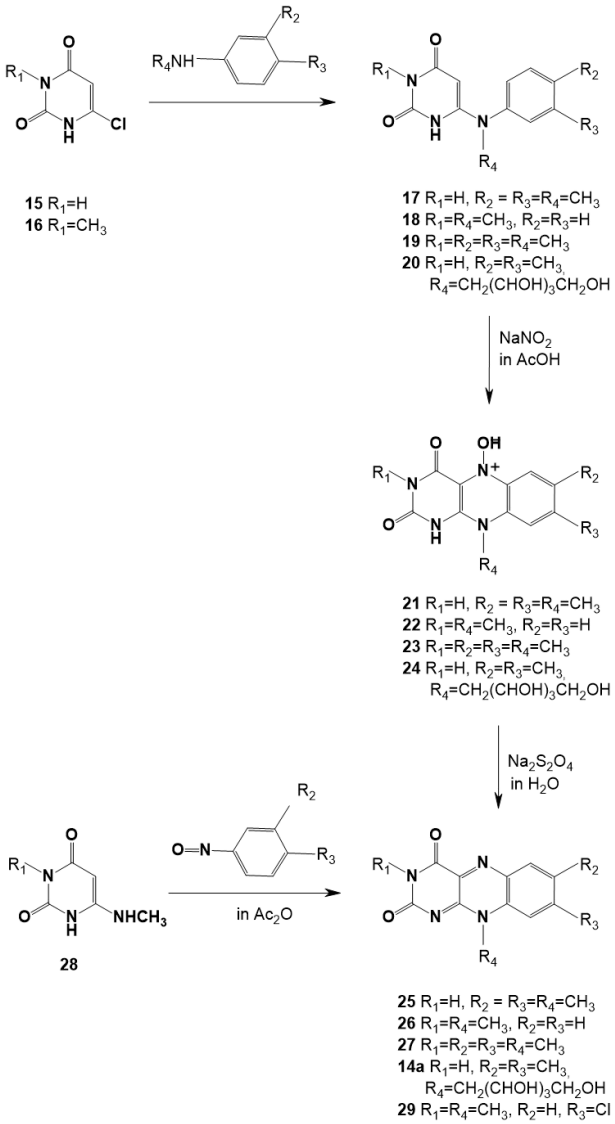
The extension of isoalloxazine synthesis to form riboflavin **14a** started with the treatment of **15** with *N*-D-ribityl-3,4-xylidine at 160 °C for 5 min to yield the desired syrup 6-(*N*-D-ribityl-3,4-xylidino)uracil **20** in excellent yield of 90 %. The resulting syrup **20** was then treated with sodium nitrate in acetic acid to generate the corresponding *N*-oxide **24** in 85 % yield. The *N*-oxide **24** was subjected to sodium dithionite in water to form the desired riboflavin **14a** in quantitative yield as depicted in Scheme 3.

In 1947, Ladenburg and co-workers [61] presented yet a much more direct and simpler method of preparing riboflavin **14a** than the older and more complicated methods. The method starts with the condensation of 27 g of 1-(D-ribitylamino)-2-*p*-nitrophenylazo-4,5-dimethylbenzene and 14.3 g of barbituric acid **31** under reflux in 180 mL dioxane and 34 mL acetic acid for 5 h and the condensation gave rise to a mixture which led to a very pale green sample with hydrochloric acid. The resulting mixture was then cooled and filtered and the solid product was further rinsed with hot water and dried again to give 21 g crude riboflavin product **14a**. The crude riboflavin **14a** was then recrystallized from boiling water or dissolved in four volumes of 18 % hydrochloric acid adding a few drops of superoxol to bleach out impurities, filtering and diluting with water to furnish pure riboflavin **14a** in reasonable yield of 65.8 % in a procedure known as the Pasternack and Brown method as indicated in Scheme 4.

Vitamin B_3 **32a,b** (nicotinamide **32a**, and nicotinic acid **32b**) in Fig. 5 is essential to cells of all living organisms and always undergoes conversion to nicotinamide adenine dinucleotide (NAD^+) **33** which is a remarkably versatile acceptor of hydride to generate the reduced form of dinucleotide, NADPH **34** [62]. Vitamin B_3 **32a,b** has been shown to significantly reduce the size of infarction following brain injury [63].

Nicotinamide riboside **35** in Fig. 6 is regarded as the new form of vitamin B_3 with unique properties and it exists as a nucleoside which results from the union of nicotinamide as well as ribose as illustrated in Fig. 6.

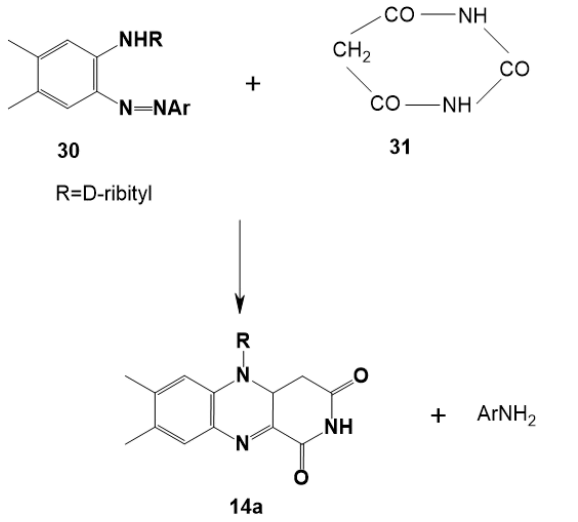
Nicotinamide riboside **35** is basically a precursor that enhances the presence of nicotinamide adenine dinucleotide (NAD^+) **33** in animal tissues such as muscle and brain and because of that it is generally considered as an active form of vitamin B_3



Scheme 3. The synthesis of isoalloxazines.

[64, 65]. It has been found that nicotinamide riboside **35** plays a significant role against excitotoxicity which is rampant in many neurological disorders where NAD^+ **33** gets depleted, thus, NR **35** gets converted or rather replenishes NAD^+ **33** when it enters cells through nucleoside transporters (NTs) [66].

Recent literature studies of the fascinating synthesis and mechanism of action of vitamin B_3 helped a great deal in revealing the interconnectedness of gastrointestinal deficiencies exhibited by the novel coronavirus patients, the production of a vast amount of reactive oxygen species (ROS), and effects of oxidative stress (OS), and as such elevated the need for a healthy diet that will help maintain and keep host eubiosis at its utmost best [67]. Vitamin B_3 deficiency which is more pronounced amongst the poor is due to low meat intake and amongst these social classes of people low levels of nicotinamide lead to diseases such as pellagra [68].



Scheme 4. A new and direct synthesis of riboflavin.

The use of vitamin B_3 to prevent inflammation against SARS-CoV-2 has been rationalized and is thought of to be a result of mitohormetic concept of anti-inflammatory activity induced by the application of 1-methylnicotinamide (1-MNA) illustrated in Fig. 7 which displays a significant physiological role in the regulation of the innate immune response.

In Fig. 7, nicotinamide (NA) is converted to 1-methylnicotinamide (1-MNA) with the aid of nicotinamide *N*-methyltransferase (NNMT). 1-MNA is then further broken down to yield pyridines, namely, 2-pyridone as well as 4-pyridone with the help of aldehyde oxidase (AOX). Hydrogen peroxide is linked to oxidative stress in the cells and thus, its presence is seen as a negative. Even though hydrogen peroxide is usually regarded as a negative, in small amounts it can be beneficial and this is referred to as mitohormesis where it induces the protective stimulation of NLRP3 inflammasome activity which increases the innate immune response during acute infection [69]. Vitamins and supplements may have an additional benefit in the fight against SARS-CoV-2 [70].

3.2 Synthesis of Nicotinamide 32a

The preparation of nicotinamide **32a** began with dissolving 121 g of 3-cyanopyridine **36** in 339.5 g of ethanol where the mixture was stirred for 30 min until 3-cyanopyridine **36** was completely dissolved and then 5 % of NaOH (7.3 g of NaOH in

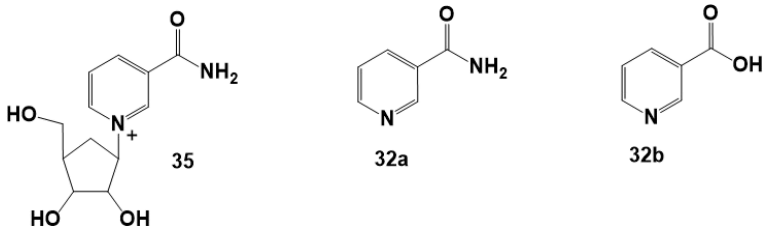


Figure 5. The depicted structures of nicotinamide riboside (a), nicotinamide (b), and nicotinic acid (c).

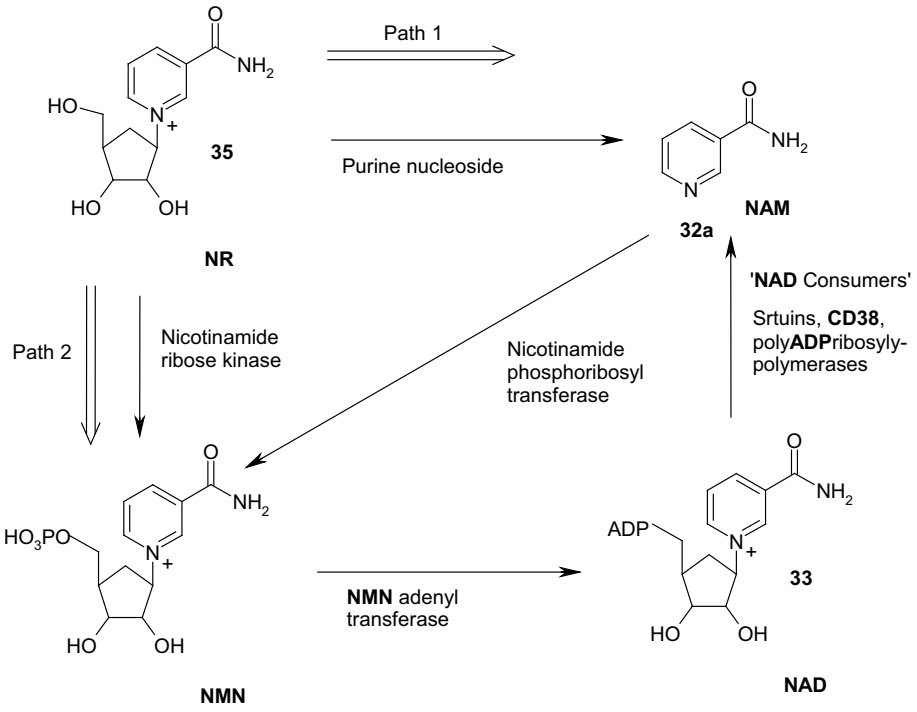


Figure 6. The different pathways involving nicotinamide riboside.

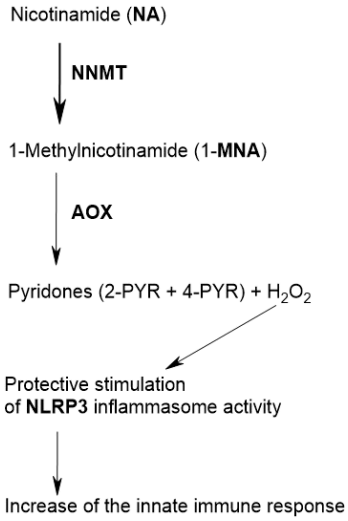
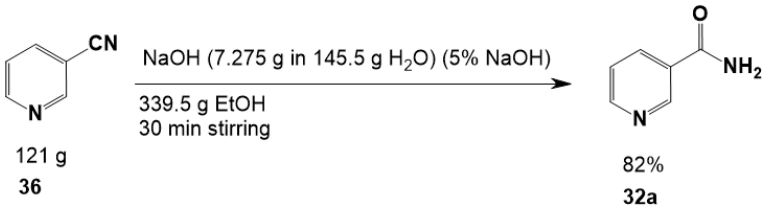


Figure 7. Motohormetic concept of immune response by 1-NMA.

145.5 g of H_2O) was added which was followed by subsequent addition of 24.2 g of MnO_2. The mixture was warmed up to 95 °C for 8 h. MnO_2 was then removed at the end of the reaction and the mixture was heated up to remove the solvent and eventually filtered to obtain the desired nicotinamide **32a** in 82 % yield as shown in Scheme 5 [71].



Scheme 5. Preparation of nicotinamide from 3-cyanopyridine.

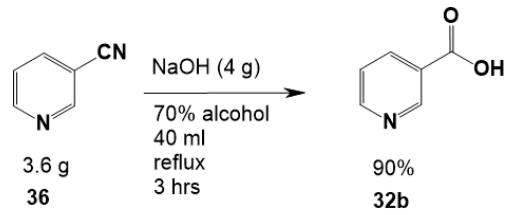
3.3 Synthesis of Nicotinic Acid 32b

Nicotinic acid **32b** was easily obtained by refluxing for 3 h 3.6 g of cyanopyridine **36** with 4 g of NaOH in 70 % alcohol. At the end of the reaction the solvent was evaporated and the resulting residue taken up in 25 mL of water. The aqueous solution was then cooled to 0 °C and then carefully neutralized using acid to yield the desired nicotinic acid **32b** in 90 % yield as indicated in Scheme 6 [72].

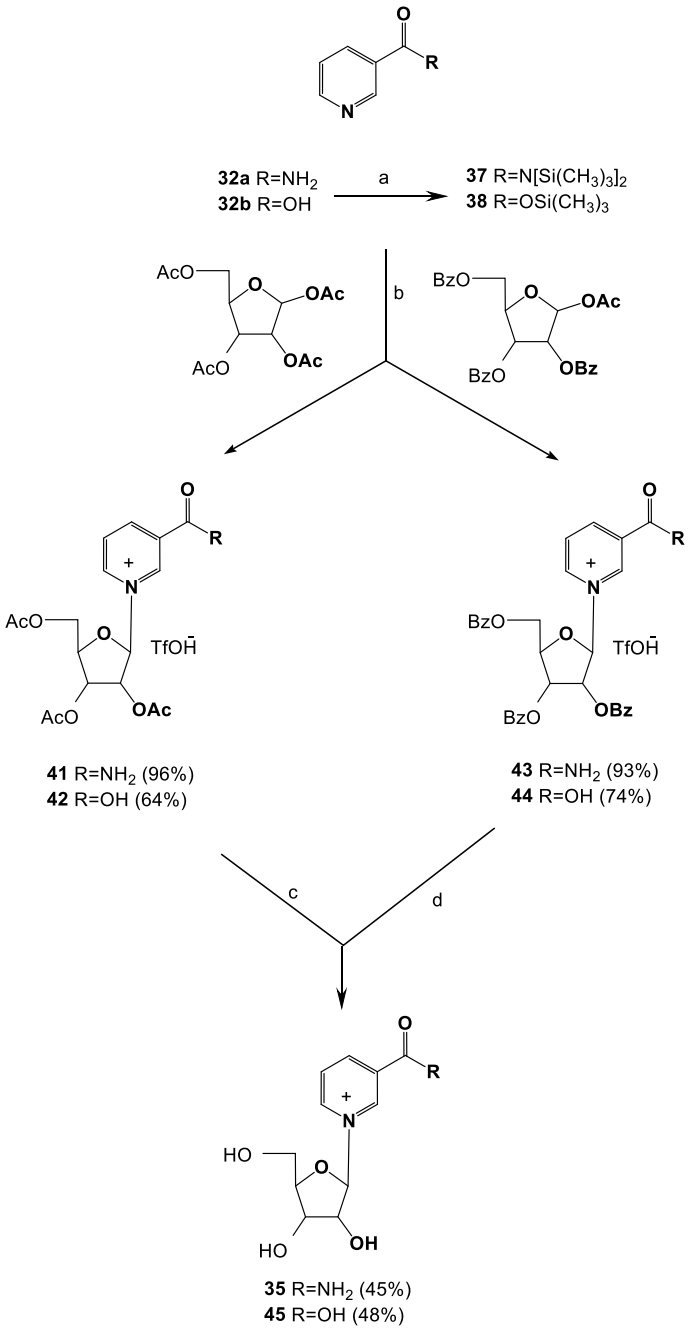
3.4 Synthesis of Nicotinamide Riboside 35

In 2004, Franchetti and co-workers [73] obtained stereoselectivity when synthesizing the target nicotinamide β-riboside **35**. The synthesis took off when dry nicotinamide **32a** and nicotinic acid **32b** were both silylated with two equivalents of TMSCl under reflux at 120 °C to furnish the corresponding intermediates **37** and **38**. The resulting intermediates **37** and **38** were then condensed under well-controlled conditions with both 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose **39** and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **40** in the presence of catalytic amounts of TMSOIf in anhydrous 1,2-dichlorethane to give rise to **41–44** in good to excellent yields (64–96 %) which were then subsequently deprotected under basic hydrolytic conditions to form the desired β-anomers of the protected N-nucleosides **35** and **45** as demonstrated in Scheme 7 [73].

It is in 1932 that Odhake first encountered vitamin B_6 **46** as a by-product while isolating rice-polishings in the rush to extract vitamin B_1. In fact, in 1938 a group of five separate scholars that include Gyorg successfully isolated compound **46** as crystals from yeast and also well characterized the structure and assigned the name of the vitamin pyridoxine **46**. Pyridoxine **46** is characterized by bearing a hydroxymethyl at position 4′. It was, however, found that vitamin B_6 **46** consisted of two other forms that were different from pyridoxine (PN) **46** by having a different group at position 4′, namely, pyridoxal (PL)



Scheme 6. Preparation of nicotinic acid from 3-cyanopyridine.



Scheme 7. Reagents and conditions: (a) TMSCl, HMDS, 120 °C, 5 h; (b) TMSOTf, $ClCH_2CH_2Cl$ anhydrous, 45 °C, 2 h; (c) NH_3/CH_3OH, −5 °C, 6 h; (d) NH_3/CH_3OH, −5 °C, 48 h.

47 which carries an aldehyde group at position 4′, and pyridoxamine (PM) **48** which carries an aminomethyl group at position 4′ as shown in Fig. 8 [74].

Their corresponding ester derivatives which act as active coenzymes are pyridoxine 5′-phosphate (PNP) **49**, pyridoxal 5′-phosphate (PLP) **50**, and pyridoxamine 5′-phosphate (PMP) **51**, respectively, as depicted in Fig. 9 [75].

Vitamin B_6 **46**, in the form of pyridoxal 5′-phosphate, a cofactor, is responsible for transsulfuration of homocysteine that takes place through cystathionine during a homocysteine catabolic pathway [76]. In other words, during the transsulfuration, two coenzymes were responsible that are pyridoxal 5′-phosphate dependent being cystathionine β-synthase as well as γ-cystathionase [77]. Humans are not able to synthesize PLP **50**, and as a result can only access it via a variety of foods that include fruits, vegetables, nuts, beans, and dairy products [78]. PLP **50** is the only derivative that assumes the role of a cofactor for enzymes as a result when the nonphosphorylated B_6 vitamers **46–48** are absorbed into the intestine. The nonphosphorylated B_6 vitamers **46–48** will undergo conversion into the active form PLP **50** with the aid of specific enzymes [79].

32a R=NH2 **32b** R=OH

High levels of homocysteine in blood is thought of to be a risk factor for early arterial disease and this is mainly due to vitamin B_6 **46**, vitamin B_{12}, or folate deficiency [80]. Apart from vitamin B_6 **46** acting as a cofactor, vitamin B_6 **46** is also responsible for a wide variety of other developmental metabolic and physiological processes and it has also been found to act as an antioxidant due to its ability to quench free oxygen radicals [81]. Vitamin B_6 **46** is the most involved nutrient with respect to bodily functions than any other nutrient, e.g., it is cited in nucleic acid synthesis, niacin formation, haem biosynthesis, and serotonin synthesis and in addition it has been mentioned as regulator of various membrane transporters. Due to its ability to bind to steroid receptors it has also been linked to modulation of hormone function together with modulation of transcription factors [82].

Given that vitamin B_6 pyridoxal 5′-phosphate (PLP) **50** serves as coenzyme in the tryptophan-serotonin pathway, deficiency in vitamin B_6 **46** is a direct cause of depression and a study to confirm that found a direct correlation between low levels of vitamin B_6 **46** in depressed patients [83]. Vitamin B_6 **46** deficiency has been suggested to be involved in a number of diseases that include autism, Alzheimer, cancer, diabetes, Down's syndrome, epilepsy,

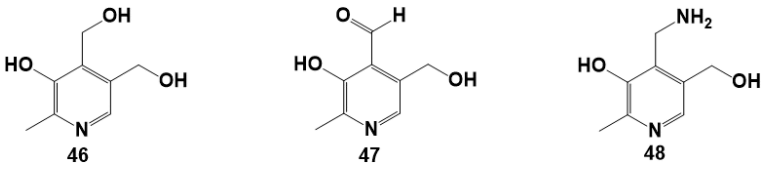


Figure 8. Pyridoxine (a), pyridoxal (b), and pyridoxamine (c).

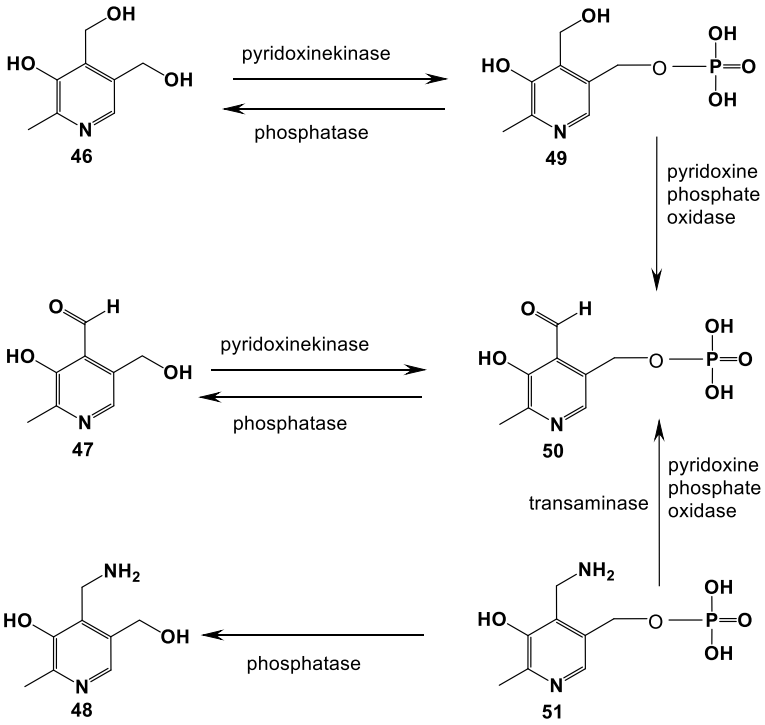


Figure 9. Interconversion of pyridoxine, pyridoxal, and pyridoxamine and their corresponding phosphonate esters.

Parkinson, and schizophrenia [84]. There has been a number of studies that have shown a positive association between high levels of vitamin B_6 **46** supplementation and reduction of cancer risk among women [85].

Elevated levels of blood homocysteine have been confirmed as a probable cause for coronary disease and so given the fact that folate as well as vitamin B_6 **46** are considered as cofactors for metabolism it stands out to reason that supplementation of the diet with folate alone or in combination with vitamin B_6 **46** or vitamin B_{12} is a necessity to lower levels of homocysteine in the blood plasma [86]. Epidemiological studies reveal that a higher intake of vitamin B_6 **46** yield better mental health [87]. Protein metabolism is dependent on vitamin B_6 **46** and is implicated in well over 100 biochemical reactions in the body and, therefore, deficiency in vitamin B_6 will lead to immune suppression in the host whereas vitamin B_6 supplementation to SARS-CoV-2 patients will help boost their immune system [88].

3.5 Synthesis of Pyridoxine 46

Harris and Folkers achieved synthesis of pyridoxine **46** via a very lengthy method that involves nitration of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone **53** which was subsequently followed by introduction of the nitro-group at position 5. The generated nitro derivative **54** was then chlorinated at position 2 to yield the chlorinated compound **55**. The chlorinated compound **55** underwent catalytic hydrogenation to give rise to amino derivative **56** which was further hydrogenated to form the diamino derivative **57**. The diamino derivative **57** was then chlorinated to yield the dichloride derivative **58** which was then treated with sulfuric acid and sodium nitrite to produce the desired product **59**. The product **59** was then treated with hydrochloric acid to yield the corresponding bromo derivative **60** which was eventually converted to the desired pyridoxine **46** using boiling water and silver chloride as illustrated in Scheme 8 [89].

3.6 Synthesis of Pyridoxal 47

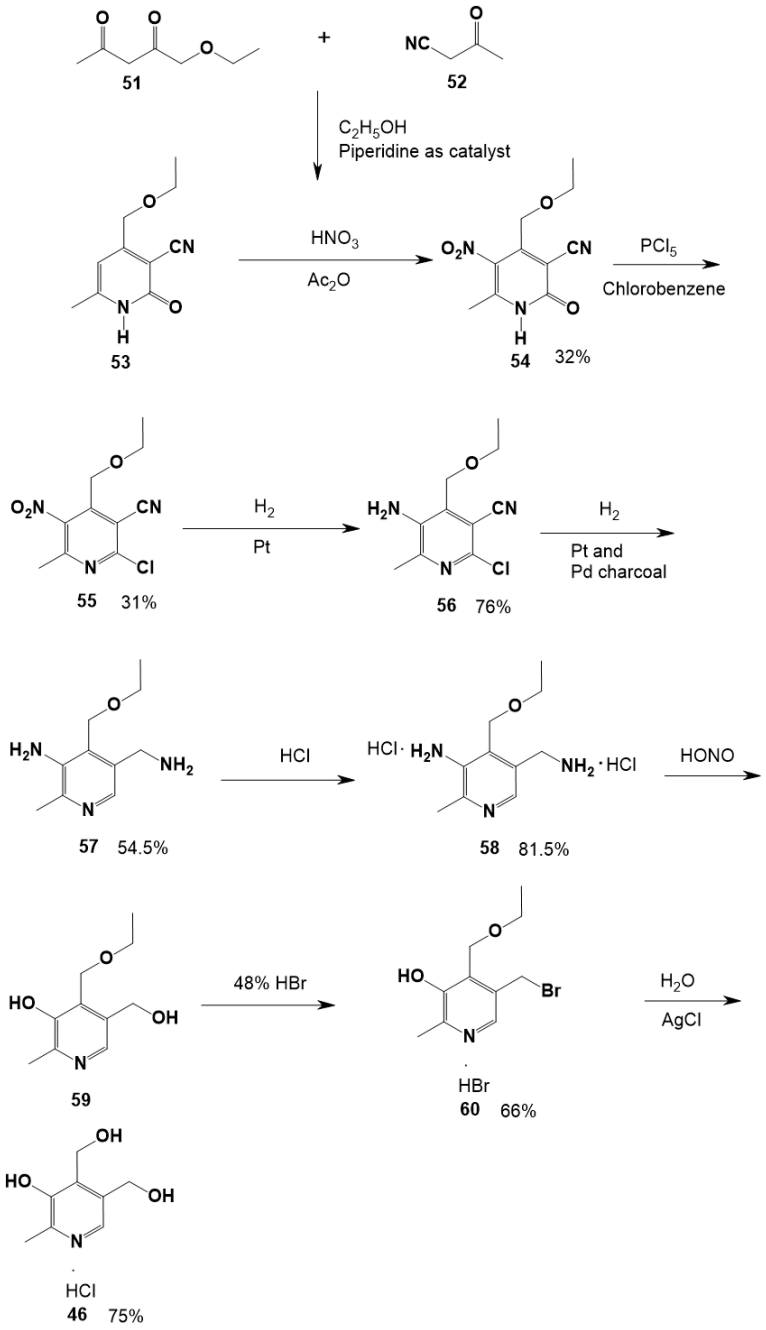
The desired aldehyde **47** was prepared by heating 144 mg of starting material **61** in 5 mL of H_2O that contains a single drop of 6*N* HCl at 50–55 °C for 5 min. The reaction mixture was then allowed to stand at room temperature for 30 min. The solution was reduced to dryness and the residue was crystallized and washed several times in acetone to give rise to the desired aldehyde **47** in excellent yield of 96 % according to Scheme 9 [90].

3.7 Synthesis of Pyridoxamine 48

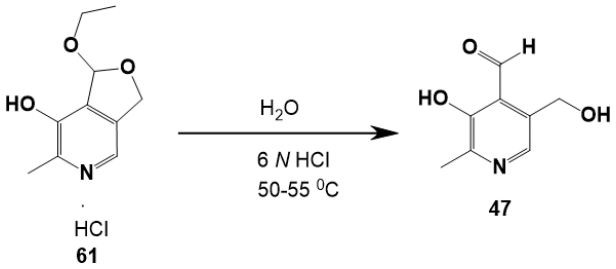
In 1944, Harris and co-workers prepared pyridoxamine **48** by heating in an autoclave at 140 °C 4-methoxymethyl derivative **62** in the presence of 400 mL of methanol and 400 mL of liquid ammonia. At the end of the reaction after 15 h, ammonia and methanol were removed and the resulting residue was then dissolved in 100 mL of water to which an excess of 6*N* sodium hydroxide was added. The excess ammonia was removed under pressure and the resulting solution was then cooled at 0 °C. Filtration was then carried out and the desired amine **48** was obtained in good yield of 71 % as shown in Scheme 10 [90].

4 Vitamin C

Vitamin C **63** is a water-soluble micronutrient that acts as an electron donor and a potent antioxidant. That is, as an antioxidant vitamin C **63** donates electrons to reactive oxygen species such as superoxide radicals, hydroxyl radicals, peroxyl radicals, and also to sulfur radicals and nitrogen-oxygen radicals; to non-radicals such as hypochlorous acid, nitrosamines, and other nitrosating compounds, nitrous acid-related derivatives,



Scheme 8. The synthesis of pyridoxine via 3-cyano-4-ethoxymethyl-6-methyl-2-pyridinone.



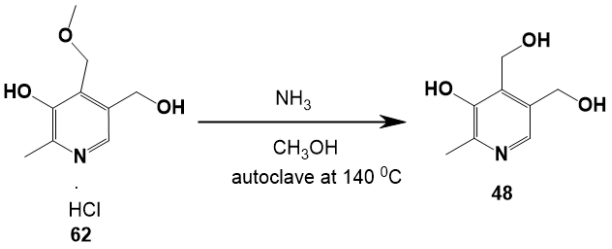
Scheme 9. The synthesis of pyridoxal.

and ozone; to compounds that are a product of radicals and non-radicals such as α-tocopheroxyl radical; and lastly to transition metal-mediated reactions involving copper and iron [91]. In simple terms, vitamin C **63** acts as a reducing agent and a potent antioxidant that also serves a role of cofactor in many biochemical reactions such as reactions catalyzed by Cu^+-dependent monooxygenases and Fe^{2+}-dependent dioxygenases [92].

It must, however, be stated that as an essential micronutrient vitamin C **63** cannot be synthesized in vivo from glucose by humans due to the fact that humans lack a certain key enzyme, L-gluconono-γ-lactose oxidase in the biosynthetic pathway [93, 94]. These free radicals have the ability to damage molecules that are necessary for proper functioning of the cell and once they exceed the cellular antioxidant defense, peroxidation of polyunsaturated fatty acids in membrane structures result. In other words, lipid peroxidation will in a chain reaction further release free radicals as well as toxic aldehydes and eventually lead to inactivation of enzymes and other cell components [95].

Ondermans-van Streaten and co-workers thoroughly explained the mitigating role played by vitamin C **63** against oxidative injury-induced microcirculatory impairment as well as against ischaemic or septic failure of associated organs, i.e., high doses of vitamin C **63** under such conditions offer a low-cost strong, multifaceted antioxidant, and robust form of resuscitation of the circulation [96]. Vitamin C **63**, which is also known as ascorbate, donates its electrons to eight enzymes, of which three enzymes take part in collagen hydroxylation, two of these enzymes play a role in carnitine biosynthesis, and the others, namely, dopamine β-monooxygenase takes part in the biosynthesis of the catecholamine hormone norepinephrine, peptidylglycine α-monooxygenase is responsible for amidation of peptide hormones, and lastly, 4-hydroxyphenylpyruvate dioxygenase that is significant in tyrosine metabolism [97].

The biosynthesis of collagen, 1-carnitine as well as the coversion of dopamine to norepinephrine are all driven by vitamin C **63**. Vitamin C deficiency has also been shown to result in scurvy, damage or fragility of blood vessels, damage of the fragility of the connective tissue, general fatigue, and eventually may lead to death [98]. Vitamin C **63** is a cofactor for a variety of enzymes that take part in the biosynthesis of collagen, carnitine, and neurotransmitters, e.g., enzymes such as procollagen dioxygenase (proline hydroxylase) and procollagen-lysine-5-dioxygenase (lysine hydroxylase) [99]. In fact, the story of vitamin C **63** begins in the early twentieth century when a compound that would cure scurvy was identified. In other words, given the fact that scurvy was linked to pneumonia, it was thought that a compound that would treat scurvy would also have an effect on pneumonia [100].



Scheme 10. Preparation of pyridoxamine using a 4-methoxymethyl derivative.

Vitamin C **63**, together with vitamin E and β-carotene are referred to as the radical scavenging antioxidants responsible for defending the body against oxidative stress, thus, preventing disease and hence maintaining health [101]. The notion that oxidative stress plays a vital role in atherogenesis invariably reveals a crucial point that both the development and progression of atherosclerosis can be hampered by antioxidants such as vitamin C **63** and α-tocopherol (the active form of vitamin E). Studies indicate an inverse relationship between antioxidant intake and the risk of cardiovascular disease [102]. Cigarette smoking has been shown to reduce serum vitamin C **63** levels and even smokers who were taking vitamin C supplements were at increased risk of hypovitaminosis C [103]. Given the threshold urinary excretion, the recommended dietary allowance for vitamin C **63** is given as 60 mg daily [104].

The chemistry of vitamin C **63** is displayed in Fig. 10, which reveals that vitamin C **63** (ascorbic acid) under physiological conditions exists as an anion **63a**. The anion **63a** donates two electrons belonging to the double bond positioned between C2 and C3. The loss of one electron during oxidation generates the free radical referred to as the ascorbate radical **63b** (semihydroascorbic acid **63b**). When ascorbate radical **63b** loses an electron, it becomes dehydroascorbic acid **63c** (DHA **63c**). DHA **63c** exists in different forms, namely, the hydrated hemiacetal form **63d** which is the dominant form. DHA **63c** forms 2,3-diketogluconic acid **63e** upon hydrolysis and this step is irreversible. The 2,3-diketogluconic acid **63e** yields several metabolic products, such as oxalate, threonate, xylose, xylonic acid, and lyxonic acid. Oxalic acid is a very important metabolic product in humans. DHA **63d** may revert back to ascorbic acid **63** by glutathione or perhaps directly to ascorbic acid **63** with the aid of enzyme-dependent mechanisms [105].

Vitamin C **63** that is labeled as an antioxidant has anti-inflammatory and immune-supportive properties. It has been reported that patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease developed acute respiratory distress syndrome (ARDS) and in 90 % of these patients levels of vitamin C **63** were undetectable [106]. During any form of infection, vitamin C **63** is needed for the purpose of destroying neutrophils and also given its large concentration within macrophages, it is, therefore, necessary for T-cell maturation, and lastly vitamin C **63** encourages phagocytosis as well as apoptosis of spent neutrophils [107].

A recent study reveals that a protocol that uses intravenously a high dosage of vitamin C **63** together with thiamine and glucocorticoid steroid such as dexamethasone could actually be considered in treating COVID-19, and given the fact it yields low risk of severe disease, it could manage the cytokine storm that is linked to SARS-CoV-2, and also it is less expensive [108]. In other words, vitamin C **63** downregulates the cytokine storm and hence protects the endothelium from oxidant injury, and it also takes part in repairing tissue [109].

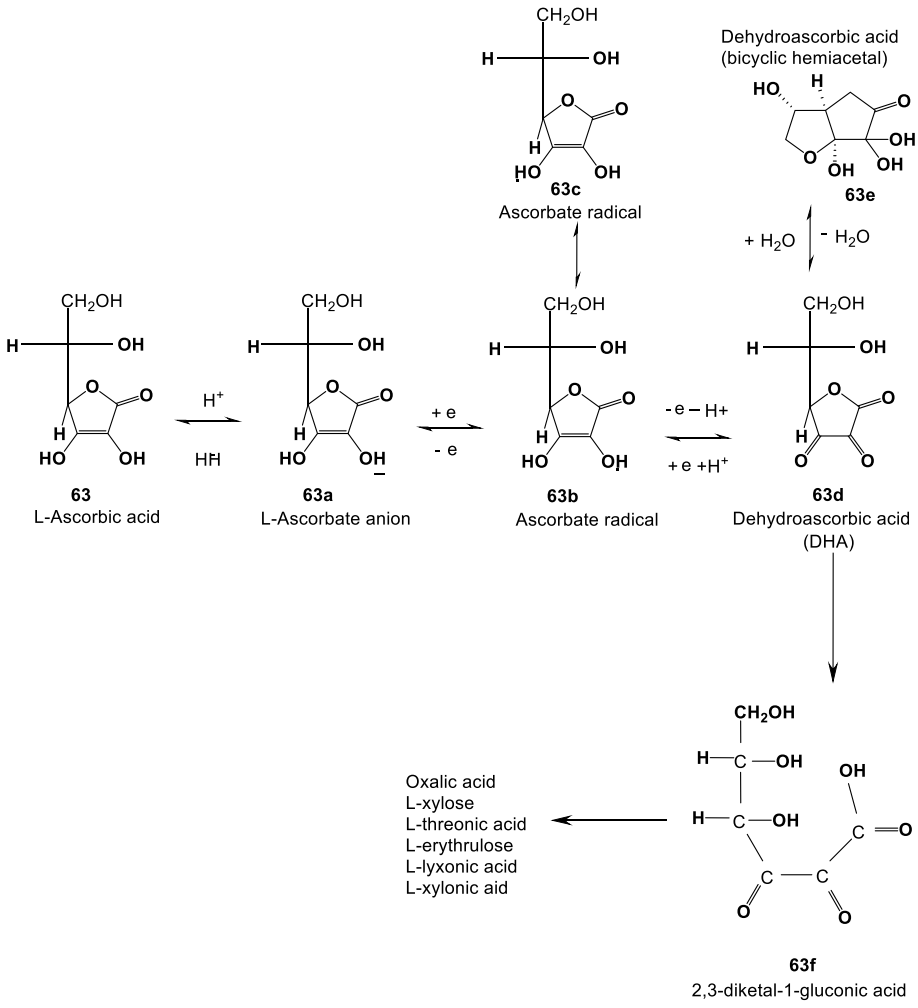


Figure 10. Metabolism of ascorbic acid.

Vitamin C plays a significant role of helping various processes of innate and adaptive immunity and by so doing helps strengthen the immunity system as whole. Administration of a set amount of vitamin C could have an effect on certain specific functions of neutrophils (ROS and TNF, IL-1 mediated), thus blocking pathways that are involved in the formation of the neutrophil extracellular trap (NETosis), and hence toning down uncontrollable inflammatory of cytokine production in the alveolar region. Vitamin C has also been hypothesized to be involved in the reduction of cytokine production in lymphocytes and macrophages; NFkB, nuclear transcription factor kappa B; inhibitory stimulus; dashed arrow, reduced effect or production. A schematic representation of action of vitamin C against SARS-CoV-2 is displayed in Fig. 11 [110].

Vitamin C, in any form, is typified in both processing as well as food preparation by its degradability. However, despite countless studies its degradability remains inconceivable [111]. Factors such as oxygen, temperature, light, pH, and storage conditions are involved in the degradation of vitamin C that occurs by both aerobic and anaerobic pathways [112]. One of the strategies to protect vitamin C from the harsh environment is by encapsulating vitamin C within a layer of wall material [113].

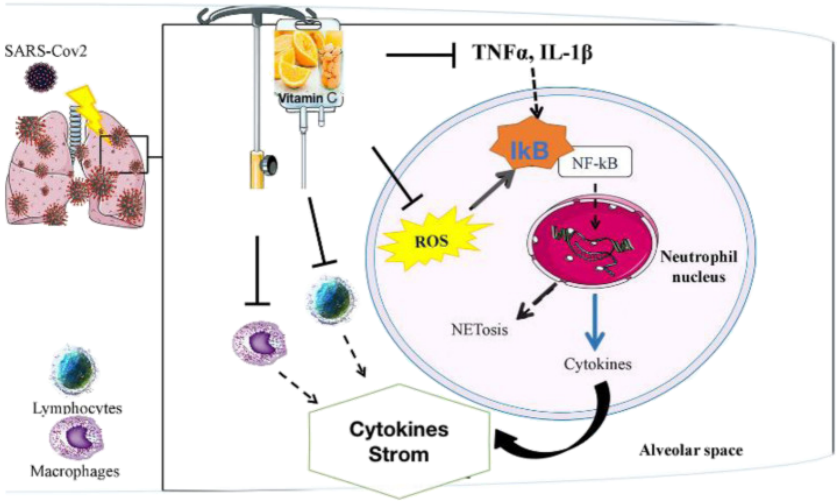
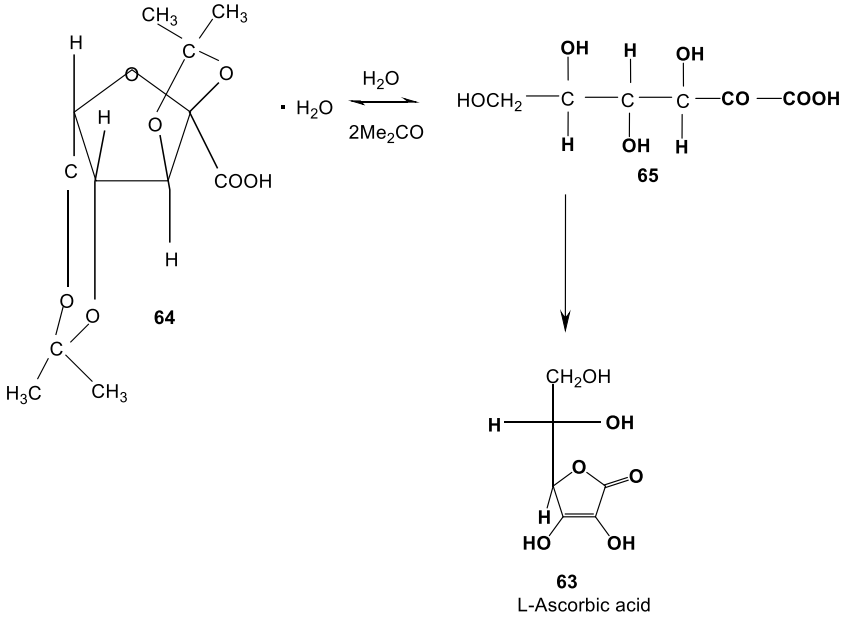


Figure 11. Administration of vitamin C to build-up specific functions of immune system.



Scheme 11. The commercial preparation of ascorbic acid using Reichstein and Grussner method.

4.1 Synthesis of Vitamin C 63

In 2001, Nadtochi and Melent'eva prepared the desired ascorbic acid **63** by using a slightly modified method than the one used by Reichstain and Grussner in 1934 [114]. The synthesis begins with the addition of 5.4 mL of HCl to a mixture of 50 g of diacetoneketogluconic acid hydrate **64** and 50 mL of toluene. The mixture is then allowed to cool and upon cooling a precipitate is formed which is then filtered and dried to generate 24.9 g of technical ascorbic acid **63**. An amount of 20 g of the resulting technical ascorbic acid **63** is then dissolved in water with a color index of 350 U and the resulting solution is then washed with 20 mL of a 1:2 toluene-acetone mixture. The aqueous layer is then separated and analyzed for color as well as ascorbic acid content which gave a color index of 276 U and ascorbic content of **63** with 19.1 g yield as indicated in Scheme 11.

5 Vitamin D

Humans obtain relatively between 10–20 % of vitamin D **66a** or **67a** from nutritional resources as well as between 80–90 % via the cutaneous synthetic route which is driven by natural sunlight [115]. In humans, vitamin D **66a** or **67a** exists in two active forms, namely, vitamin D_3 **66a** which is also referred to as cholecalciferol **66a**, the preparation of which takes place in the skin just after the skin has been exposed to sunlight or perhaps UV light, and vitamin D_2 **67a** which is obtained as a nutrient that has itself been irradiated. Fig. 12 shows the structures of vitamin D_3 **66a** and vitamin D_2 **67a** together with their accompanying precursors, namely, 7-dehydrocholesterol **66b** and ergosterol **67b**, respectively [116, 117].

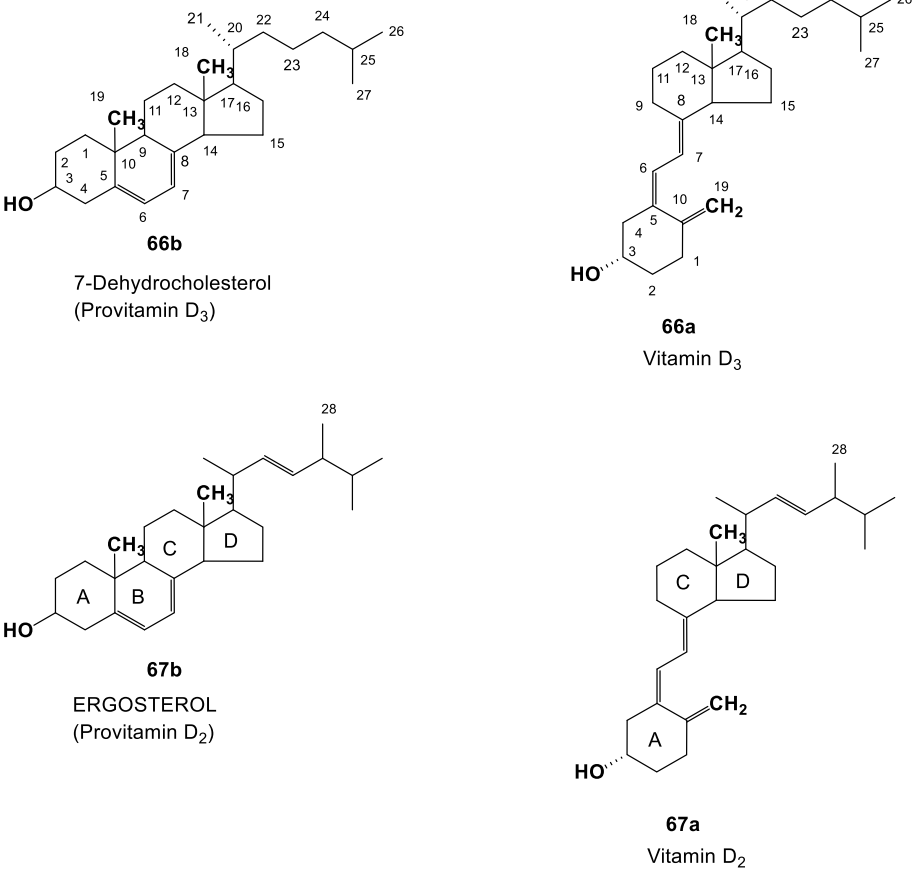


Figure 12. Structural similarities and differences between vitamin D_3 and vitamin D_3.

Vitamin D **66a** or **67a** plays a crucial role in the regulation of calcium-phosphate homeostasis as well as in the control of bone turnover, that is, skeletal health during growth and in adult age entirely depends on it and as such its lack thereof results in rickets [118]. In fact, vitamin D **66a** or **67a** is technically not a vitamin instead a prohormone formed as a result of irradiation of the skin by sunlight or UV rays in a reaction that converts 7-dehydrocholesterol **66b** into vitamin D_3 **66a**, which is closely related to that of classic steroid hormones such as estradiol, cortisol, and aldosterone given the fact that they all share the same ring structure (cylcopentaneperhydrophenathrene ring) with vitamin D_3 **66a** having a broken 9,10-carbon-carbon bond [119].

Vitamin D **66a** or **67a**, also referrered to as 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$], has unfolded from just being a nutrient into the role of being a hormone that takes complex roles in the endocrine system such as directing homeostasis, furnishing bone integrity, modulating growth of cells, and being responsible in the differentian of cells in a vast array of tissues [120]. Apart from the empirical evidence of vitamin D **66a** or **67a** in skeletal health, there is also overwhelming evidence of immune disorders that occur as a result of lack of vitamin D **66a** or **67a** [121]. Vitamin D_3 **66a** or **67a** acts as a hormone that is responsible for relaying messages to the intestines to enforce intestines to actively perform their function of increasing the absorption of calcium and phosphorus [122].

High prevalence of vitamin D deficiency is found in all race classifications and may account for a plethora of cancer types such as breast, colon, ovarian, and prostate cancer [123]. Vitamin D **66a** or **67a** which is a hormonal metabolite and in particular, 1α,25-dihydroxyvitamin D_3 **66a** or **67a** (1,25 D) is responsible for triggering biological responses by binding to the vitamin D receptor (VDR). As soon as the vitamin D receptor (VDR) is housed by vitamin D_3, it then interacts with another receptor called the retinoid X receptor (RXR) to yield a heterodimer that then binds to vitamin D responsive elements in the gene area controlled by vitamin D_3. The VDR-RXR is basically responsible for modulating the transcription of genes that encode proteins that allow the normal functions of vitamin D **66a** or **67a** which include signalling intestinal calcium and phosphate absorption to affect skeletal and calcium homeostasis [124].

Vitamin D deficiency has also been linked to increased risk of type 1 diabetes mellitus, cardiovascular disease, cancers of certain types, declining cognitive ability, depression, complications in pregnancy, autoimmune diseases, allergy, and frailty and as such vitamin D deficiency has been recognized as a pandemic of significant proportions [125]. The discovery of the presence of 1α,25-dihydroxy vitamin D_3 **66a** or **67a** in tissues such as pancreatic beta cells and immune cells suggests a correlation between the increased prevalence of type 2 diabetes and vitamin D deficiency, that is, it has been established that synthesis of insulin and its secretion in beta cells was impaired coming from vitamin D deficient animals and this could only be corrected or reversed if vitamin D levels were returned to normal [126].

Vitamin D deficiency is prevalent amongst the community-dwelling elderly in the developed countries positioned geographically in higher latitudes, amongst institutionalized elderly, geriatric patients, and also amongst patients suffering from high fractures [127]. Public health perspective suggests that healthcare workers need to target infants, children, adolescents, pregnant women, the elderly and the institutionalized people in order to manage vitamin D insufficiency and as such encourage these groups to take vitamin D supplements, eat oily fish, encourage sunlight exposure, and also develop a more robust approach to vitamin D supplementation [128].

The pivotal role played by vitamin D **66a** or **67a** in the prevention or treatment of acute respiratory infections has always been a subject of interest since the 1930s as exemplified by the study of cod liver oil as a means to drop industrial absenteeism which was due to the common cold. Given the striking resem-

blance of risk factors due to severe Covid-19 as well as those of vitamin D deficiency and added to these, factors such as obesity, older age, and Black or Asian ethnic origin have all brought hope for scientists to consider vitamin D supplementation as perhaps a promise that could be held as a preventive or therapeutic agent for Covid-19 [129].

The ability of vitamin D **66a** or **67a** to display a variety of characteristics such as immunomodulatory, anti-inflammatory, antifibrotic, and antioxidant has also drawn vitamin D **66a** or **67a** as a potential immunomodulator that could alleviate severity and hence improve outcomes of SARS-CoV-2 given the current lack of knowledge that exists in response to SARS-CoV-2 [130]. In fact, in the fight against SARS-CoV-2, vitamin D **66a** or **67a** has been shown as a factor in regard to cytokine storm and as such it indicates in advance that it will foreshadow and arrest the serious consequences of COVID-19 disease [131].

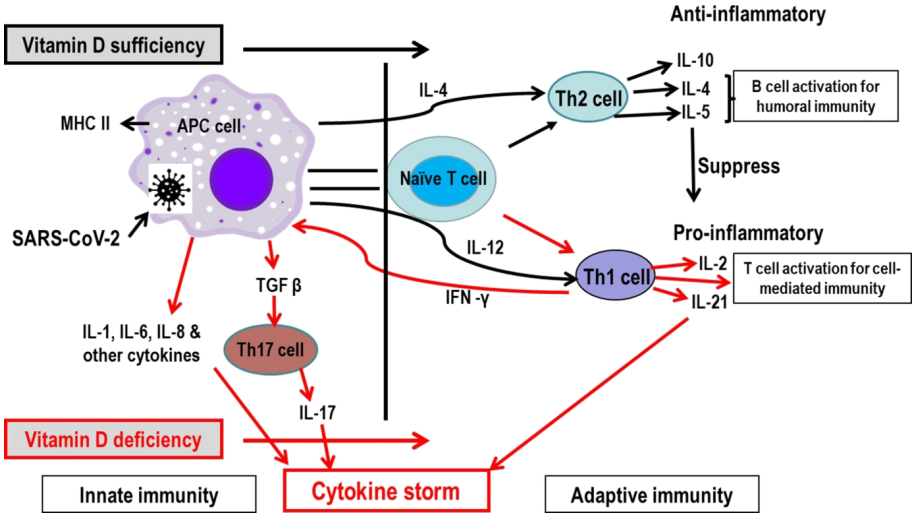


Figure 13. Possible pathway of vitamin D-modulated immunity in reducing cytokine storm in patients with SARS-CoV-2 infection.

SARS-CoV-2 infection brings about antigen-presenting cells (APCs) activation for phagocytosis of SARS-CoV-2, thus allowing the cell type to trigger naive T-(Th-0) cells. In the presence of adequate vitamin D, the naive T-cells are then driven towards T-helper 2 (Th2) cell as opposed to Th1 cells resulting in the promotion of anti-inflammatory cytokines that include production of IL-10, IL-5, and IL-4 which suppress the secretion of pro-inflammatory cytokines such as IL-6, IL-2, IF, and IFN-8. All this comes to effect as a result of downregulation of Th1 cells. The opposite is true if there is vitamin D insufficiency where the naive T cell will be driven towards upregulation of Th1 cell response which will eventually lead to hyper-inflammation/cytokine storm.

On the other hand, optimum levels of vitamin D are responsible for downregulating Th17-cell response and also hamper differentiation of naive T-cells into Th17-cell types which decreases the synthesis of IL-12 which subsequently reduces the production of pro-inflammatory cytokines that include IL-6, IL-17, and IL-23. A schematic representation of action of vitamin D against SARS-CoV-2 is given in Fig. 13 [132].

The stability of vitamin D_3 suffers a great deal in aqueous media and, thus, vitamin D_3 medicines and supplements have shorter shelf lives of one to two years. Various factors such as exposure to light, humidity, oxygen, temperature, and pH are responsible [133]. However, vitamin D shows some degree of stability when it comes to oxidation and acid, and the stability suffers under various factors such as light, pH, storage time, temperature, and humidity [134]. Encapsulation has been pointed out as desirable delivery approach not only to improve on stability but also preserve bioactivity,, and greatly enhance its absorption in beverage systems [135].

5.1 Synthesis of Vitamin D 66a

Cholesterol **68** (30 g, 7.76 mmol) which was dissolved in 20 mL of pyridine was then treated with acetic anhydride (5.0 mL, 52.9 mmol) and the resulting mixture was stirred at 45 °C for 15 h. The reaction was stopped by adding ice and the mixture was further stirred for 1 h, then extracted with chloroform, washed with 2N aqueous HCl, and reduced under pressure. The resulting product was recrystallized using ethanol to form the compound **69** in 98 % yield. The acetylated compound **69** (3.0 g, 7.00 mmol) was then disslolved in 80 mL of cyclohexane at 65 °C upon which NBS (1.868 g, 10.49 mmol) and then the resulting mixture was stirred under reflux conditions at 90 °C for 1 h. The reaction mixture was then allowed to cool to room temperature, 100 mL of water was added, and the solution stirred for 1 h. The mixture was then extracted using *n*-hexane, then washed with water and reduced under pressure.

To the resulting mixture, a 1.0 M solution of tetrabutylammonium fluoride in THF (10.5 mL) was added and stirred at room temperature overnight. The reaction product was extracted using *n*-hexane, then washed with water, reduced under pressure, and the main product was separated using silica gel column chromatography (ethyl acetate:*n*-hexane 1:10) to obtain the desired compound **70**. Compound **70** was dissolved in a mixture of dichloromethane (8 mL) and methanol (30 mL) and then 28 % NaOMe in MeOH was added until pH 10. The resulting solution was stirred for 2 h at room temperature. The reaction mixture was evaporated under reduced pressure and the main product was separated using silica gel chromatography (ethyl acetate:*n*-hexane 1:4) to obtain the corresponding compound **71** in 62 % yield.

Compound **71** (20 mg, 0.05 mmol) was then dissolved in 0.1 % 3-tetra-butyl-4-hydroxanisole (BHA) in cyclohexane (2 mL) and transferred to a petri dish. While stirring the mixture in a petri dish covered with a polyvinyldene chloride food wrap, the mixture was irradiated with UV at 280 nm (9.03 mW cm^{-2}) for 1 h. After the reaction was concentrated, the main product was separated using silica gel column chro-

matography (ethyl acetate:*n*-hexane 1:4) to obtain compound **72** in 25 % yield. Compound **72** (5.02 mg, 0.013 mmol) was dissolved in 0.1 % BHA in cyclohexane (2 mL) and the mixture was stirred under reflux conditions at 100 °C for 1 h. After the reaction mixture was concentrated, the main product was separated using silica gel column chromatography (ethyl acetate:*n*-hexane 1:4) to obtain the vitamin D_3 **66a** in poor yield of 41 % according to Scheme 12 [136].

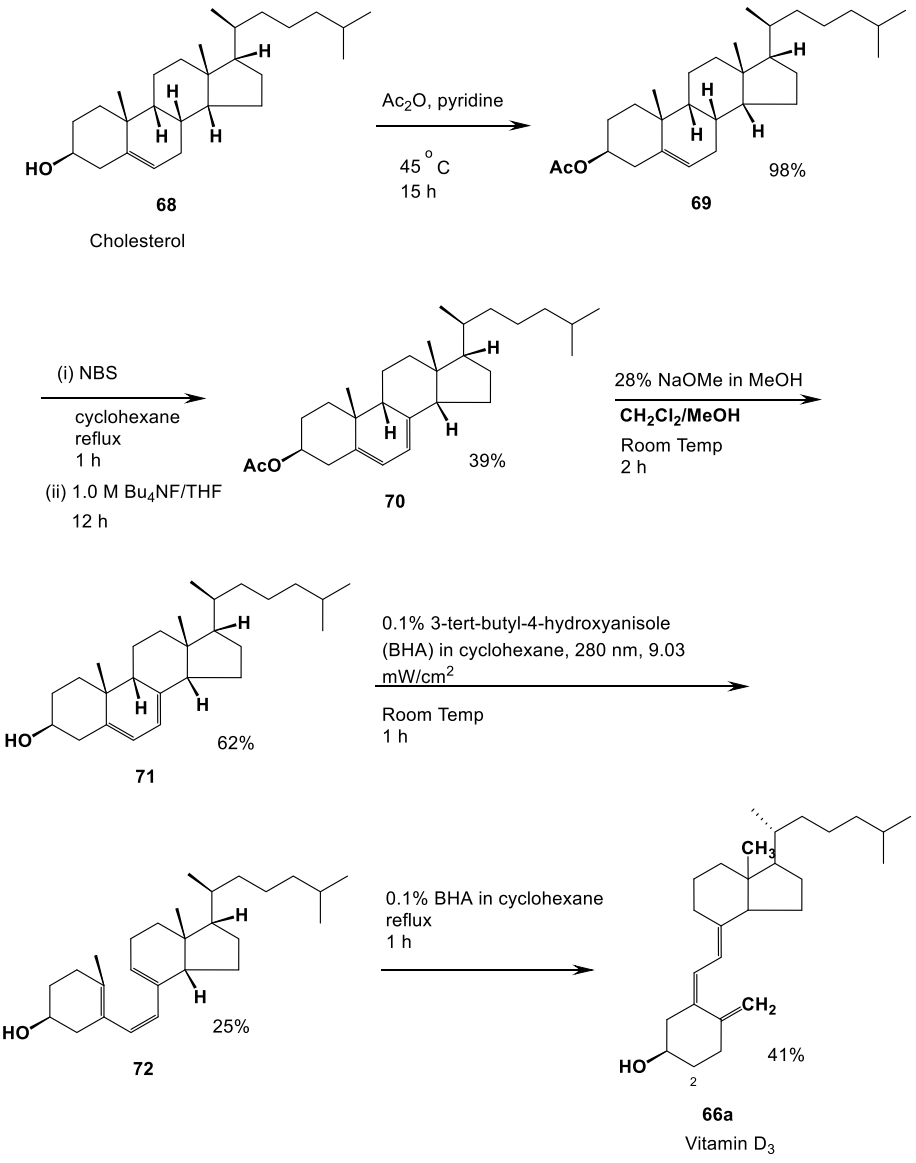
6 Vitamin E

Vitamin E **73a-h** was discovered in 1922 by Evans and Bishop as a micronutrient responsible for reproduction in rats [137]. It is important to note that out of the four tocopherols (**73a,c,e**, and **g**) as well as the four tocotrienols (**73b,d,f**, and **h**) which have been designated as α-, β-, γ-, and δ-tocopherols that are found in food sources, it is only the α-tocopherol **73a** that meets human vitamin E requirements [138]. It is thought that vitamins which act as antioxidants such as vitamin C **63** and vitamin E **73a-h** and also caretenoids are able to prevent atherosclerosis by being able to block oxidative modification of low-density lipoprotein (LDL) which may invariably be selectively utilized by monocytes in the arterial wall [139].

Vitamin E **73a-h** is a term that denotes a group of eight naturally occurring potent, essential, lipid-soluble, chain-breaking antioxidants. Structural elucidation demonstrates that molecules with vitamin E antioxidant activity consist of four tocopherols **73a,c,e**, and **g** (depicted as α-, β-, γ-, and δ-) and four tocotrienols **73b,d,f**, and **h** (denoted as α-, β-, γ-, and δ-) as illustrated in Fig. 14 [138, 140].

The different forms of vitamin E **73a-h** display antioxidant activities and as a major lipid-soluble antioxidant play a significant role in scavenging peroxy radicals and also terminating the oxidation of polyunsaturated fatty acids (PUFAs), that is, the peroxy radicals react mainly with α-tocopherol as opposed to lipid hydroperoxide and, thus, by so doing the chain reaction steps of peroxyl radical production is terminated, and any further oxidation of PUFAs in the membrane is prevented [141]. In fact, the association of vitamin E activity and its molecular function as an antioxidant was first shown by Olcott and co-workers in 1937 and in the experiments carried out it was established that an unsaponifiable fraction from lettuce oil inhibited the antioxidation of lard. Studies, thereafter, concluded that vitamin E **73a-h** was indeed able to prevent the oxidation conversion of membrane and lipoprotein polyunsaturated fat (LH) into lipid hydroperoxides (LOOH) [142].

It has been established that vitamin E **73a-h** stimulates the body's defence and thereby increases both humoral and cell immune responses and also phagocytic functions [143]. Added to the role of vitamin E **73a-h** as a potent antioxidant, vitamin E **73a-h** also displays a variety of pertinent functions that span from immune function, control of inflammation, regulation of gene expression, and cognitive performance and, therefore, vitamin E deficiency is characterized by anaemia, ataxia, and peripheral neuropathy and due to limited intake of food sources as well as high preva-



Scheme 12. The synthesis of vitamin D_3 from cholesterol.

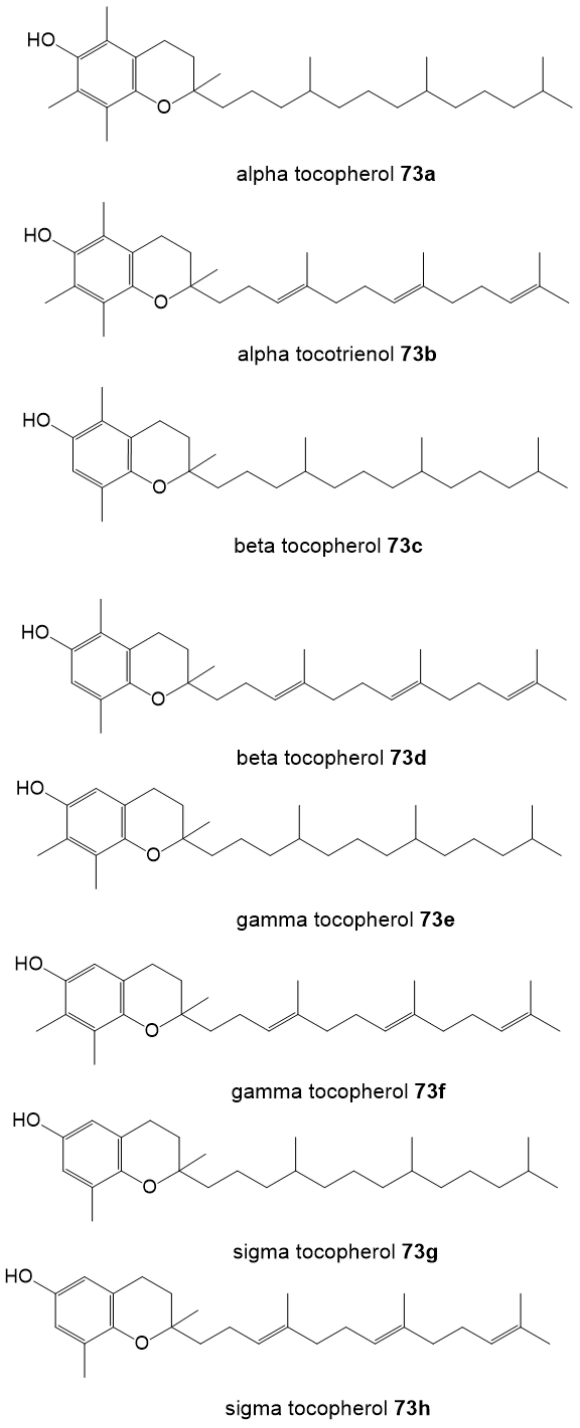


Figure 14. Naturally occurring forms of vitamin E.

lence of oxidative stressors as a result of HIV infection and diseases such as malaria, populations in third world countries are at greater risk of vitamin E deficiency [144].

Vitamin E supplementation helps elevate the activity of helper T lymphocytes and also improves vaccine response. Several studies concur that vitamin E supplementation greatly reduces the risk of respiratory tract infections whilst it also curtails the duration of respiratory tract infections among adults [145]. Vitamin E is responsible for reducing NF-kB binding activity into the DNA and by so doing without exception downregulating the production of a pro-inflammatory cytokine that include IL-6, IL-8, IL-12, and COX-2 which are all responsible for severe forms of COVID-19. A schematic representation is shown in Fig. 15 [146]. Use of vitamin E in combination with co-antioxidants such as vitamin C have been employed to enhance antioxidant effects whilst at same time increasing the stability of vitamin E [147].

6.1 Synthesis of Vitamin E

In 2007, Bonrath and co-workers were able to easily prepare the desired α-tocopherol **73a** by transferring trimethylhydroquinone **74** or its monoacetylated derivative **75** into the corresponding desired tocopherol **73a** or its accompanying derivative tocopheryl acetate **79** by using rare earth metals such as $Gd(OTf)_3$ as illustrated in Scheme 13. The reaction was carried out using several solvent systems such as biphasic systems, especially solvent systems based on ethylene, propylene carbonate and hexane, heptanes or octane. Temperatures were set between 80–160 °C. The reaction could be carried out at a substrate-catalyst-ration (s/c) of 1000 and the products **73a,79** were isolated in 95 % yield after using bulb-to-bulb distillation as indicated in Scheme 13 [148].

7 Conclusions

The commercial availability of vitamins seen in the production of thousands of tons explains the importance of vitamins in biological systems. However, the synthesis of vitamins and their derivatives suffer from a lot of drawbacks such as formation of by-products in high yields.

In this review, a variety of reactions have been carried in the synthesis of various vitamins, for example: in the synthesis of vitamin A, a Reformatksy reaction is carried out on β-ionone to increase the length of the unsaturated chain. This is then followed by the interconversion of the ester moiety to the corresponding carboxylic acid by a known process of saponification and then lastly by carrying out an alkylation to yield the corresponding key intermediate ketone of 18-C atoms. The processes are then repeated to yield the 21-C ketone.

The synthesis of vitamin B_2 involves synthesis of isoalloxazines which are then transformed to riboflavin. A direct synthesis of riboflavin was carried out by Ladenburg and co-workers in which D-ribityl was condensed with barbituric acid and this method proved to be far superior to the older and more complex methods.

The synthesis of vitamin D involved acetylation of cholesterol, followed by hydrogenation of the B-ring, deacetylation, ring-opening of the B-ring, and lastly formation of vitamin D through treatment with *tert*-butyl-4-hydroxyanisole.

And lastly, the synthesis of vitamin E involves condensation of dimethylhydroquinone with isophytol to give rise to α-tocopherol and its derivative. In the current fight against Covid-19, novel methods of synthesizing vitamins and their derivatives are urgently needed in the on-going fight against this pandemic.

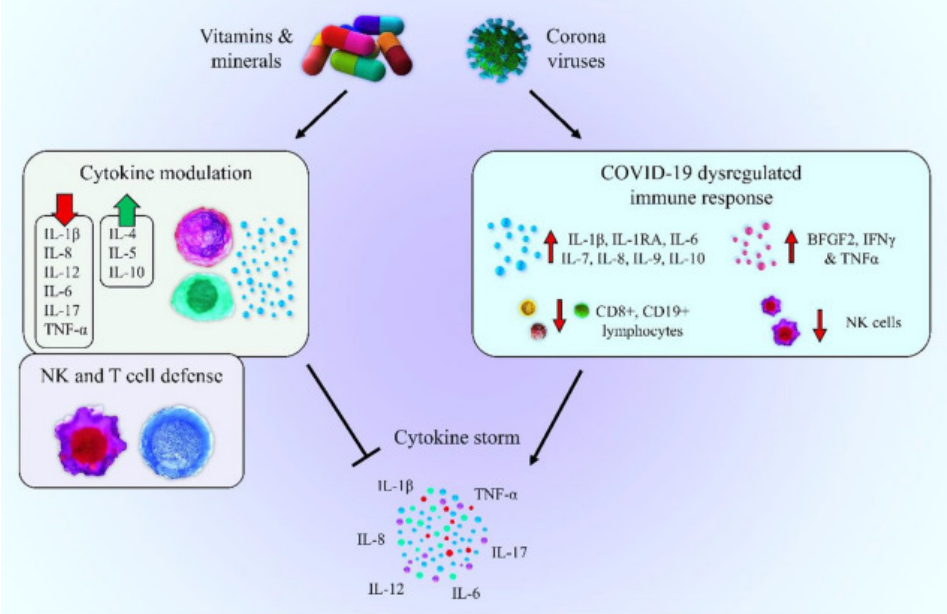


Figure 15. A potential role of vitamins and minerals in the prevention of cytokine storm during COVID-19 infection.

Conflicts of Interest

The authors declare no conflict of interest.

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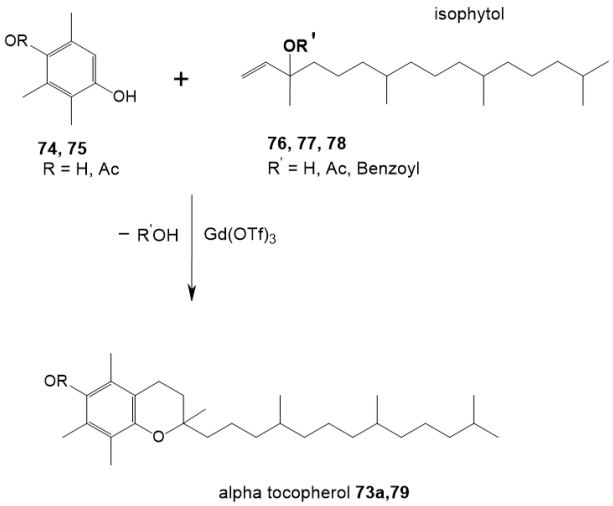

Scheme 13. Preparation of alpha tocopherol.

Abbreviations

ACDH	acyl-CoA dehydrogenase
ACE2	angiotensin-converting enzyme 2
ALRT	acute lower respiratory infection
AOX	aldehyde oxidase
BHA	tetrabutyl-4-hydroxanisole
COX	cytochrome oxidate
COX-2	cyclooxygenase-2
CoVXCZ21	coronavirusXCZ21
Covid-19	coronavirus
DHA	dehydroascorbic acid
DNA	deoxyribonucleic acid
FAD	flavin adenine dinucleotide
FMN	flavin mononucleotide

GHS	glutathione
GSSG	glutathione disulfide
HIV	human immunodeficiency virus
ICTV	International Committee on Taxonomy of Viruses
LOOH	hydroperoxide
MERS	Middle East respiratory syndrome
1-MNA	1-methylnicotinamide
NA	nicotinamide
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NETosis	neutrophil extracellular trap
2019-nCoV	2019 novel coronavirus
NSG	nidovirales study group
NT	nucleoside transporter
OS	oxidative stress
OXPHOS	oxidative phosphorylation
PRT	Mirasol pathogen reduction technology system for platelets and plasma
PUFA	polyunsaturated fatty acid
RNA	ribonucleic acid
ROS	reactive oxygen species
RTD	riboflavin transporter deficiency
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SARS-CoV	severe acute respiratory syndrome-coronavirus
SCAD	short-chain acyl-CoA dehydrogenase
TMSCl	trimethylsilyl chloride
TMSOIf	trimethylsilylfluoromethanesulfonate
WHO	World Health Organisation
VAD	vitamin A deficiency
VDR	vitamin D receptor
VDR-RXR	vitamin D receptor-retinoid X receptor

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