Trop J Nat Prod Res, September 2021; 5(9):1521-1527 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

Tropical Fruits and Vegetables as Immune Boosters against Coronavirus Disease (COVID-19): Call for Cautious Optimism

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ARTICLE INFO

Article history:
Received 23 April 2021
Revised 27 July 2021
Accepted 11 September 2021
Published online 02 October 2021

ABSTRACT

The novel coronavirus disease (COVID-19) continues as the major health challenge of today, primarily due to a delay in global access to definitive therapeutic interventions.
Therefore, prevention still remains the major containment option globally, even as the race against time to develop lasting therapeutics continues. One of such preventive approaches being advocated is the maintenance of healthy diets to boost the immune system. Specifically, in sub-Saharan Africa, this option is receiving huge attention owing to her richness in tropical foods such as fruits and vegetables with immune-boosting properties. However, while fruits and vegetables score high as immune boosters, it is important to properly lay out the facts in order to be well informed. Therefore, this short-review outline some findings supporting tropical fruits and vegetables as rich sources of bioactive phytochemicals including phenolic compounds with immune-boosting properties alongside the effect of processing/culinary practices on such properties which could significantly influence their overall medicinal properties.
This review chronicles some tropical fruits and vegetables as well as their therapeutic properties. Also, the influence of culinary practices/processing methods on their bioactive components and therapeutic properties were presented. Fruits and vegetables remain a rich source of antioxidant and anti-inflammatory phytochemicals that have been widely acclaimed to help in the management of some degenerative diseases and boost the immune system. However, it is important to be well informed on how various processing and culinary practices could influence the medicinal properties of these foods in order to be able to explore them for their maximum benefits.

***Keywords*:** Coronavirus, Functional foods, Immunity, Food processing, Covid-19, Polyphenols.

Introduction

The pandemic caused by the novel coronavirus disease (COVID - 19) continues to be the major health challenge of today. As at July,2021, the virus has been officially reported to infect over one hundred and ninety four million people globally according to the data of World Health Organization (WHO) which indicated more than four million deaths.[1] Like many other pandemics of the past, a delay in global access to immediate definitive drugs or vaccines make prevention the first-line containment option globally; according to WHO, just a little over three million, six hundred and ninety six thousand vaccine doses have been administered so far.[1] Synonymous with several infections, the immune system is the first and the main line of defense for the human body against the severe acute respiratory syndrome coronavirus (SARS-COV-2) infection responsible for the COVID-19 disease. The numerous tolls the virus takes on the patient's immune system have clearly shown that a robust immune system for proper immune tolerance and/or response to the virus is crucial for survival of the host.
Studies have shown that COVID-19 patients exhibit mild-to-severe immune responses, including lymphocytopenia, leukopenia, depleted CD-4 count and increased levels of plasma pro-inflammatory cytokines that are reasoned to promote disease severity.[2] This is supported by the fact that emerging data has shown that the disease fatality is dependent on some immune-related factors, especially age and co-morbidities.[2] In many hard-hit countries, the aged (> 60 years) share the largest proportion of the death rate. This can be associated with the fact that immune systems are generally weakened as ageing progresses. Furthermore, disease conditions such as cancer, kidney diseases, diabetes, hypertension and others, which inadvertently result in immunosuppression has been classified as co-morbidies of COVID-19 disease.[3] Consequently, both aforementioned groups have taken the largest part of the fatality resulting from the disease and classified as the ´high-risk´ groups globally. In view of this, immune-boosting therapies are being advocated as a major line of defense against this ravaging viral infection.

The Pathogenesis of Coronavirus Disease (COVID-19)
The SARS-CoV-2 is a positive-stranded RNA virus of the Betacoronavirus genus, which is embedded with spike glycoproteins.[4] The virus has been shown to invade the epithelial cells of the alveolar through mainly Angiotensin-converting enzyme 2 (ACE2).[5] Cell binding and entry of the virus are thus mediated by the spike proteins (Figure 1). Infection occurs when the virus binds to a host cell through its target receptor; the S1 sub-unit of the spike protein contains the receptor binding domain that binds to the peptidase domain of ACE2.[6] Active replication and release of the virus in the lung cells could lead to non-specific symptoms such as fever, myalgia, headache, and respiratory symptoms.[7] The distribution of ACE2 receptors in most tissues may explain the sites of infection and symptoms in patients. For example, the ACE2 receptor is found on the epithelium of other organs such as the intestine and endothelial cells in the kidney and

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Citation: Oboh G, Ogunsuyi OB,[2] Oyeleye SI, Adefegha SA. Tropical Fruits and Vegetables as Immune Boosters against Coronavirus (COVID-19) Disease: Call for Cautious Optimism. Trop J Nat Prod Res. 2021; 5(9):1521-1527. doi.org/10.26538/tjnpr/v5i9.1

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ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

blood vessels, and may explain gastrointestinal symptoms and cardiovascular complications.[8] In addition, lymphocytic endotheliitis has been observed in postmortem examinations of the lung, heart, kidney, and liver as well as liver cell necrosis and myocardial infarction in patients who have died of COVID-19.[6] These findings indicate that the virus directly affects many organs, as also seen in SARS-CoV-1 and influenza infections.[9]

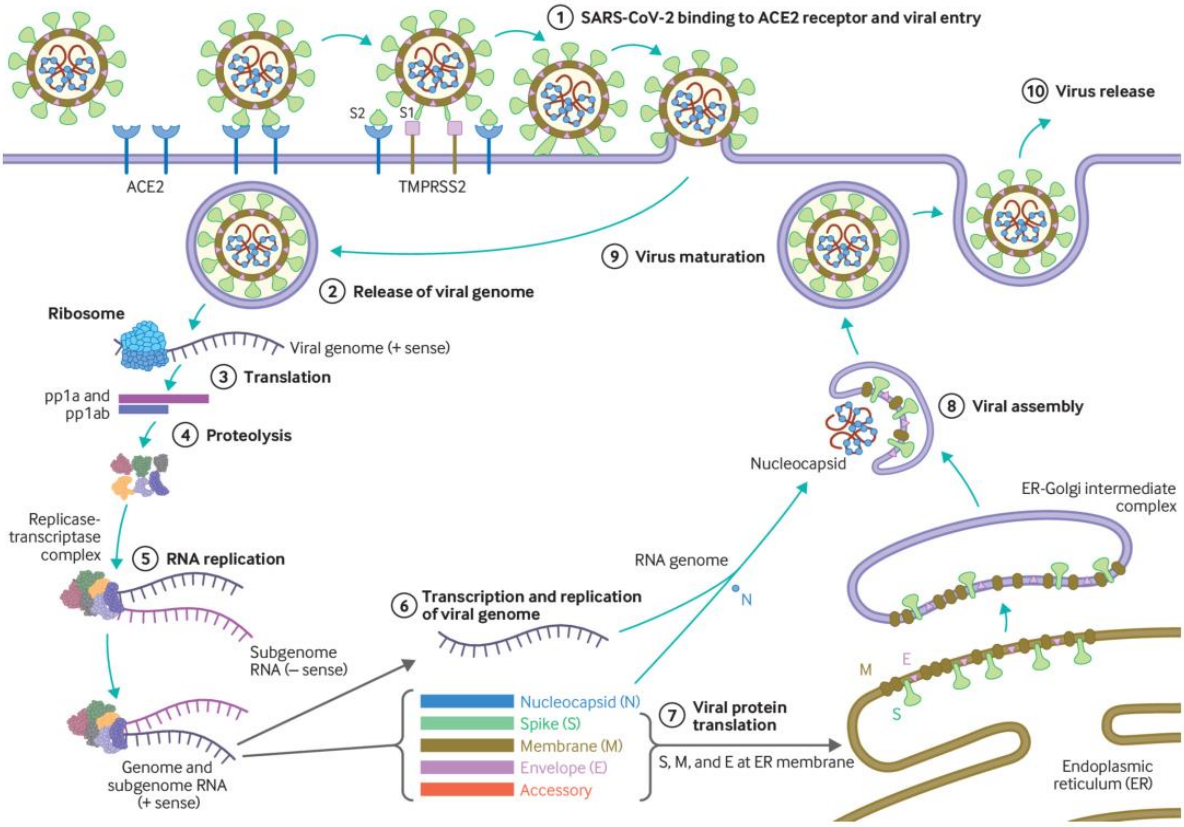

Figure 1: ACE2 serves as the target cell receptor in the host for the virus which works together with the host's cell surface protein (transmembrane serine protease 2), mainly expressed in the airway epithelial cells and vascular endothelial cells. Consequent upon binging of the virus, membrane fusion follows and the viral genome is released into the host cytoplasm (2). This is followed by viral replication, viral assembly, maturation and virus release as illustrated in stages 3-7) (Figure and Illustrations sourced from Cevik *et al*., [7]).

Human Immune System and COVID-19

The immediate response of the host to viral infections and its clearance heavily relies on type I interferon (T1IFN) expression.[10] Expressions of this T1IFN and down-stream signals help modulate cell responses and reprogram the cells of the body into an "antiviral state", subsequently promoting infection control and pathogen clearance.[11] However, in a proportion of infected individuals, SARS-CoV, MERS-CoV and likely SARS-CoV2 evade immune system recognition through suppression of these mechanisms, a phenomenon associated with more severe disease and poorer prognosis.[12.13.14] Subsequently, novel coronaviruses have the ability to counteract T1IFN signaling through the inhibition of signal transducer and activator of transcription (STAT) family transcription factor phosphorylation.[15] As a result, suppression of innate immune mechanisms in infected epithelial cells and, to some extent, infected monocytes/macrophages allow these novel coronaviruses to proliferate without triggering the innate antiviral response machinery of these cells.

However, it is being suggested that a robust immune system will offer efficient immune tolerance against the disease and in the case of infection, a good immune response to fight-off the infection.[2,3] It has been discovered that several vitamins and trace elements are essential for the normal functioning of the immune system.[16] Vitamin A and D supplementation has been recognized to increase immunity of pediatric patients following influenza vaccination.[17] A high dose Zinc supplementation has shown immune enhancement of patients with torquetenovirus (TTV).[18] Likewise, selenium supplementation has shown a positive response after an influenza vaccination challenge.[19]

Furthermore, several functional foods, nutraceuticals and probiotics have also shown a supportive role in enhancing immune responses.[20,21] In this regard, functional foods, especially fruits and vegetables have been flagged as the excellent immune-boosters.[3] Fruits and vegetables are rich dietary sources of various immune-boosting natural chemicals such as vitamins, and minerals as well as non-nutrient phytochemicals, including carotenoids, polyphenol and flavonoids (including anthocyanins, flavanols, flavones and flavanones).[22-25] These phytochemicals can have profound effects on cellular growth and differentiation, and are needed for the optimal functioning of the immune system. The most well-known antioxidants are polyphenols, vitamins A, C and E, beta carotene, and selenium. Citrus fruits and their juices, berries, dark green vegetables (spinach, asparagus, green peppers, brussel sprouts, broccoli, watercress, other greens), red and yellow peppers, tomatoes, pineapple, cantaloupe, mangos, papaya and guava are good source of vitamin C, while vegetable oils such as olive, soybean, corn, cottonseed and sunflower, nuts and nut butters, seeds, whole grains, wheat, wheat germ, brown rice, oatmeal, soybeans, sweet potatoes, legumes (beans, lentils, split peas) and dark leafy green vegetables are good sources of vitamin E. Selenium can be obtained by eating Brazil nuts, brewer's yeast, oatmeal, brown rice,

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

chicken, eggs, dairy products, garlic, molasses, onions, salmon, seafood, tuna, wheat germ, whole grains and most vegetables. Variety of dark orange, red, yellow and green vegetables and fruits such as broccoli, kale, spinach, sweet potatoes, apple, carrots, red and yellow peppers, apricots, cantaloupe and mangos are good sources of ß-carotene (for more detailed review on plant antioxidant sources see [24, 26, 27, 28]. However, while fruits and vegetables score high as excellent immune boosters it is important to properly lay out the facts in order for the general public to be better informed.

Optimism for fruits and vegetables as immune boosters

The medicinal benefits of several fruits and vegetables have been attributed to their constituent antioxidant phytochemicals. The antioxidants are critical at fighting-off the deleterious damages of free radicals and the consequential oxidative stress which are linked to numerous diseases. While free radicals can be as a result of some natural processes such as ageing and respiration, more comes from exposure to environmental toxicants like cigarette smoke and some harmful pesticides. However, free radicals at amount below the ´harmful threshold´ have their physiological roles such as in cell-to-cell communication and immune cell functions. To maintain these free radicals below this threshold, the human body is equipped with antioxidant defense systems that deactivate these highly reactive radicals. These antioxidants can also be obtained from foods such as fruits and vegetables. However, when these free radicals overwhelm the body's antioxidant defense system, it pushes above the harmful threshold to initiate damages that lead to several diseases.[29,30] This is why consumption of foods such as fruits and vegetables rich in natural antioxidants are often advocated to complement the body's antioxidant defense system. Furthermore, antioxidants are very crucial for proper immune functions.[27, 31,32] As earlier stated, free radicals are by-products of some immune reactions and as such, elevated immune response due to a viral infection will be expected to elicit tremendous elevation in free radical production which can eventually circumvent immune functions and damage other vital physiological processes.[31] Therefore, boosting the immune system may provide the opportunity of sparing the infectious agents and staying healthy. The mechanisms by which these natural foods and herbs can boost the immune systems includes enhancement of anti-inflammatory functions, reduction of pro-inflammatory mediators, regulation of cell-mediated immunity, modulation of antigen-presenting cellular function as well as alleviation of innate and adaptive immune response communication. Thus, helping the entire populace to ´indirectly vaccinate´ themselves naturally against infectious diseases such as the coronavirus. Consumption of adequate antioxidant-rich foods such as fruit and vegetable is one of the cornerstones of a healthy diet, and may enhance immunity against infectious diseases as well as provide protection against several chronic diseases including cardiovascular disease, diabetes, obesity, neurodegenerative diseases and several cancers.

Previous studies have reported the antioxidant properties of numerous tropical fruits and vegetables; particularly green leafy vegetables, vegetable fruits, spices and fruits.[24, 33] Tropical green leafy vegetables including Water bitter leaf (*Struchium sparganophora),* Amaranthus *(Amaranthus cruentus),* Pumpkin leaf *(Telfairia occidentalis),* Jute leaf *(Corchorus olitorius),* Sweet basil *(Ocimum gratissimum),* Water leaf *(Talinum triangulare),* Jerusalem leaf *(Cnidoscolous aconitifolius)* and Bitter leaf *(Vernonia amygdalina*) are rich in phytochemicals that could exert interesting antioxidant activities.[24] The polar extracts of the vegetables have higher antioxidant properties than non-polar extracts. Sweet basil leaf had the highest antioxidant properties, while 'water leaf' had the lowest antioxidant properties.[24] The polar constituents of these vegetables, containing ascorbic acid, phenols and flavonoids, appear to have the highest antioxidant properties, as typified by the increased free radical scavenging, reducing power and Fe (II) chelating abilities.

Furthermore, in a study that ranked some commonly-consumed fruits based on their antioxidant properties, all the fruits exhibited high antioxidant properties; however, African star apple, guava, and cashew had the highest radical scavenging abilities.[24] Quercetin is present in all the fruits while gallic acid, catechin, epicatechin, rutin, and chlorogenic acid are other phenolic constituents in most of the fruits.[24] Ginger and turmeric rhizomes popularly used as spices have also been reported to exhibit anti-inflammatory properties.[34] Studies have shown that COVID-19 patients exhibit increased levels of plasma pro-inflammatory cytokines (such as IL1-β, IL7-10 and TNFα among others) that are reasoned to promote the disease severity. [2] Therefore, approaches that improve immune responses/tolerance by boosting immune cells and show tolerable anti-inflammatory responses are also being explored for combating this disease. The bioactivity attributed to individual antioxidant nutrients alone does not explain the observed health benefits of diets rich in fruits and vegetables in diseased states. Reports from several clinical trials conducted within the last four decades have shown that these compounds, when taken in isolation, do not appear to have consistent preventive effects. This suggests that the additive and synergistic effects of phytochemicals in food are responsible for the potent antioxidant and anti-cancer activities, and that the benefit of a diet rich in fruits and vegetables accrues from the complex mixture of phytochemicals present in whole foods.[35]

Fruits and vegetable in the potential management of COVID-19 co-morbidities

According to the report of Jayawardena,[3] diseases such as cancer, diabetes, hypertension and other degenerative diseases compromise the immune system, thus accelerating the fatality of the COVID-19 disease. This could also be supported by the findings of Yang[36] and Fang,[37] that the common comorbidities of 32 non-survivors from a group of 52 patients with COVID-19 were cerebrovascular diseases (22%) and diabetes (22%). From the study of Guan *et al*.,[38] among 1,099 patients with confirmed cases of COVID-19, 173 had severe disease with comorbidities of hypertension (23.7%), diabetes mellitus (16·2 %), coronary heart diseases (5.8%), and cerebrovascular disease (2.3%). Therefore, attempting to attend to the underlying factor or symptoms of these diseases could be of great help in boosting the immune system and COVID -19 management. Interestingly, several studies have shown that consumption of fruits and vegetables are not only beneficial in controlling the symptoms of these diseases, but also in their treatment/management.

The leaves of Jute (*Corchorus spp*.), *Amaranthus cruentus*, *Struchium sparganophora*, *Clerodendrum voluble*, Fireweed (*Crassocephalum crepidioides*), *Lasianthera Africana*, pumpkin (*Telfairia occidentalis*), *Moringa oleifera*, Avocado Pear *(Persea Americana)* Leaf and African Padauk (*Pterocarpus soyauxii*) possess the ability to control blood glucose via their abilities to inhibits α-amylase and α-glucosidase activities.[39-42] The leaves of sweet basil (*Ocimum basilicum* L.), guava (*Psidium guajava* L.) leaf, *Vernonia amygdalina*, *Telfairia occidentalis*, *Lasianthera africana*, *Talinum triangulare*, Bitter gourd (*Momordica charantia* L) *and Amaranthus hybridus* have also been shown to be effective in the management of hypertension.[41,43]

Fruits including plantain fruit (*Musa paradisiaca*), tomatoes (*Trichosanthes cucumerina* and *Lycopersicon esculentum*), peels and juices from grapefruit (*Citrus paradisi*), lemon (*Citrus limon*), Shaddock (*Citrus maxima*), orange (*Citrus sinensis*) and lime (*Citrus aurantifolia*) fruits, African pear (*Dacryodes edulis*) fruit, *Persea americana* fruit and varieties of pepper fruits (*Capsicum annuum* var. *grossum*, *C. annuum* var. abbreviatum, and *C. annuum* var. accuminatum) have been reported to ameliorate the incidence of diabetes and hypertension. [40, 44-47] Furthermore, the extracts from some citrus [grapefruit (*Citrus paradisi*), orange (*Citrus sinensis*) and shaddock (*Citrus maxima*)] peel were reported to repressed some cancer related enzymes.[48, 49] These potentials could be accrued to their bioactive components such as polyphenols, terpene, terpenoid, alkaloid, among others, which also double as antioxidant compounds. Therefore, not only can these constituents serve as an excellent source to boost the immune system, but can also have potential in the management of COVID-19 co-morbidities.

The need for cautious optimism

Tropical fruits and vegetables have attracted lots of attention for their health promoting benefits. Similarly, they have also attracted attention on how various processing methods influence such medicinal

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

properties. It is important to note that the availability of the medicinal properties inherent in these functional foods is dependent on a number of factors including post-harvest processing, storage and culinary practices (see Table 1 for some common tropical fruits and vegetables and their associated culinary/processing methods). Therefore, without prejudice to the immunomodulatory benefits of fruits and vegetables earlier discussed, there is however, a need for careful evaluation. Several studies have called for caution in direct application of the antioxidant properties of some food samples without taking into consideration other processing factors.[33, 50-52] This is more so because most antioxidant-rich plant foods are often investigated in a state quite different from how it is traditionally consumed. This means that often, the cultural culinary practices are not taken into considerations and post-harvest conditions not fully stated.

Regarding the effects of post-harvest processing, it was observed for example, that while both ripe and unripe peppers (*Capsicum annuum* L.) extracts had high antioxidant properties, ripening processes enhanced the antioxidant properties of pepper.[24] Considering culinary practices, Chuah,[52] investigated three cooking methods(microwave heating, stir-frying and boiling in water) on five varieties of pepper (*Capsicum annuum* L.) and observed a marked decrease in the total phenol and vitamin C contents, as well as radical scavenging ability in water boiled samples compared to the raw form. They went further to recommend stir-frying and microwave heating as better cooking methods while suggesting reduced time and water volume for cooking in water. In another study, Oboh & Rocha, [53] reported that removing the seed from pepper, amounted to about fifty percent loss in the total phenol content, and consequently, led to the reduction in antioxidant activity. This study was informed based on some cultural culinary practices such as in Nigeria for example; where some individuals make use of whole pepper in food preparations, while some discard the seed and utilize the flesh alone in order to reduce the "hotness" of the pepper. Nevertheless, others prefer mainly the seed because it is the "hot" part of the pepper fruit. In yet another study, it was observed that the combination of three pepper varieties (*C. annuum var. grossum, C. annuum var. abbreviatum, and C. annuum var. accuminatum)* in equal proportions exhibited additive antioxidant properties.[26]

Still in regards to culinary practices, green leafy vegetables are not always consumed in their fresh form unlike fruits; they are usually processed before consumption. It is common to either blanch vegetables or steam-cook them. Several studies on tropical vegetables[24] revealed that blanching may enhance the phenol content. However, decrease in their vitamin C contents, reducing property and free radical scavenging ability of most of the vegetables studied were observed. This indicates that blanching leads to loss of antioxidant properties of the vegetables. Therefore, a balance must be reached between palatability, nutrition, health and body cell protection. In a similar study on sun-drying of green leafy vegetables, which is a popular local practice in sub-Saharan Africa, as a way of preserving green leafy vegetables for future use, it was observed that sun-drying alter bioactive phytochemicals and antioxidant properties of such vegetables.[54, 55] It is interesting to note that most processing methods of green leafy vegetables, including blanching, steam cooking and sun drying decreased vitamin C content of the vegetables. However, if the processing methods are carried out within a short period, they may enhance phenolic contents, increase metal reducing properties, radical scavenging ability and overall antioxidant activity of the vegetables.

Table 1: Some tropical fruits and vegetables discussed in this review and their predominate culinary practice

Common culinary practice	Fruits	Vegetables
Raw	Banana, carrot, breadfruit, avocado, pineapple, pawpaw, guava, citrus, cashew	Onion, garlic, ginger, cucumber, cabbage
Boiling/steaming in water	Avocado, carrot, tomatoes, pepper, plantain	Water bitter leaf, amaranthus, pumpkin leaf, jute leaf, sweet basil, water leaf, Jerusalem leaf, bitter leaf, onion, garlic, ginger, turmeric
Frying	Carrot, tomatoes, pepper, plantain	Onion, garlic, ginger, turmeric

Figure 2: Fruits investigated for their medicinal properties [55]

Fruits have been identified as a nutritious naturally occurring food and in recognition of this, national and international health and nutrition agencies recommended the consumption of fruit. Studies have shown that fruits are rich sources of antioxidants such as flavonoids, carotenoids, hydroxycinnamic acids, and so on. Studies[56, 57] had ranked thirteen commonly consumed tropical fruits {Banana (*Musa paradisaca*), Carrot (*Daucus carota*), Avocado pear (*Persia americana*), Pineapple (*Ananas comosus*), Pawpaw (*Carica papaya*), Guava (*Psidium Guajava*), Tomatoes (*Lycopersicon esculentum*), African star apple (*Chrysophyllum albidum*), Watermelon (*Citrullis lanatus*), Orange (*Citrus sinensis*), Cashew (*Anacardium occidentale*), Soursop (*Annona muricata*), Breadfruit (*Artocarpus altilis*)} based on their antioxidant properties (Figure 2). The findings indicated that all the fruits exhibited high antioxidant properties as exemplified by their radical scavenging abilities; however, African star apple, guava and cashew have the highest radical scavenging abilities. It was also reported that quercetin is present in all the fruits while gallic acid, catechin, epicatechin, rutin, and chlorogenic acid can be found in other phenolic constituents in most of the fruits.

Conclusion

Fruits and vegetables remain a rich source of antioxidant and anti-inflammatory phytochemicals that have been widely acclaimed to help in the management of some degenerative diseases and boost the immune system. Furthermore, they remain one of the cheapest natural sources of antioxidants for the general public especially in sub-Saharan Africa. However, it is important to be well informed on how various processing and culinary practices could influence the medicinal properties of these foods in order to be able to explore them for their maximum benefits. In addition, while boosting human immune system through ´right´ consumption of fruits and vegetables could help improve the immune tolerance and response to the novel coronavirus disease, no current scientific evidence suggests them as absolute preventive or curative therapy and as such, all other preventive and curative guidelines as prescribed by the relevant health authorities should be adhered to.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors acknowledge the management of The Federal University of Technology, Akure for commissioning this timely review study.

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ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

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