Review

Natural Products with Therapeutic Action in Diabetes: A Coadjuvant Alternative Against COVID-19?

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Natural Products with Therapeutic Action in Diabetes: A Coadjuvant Alternative Against COVID-19?

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Abstract: From the time that, in March, 2020, the World Health Organization (WHO) declared the acute respiratory syndrome caused by Coronavirus-2 (SARS-CoV-2), better known as COVID-19, a pandemic, an effective treatment has been sought, without achieving this at 100%. SARS-CoV-2 mainly affects the respiratory airways, but it is also known to damage various organs and systems, giving rise to a slight symptomatology up to, even, death in some cases. Unfortunately, high comorbility has also been found, which is associated with chronic-degenerative diseases that raises the risk of mortality in patients. In this review, a description is made of some common factors in patients affected by COVID-19 with a diagnosis of prior diabetes. In this regard, the therapeutic effects are described of some plant species and their secondary metabolites that, in some previous studies, have demonstrated, to exert certain effects in patients diagnosed with diabetes, emphasizing that, while different vaccines are now available to meet the challenge of the pandemic, the information collected in this work could be useful in the search for alternative clinical therapies based on Traditional Medicine and on the chemistry of some plant-derived secondary metabolites in patients affected by COVID-19 and diabetes.

Keywords: COVID-19; diabetes; natural products; therapeutic effect

1. Introduction

On March 11, 2020, the World Health Organization (WHO) announced that a disease similar to Severe Acute Respiratory Syndrome (SARS) had become a problem of world health. Tedros Adhanom Ghebreyesus, head of this organism, added: "We can expect that the number of cases or deaths and countries affected will increase in the following days and weeks" [1]. Since that date, the number of contagions increased exponentially in Asia, Europe, and later in America, and then efforts began to treat the disease, to contain it, and to diminish the number of deaths. However, there is no satisfactory treatment to date, although in emerging fashion, some vaccines have been approved to confront the pandemic.

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2. COVID-19: Signs and Symptoms

The causal agent of COVID-19, a new variant of the SARS-CoV-2 CoronaViruses (CoV), was detected for the first time in December 2019 in the city of Wuhan, People's Republic of China (PRC) 2–6]. Taxonomically, it belongs to the Coronaviridae family, which includes other viruses such as SARS and (MERS) [7–12], and is constituted by four structural proteins: spike (S), Envelope (E), Membrane (M), and Nucleocapside (N) [9,13,14]. This pathogen is transmitted by means of droplets of saliva or other fluids contained in the sneeze in direct contact with contaminated surfaces, the cough or the breathing of contaminated persons [15]. Little is known about the mechanisms utilized to establish it in the body, but the studies reveal that this is carried out in the respiratory airways and the lungs where the S1-subtype of the S proteins bind with the host cells Angiotensin-Converting Enzyme 2 (ACE2) that, together with some leptins, become the SARS-CoV-2 receptor [7,16–19]. Proteins such as neuropilin-1, which is in the endothelial cells that line the nasal cavity also favor the entry of this pathogen, not only to the respiratory airways, but also to the central nervous system (CNS) [20,21]. In addition, this panorama can become more dangerous if the patient has some alteration of the immune system [22–24]. Once established in the body of the host, this can remain asymptomatic or can present slight signs and symptoms such as cough, fever, weakness and generalized malaise, throat pain, loss of the sense of taste and smell, difficulty in breathing, pain in different parts of the body such as muscular pain, cephalea, chest pain, loss of speech, among others [25,30]. There may be more severe symptoms, such as diarrhea, hepatic and cardiac lesions, pneumonia, pulmonary hyperplasia, sepsis, uncontrolled inflammation of the attacked tissues due to the failure of the immune system, respiratory failure, thrombosis, and alterations in the CNS [3,31–38], which endanger the life of the patient (Figure 1).

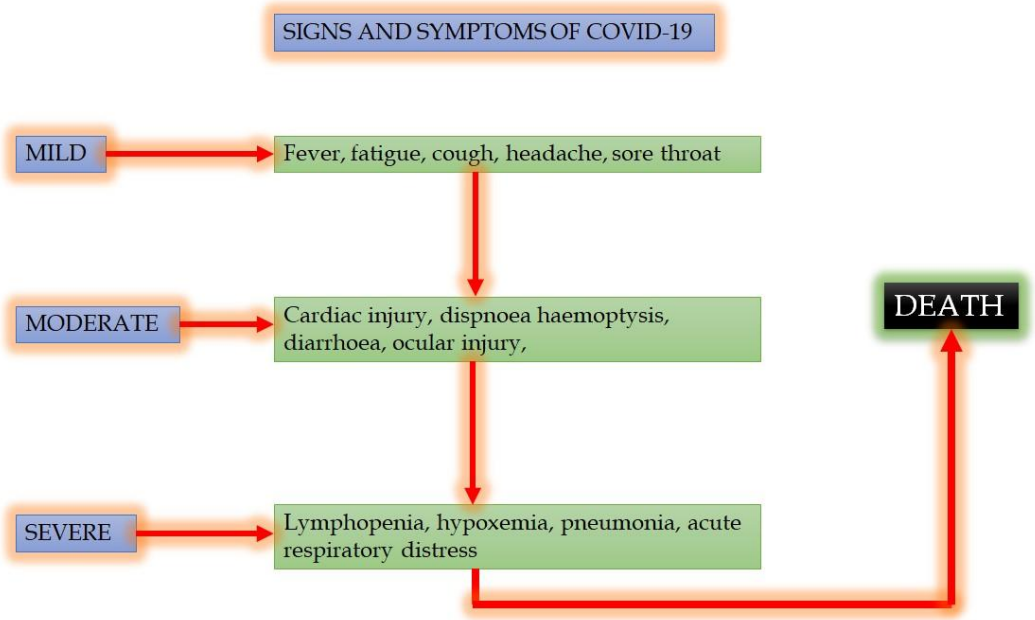

Figure 1. Progression of signs and symptoms of COVID-19, from mild to severe and that cause death in the patient.

3. Treatment of COVID-19

From the beginning and the declaration of the pandemic, therapies have been sought for an adequate treatment of the disease. However, up to October 2020, there was no effective treatment and only very strict measures of hygiene and of social isolation were implemented. Many companies throughout the world focused on creating a vaccine against SARS-CoV-2; currently, some of these have been administered to health-care workers since December 2020. Although the mortality rate of this pandemic is relatively low, there were 1.3 million deaths by mid-November 2020; it is noteworthy

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that the majority of persons who died presented some chronic pathology, rendering them more susceptible [39]. Among the treatments that have been utilized to cope with the pandemic we are able to cite the antivirals Ribavirin, Remdesivir [40–42], Interferon alpha [43–46], Cyclophilin inhibitors such as Cyclosporin A [47–50], glycosylation inhibitors such as Chloroquine [51–54], Kinase inhibitors such as Imatinib [55–57], and some monoclonal antibodies that can be employed in vaccines [58,60]. Nonetheless, none of these treatments have proven to be completely effective to diminish the severity of this pandemic.

4. Comorbility

Unfortunately, other factors have been discovered that have been added to the lethality of COVID-19. Age is one of these factors, in various countries, is for people over 44 years old [3,61–65]. Another determinant factor are chronic illnesses in the patients, such as diverse respiratory diseases of the Chronic Obstructive Pulmonary Disease (COPD) type [66–71], asthma [72,73], chronic kidney disease [74,75], cardiovascular disease [76–81], hypertension [82–85], and obesity [86–96], as well as diverse forms of diabetes [97–105].

4.1. Diabetes and COVID-19

Diabetes mellitus is one of the pandemics that have been increasing dramatically in recent decades; the incidence is no longer exclusive to developed countries, in that various developing countries are now among those in which this metabolic problem is considered a national health problem [106]. The principal sign of diabetes is the elevation of blood glucose levels as a result of different issues including deficient production of insulin, to the lack of response to insulin by the insulin receptors, a deficiency in insulin transporters, or even problems in the immune system [107–111].

Several studies have found that, among the diverse comorbilities that contribute to the mortality of patients with COVID-19, diabetes occupies one of the first places, and it has been proposed that this is due to in these patients, there is a high expression of the angiotensin-converting enzyme 2 receptor (ACE2), which increases mortality up to 2-fold [105,112]- Other studies go further and have proposed that this ACE2 receptor is also highly expressed in the pancreatic cells, and that therefore, SARS-CoV-2 virus would affect the pancreas, causing more severe hyperglycemia [113,114]. At present there is no pharmacological cure in cases of diabetes mellitus, as well as for COVID-19. There are drugs that aid in controlling blood glucose levels in diabetic patients and, as noted in previous paragraphs, palliative therapies are being studied for the signs and symptoms of the disorder cause by the SARS-COV-2 virus. In this respect, although at the moment of writing these lines, the first vaccines against SARS-CoV-2 are being approved, some studies mention that the use of alternative therapies related with the secondary metabolites of different plants could be a useful coadjuvant in diabetic patients infected with SARS-CoV-2.

4.2. Secondary Metabolites with a Potential Effect on Diabetic Patients COVID-19

One example of a secondary metabolite that has been used for diverse respiratory pathologies caused by SARS-CoV-2-like viruses and that also have been assayed previously in diabetes is resveratrol, a compound obtained from diverse plant species such as the grape. Evidence was found that this metabolite significantly inhibits the *in-vitro* replication of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) through the inhibition the production of RNA; it has also been reported that it diminishes the expression of the MERS-CoV nucleocapside, a protein essential for its replication [115,120]. Perhaps the key to the clinical effectiveness of resveratrol in diabetes and COVID-19-related disorders is associated with the antioxidant properties. On this regard, it should be taken into consideration that in many chronic-degenerative and in viral-type diseases, an imbalance in oxide-reduction reactions can be present as a risk factor, which can produce free radicals that aggravate such illnesses [121,122]. In most of the cases, when these oxidative imbalances are

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present and there is an increase of free radicals, endogenous mechanisms are activated to diminish the concentrations of these radicals by means of the so-called endogenous antioxidant agents, such as the enzymes catalase, glutathione peroxidase, and superoxide dismutase, among others [123]. In patients with COVID-19, the so-called "cytokine storm" presents, which leads to states of hyperinflammation, which in turn leads to the generation of free radicals, aggravating the pathological state in these patients as well as in those previously diagnosed with diabetes [124]. In normal health conditions, under stressful conditions, for example physical exercise, the antioxidant protector system is activated that is modulated by the Nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor, which regulates the endogenous antioxidant response as a natural defense under physiological as well as chronic pathological conditions including diabetes [125–127]. Based on the latter, such as alternatives to the pharmacological treatment of patients with COVID-19 and, while the massive production is achieved of the different vaccines that are already being applied, in some countries the proposal is being implemented of nutritional changes in these patients, using the traditional ethnomedical knowledge of natural products. China can be cited as an example, where the State Administration of Traditional Chinese Medicine reports that the administration of a traditional remedy known as the "Qingfei Paidu Decoction", which is elaborated with *Ephedra*, *Almond*, *Polyporus*, and *Citrus aurantium*, among other natural products, exhibited an effectivity rate higher than 90% in patients with COVID-19 [9]. Another example is found in Mexico, a country with a very ancient and widely extended herbolistic tradition where popular writings are beginning to be published, inviting the population to protect itself from SARS-CoV-2 by changing the nutritional customs and using herbal remedies as prophylactics [128]. In addition, a study carried out in patients in the Mexican health sector reports that the drug Nasoil®, which possesses, among its active components, the *Asclepias curassavica* extract, increases the respiratory capacity of patients [129].

All this evidence leads us to think that several of the products focusing on patients with diabetes that were cited in diverse publications could be effective in patients with COVID-19 thanks to its antioxidant properties. For this reason, we will present herein a brief description of some of these natural products or secondary metabolites with potential use in these patients.

4.2.1. Copper and N-Acetylcysteine

Copper possess multiple properties, among which antiviral activity and the inhibition of inflammatory processes are highlighted. On the other hand, N-acetylcysteine is a precursor of the amino acid L-cysteine, which acts as a free radical scavenger of Reactive Oxygen Species. It has been proposed that the combination of these would aid in diminishing the severity of the inflammatory events in the respiratory airways of patients with COVID-19 [129]. In this case, one should bear in mind that N-acetylcysteine has also been utilized in studies for the treatment of diabetes; for example, it can be mentioned that the administration of N-acetylcysteine in C57BL/6J mice t treated with Streptozotocin (STZ) activates the endogenous antioxidant systems and protects against thrombotic events [130], while promoting the peripheral uptake of glucose and diminishing plasma and hepatic cholesterol in models with diabetic animals [131].

4.2.2. Quercetin

This is a flavonoid widely found in diverse plants species with anti-inflammatory, anticancer, and antioxidant properties [132,133]. Paradoxically, quercetin could possess pro-oxidant effects, but there is evidence that, when administered with vitamin C, it could diminish this risk in patients with COVID-19 [133]. When administered in animals with diabetes, it was found that it diminishes the levels of lipid peroxidation [134,135]. In addition, quercetin has the advantage of penetrating the Blood-Brain Barrier (BBB), something that could be beneficial in diabetic patients recovering from COVID-19 [136].

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4.2.3. *Houttuynia cordata*

This is a perennial herbaceous plant of the *Saururaceae* Family of Asian origin, with evidence of its effectiveness in respiratory disorders such as pneumonia. A study indicates that *Houttuynia cordata* exerts an inhibitory effect on the 3C-like protease (3CLpro) and on the RNA-dependent RNA polymerase (RdRp) of SARS CoV [137]. There is also evidence that the aqueous extract of this plant, administered together with metformin, inhibits the production of inflammatory cytokines and diminishes the degree of glucose tolerance in mice fed with a carbohydrate-rich diet [138]. Another study demonstrated that the administration of the alcoholic extract of *Houttuynia cordata* increased the plasma levels of insulin, something that was related with an upregulation in the expression of the GLUT-2 and GLUT-4 transporters of the glucose [139].

4.2.4. *Laurus nobilis*

A case that attracts out attention is one that was reported in Italy. The majority of SARS-CoV-2 contagions were concentrated in the northern part of the country, while in the South few cases had been detected in May 2020 [140]. It is proposed that this could have been due to that, in the South of Italy, there are more wooded zones with different species such as *Laurus nobilis*, which is a typically Mediterranea tree, this specie could possess a protector effect due to the emission of volatile organic immunomodulatory compounds. In the study of potentially protector compounds, by means of *in-silico* analysis in *Laurus nobilis*, the authors described a potential activity of the laurusides against COVID-19 [140,141]. *L. nobilis* specie is widely distributed worldwide and has also been associated with beneficial effects in reducing glycemia when its triturated leaves (powder) have been supplemented in cookies in diabetic subjects [142]. Something similar was also found using capsules containing between 1 and 3 g of the leaves extract of *L. nobilis* that were administered to patients with type 2 diabetes [143]. In our laboratory, we are currently working with the methanolic extract of *L. nobilis* in mice treated with Streptozotocin, and it was found that after the intragastric (i.g.) administration of this extract during 6 weeks, the rise in the blood glucose levels was avoided in hyperglycemic animals (Figure 2).

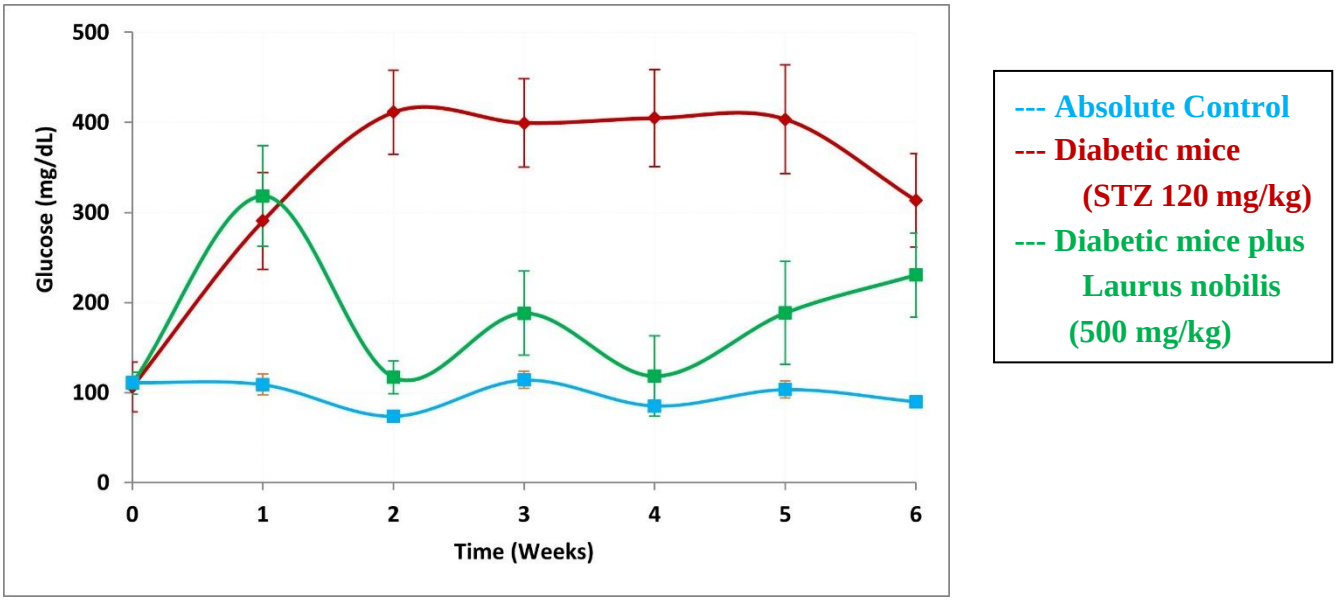

Figure 2. Blood glucose in mice under different treatments for 6 weeks. **P* <0.05 Diabetic mice plus *L. nobilis* vs. diabetic mice from week 1. Two-way repeated measures Analysis of VAriance (ANOVA) (own data).

4.2.5. Naringenin

Naringenin is a flavonoid found in diverse citric plants, such as orange and grapefruit, with antiviral, anti-inflammatory, and antioxidant properties. Recently, it was determined that it is capable

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of inhibiting the protease 3CLpro, and it recude the activity of ACE2 receptors in molecular docking studies [144,145]. It is logical to think that, due to its antioxidant properties, it could also exert a therapeutic effect on diabetic patients. In effect there is a review article on these actions in diverse *in-vitro* and animal models, finding that this is achieved because of the capacity of increasing glucose uptake tissues such as muscle [146]. Another study reports that naringenin, in 25-50-mg/kg doses combined with Lisinopril (10 mg/kg) in rats treated with Streptozotocin attenuated renal oxidative stress [147].

4.2.6. Naringin

Molecular docking studies showed that there has been evidence that naringin, a flavonoid-like compound present in various citrics such as orange, was capable of inhibiting the protease (6LU7) of SARS-CoV-2s due to its antioxidant and anti-inflammatory properties [148,149]. On the other hand, it was also found that naringin increased the expression of mRNA and protein of transcription factor FoxM1 in pancreatic beta cells in diabetic rats, while it diminished the blood values of some parameters such as glucose [150], glucose-6-fosfatase activity, and an uptake of blood glucose by peripheral tissues such as skeletal muscle [151].

4.2.7. *Azadirachta indica*

As mentioned in previous paragraphs, our Laboratory has been focused on searching for alternative therapies for ther treatment of diabetes. Since 2006, we have utilized a great variety of extracts of plant origin in chemical models of diabetes in mice. We have found various plants with a clear glucose-lowering effect on these models, such as *Moringa oleifera*, *Passiflora edulis*, and *Azadirachta indica*, all with high antioxidant activity and perhaps possessing promoter effects in improvement glucose uptake [152]. In this way, we focus on specialized literature about the possible effects of *A. indica* or its active metabolites against COVID-19, finding seven publications which highlighted that some of the secondary metabolites of this tree can inhibit the expression of the M and E proteins of the virus. Within secondary metabolites are mentioned nimocin, phytosterol, beta-amyrin, and nimbolin-A, among others, are mentioned. These recent works are summed up in Table 1 [153–159].

Table 1. Studies on *Azadirachta indica* and COVID-19.

Authors	Study type	Findings
Borkotoky and Banerjee, 2020 [153]	Docking and simulation methods to identify small molecule inhibitors of SARS-CoV-2 Membrane (M) and Envelope (E) proteins, which are essential for virus assembly and budding.	Of the 70 compounds monitored, we found that five compounds interacted with protein E and two interacted with protein M (nimocin and nimbolin)
Khan et al., 2020 [154]	PCR studies in humans to compare the effectiveness of an oral solution based on *A. indica* with other substances	Reduction of the intraviral oral burden confirmed with real time-PCR i
Adithya et al., 2020 [155]	Comparative study comparing information on Ayurvedic Medicine and its antiviral effects	Seven of the plants most used in Ayurvedic Medicine are mentioned (including *A. indica*) have antiviral potential
Garg et al., 2020 [156]	Molecular docking of the 38 bioactive compounds of five plants effective against SARS-COV-2.	Some of the compounds, such as nimbin, inhibit inhibin the expression of the protein M^{pro} of COVID-19

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Ogidigo et al., 2020 [157]	Computer study of the compounds of two plants with antiviral properties compared with FDA drugs-of-reference	Six compounds including nimbolin had strong inhibitory reactions with the M^{pro} of COVID-19
Baildya et al., 2021 [158]	Molecular docking and molecular dynamic study of the extracts of different parts *A. indica* against PLpro del COVID-19	All compounds presented inhibition in the protein PLpro (above all DesaCetylGedunin (DCG), found in Neem seed)
Parida et al., 2020 [159]	molecular dynamic study on the effectiveness of 55 Ayurvedic on SARS-COV-2	Withanolide R and 2,3-Dihydrowithaferin A were the compounds that interacted with the proteases and the spikes of the virus, but more evaluation is required

4.2.8. Vitamin C

Several years ago, it was determined that the vitamin C (ascorbate), contained in many fruits (e.g., orange, grapefruit, lemon), has many pharmacological and therapeutic properties. For example, it is a metabolite with antioxidant properties that, in diabetic patients, is found at low plasma levels, which increases glucose intolerance [160,161]. To these properties we must add the properties of being capable of increasing the production of the PGE1 and PGI2 and promoting the formation of lipoxin A4, which in turn also possesses anti-inflammatory and antioxidant properties with the consequent therapeutic benefit for patients with diabetes or with other associated pathologies [162]. These properties can contribute to the cytokine storm that has been described in patients with COVID-19; in fact, there is evidence that the intravenous administration of vitamin C at high doses for various days in these patients reduces the probabilities of their being admitted to intensive care units as well as the mortality rate of [163]. Other results reported with these high doses of vitamin C (e.g., 12 g) in reference to the cytokine storm is a reduction of Interleukin 6 (IL-6) and Interleukin 10 (IL-10), as well as an increase in the number of assisted ventilation-free days in patients with COVID-19 [164].

5. Conclusions

We described the recent findings on alternative therapies in the treatment of COVID-19 and diabetes. However, we think that several of the examples described in this review deserve to be taken into account once that effective therapies are established against both pathologies, in that surely physicians will confront both in their patients sooner or later. Several of the examples of cited contain information on the antiviral and hypoglycemic activity of secondary metabolites or natural extracts of plants that have been in use for a long time in Traditional Medicine. It is a good time to pick up again and reevaluate the potential that these compounds have for health, in order for them to taken into account, not only in the search for effective drugs for treatment, but also for their inclusion in prophylactic measures from the nutritional level or nutritional supplementation in each country, above all in those considered as developing nations. At the time of writing these lines, the first vaccines against SARS-CoV-2 are arriving at diverse parts of the world to be administered to health personnel in the first line of defense against the pandemic. Notwithstanding this, it will be several months before the greater part of the population will be protected against the virus, and although safety is lacking in terms of there not being secondary adverse effects due to the utilization in record time of these vaccines in humans. We think that this opens up the possibility of continuing to search for alternate therapies that are clinically safe and with ease-of-access in the population in general. Therefore, it can be affirmed that the review article that took shape in this writing still has continuity and could be expanded in the near future.

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Perspectives

Despite of the development of the vaccine against SARS-CoV-2, it is vital to continue efforts in the search for molecules that improving the patients' quality life, while they have COVID-19 and also when they overcome the disease the diabetes persist. On the other hand, diabetes is a critical factor in the survival of patients who are facing this pathogen. It would be convenient count on drugs that can aid to overcoming these pandemics simultaneously and improve their life expectancy, providing a better better treatment and with the employment of fewer drugs because the abuse of drugs has repercussions on health, on generating processes of toxicity in diverse organs, such as liver, kidney, and digestive tract. In this regard, this review has the aim of serve as a base for the elaboration of research projects focused on the clinical evaluation of the beneficial effects of some natural products or nutritional supplements that can function as auxiliaries in diabetic patiens with COVID-19.

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