Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Herbal medications and natural products for patients with covid-19 and diabetes mellitus: Potentials and challenges

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ABSTRACT

Background: The presence of diabetes mellitus (DM) among COVID-19 patients is associated with increased hospitalization, morbidity, and mortality. Evidence has shown that hyperglycemia potentiates SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection and plays a central role in severe COVID-19 and diabetes comorbidity. In this review, we explore the therapeutic potentials of herbal medications and natural products in the management of COVID-19 and DM comorbidity and the challenges associated with the preexisting or concurrent use of these substances.

Methods: Research papers that were published from January 2016 to December 2021 were retrieved from PubMed, ScienceDirect, and Google Scholar databases. Papers reporting clinical evidence of antidiabetic activities and any available evidence of the anti-COVID-19 potential of ten selected natural products were retrieved and analyzed for discussion in this review.

Results: A total of 548 papers (73 clinical trials on the antidiabetic activities of the selected natural products and 475 research and review articles on their anti-COVID-19 potential) were retrieved from the literature search for further analysis. A total of 517 articles (reviews and less relevant research papers) were excluded. A cumulative sum of thirty-one (31) research papers (20 clinical trials and 10 others) met the criteria and have been discussed in this review.

Conclusion: The findings of this review suggest that phenolic compounds are the most promising phytochemicals in the management of COVID-19 and DM comorbidity. Curcumin and propolis have shown substantial evidence against COVID-19 and DM in humans and are thus, considered the best potential therapeutic options.

Introduction

The coronavirus disease 2019 (COVID-19) is the most recent global pandemic of the 21st century. According to the World Health Organization (WHO, 2021), the global death toll of COVID-19 exceeds five million in two years, indicating a mortality rate of more than two and a half million *per* annum. Studies have shown that the majority of those who did not survive had pre-existing comorbidities such as

Abbreviations: 8-OHDG, 8-hydroxy-2'-deoxyguanosine; ACE2, Angiotensin-converting enzyme 2; ADMA, asymmetric de-methyl-arginine; DM, diabetes mellitus; FBS, fasting blood sugar; GLUT-4, glucose transporter-4; GSK-3β, glycogen synthase kinase-3β; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; hs-CRP, high-sensitivity C-reactive protein; IAPP, islet amyloid polypeptide; IFN, interferon; IFNAR2, interferon-alpha receptor 2; IL-6, interleukin-6; ARDS, acute respiratory distress syndrome; LDL, low-density lipoprotein; MDA, malondialdehyde; PLpro, papain-like protease; PON1, paraoxonase-1; RBD, receptor-binding domain; Mpro, main protease; RCT, randomized control trial; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SFJDC, Shufeng Jiedu Capsule; T1D, type 1 diabetes; T2D, type 2 diabetes; TAC, total antioxidant capacity; TMPRSS2, transmembrane protease serine 2.

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diabetes mellitus (DM), hypertension, obesity, and cardiovascular diseases as well as DM complications such as heart failure and chronic kidney diseases (de Almeida-Pititto et al., 2020; Fang et al., 2020; . Lim et al., 2021; Muniyappa and Gubbi, 2020).

COVID-19 pathophysiology begins with an infection resulting from a stepwise invasion and activation of a virus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in the host cells (Astuti and Ysrafil, 2020; Hu et al., 2020). Like its homolog (SARS CoV), SARS-CoV-2 is a novel strain of coronaviruses that also gains access to human cells by binding to a type 1 transmembrane protein known as angiotensin converting enzyme 2 (ACE2) found on the host cell's plasma membrane (Davidson *et al.*, 2020; Wu *et al.*, 2020). Of note, although the virus primarily attacks the lungs, SARS-CoV-2 infection in some patients is systemic and may result in multiorgan failure because ACE2 receptors are expressed in other organs of the body including the brain, pancreas, heart, gut, liver, and kidney (Gavriatopoulou et al., 2020; Xu et al., 2020).

Herbal medications have been used to treat DM since time immemorial, and a bunch of antidiabetic natural products has shown promising therapeutic potential against COVID-19 (Abubakar et al., 2021; Omrani et al., 2021). However, detailed information on the toxicity profile, dosage, efficacy, chemical composition, and mechanism of action of most of these compounds is lacking (Yang, 2020). Hence, concurrent use of these medications in patients with COVID-19 and diabetes comorbidity may predispose them to long-term complications, which can aggravate the existing precarious conditions. Moreover, previous exposure to these treatments may have a cumulative impact on COVID-19 patients with DM comorbidity. In this review, we highlighted recent advances in the use of herbal medications and natural products in the treatment of COVID-19 and DM and identified some substances that may be better therapeutic options in addressing the comorbidity. We also raised concerns on the concurrent and or pre-existing use of these products and the possible ways to address these concerns.

COVID-19 and diabetes: the underlying mechanisms of the comorbidity

Substantial evidence has shown that there were significantly higher disease severity and mortality in COVID-19 patients with DM compared to non-diabetic patients (Erener, 2020; Fang et al., 2020; Muniyappa and Gubbi, 2020). Several mechanisms have been put forward to explain this observation: they include but are not limited to enhancement of viral reception, reduction in viral clearance, impaired innate and adaptive immunity, enhanced inflammatory responses, and preexisting comorbidities resulting from DM secondary complications (de Almeida-Pititto et al., 2020; Muniyappa and Gubbi, 2020).

Diabetes-induced upregulated ACE2 expression may enhance SARS-CoV-2 invasion

There seems to be a correlation between diabetes and upregulated ACE2 gene expression in different diabetic models (Rao et al., 2020). For instance, there was a significant upregulation of ACE2 expression in the livers of type 2 diabetes (T2D) patients compared to non-diabetic human subjects (Soldo et al., 2020). In addition, ACE2 expression was significantly upregulated in the epicardial fat biopsies of T2D patients who underwent an open-heart surgery; T2D was associated with the ACE2 upregulation observed in the subjects and the results were more significant in patients with diabetes and obesity (Couselo-Seijas et al., 2020). Altogether, these findings signify that DM is a risk factor for upregulated ACE2 gene expression in various tissues of diabetic patients, which may facilitate SARS-CoV-2 binding and activation in those tissues, resulting in the multiorgan failure observed in COVID-19 patients with DM comorbidity.

Post-infectious downregulation of ACE2 may exacerbate the comorbidity

Although diabetic human subjects have shown an upregulated ACE2 expression before SARS-CoV-2 infection, the protein's intrinsic biological activity could diminish when COVID-19 manifests. Evidence suggests that the downregulation may result from an increased viral binding on the receptor and chronic hyperglycemia due to diabetes (Bornstein et al., 2020; Datta et al., 2020). It has been reported that uncontrolled hyperglycemia in diabetic and non-diabetic patients may induce glycosylation of the host ACE2 and the viral S-protein (Brufsky, 2020). Interestingly, S-protein and ACE2 glycosylation substantially enhance viral-ACE2 binding and thus, viral reception (Mehdipour and Hummer, 2021). Moreover, glycans induce a conformational change on the ACE2 holoenzyme (Bernardi et al., 2020), which may cause a loss of catalytic activity. Thus, both hyperglycemia and SARS-CoV-2 binding could downregulate ACE2's catalytic function. One possible detrimental consequence of ACE2 downregulation is multiorgan dysfunction brought about by an impairment in the renin-angiotensin system (RAS), which regulates the cardiovascular system and body fluids homeostasis, and plays a significant role in the pathogenesis of cardiometabolic diseases such as hypertension and DM (Đambić, 2020; Ni et al., 2020). Noteworthy, the RAS is already implicated in the development of the vascular complications of DM (Hsueh and Wyne, 2011). Therefore, its downregulation in COVID-19 patients with DM implies a double hit (Tseng et al., 2020), and such patients may likely have severe disease or die due to the exacerbated DM-COVID-19 complications.

Immune perturbations and viral clearance in diabetic COVD-19 patients

Innate immunity is the first line of defense against pathogens including SARS-CoV-2 (Lee et al., 2020). However, SARS-CoV-2 evades the host's innate immune surveillance by interfering with or delaying interferon types I and III (IFN-1 and INF-III) signaling (Kasuga et al., 2021; Lowery et al., 2021). Similarly, an analysis of human peripheral blood mononuclear cells has shown that hyperglycemia inhibits IFN-1 production and signaling (Hu et al., 2018). Thus, hyperglycemia may weaken the host's innate immune response to the virus by interfering with interferon signaling, and could ultimately lead to reduced viral clearance.

A hallmark of SARS-CoV-2 infection, which has been associated with disease severity is lymphopenia (Chen and John Wherry, 2020). Accordingly, lower lymphocyte count has been reported in COVID-19 patients with T2D compared to non-diabetic patients (Cheng et al., 2020; Wu and Gao, 2020), indicating that DM may be a risk factor for lymphopenia and therefore infection severity in these patients. Moreover, alveolar macrophages, natural killer cells, dendritic cells, and inflammatory monocyte-macrophages are primary IFN producers in respiratory virus infections (Lowery et al., 2021). Therefore, the delayed and limited interferon signaling in SARS-CoV-2 infection could be attributed to the reduced lymphocyte count observed in COVID-19 patients with DM comorbidity. Furthermore, another study has shown that critically ill COVID-19 patients with DM comorbidity had prolonged viral shedding, which according to the researchers could be due to compromised innate immunity, cytokine storm, or downregulation of ACE2 (Buetti et al., 2020). Apart from early response to infection, a fundamental function of innate immunity is the activation or priming of adaptive immunity; hence, the delayed IFN signaling in severe SARS-CoV-2 infection leads to poor priming of the adaptive immune response and determines the success of the infection (Sette and Crotty, 2021). Increasing evidence suggests that another culprit behind severe COVID-19 pathology and mortality is the cytokine storm, which is a prerequisite to ARDS, multiorgan organ failure and ultimately death (Ragab et al., 2020; Ye et al., 2020). Unfortunately, this form of systemic inflammatory response is also central to the pathogenesis and development of DM, especially T2D (Böni-Schnetzler and Meier, 2019; Randeria et al., 2019; Tsalamandris et al., 2019). Therefore, COVID-19 patients

with DM comorbidity are at a greater risk of exacerbated inflammatory responses and therefore cytokine storm (Forcados et al., 2021). For instance, in a study involving COVID-19 patients with DM and associated comorbidities, diabetic patients with no other comorbidities have shown elevated levels of interleukin-6 and C-reactive protein as well as an aggravated risk of tissue injury compared to non-diabetic patients (Guo et al., 2020).

In a nutshell, it is inferable from these findings that DM is a risk factor for hyperglycemia-induced impaired immunity, which is a prerequisite to cytokine storm, reduced viral clearance, and uncontrolled viral shedding in diabetic COVID-19 patients.

Methods

Ten natural products (astaxanthin, curcumin, genistein, hesperidin, oleanolic acid, pomegranate, propolis, quercetin, resveratrol, and rutin) were selected based on a preliminary literature search as well as the previous knowledge and opinion of the authors. An advanced literature search was conducted on PubMed and google scholar with the following combinations of keywords appearing in the title or abstract of the targeted papers: "diabetes and astaxanthin", "diabetes and curcumin", "diabetes and genistein", "diabetes and hesperidin", "diabetes and oleanolic acid", "diabetes and quercetin", "diabetes and pomegranate", "diabetes and propolis", "diabetes and resveratrol", "diabetes and rutin". Research papers published from January 2016 to December 2021 were searched. The search result was then filtered to include only clinical trials reporting the antidiabetic roles of the selected natural products or their bioactive components in humans. Further literature searches were conducted on PubMed, Google Scholar, and ScienceDirect databases using a combination of keywords (separately for each) as follows: "COVID-19 and astaxanthin", "COVID-19 and curcumin", "COVID-19 and genistein", "COVID-19 and hesperidin", "COVID-19 and oleanolic acid", "COVID-19 and quercetin", "COVID-19 and pomegranate", "COVID-19 and propolis", "COVID-19 and resveratrol", "COVID-19 and rutin". The search result was filtered to return only papers with any of the ten selected natural products and COVID-19 in the title or abstract. Research papers reporting any available evidence of the therapeutic potential of these substances against COVID-19 were retained with an emphasis on the most recent papers and clinical trials. Reviews were excluded but systematic reviews and meta-analyses, as well as other relevant ones, were used where necessary to elaborate the main text of this paper.

Results

The initial search resulted in 2, 101 searched items which were reduced to 73 clinical trials after filtering. A total of sixteen (16) most relevant research papers (Abdollahi et al., 2019; Afsharpour et al., 2019; Braxas et al., 2019; Homayouni et al., 2018, 2017; Khajebishak et al., 2019; Mashhadi et al., 2018; Ragheb et al., 2020; Santos-Lozano et al., 2019; Seyed Hashemi et al., 2021; Shokri-Mashhadi et al., 2021; Tabatabaie et al., 2020; Thota et al., 2020; Urakaze et al., 2021; Yao et al., 2019; Zhao et al., 2016) reporting clinical evidence of antidiabetic properties of the ten selected natural products met the criteria and were included in this review (57 less relevant ones were excluded). The second phase of the literature search resulted in 475 search items and only fifteen (15) most relevant additional research papers (de Ligt et al., 2021; di Pierro et al., 2021; Elfiky, 2021; Hassaniazad et al., 2021; Kosari et al., 2021; Kumar et al., 2021; Marín-Palma et al., 2021; Pasquereau et al., 2021; Patel et al., 2021; Pendyala et al., 2021; Rahman et al., 2021; Refaat et al., 2021; Silveira et al., 2021; Tallei et al., 2020; Tito et al., 2021) reporting any available evidence of the anti-COVID-19 potential of these substances were also selected (460 articles comprising reviews and other less relevant papers were excluded). A cumulative sum of thirty-one (31) papers was retained and discussed in this review.

Herbal medications and natural products in the management of COVID-19 and DM

The use of herbal remedies in the management of SARS-CoV-2 infection is becoming popular in some parts of the world, especially in China, where the infection originated. Although its effectiveness is inconclusive, the use of Chinese herbal formulations for COVID-19 treatment has been supportive, particularly in relieving symptoms, slowing disease progression, and reducing the duration of hospitalization (Chan et al., 2020; Zhou et al., 2021). Researches exploring the anti-COVID-19 potential of herbs are ongoing, and a great deal of them have shown promising potential. Meanwhile, systemic reviews and meta-analyses suggest that herbal preparations are more effective as supporting agents when combined with the western treatment (Ang et al., 2020; Liang et al., 2020; Zhou et al., 2021).

Bioactive compounds from herbs are emerging as potential therapies for COVID-19. These compounds are plants' secondary metabolites mainly in the category of alkaloids, terpenoids, or phenolic compounds. Recent data has reported a bunch of these compounds with different mechanisms of action on the SARS-CoV-2 virus (Abubakar et al., 2021; Augusti et al., 2021; Omrani et al., 2021; Solnier and Fladerer, 2020; Xian et al., 2020). Some natural products (mainly flavonoids) have the potential to antagonize viral reception and activation by modulating the ACE2 receptor via the spike-receptor-binding domain/TMPRSS2/ACE2 axis (Abubakar *et al.*, 2021). Others act as potential inhibitors of viral replication and maturation by targeting the SARS-CoV-2 Mpro and other essential enzymes involved in the process (Omrani et al., 2021). Another important approach is the use of plant-based natural products with the antioxidant capacity to mitigate oxidative stress and inflammation, which are important risk factors in COVID-19 pathogenesis and that of its comorbidities including DM (Forcados et al., 2021). Importantly, increasing evidence points towards phytochemicals targeting membrane lipids in COVID-19 therapy (Pawar et al., 2021).

There are already enough reviews on the use of natural products from herbal preparations in the treatment of DM including systematic reviews and meta-analyses (Andrade et al., 2020; Bilal et al., 2018; Jacob and Narendhirakannan, 2019; Kooti et al., 2016; Kumar et al., 2021; Pang et al., 2019; Zheng et al., 2020; Zhou et al., 2021). However, only a few of the numerous antidiabetic herbs have been clinically evaluated for their efficacy and safety, and their success in ameliorating diabetes has been attributed to their phytochemical constituents such as phenolic compounds, flavonoids, terpenoids, and coumarins (Kumar et al., 2021). Moreover, depending on their phytoconstituents, the antidiabetic mechanism of action exhibited by these plants is very broad and includes reduction of blood glucose levels by mitigating insulin resistance, improving insulin signaling, upregulation of glucose transporters, and stimulation of β-cells to release insulin; slowing down carbohydrate digestion and absorption by inhibiting α-amylase and α-glucosidase; increasing glucose oxidation and storage by stimulating glucose 6-phosphate dehydrogenase, glutathione synthase, and inhibiting glycogen synthase kinase-3β (GSK-3β); lowering adipogenesis, visceral adiposity, body weight and fat mass (Andrade et al., 2020; Bustos et al., 2020). In addition, some of these plants harbor bioactive components with hypolipidemic, antioxidant, and anti-inflammatory effects, and thus, can reduce the risk of DM fueled by oxidative stress and inflammation (Pang et al., 2019). Importantly, emerging evidence suggests that changes in the gut microbiome composition are implicated in the pathogenesis of DM especially T2D (Gurung et al., 2020; Zhang et al., 2021, 2020), and some bioactive components of the herbs used in the treatment of T2D help improve the dysbiosis of the gut microbiota (Fig. 1) (Carrera-Quintanar et al., 2018; Zheng et al., 2020). Here, we discussed a few bioactive compounds found in medicinal herbs and other natural products, which have been recently reported to have anti-diabetic properties as well as anti-COVID-19 potential with an emphasis on clinical trials.

Astaxanthin is a carotenoid synthesized naturally by *Haematococcus*

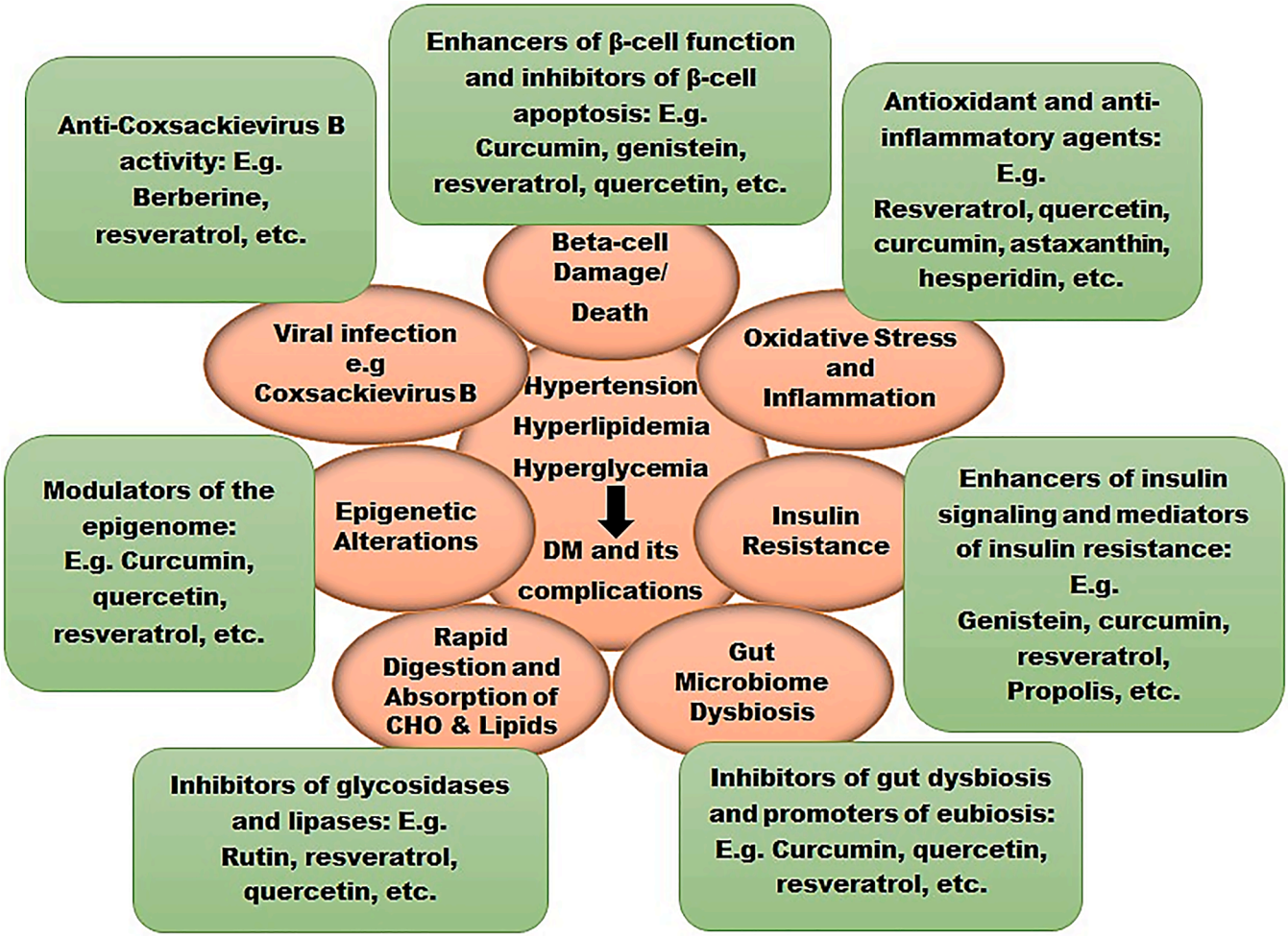


Fig. 1. Mechanism of antidiabetic properties of natural products. The figure illustrates the various mechanisms through which natural products mitigate the risk factors associated with the development and progression of diabetes mellitus and its complications.

pluvialis and some yeast species. A randomized controlled clinical trial (RCT) reported that supplementation with 8 mg astaxanthin tablets once daily for 8 weeks resulted in elevated levels of serum adiponectin as well as decreased visceral body fat mass, systolic blood pressure, serum triglyceride, very-low-density lipoprotein cholesterol, plasma glucose and significantly reduced serum fructosamine concentration in T2D patients compared to placebo (Mashhadi et al., 2018). Another RCT documented that a 12 weeks supplementation with 12 mg astaxanthin once daily led to significantly reduced levels of blood glucose after 2 h of 75 g oral glucose tolerance test (OGTT); glycated hemoglobin and malondialdehyde-modified low-density lipoprotein were also reduced in the studied healthy prediabetic human subjects compared to placebo (Urakaze et al., 2021). Moreover, a mechanistic study in which T2D patients were supplemented with 8 mg *per* day oral astaxanthin for 8 weeks has shown that it could reduce plasma levels of MDA (malondialdehyde) and IL-6 (interleukin-6) by downregulating miR-146a (microRNA-146a) gene expression; miR-146a is found to be upregulated in hyperglycemic and diabetic patients (Shokri-Mashhadi et al., 2021). Regarding COVID-19, *in silico* data reported that astaxanthin has the potential to bind the SARS-CoV-2 PLpro with a binding energy of -9.3 Kcal/mol (Pendyala et al., 2021). Astaxanthin could, therefore, be considered a suitable herbal-based remedy in the management of COVID-19 and DM comorbidity.

Curcumin is a hydrophobic polyphenol primarily found in turmeric (*Curcuma longa L.*). A study involving healthy volunteers who are at a high risk of developing T2D reported that dietary supplementation with 180 mg *per* day curcumin for 12 weeks mediated insulin resistance in the treated subjects by reducing the circulating levels of islet amyloid polypeptide (IAPP) and GSK-3β (Thota et al., 2020). Moreover, in a recent systematic review and meta-analysis of RCTs on the effect of curcumin on glycemic and lipid profile in subjects with uncomplicated T2D, curcumin treatment is associated with a significant reduction in the glycosylated hemoglobin (HbA1c), homeostasis model assessment (HOMA), and low-density lipoprotein (LDL) in the treated subjects compared to placebo (Altobelli et al., 2021). Similarly, *in silico* and *in vitro* data has shown that curcumin has the potential to bind SARS-CoV-2 S-protein as well as ACE2 via covalent interactions (Shanmugarajan et al., 2020; Patel et al., 2021), and clinical trials to check the effectiveness of various formulations of curcumin in COVID-19 patients are in progress. Interestingly, a recent study has shown that a pre-post-infection treatment with curcumin (10 μg/mL) in Vero E6 cells infected with the D614G strain and the Delta variant of SARS-CoV-2 has shown a strong antiviral effect against these viruses with an efficiency of 99.0% and 99.8% respectively (Marín-Palma et al., 2021). According to the study, curcumin treatment also ameliorated the SARS-CoV-2 infection-mediated release of the pro-inflammatory cytokines (IL-1β, IL-6, and IL-8) by the peripheral blood mononuclear cells (Marín-Palma et al., 2021). Furthermore, a recent triple-blind, RCT reported that supplementation with the nano-curcumin (Sinacurcumin®) soft gel 40 mg, four times daily (after breakfast, lunch, dinner, and before bedtime) for 2 weeks resulted in decreased serum levels of the proinflammatory cytokines (IFN-γ and IL-17) as well as downregulations of some genes associated with T-cells response (*TBX21* and *FOXP3*) in the treated subjects compared to placebo (Hassaniazad et al., 2021). These

observations signify that the antiviral, as well as anti-inflammatory effects of curcumin, can be employed against COVID-19 and thus, have proven the promising therapeutic potential of curcumin in diabetic COVID-19 patients.

Genistein is a 7-hydroxyisoflavone with additional hydroxy groups at positions 5 and 4′ originally isolated from *Genista tinctoria* and commonly found in soy products. It is a phytoestrogenic isoflavone with antioxidant properties. An RCT involving type 2 diabetic postmenopausal women reported that 12-week treatment with 108 mg *per* day genistein capsules significantly reduced serum levels of fasting blood glucose (FBS), HbA1c, serum triglyceride (TG), and MDA, and increased total antioxidant capacity compared with the placebo (Braxas et al., 2019). On the other hand, a molecular docking experiment has shown that genistein has a moderate affinity to the receptor-binding domain of the cell surface heat-shock protein, one of the host's membrane proteins that are known to facilitate SARS-CoV-2 binding and activation (Elfiky, 2021). These findings present genistein as a potential biotherapeutic phytochemical in the management of COVID-19 and DM comorbidity.

Hesperidin, a powerful antioxidant, is a flavanone glycoside primarily found in citrus fruits. In an RCT involving 64 T2D patients, a 6 weeks supplementation with 500 mg *per* day hesperidin capsules resulted in significantly decreased blood pressure and inflammatory biomarkers (tumor necrosis factor-alpha, interleukin 6, and high-sensitivity C-reactive protein) as well as increased total antioxidant capacity (TAC) (Homayouni et al., 2018). A similar study reported that hesperidin ameliorated oxidative DNA damage and lipid peroxidation by lowering the serum levels of MDA, 8-hydroxydeoxyguanosine, and fructosamine as well as increasing the TAC of T2D patients compared to placebo (Homayouni et al., 2017). Likewise against COIVD-19, hesperidin has shown greater binding affinity to SARS-CoV-2 S-protein compared to drug candidates such as chloroquine and hydroxychloroquine (Tallei et al., 2020). It is inferable from these observations that hesperidin is a potential therapeutic agent in diabetic COVID-19 patients.

Oleanolic acid (OA) is a pentacyclic triterpenoid that is commonly found in abundance in the Oleaceae family of flowering shrubs such as the olive plant, *Olea europaea (Linn.)* (Ayeleso et al., 2017). An RCT reported that a 30-month supplementation with 55 mL per day of OA-enriched olive oil (equivalent dose 30 mg OA *per* day) reduces the risk of developing diabetes in prediabetic human subjects compared to placebo (Santos-Lozano et al., 2019). Similarly, results from molecular docking experiments suggest that OA could be a potent inhibitor of SARS-CoV-2 Mpro (Kumar et al., 2021). OA could thus, be considered as a treatment option in diabetic COVID-19 patients.

Pomegranate (*Punica granatum L.*), is a fruit native to the Middle East whose peel, flower, juice, and seed extracts have been reported to contain anti-diabetic phytochemicals with the potential to fight T2D including punicalagin and ellagic, gallic, oleanolic, ursolic, and uallic acids as well as tannins and anthocyanins (Banihani et al., 2013). For example, a randomized control trial (RCT) involving 52 obese T2D patients conducted in Iran has shown that an eight weeks treatment with 1 g daily pomegranate seed oil resulted in significantly upregulated glucose transporter-4 (GLUT-4) gene expression as well as reduced FBS in these patients compared to placebo (Khajebishak et al., 2019). In a more recently published prospective randomized double-blind placebo-controlled clinical trial, an eight weeks treatment with 5 g pomegranate seed powder (twice daily) led to significantly reduced FBS, HbA1c, total cholesterol, and TG in T2D patients compared to placebo (Seyed Hashemi et al., 2021). Regarding COVID-19, bioactive components of pomegranate peel extract namely punicalin and punicalagin (the major polyphenols) as well as urolithin A (a major metabolite), have shown the potential to inhibit SARCoV-2 binding on ACE2 receptors *in silico* and *in vitro* (Tito et al., 2021). These findings suggest the antidiabetic and anti-COVID-19 potential of the various forms of pomegranate extracts and thus, its suitability for managing diabetic COVID-19 patients.

RCTs in human subjects have proven the antidiabetic properties of propolis (Afsharpour et al., 2019; Samadi et al., 2017; Zakerkish et al., 2019; Zhao et al., 2016), a resinous material produced by honey bees from plant exudates that have been used by Egyptians and Greeks as a herbal medication thousands of years ago. For instance, in one of these studies, a 1500 mg daily (500 mg thrice a day) supplementation with Iranian propolis capsules for two months resulted in significantly reduced FBS, 2-hours postprandial glucose, insulin, insulin resistance, and HbA1c levels in the blood of T2D patients compared to placebo (Afsharpour et al., 2019). In another study, a 900 mg *per* day supplementation with the Brazilian green propolis capsules for 18 weeks improved the antioxidant function by increasing the levels of glutathione and total polyphenols as well as decreasing serum carbonyls and lactate dehydrogenase activity in T2D patients compared to placebo (Zhao et al., 2016). Moreover, recent systematic reviews and meta-analyses of these clinical trials have cumulatively reported the antidiabetic properties of various forms of propolis supplements in T2D patients (Gheflati et al., 2021; Hallajzadeh et al., 2021). Similarly, some natural products found in the Egyptian propolis have the potential to inhibit the signaling pathways involved in SARCoV-2 binding and entry into the host cells *in silico and in vivo* (Berretta et al., 2020). For instance, in a study to unveil the anti-SARS-CoV-2 potential of flavonoids components of Egyptian propolis, all the propolis components showed high affinity to the viral Mpro *in silico* (rutin and caffeic acid phenethyl ester showed the highest affinity) compared to the antiviral drug candidates, Avigan, Hydroxychloroquine and Remdesivir (Refaat et al., 2021). Moreover, a 7 days supplementation with Propomax®/EPP-AF® capsules (a dehydrated Standardized Brazilian Green Propolis Extract), 400 mg daily (one 100 mg capsule, four times a day) or 800 mg daily (two 100 mg capsules, four times a day) reduced the duration of hospitalization in COVID-19 patients compared to a placebo receiving standard care without propolis supplementation (Silveira et al., 2021). In addition, another 6 days of oral supplementation with a 10 mL syrup (a solution of 1.6 mg methanolic extract of *Hyoscyamus niger L.* and 450 mg of Iranian propolis) three times daily ameliorated some of the clinical symptoms of COVID-19 including dry cough, shortness of breath, sore throat, chest pain, fever, dizziness, headache, abdominal pain, and diarrhea in COVID-19 patients compared to placebo (Kosari et al., 2021). Propolis is, therefore, considered a potentially potent therapeutic agent against COVID-19 and DM comorbidity.

Quercetin is a flavonoid found in many fruits and vegetables including onions (*Allium cepa L.*). Although evidence reporting the antidiabetic properties of quercetin in animal models is sufficient, clinical data supporting these findings is lacking in the existing literature (Shi et al., 2019). However, a study investigating the relationship between dietary quercetin intake and the prevalence of T2D among Chinese adults has reported a protective role of the compound against the development of T2D (Yao et al., 2019). Moreover, quercetin is an anti-inflammatory agent, which regulates some genes involved in the transport of cholesterol. In combination with fenofibrate (a cholesterol-lowering drug), quercetin has the potential to synergistically reduce cholesterol accumulation in macrophages, and thus, might be useful in COVID-19 treatment (Pawar et al., 2021). Recently, a 2-week, randomized, open-label, and controlled clinical study has shown that a 14 days (1500 mg daily in the first 7 days and 1000 mg daily in the last 7 days) treatment with Quercetin Phytosome® tablet (a novel bioavailable form of quercetin) accelerated viral clearance and reduced symptom severity among COVD-19 patients (Di Pierro et al., 2021). Considering the lack of clinical evidence on the antidiabetic properties of quercetin, the above human study provides the basis to further explore the combined antidiabetic and anti-COVID-19 potential of the compound in humans. Thus, making quercetin a prime therapeutic agent in addressing COVID-19 and diabetes comorbidity.

Meta-analysis of RCTs has shown that treatment with resveratrol, a polyphenol found in the skin of fruits such as grapes (*Vitis vinifera L.*) and

berries such as blueberry (*Vaccinium myrtillus L.*), improved FBS, insulin levels, and insulin resistance in T2D patients (Zhu et al., 2017). The results were more significant in patients treated with ≥100 mg/kg of the compound (Zhu et al., 2017). In a more recent RCT, an eight-week treatment with 1000 mg/day (500 mg twice daily) trans-resveratrol capsules in T2D patients resulted in decreased FBS as well as increased high-density lipoprotein (HDL) and insulin levels (Abdollahi et al., 2019). Moreover, a more recent study has reported significantly decreased serum levels of asymmetric de-methyl-arginine (ADMA) and an increased paraoxonase-1 (PON1) activity in T2D patients treated with 1000 mg per day resveratrol capsules for 8 weeks (Tabatabaie et al., 2020). Likewise, a study reported that 30 days of supplementation with 150 mg *per* day *trans*-resveratrol reduces ACE2 and leptin gene expression in the abdominal subcutaneous adipose tissue of obese male human subjects compared to placebo (de Ligt et al., 2021). In addition, treatment with a solution containing 200 mM resveratrol is reported to inhibit SARS-CoV-2 replication in Vero E6 cells with a significant reduction in the viral titer (Pasquereau et al., 2021). Thus, resveratrol is indeed a potential therapeutic option in diabetic COVID-19 subjects.

Rutin (quercetin-3-O-rutinoside) is a quercetin derivative with the disaccharide rutinose (α- L -rhamnopyranosyl–β- D -glucopyranose) attached to the quercetin ring. Evidence has shown that a three times daily supplementation with RUTA C 60 ®, a tablet containing rutin (60 mg), and vitamin C (160 mg) for eight weeks significantly reduced the percent change in FBS levels in T2D patients compared to placebo (Ragheb et al., 2020). Similarly, *in silico* experiments have shown that rutin has the potential to inhibit some essential proteins of SARS-CoV-2 including the main protease (Mpro), RNA-dependent RNA polymerase (RdRp), papain-like protease (PLpro), and spike (S)-protein. The compound shows the strongest binding affinity with the Mpro by having the least binding energy of about -8.9 Kcal/mol (Rahman et al., 2021). Based on these observations, rutin could be considered as a therapeutic option in the management of diabetic COVID-19 patients. Table 1 summarizes the ten selected herbal medications/natural products and their therapeutic potential in the management of COVID-19 and DM comorbidity.

The traditional Chinese medicine, Shufeng Jiedu Capsule (SFJDC), is a herbal formulation of eight medicinal plants (*Ephedrae Herba, Gypsum Fibrosum, Mori Cortex, Scutellariae Radix, Lepidii Semen, Lonicerae Japonicae Flos, Scrophulariae Radix, Moutan Cortex, Rehmanniae Radix, Atractylodis Macrocephalae Rhizoma, and Cimicifugae Rhizoma*) and is a commonly used antiviral and anti-inflammatory drug in China (Feng et al., 2022; Xia et al., 2018, 2021). Evidence has shown that SFJDC is rich in flavonoids mainly quercetin and resveratrol with a concentration of about 0.18% and 0.154% respectively (Xia et al., 2018). A clinical study reported that a combination of standard antiviral therapy and oral supplementation with 0.2 ml SFJDC extract *per* 10 g body weight once daily for 4 days reduced the clinical recovery time as well as the duration of cough and fatigue in COVID-19 patients compared to the groups with the standard therapy only (Xia et al., 2021). Moreover, a recent mechanistic study reveals that three times daily supplementation with 12 g or 24 g SFJDC granules exerts an anti-inflammatory effect in COVID-19 patients by suppressing some genes involved in the nuclear factor kappa B (NF-κB) signaling and the altered genes are mainly the targets of three of the bioactive components of SFJDC (quercetin, kaempferol, and luteolin) (Feng et al., 2022). According to the study, molecular docking experiments reveal that the ligands of the three compounds had strong interactions with NF-κB, p65, and IκBα (Feng et al., 2022). It is noteworthy that although there is dearth of clinical evidence on the antidiabetic role of SFJDC, some of its bioactive components have been evaluated as potential anti diabetic in humans. This herbal formulation is, therefore, considered a potential therapeutic option against COVID-19 and DM comorbidity. However, due to lack of clinical evidence on the antidiabetic role of SFJDC, the substance is not regarded among the ten selected natural products discussed in this paper. Further research could perhaps explore its antidiabetic potential.

COVID-19 and DM: potentials and challenges on the use of herbal medications and natural products

Considering the exponential rise in the number of cases and death toll of COVID-19, the need of the hour is to urgently provide effective therapeutics to tackle the pandemic. Recently, Gaziano *et al.*, (2021) proposed drug repurposing as a promising alternative to address the urgent need for therapeutics in the management of COVID-19 (Gaziano et al., 2021). The researchers proposed that existing drugs targeting ACE2 and interferon-alpha receptor 2 (IFNAR2) that have been clinically evaluated could have greater potential compared to those yet to undergo clinical trials. For instance, the antiviral properties of the antimalarial drug chloroquine have been clinically evaluated, and because of its immunomodulatory properties, the drug has been proposed as a promising therapeutic agent against COVID-19 (Zhou et al., 2020). Similarly, a molecular docking experiment has recently identified some already established antidiabetic drugs including repaglinide, canagliflozin, glipizide, gliquidone, glimepiride, and linagliptin as promising inhibitors of SARS-CoV-2 Mpro (Qu et al., 2021). In this regard, a similar approach for phytochemicals could be a paramount alternative in the management of COVID-19 in patients with DM comorbidity.

To achieve reasonable efficacy, safety, and bioavailability in the use of conventional drugs, herbal medications, or natural products, efficient delivery vehicles need to be employed. Recently, extracellular vehicles (ECVs) have been proposed as a next-generation drug delivery platform (Herrmann et al., 2021). Moreover, Yan *et al.*, (2021) have recently reviewed some therapeutic approaches that involve the use of ECVs in the treatment of COVID-19 (Yan et al., 2021). Accordingly, in a recent study conducted to examine the antioxidative synergistic effects of melatonin and resveratrol encapsulated by solid lipid nanocarriers against the pure antioxidant combination (melatonin + resveratrol without lipid encapsulation), the encapsulated treatment reduced the levels of reactive oxygen species in the treated oocytes (compared to the pure compounds) through an enhanced intracellular penetration (Aghaz et al., 2021). Similarly, an optimized liposomal formulation of propolis has shown better inhibitory effects against the SARS-CoV-2 Mpro compared with the pure Egyptian propolis extract *in vitro* (Refaat et al., 2021), indicating that liposomal encapsulation could enhance the antiviral effects of propolis against COVID-19. Putting these observations together, we may conclude that ECVs could enhance the pharmacological properties and treatment efficiency of natural products in the management of COVID-19.

Owing to the role of IFNs in combating viral infections including SARS-CoV-2, stimulation of IFN signaling has been proposed as a potential prophylactic and therapeutic target for COVID-19 (Li et al., 2021; Major et al., 2020). It has been reported that activation of the stimulator of interferon genes (STING) triggers a multi-dimensional IFN-I response that augments innate and adaptive immune responses (Li et al., 2021). Moreover, recent evidence has shown that treatment of human lung epithelial cells with IFNs blocks SARS-CoV-2 infection (Li et al., 2021). In addition, the researchers also reported that a STING agonist known as diABZI significantly inhibits SARS-CoV-2 infection by potentiating an innate immune response involving IFN signaling (Li et al., 2021). Similarly, phytochemicals such as resveratrol, genistein, and quercetin have shown a dose-dependent stimulatory role on IFN signaling in the human HeLa cell lines (Vlasova et al., 2019). Interestingly, the antidiabetic and anti-COVID-19 potential of these compounds has been reported earlier in this review. Thus, natural products with IFN signaling enhancement capacity may be of paramount importance in the prophylaxis and treatment of COVID-19 in patients with DM-associated immunodeficiency. Fig. 2 summarizes crosstalk between COVID-19 and DM as well as the potential therapeutic targets of phytochemicals in addressing the comorbidity.

The major concerns in using herbal preparations for COVID-19 therapy lie in their safety, efficacy, dosage, action mechanism,

Table 1
Natural products with clinical evidence of antidiabetic activities and anti-COVID-19 potential.

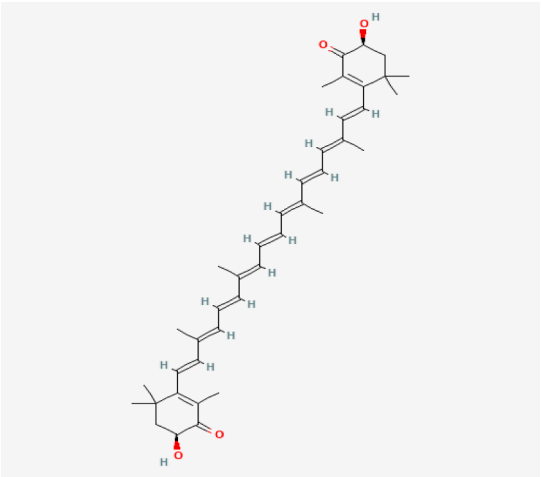
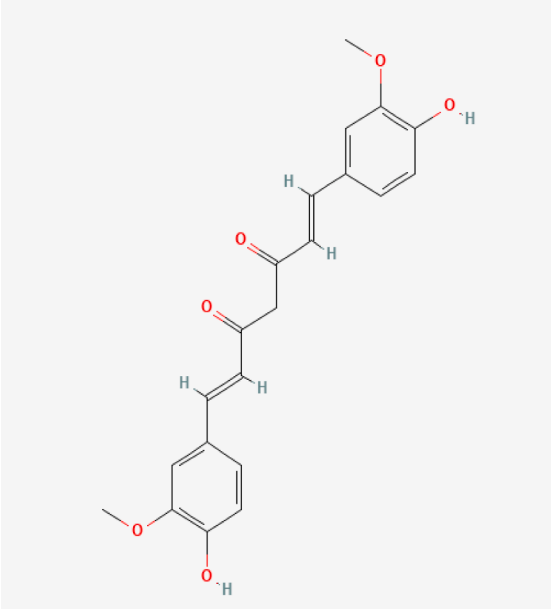
S/No	Type of supplement (Dosage and duration of treatment)	Bioactive component (type of chemical compound)	Chemical structure of the bioactive component (PubChem web reference)	Type of study (Subjects/targets)	Effect of supplement in diabetic patients/anti-COVID-19 potential of the bioactive compound (references)
1	a. Astaxanthin tablets (8 mg once daily for 2 months) b. Astaxanthin tablets (12 mg once daily for 3 months) a. Astaxanthin tablets (8 mg once daily for 2 months) c. Astaxanthin ligand.	a. Astaxanthin (Carotenoid) b. Astaxanthin (Carotenoid) c. Astaxanthin (Carotenoid) d. Astaxanthin (Carotenoid)	 Astaxanthin (https://pubchem.ncbi.nlm.nih.gov/compound/Astaxanthin#section=2D-Structure)	a. RCT (T2D patients) b. RCT (prediabetic healthy volunteers) c. RCT (T2D patients) d. *in silico* (SARS-CoV-2 protein)	a. Serum adiponectin↑, visceral body fat↓, systolic blood pressure↓, plasma glucose↓, serum triglyceride↓, serum VLDL-C↓, serum fructosamine↓ (Mashhadi et al., 2018). b. Blood glucose after 2 h OGTT↓, glycated hemoglobin ↓, MDA-modified LDL↓, (Urakaze et al., 2021). c. Plasma MDA↓, IL-6↓, miRNA-146a expression↓ (Shokri-Mashhadi et al., 2021) d. PLpro binding (Pendyala et al., 2021)
2	a. Curcumin tablets (180 mg per day for 3 months) b. Curcumin ligand. c. Curcumin solution (10 μg/mL) d. Sinacurcumin® soft gel (4 mg four times daily for 2 weeks)	a. Curcumin (Polyphenol) b. Curcumin (polyphenol) c. Curcumin (Polyphenol) d. Curcumin (Polyphenol)	 Curcumin (https://pubchem.ncbi.nlm.nih.gov/compound/curcumin#section=2D-Structure)	a. RCT (healthy volunteers who are at a high risk of developing T2D) b. *in silico* (SARS-CoV-2 and host proteins) c. *In vitro* (Vero E6 cells) d. RCT (COVID-19 patients)	a. IAPP↓, GSK-3β↓, insulin resistance↓ (Thota et al., 2020). b. Binds to host ACE2 and SARS-CoV-2 S-protein (Patel et al., 2021; Shanmugarajan et al., 2020) c. IL-1β↓, IL-6↓, and IL-8↓, 99.0% D614G strain of SARS-CoV-2↓, 99.8% Delta variant of SARS-CoV-2↓ (Marín-Palma et al., 2021). d. IFN-γ↓, IL-17↓, *TBX21* gene expression↓, *FOXP3* gene expression↓ (Hassaniazad et al., 2021).

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Table 1 (*continued*)

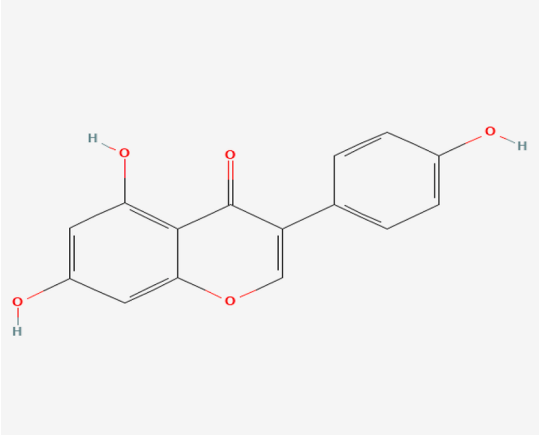
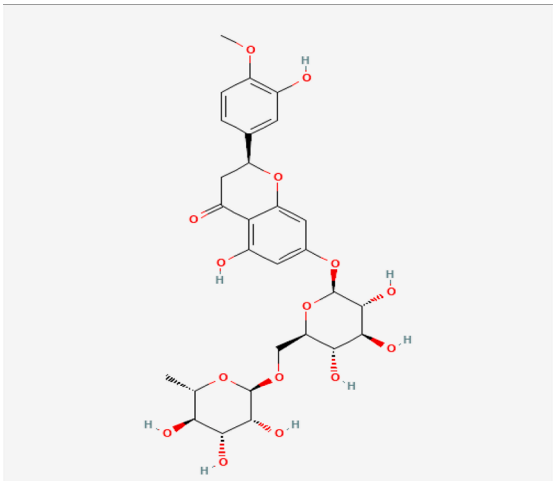
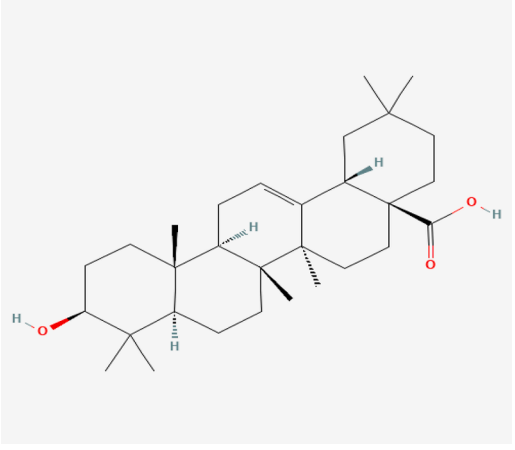
S/No	Type of supplement (Dosage and duration of treatment)	Bioactive component (type of chemical compound)	Chemical structure of the bioactive component (PubChem web reference)	Type of study (Subjects/targets)	Effect of supplement in diabetic patients/anti-COVID-19 potential of the bioactive compound (references)
3	a. Genistein capsules (108 mg per day for 3 months). b. Genistein ligand.	a. Genistein (Isoflavone) b. Genistein (Isoflavone)	 Genistein (https://pubchem.ncbi.nlm.nih.gov/compound/genistein#section=2D-Structure)	a. RCT (Diabetic post-menopausal women) b. *in silico* (host membrane protein)	a. FBS↓, triglycerides↓, MDA↓, glycated hemoglobin↓, TAC↑ (Braxas et al., 2019). b. Binds to the host's cell surface heat-shock protein (Elfiky, 2021)
4	a. Hesperidin capsules (500 mg *per* day for 6 weeks). b. Hesperidin capsules (500 mg *per* day for 6 weeks). c. Hesperidin ligand.	a. Hesperidin (Flavanone glycoside)b. Hesperidin (Flavanone glycoside)c. Hesperidin (Flavanone glycoside)	 Hesperidin https://pubchem.ncbi.nlm.nih.gov/compound/hesperidin	a. RCT (T2D patients) b. RCT (T2D patients) c. *in silico* (SARS-CoV-2 protein)	a. BP↓, TNF-α↓, IL-6↓, hs-CRP↓, TAC↑ (Homayouni et al., 2018). b. MDA↓, fructosamine↓, 8-OHDG↓, TAC↑ (Homayouni et al., 2017). c. S-protein binding (Tallei et al., 2020).
5	a. Oleanolic acid-enriched olive oil (55 mL ≡ 30 mg Oleanolic acid *per* day for 30 months) b. Oleanolic acid ligand.	a. Oleanolic acid (Terpenoid) b. Oleanolic acid (Terpenoid)	 Oleanolic acid (https://pubchem.ncbi.nlm.nih.gov/compound/Oleanolic-acid#section=2D-Structure)	a. RCT (Prediabetic humans) b. *in silico* (SARS-CoV-2 protein)	a. Risk of diabetes↓ (Santos-Lozano et al., 2019). b. Binds SARS-CoV-2 Mpro (Kumar et al., 2021).

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Table 1 (*continued*)

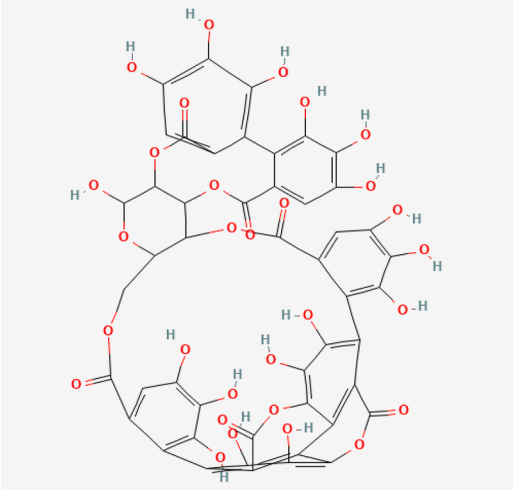
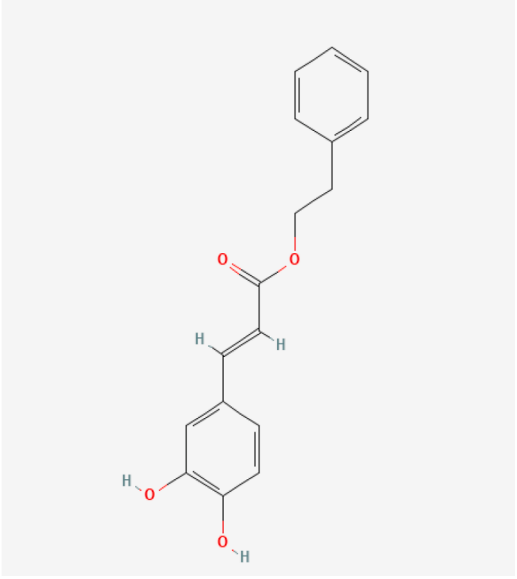
S/No	Type of supplement (Dosage and duration of treatment)	Bioactive component (type of chemical compound)	Chemical structure of the bioactive component (PubChem web reference)	Type of study (Subjects/targets)	Effect of supplement in diabetic patients/anti-COVID-19 potential of the bioactive compound (references)
6	a. Pomegranate (*Punica granatum L.*) seed oil (1 g daily for 2 months). b. Pomegranate (*Punica granatum L.*) seed powder (5 g twice daily for 2 months). c. pomegranate peel extract (bioactive ligands)	a. Pomegranate seed oil b. Pomegranate seed powder a. Punicalagin (Phenolic)	 Punicalgin https://pubchem.ncbi.nlm.nih.gov/compound/Punicalagin#section=2D-Structure	a. RCT (T2D patients) b. RCT (T2D patients) c. *in silico* and *in vitro* (SARS-CoV-2 and host proteins)	a. GLUT-4 gene expression↑, FBS↓ (Khajebishak et al., 2019). b. FBS↓, glycated hemoglobin↓, total cholesterol↓, triglycerides↓ (Seyed Hashemi et al., 2021). c. Inhibits SARS-CoV-2 binding to ACE2 (Tito et al., 2021).
7	a. Iranian propolis capsules (500 mg 3 times daily for 2 months). b. Brazilian green propolis capsules (900 mg daily for 18 weeks). c. Egyptian propolis (bioactive ligands) d. Propomax®/EPP-AF® capsules (400/800 mg daily for a week) e. 450 mg of Iranian propolis + 1.6 mg methanolic extract of *Hyoscyamus niger L* (10 mL of the solution 3 times daily for 6 days)	a. Iranian propolis b. Brazilian green propolis c. Rutin (flavonoid) and Caffeic acid phenethyl ester (phenolic) d. Brazilian green propolis e. Iranian propolis and *Hyoscyamus niger L*	 Caffeic acid phenethyl ester (https://pubchem.ncbi.nlm.nih.gov/compound/Caffeic-acid-phenethyl-ester#section=2D-Structure) See rutin structure at No 10	a. RCT (T2D patients) b. RCT (T2D patients) c. *in silico* (SARS-CoV-2 protein) d. RCT (COVID-19 patients) e. RCT (COVID-19 patients)	a. FBS, PBS↓, insulin↓, insulin resistance↓, glycated hemoglobin↓ (Afsharpour et al., 2019). b. Serum GSH↑, total polyphenols↑, carbonyls↓, LDH↓ (Zhao et al., 2016). c. Bind to SARS-CoV-2 Mpro (Refaat et al., 2021) d. Duration of hospitalization↓ (Silveira et al., 2021) e. Dry cough↓, dyspnea↓, sore throat↓, chest pain↓, fever↓, dizziness↓, headache↓, abdominal pain↓, diarrhea↓ (Kosari et al., 2021).

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Table 1 (*continued*)

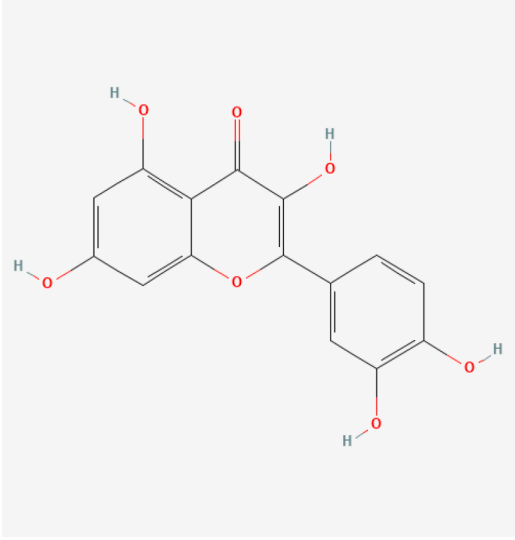
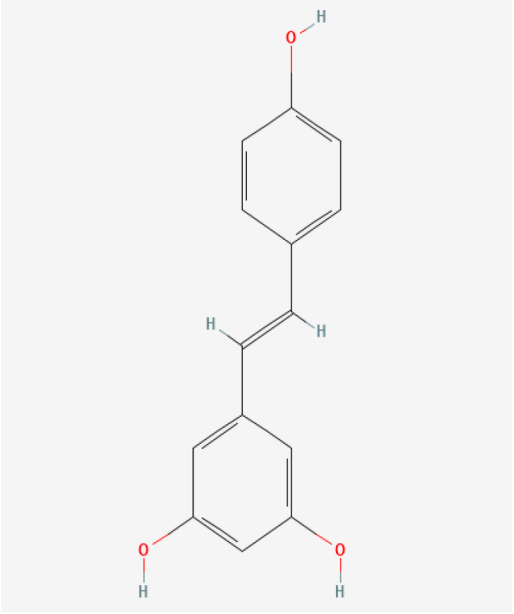
S/No	Type of supplement (Dosage and duration of treatment)	Bioactive component (type of chemical compound)	Chemical structure of the bioactive component (PubChem web reference)	Type of study (Subjects/targets)	Effect of supplement in diabetic patients/anti-COVID-19 potential of the bioactive compound (references)
8	a. Dietary Quercetin b. Quercetin Phytosome® (1500 mg daily for 7 days + 1000 mg daily for 7 days)	a. Quercetin (flavonoid) b. Quercetin (flavonoid)	 Quercetin (https://pubchem.ncbi.nlm.nih.gov/compound/quercetin#section=Structures)	a. RCT (normal Chinese adults) b. RCT (COVID-19 patients)	a. Protection against T2D (Yao et al., 2019) b. COVID-19 symptoms↓, viral clearance↑ (Di Pierro et al., 2021).
9	a. *Trans*-resveratrol capsules (500 mg twice daily for 2 months). b. Purified resveratrol capsules (500 mg twice daily for 2 months). c. *Trans*-resveratrol capsules (150 mg daily for 1 month). d. 200 mM resveratrol (in solution)	a. Resveratrol (polyphenol) b. Resveratrol (polyphenol) c. Resveratrol (polyphenol) d. Resveratrol (polyphenol)	 Resveratrol (https://pubchem.ncbi.nlm.nih.gov/compound/resveratrol)	a. RCT (T2D patients) b. RCT (T2D patients) c. RCT (obese male humans) d. *In vitro* (Vero E6 cells)	a. FBS↓, HDL↑, insulin↑, (Abdollahi et al., 2019). a. ADMA↓, PON1↓ (Tabatabaie et al., 2020). c. ACE2 expression↓ (de Ligt et al., 2021). d. SARS-CoV-2 replication↓, viral titer↓, cytotoxicity of host cells↓ (Pasquereau et al., 2021).

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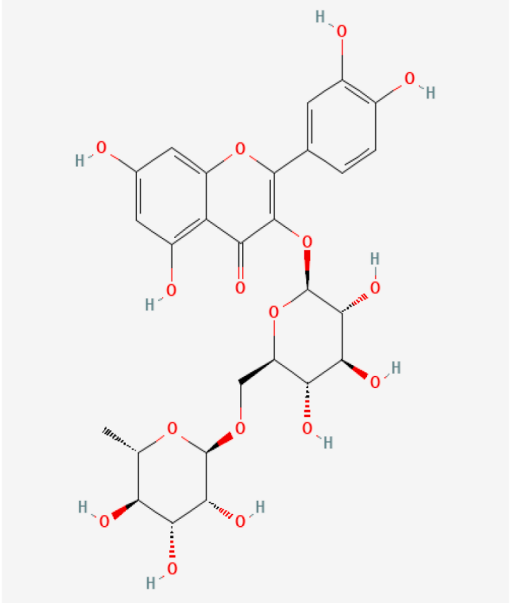
Table 1 (*continued*)

S/No	Type of supplement (Dosage and duration of treatment)	Bioactive component (type of chemical compound)	Chemical structure of the bioactive component (PubChem web reference)	Type of study (Subjects/targets)	Effect of supplement in diabetic patients/anti-COVID-19 potential of the bioactive compound (references)
10.	a. RUTA C 60 ® (60 mg Rutin + 160 mg vitamin C three times daily for 2 months) b. Rutin ligand	a. Rutin (flavonoid) and Vitamin C b. Rutin (flavonoid)	 Rutin (https://pubchem.ncbi.nlm.nih.gov/compound/rutin#section=2D-Structure)	a. RCT (T2D patients) b. *in silico* (SARS-CoV-2 protein)	a. %Change in FBS↓ (Ragheb et al., 2020). b. Binds SARS-CoV-2 Mpro, PLpro, RdRp, and S-protein (Rahman et al., 2021)

The table presents some herbal extracts/natural products or their bioactive compounds whose antidiabetic properties have been studied in human subjects, and have shown promising potentials in fighting COVID-19. ↑, increase; ↓, decrease; ACE2, Angiotensin-converting enzyme 2; ADMA, asymmetric de-methyl-arginine; FBS, fasting blood sugar; GLUT-4, glucose transporter-4; GSK-3β, glycogen synthase kinase-3β; hs-CRP, high-sensitivity C-reactive protein; HOMA' homeostasis model assessment; HDL, high-density lipoprotein; IAPP, islet amyloid polypeptide; IL-6, interleukin-6; LDL, low-density lipoprotein; MDA, malondialdehyde; miRNA-146a, microRNA-146a; OGTT, oral glucose tolerance test; PON1, paraoxonase-1; RCT, randomized controlled trial; T2D, type 2 diabetes; TAC, total antioxidant capacity; 8-OHDG, 8-hydroxy-2'-deoxyguanosine.

variable composition, and extraction methods, which are yet to be fully explored (Lim et al., 2021; Yang, 2020). Moreover, the few bioactive compounds proposed to be beneficial in fighting COVID-19 are based on *in silico* experiments. In other words, the majority of them have not been tested *in vitro* or *in vivo* (preclinical), let alone clinical trials. Such compounds although may be effective against COVID-19, may still have side effects that could lead to complications, especially in patients with pre-existing comorbidities like DM.

For instance, one of the proposed therapeutic targets of phytochemicals in COVID-19 treatment is the ACE2 receptor (Abubakar et al., 2021). It has been reported earlier that the downregulation of ACE2 disturbs the RAS and is associated with the progression of DM and its complications (Đambić, 2020; Ni et al., 2020; Shukla and Banerjee, 2021). Thus, chronic exposure to herbal remedies containing natural products with ACE2 binding potential could further dysregulate the RAS pathways since the normal physiological role of ACE2 in these patients is already suppressed by SARS-CoV-2 binding (Tseng et al., 2020). The treatment may therefore lead to serious COVD-19 and diabetes comorbidity with severe complications that may be fatal. Furthermore, whether natural products targeting ACE2 may interact with antidiabetic drugs that modulate the intrinsic activity of ACE2 is another critical concern, and such interaction is worth evaluating in the case of combined treatment.

Although most bioactive compounds present in herbal remedies are considered safe, only a few of them have a well-established toxicity profile, and some of these compounds may interact with conventional drugs thereby affecting their pharmacological properties (Oga et al., 2016). For instance, epigallocatechin gallate, a potential SARS-CoV-2 S-glycoprotein antagonist with antidiabetic properties is reported to be hepatotoxic at high oral doses in mice (Lambert et al., 2010). Being the metabolic hub of the body, liver damage in COVID-19 patients with DM comorbidity may worsen metabolic syndrome, leading to exacerbated complications. Similarly, nimbolin A, nimocin, and cycloartanols, the bioactive components of the neem (*Azadirachta indica A.Juss.*) have shown the potential to bind the E and M glycoproteins of SARS-CoV-2 (Borkotoky and Banerjee, 2021). However, Lim *et al.*, (2021) have reported some toxic effects of neem leaf extract in humans, including renal injury (an earlier reported complication in COVID-19 patients with DM comorbidity) (Lim *et al.*, 2021). Moreover, the potent antioxidant and anti-inflammatory agent, glycyrrhizin, has shown an inhibitory role against SARS-CoV-2 Mpro *in vitro* (van de Sand et al., 2021). However, a previous study has shown that glycyrrhizin decreased serum testosterone concentrations in male patients with T2D and chronic hepatitis, which according to the researchers may lead to atherosclerosis, insulin resistance, sexual dysfunction, and decreased libido in men (Fukui et al., 2003). This finding implies that concurrent treatment with glycyrrhizin in COVID-19 patients with DM comorbidity could have adverse health outcomes on the patients. It is mentionable that research on the toxicity profile of plant-derived bioactive compounds is lacking in the existing literature. Therefore, considering the increasing demand for these substances due to the present pandemic, studies aimed to ascertain their safety are warranted. Recent data is suggesting that some potential anti-COVID-19 bioactive compounds with established antioxidant, anti-inflammatory, and anti-diabetic properties such as curcumin, quercetin, resveratrol, and epigallocatechin gallate are important modulators of the epigenome (Cione et al., 2019; Ramírez-Alarcón et al.,

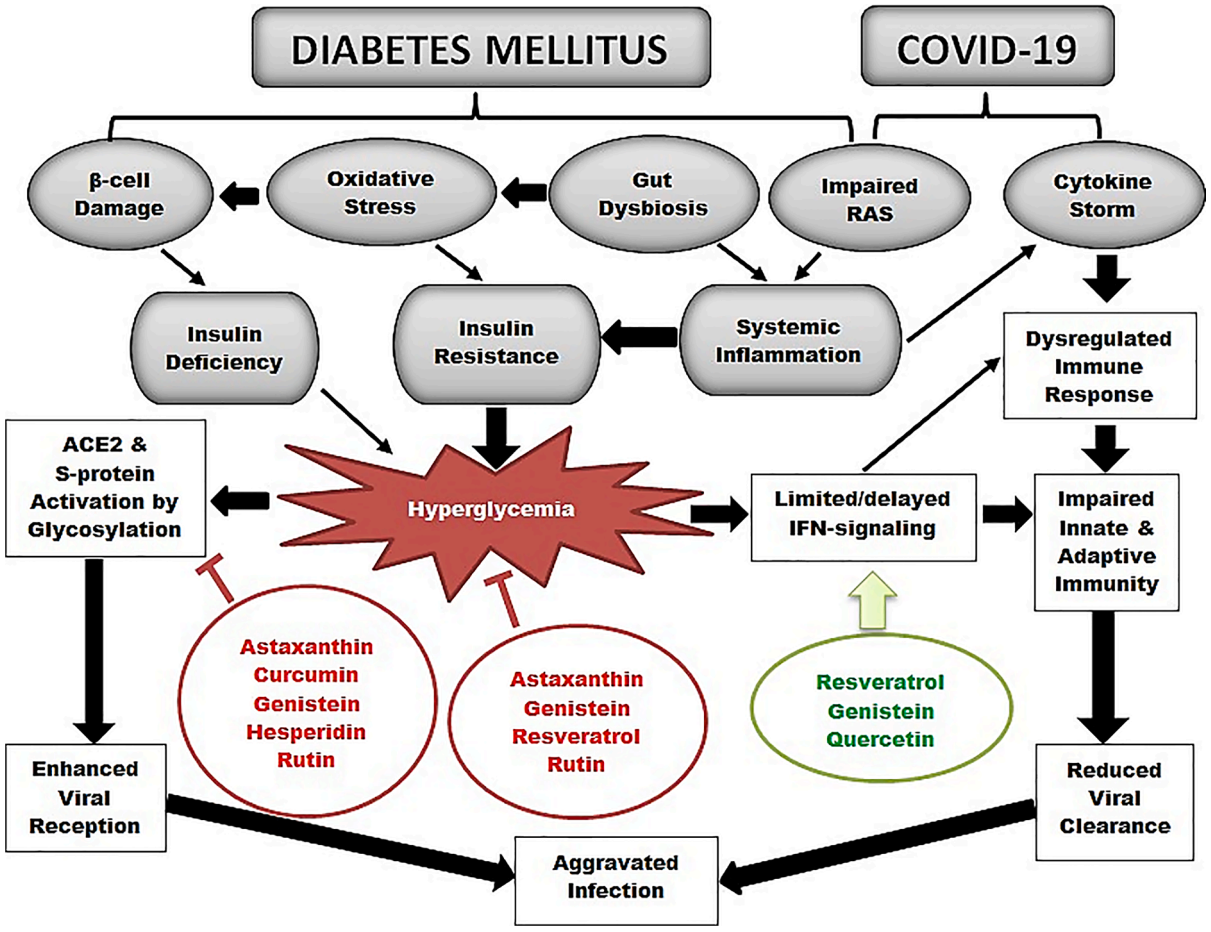


Fig. 2. Crosstalk between SARS-CoV-2 infection and diabetes mellitus (DM) showing the potential therapeutic targets of phytochemicals.

2021; Saleh et al., 2021). However, evidence on whether chronic exposure to high doses of these compounds may cause aberrant epigenetic reprogramming is lacking in the existing literature. Accordingly, another critical concern is the long-term consequences of previous exposure to substandard or toxic doses of these compounds, which may have a cumulative effect with the concurrent exposure.

Due to the ability of phytochemicals to modulate the gut microbial signature of an individual, another possible long-term detrimental consequence of preexisting chronic exposure to toxic doses of herbal remedies is the dysbiosis of the gut microbiota. It has been reported that the right composition of the gut microbiome may enhance the pharmacological properties of natural products in COVID-19 patients (Augusti et al., 2021), and changes in the gut microbiome have been implicated in the pathophysiology of DM, especially T2D (Gurung et al., 2020). Moreover, owing to the role of gut flora in immune response and inflammation, a recent paper has demonstrated how alterations in the gut microbial populations could be a critical determinant of the clinical outcomes in COVID-19 patients with DM and related sequelae (Chattopadhyay and Shankar, 2021). Therefore, alterations in the gut microbiome due to previous exposure to toxic doses or substandard preparations of herbal medications may exacerbate COVID-19 and diabetes comorbidity and may affect treatment with phytochemicals.

Conclusions and Perspectives

Bioactive components of herbal extracts and natural products with anti-COVID-19 potential whose antidiabetic properties have been clinically evaluated could be promising in managing COVID-19 and DM comorbidity. Ten (10) selected natural products comprising six phenolic compounds (curcumin, genistein, hesperidin, quercetin, resveratrol, and rutin), a carotenoid (astaxanthin), a terpenoid (oleanolic acid), pomegranate, and propolis have met the above criteria, and phenolic compounds appear to be the most promising phytochemicals. Of particular note, curcumin and propolis have shown sufficient evidence against COVID-19 and DM in humans and are thus, considered the best therapeutic options. More clinical trials are, therefore, warranted to fully explore the therapeutic potential of these substances.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phyplu.2022.100280.

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