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REVIEW

Herbal Medicines as Complementary Therapy for Managing Complications in COVID-19 Patients with Diabetes Mellitus

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Abstract: Diabetes mellitus (DM) is recognized and classified as a group of conditions marked by persistent high blood glucose levels. It is also an inflammatory condition that may influence concurrent disease states, including Coronavirus Disease 2019 (COVID-19). Currently, no effective drug has been found to treat COVID-19, especially in DM patients. Many herbal medicines, such as the well-known *Andrographis paniculata*, have been explored as drugs and complementary therapies due to their antidiabetic, antibacterial, antiviral, anti-inflammatory, and immunomodulatory effects. This study aimed to examine the potential of herbal medicines as complementary therapy in DM patients with COVID-19 complications, drawing from in-vitro and in-vivo investigations. This study analyzed articles published within the last 15 years using keywords including "herbal medicines", "COVID-19", "Diabetes Mellitus", "antidiabetics", "antiviral", and "anti-inflammatory". The results showed that several herbal medicines could serve as complementary therapy for DM patients with COVID-19 complications. These include *Andrographis paniculata, Ageratum conyzoides, Artocarpus altilis, Centella asiatica, Momordica charantia, Persea gratissima, Phyllanthus urinaria, Physalis angulata, Tinospora cordifolia*, and *Zingiber zerumbet*. Herbal medicines may serve as a complementary therapy for DM patients with COVID-19, but these claims need experimental validation in infection models and among affected patients.

Keywords: COVID-19, diabetes mellitus, antidiabetic, immunomodulator, anti-inflammatory, herbal medicines

Introduction

The worldwide outbreak of the Coronavirus Disease 2019 (COVID-19) towards the end of 2019 is significantly disrupting various human activities, especially within the healthcare sector.[1,2] It is a respiratory condition caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. People grappling with chronic conditions such as Diabetes Mellitus (DM) often have an elevated mortality rate, a phenomenon attributed to the effects of COVID-19 on the immune system. Additionally, the novel coronavirus targets essential organs including the lungs, brain, kidneys, and heart. These repercussions are implicated in the heightened vulnerability and comorbidity observed in people with chronic illnesses who contract COVID-19.[3] The COVID-19 pandemic has impacted daily life not only through infections but also through lockdowns and restrictions. These changes have disrupted lifestyle routines, particularly affecting diabetic patients by complicating blood glucose control and overall health.[4,5]

DM is a syndrome characterized by signs and symptoms of prolonged high blood glucose.[6] According to the 2019 International Diabetes Federation report, the global prevalence of DM is 463 million people, with projections expected to reach 578 million by 2030 and 700 million by 2045. It is estimated that approximately 20% to 50% of COVID-19 patients have DM, a rate significantly higher than the global incidence of the disease.[7]

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In SARS-CoV-2 infection, the host cell plays a crucial role in cross-species transmission. After the host is exposed to the virus, the spike proteins on the surface of SARS-CoV-2 attach to cells that express specific receptors. The protease of the host cell then breaks down the spike protein, enabling the virus to penetrate the cell and replicate.[8,9] Angiotensin-converting enzyme-2 (ACE-2) has been recognized as a primary receptor for both SARS-CoV and SARS-CoV-2. It is extensively expressed in various tissues, including the respiratory tract, intestines, kidneys, heart, brain neurons, arterial and venous endothelium, pancreas, and immune cells.[8,10]

COVID-19 initially became a pandemic in March 2020, and until early November 2021, it has infected 254 million people worldwide and has a two-way relationship with DM. Patients with COVID-19 have also shown severe metabolic complications from pre-existing DM, including hyperosmolarity and diabetic ketoacidosis requiring high doses of insulin. In Italy, the mortality rate among COVID-19 patients with DM is 36%.[11] The relation between infection and DM has long been recognized clinically. Diabetes impairs the immune system, making individuals more susceptible to infections like COVID-19.[12] It also promotes chronic inflammation, increasing the risk of a severe cytokine storm. Diabetic patients have higher levels of ACE2 receptors, which SARS-CoV-2 uses to enter cells, and this is linked to altered glucose metabolism.[13] Additionally, diabetes causes endothelial dysfunction and raises the risk of blood clots, further complicating COVID-19 outcomes.[14,15]

Although significant progress has been made in developing anti-SARS-CoV-2 inhibitors, many of these drugs need to be evaluated in terms of side effects or pharmacoeconomics aspect. Ritonavir has numerous drug-drug interactions that necessitate careful evaluation before use,[11,16] and Paxlovid is costly, priced at $530 for each 5-day treatment course.[17] In addition, before the development and widespread distribution of COVID-19 vaccines and in the absence of specific antiviral therapies, especially among DM patients, there was heightened interest in alternative and complementary treatments, including herbal medicines. Some herbal medicines were proposed as potential complementary therapy based on antiviral and anti-inflammatory properties. Herbal medicines, which have a long history in traditional medicine, have the potential to aid in symptom relief, enhance recovery, and strengthen the immune system. While no herbal remedy has been consistently proven effective for treating COVID-19, recent studies have identified promising candidates.[18–20] Some natural compounds, especially flavonoids, may block viral entry by modulating the ACE2 receptor through the spike-RBD/TMPRSS2/ACE2 axis.[21] Additionally, several herbs have multi-functional effects, offering antiviral, anti-inflammatory, antidiabetic, and immunomodulatory benefits.[18–20]The main objective of this review was to examine the scientific evidence of herbal medicines used as complementary therapy in DM patients with COVID-19 complications. This review discusses the potency of herbal medicines in in-vivo and in-vitro studies using animal and human models.

Methods

The articles were selected based on the inclusion criteria formulated, including journals published in the last 15 years (2008–2023), written in Indonesian and English, available as full-text articles and abstracts. The keywords used were "herbal medicines", "COVID-19", "DM", "antidiabetics", "antiviral", and "anti-inflammatory".

After determining the article search criteria, a search was performed using a predetermined database. The next step was to select articles from the 138 obtained according to the topic and study questions. The article selection mechanism was performed by formulating inclusion criteria. Meanwhile, non-English, reviews, unrelated studies, were excluded. After sorting the articles according to the inclusion criteria, a screening was conducted to re-check whether the contents of the 93 selected articles were in accordance with the pre-set study questions. The 25 articles which satisfied the inclusion criteria were then analyzed. In addition, a screening chart for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Scoping Review (PRISMA) (Figure 1).

Results and Discussion

COVID-19 Effects on Diabetes Mellitus

COVID-19 infects almost all ages but the currently available data show that the elderly and people with comorbidities have a higher risk and worse complications. These comorbidities include hypertension, DM, cardiovascular disease, and

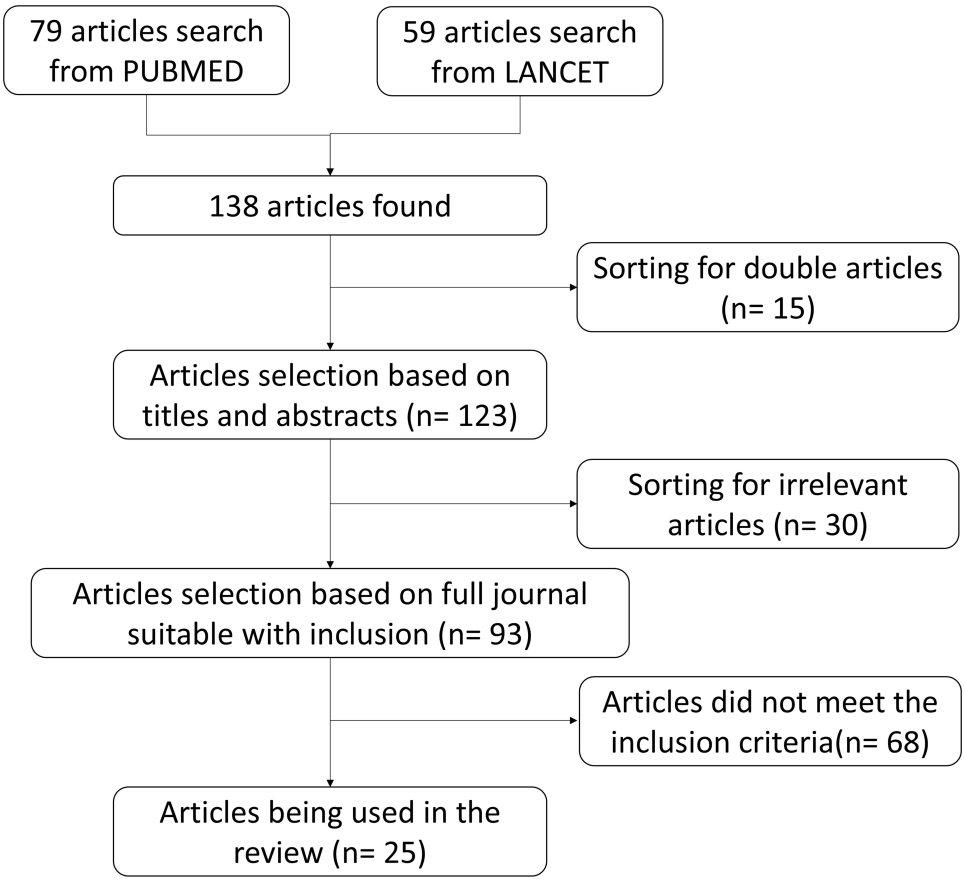

Figure 1 PRISMA Chart.

chronic lung disease. COVID-19 is found in about 8% of cases, especially in patients with DM. The worldwide outbreak of COVID-19 started at the end of 2019, significantly disrupting various human activities, especially within the healthcare sector.[1,2] Not only the infection of COVID-19 itself, but lockdowns have also influenced dietary habits, leading to higher glucose intake, as well as increased stress and depression, which can trigger systemic inflammation. Given these challenges, herbal and nutritional interventions may provide supportive benefits by helping manage diabetes and enhancing immune function, potentially helping diabetic individuals better cope with COVID-19 risks.[4,5,22]

The relation between infection and DM has long been recognized clinically. Infections, primarily pneumonia and influenza, are often found in older people with T2DM.[16] However, it remains debatable whether DM increases susceptibility and the outcome of infection or whether cardiovascular and renal diseases are the primary factors at play.

DM is a long-term inflammatory condition marked by various metabolic and vascular disorders that can impact our response to infections. Elevated blood glucose levels and insulin resistance increase the synthesis of advanced glycated end products and pro-inflammatory cytokines, which play a role in mediating tissue inflammation.[12] This inflammatory process could be the underlying mechanism for the increased susceptibility to infections and poorer outcomes. DM patients are generally characterized by elevated levels of pro-inflammatory cytokines, such as C-reactive proteins (CRP) and interleukin-6 (IL-6). Additionally, these patients show increased coagulation activity, indicated by higher concentrations of d-dimer, which correlates with disease severity.[14,15]

In a study conducted in China, 39 SARS-CoV patients without a history of DM, who did not receive steroid treatment, were compared to 39 matched healthy siblings. The results showed that 20 patients developed DM during hospital stay. In addition, immunostaining for ACE-2 is also commonly found in pancreatic islets, suggesting SARS-CoV can also damage pancreatic islets, causing DM due to insulin deficiency.[23] Although additional evidence is required, pancreatic damage may also occur and could have a more severe impact on DM patients with COVID-19.

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WHO announced therapeutic recommendations for therapeutics in September 2021, including casirivimab and imdevimab for neutralizing monoclonal antibodies, IL-6 receptor blockers, and systemic corticosteroids.[24,25] There is currently no data on the best management strategies for DM patients infected with SARS-CoV-2 or for COVID-19 patients experiencing glycemic decompensation. Therefore, it is necessary to consider alternative interventions, including herbal or traditional medicines, as supplementary options to conventional DM therapy for COVID-19 patients.

Herbal Medicines as Complementary Therapy in Diabetes Patients with COVID-19

According to the World Health Organization (WHO), traditional medicines refer to the knowledge, skills, and practices rooted in the theories, beliefs, and experiences of various cultures, used for maintaining health and for the prevention, diagnosis, enhancement, or treatment of physical and mental diseases.[26] Traditional Chinese Medicine (TCM) is a significant example of how ancient and accumulated knowledge is used in a holistic approach within contemporary healthcare.[27] Most TCM consists of a single plant or a mixture of various herbal medicines widely known to have many pharmacological activities. Sambiloto (*Andrographis paniculata*) extract is an example of herbal medicines with pharmacological activity including antidiabetic, antibacterial, antiviral, anti-inflammatory, and immunomodulator often used as an alternative DM therapy.

In 2003, TCM was used to treat various viral infections, including SARS, Middle East Respiratory Syndrome (MERS), Asian lineage avian influenza A (H7N9), avian influenza A (H1N1), Ebola virus, and others.[28] TCM has also been advocated as a remedy for COVID-19 in the "New Coronavirus Pneumonia Diagnosis and Treatment Plan" (Trial Version Five).[28] Nourishment and herbs demonstrate antiviral and immunomodulatory activities, for instance, *Aloe vera, Ganoderma lucidum* (lingzhi mushroom), *Panax ginseng* (ginseng), and *Scutellaria baicalensis* (Chinese skullcap) have demonstrated immunomodulatory properties.[29] The actions selectively stimulate cytokines, enhancing the ability to kill abnormal cells by intensifying macrophage actions and activating lymphocytes. Furthermore, wheat bran, rice bran, *Echinacea purpurea, Plumbago zeylanica* (Ceylon leadwort), *Lawsonia alba* (hina), and *Cissampelos pareira Linn* (velvetleaf) have been studied for the ability to enhance immunomodulatory properties by promoting phagocytosis. Eucalyptus essential oil has also been reported for the ability to enhance the innate cell-mediated immune response and may serve as an immunoregulatory agent against viruses responsible for infectious diseases.[30,31]

Since the spread of coronavirus, especially COVID-19, allopathic therapy has been used to cure 99 patients in Wuhan Jinyintan Hospital including intravenous immunoglobulin (27%), oxygen (75%), antiviral (76%), and antibiotic (71%).[32] The US Food and Drug Administration (FDA) has not yet approved any specific drug for COVID-19 therapy. However, many studies continuously discover effective COVID-19 therapy using herbal medicines known for antiviral, anti-inflammatory, immunomodulatory, and antidiabetic activity. These herbal medicines could serve as complementary therapy for DM patients facing complications related to COVID-19.

A specific antiviral treatment for COVID-19 has not yet been determined.[33] Therefore, several approaches have been suggested, such as using convalescent plasma and interferon (IFN), together with IL-6 receptor inhibitors to reduce the cytokine storm.[34] Chloroquine and hydroxychloroquine also play roles in inhibiting endocytosis-mediated viral entry, endosomal acidification, and ACE-2 glycosylation.[35–37] Ivermectin also inhibits the nuclear transport of viral proteins.[38,39] On June 17, 2020, WHO announced to stop using chloroquine and hydroxychloroquine for COVID-19 therapy. This recommendation was founded on six trials with 6000 participants who were not infected with SARS-CoV -2, as well as 30 trials with more than 10,000 COVID-19 patients. WHO reported that Chloroquine and hydroxychloroquine did not lower mortality rates, and may even heighten the risk of heart rhythm issues, kidney damage, blood and lymph disorders, liver complications, and failures. These drugs are safe for use in patients with malaria or autoimmune diseases, but not COVID-19.[24,37,40]

Antivirals targeting protease inhibitor proteins and nucleotide or nucleoside analogs that work to block viral RNA synthesis have been recognized for treating SARS-CoV-2 infection.[41–44] Nucleoside analogs are a class of drugs that inhibit reverse transcription and represent some of the most effective antiviral agents for fighting SARS-CoV-2 infection.[45] The antiviral and antidiabetic effects of herbal medicines, particularly quercetin, against influenza and SARS-CoV viruses have been validated through the inhibition of SARS-CoV 3-chymotrypsin-like protease (3CLpro) expression in *Pichia pastoris*.[46,47]

Anti-Inflammatory and Immunomodulatory Activity of Herbal Medicines in COVID-19 and Patients with Diabetes

Patients with DM are more susceptible to bacteria or viral infections and have a more severe disease course than non-diabetic people.[48] Previous studies showed an increased risk of COVID-19 severity in patients with T2DM along with a higher rate of morbidity and mortality.[49–52] Some mechanisms that trigger this increasing severity are DM-associated endothelial dysfunction, decreased viral immunity, and a compromised immune system.[53,54] A population-based cohort study reported a rise in COVID-19-related deaths among DM patients (both type 1 and type 2) compared to the period before the pandemic.[55]

SARS-CoV-2 infection affects multi-organ systems and influences ACE-2 receptor expression. Recent studies reported that viral infection of pancreatic endocrine and exocrine cells caused changes in morphology, translation mechanism, and functional aspects of the pancreas, leading to impaired insulin secretion.[56,57] Inflammatory responses were also linked to increased blood glucose levels. The activities of macrophages and monocytes in the immune response and viral infection resulted in a worse prognosis for COVID-19 patients. An in-vitro study reported increased viral load, as well as ACE-2 and interleukin expression in DM patients infected with SARS-CoV-2.[58] Clinical data also reported increased glucose levels, cytokines, and immune responses. DM patients with COVID-19 show an increased proportion of T-helper cells, a lower percentage of T-cytotoxic cells, as well as higher serum levels of IL-2, IL-6, IL-10, and IFN-γ.[59]

Maintaining blood glucose levels within the normal range can enhance the prognosis and survival rate.[50] However, when selecting a glucose-lowering agent for DM patients with COVID-19, it is necessary to consider clinical factors, comorbidities, and the mechanisms of concomitant drugs administered to treat other symptoms. The absence of an optimal drug for DM and the diminished effectiveness of oral medications are currently concerns for disease progression. Although these drugs are essential in managing DM, the reduced efficacy in maintaining glucose homeostasis over time and the associated side effects have restricted use.[60] In this context, plant extracts and plant-derived compounds that possess antioxidant and immunomodulatory properties could act as a complementary or alternative therapy to help reduce and/or prevent complications related to congenital DM.[20,61]

Except for respiratory failure, critically ill COVID-19 patients share features in common with previous studies. One feature is having a very high inflammatory parameter, including CRP, pro-inflammatory cytokines such as IL-6, IL-8, Tumor necrosis factor alpha (TNF-α) and others, immune system destruction indicated by spleen and lymph node atrophy, and reduction of lymphocytes in lymphoid organs.[62,63] Meanwhile, herbal medicines, which have anti-inflammatory and immunomodulatory activities such as *Panax ginseng*, inhibit cytokine production and viral replication, bio-inflammatory marker production and heighten immunity by increasing antibodies in the body. *Centella asiatica* has various pharmacological activities, including antihyperglycemic effects in obese diabetic rats, anti-inflammatory and analgesic activity based on chemical-induced animal behavior tests, as well as therapeutic activity on liver and kidney enzymes associated with oxidation of glucose and amino acids affected by DM. This plant significantly reduced renal levels of malondialdehyde (33%), IFN-γ (42%) and TNF-α (78%). Treatment with *Centella asiatica* also significantly enhanced the antioxidant status of the kidneys and brain in obese diabetic rats.[64]

Herbal medicines currently remain a favorite alternative and complementary therapy in many countries, along with allopathic therapy. Although herbal medicines can be complementary therapy in DM and COVID-19 patients, further studies are needed regarding efficacy, effectiveness, dosage, and toxicity. While reviewing the effectiveness of therapy, efficacy, and side effects of using herbal medicines in DM patients with COVID-19 complications, it is also necessary to monitor blood glucose levels closely and thoroughly to avoid drug interactions that can worsen symptoms and other unwanted outcomes.[65]

Although hyperglycemia is typically the primary concern, other factors should not be ignored. These include the possibility of a hypoglycemic reaction resulting from the interaction between drug therapy, the symptoms often experienced by DM patients, and COVID-19 viral pathogenesis. Therefore, it is also necessary to develop careful and effective therapeutic formulations along with strict and optimal glucose level measurements for DM patients infected with COVID-19 to obtain the desired results.

Some studies reported that using insulin can decrease severity and mortality rates. These results were due to the anti-inflammatory and immunomodulatory activity as well as decreased blood glucose levels in DM patients[66,67] However, other studies claimed that insulin administration could worsen the clinical profile of DM patients with COVID-19. This condition correlated with poor prognosis caused by insulin-mediated inhibition of disintegrin and metalloproteinase domain-containing protein 17 (ADAM17), facilitating proteolytic cleavage and release of the active ectodomain of ACE-2. Therefore, it elevated the activities of ACE-2 in SARS-CoV-2 infection.[68,69]

Recent studies reported decreasing mortality rates among DM patients infected with SARS-CoV-2 who were administered metformin to maintain blood glucose levels. This decrease was potentially due to the mammalian target of rapamycin (mTOR) inhibitory effects of metformin.[70] Studies have suggested that metformin may interfere with the interaction between host cells and viral proteins regulating replication, assembly, and pathogenesis.[71,72] The immunomodulatory mechanisms of metformin are inhibiting monocyte-macrophage differentiation, pro-inflammatory expression of activated macrophages, as well as differentiation of T-cells into regulatory and memory T-cells. However, some issues arose when the FDA recalled metformin in 2020. The concern was related to nitrosamine impurity findings in some metformin extended-release products. These results caused many patients to find natural and effective alternatives to metformin with similar active components.[73] Some active components that can replace metformin are berberine and N-acetyl-cysteine (NAC).

Table 1 shows some herbal medicines with antidiabetic properties as well as other pharmacological activities related to COVID-19. Although this review provides preliminary data on the medicinal plants that can be used as complementary therapy for DM patients with COVID-19 complications, it did not discuss safety profiles, potential side effects, or interactions of herbal medicines with conventional medications due to limited references on the mentioned topic. Some other herbal medicines showed antidiabetic effects and can be used as alternatives for DM patients with COVID-19 complications (Table 1).

Among the various herbal medicines discussed in this review, several have shown promising potential as complementary therapy for COVID-19 patients with DM complications. However, determining the most effective is challenging due to the differences in methodologies, designs, and experimental conditions used across the studies. The variability in dosages, models (animal vs human), and outcome measures further complicates direct comparisons between herbal medicines.

Table 1 Potential Herbal Medicines That Could Be Used as Complementary Therapy for DM Patients with COVID-19 Complications

Herbal medicines	Bioactive compound	Pharmacology activity	Result	Experimental testing	References
Andrographis paniculata	Andrographolide	Antidiabetic	Andrographolide extracts significantly reduced blood glucose, triglyceride and LDL.	Animal model	[74]
		Anti-inflammatory	The extract has anti-inflammatory effects by inhibiting NF-kB and reducing TNF-α, IL-6, MIP-2 and NO secretion in macrophages.		[75]
Ageratum conyzoides	Polymethoxyflavones, flavonoid, tannins, and terpenoids	Antidiabetic	Aqueous extracts of *Ageratum conyzoides* showed significant hypoglycemic effects.	Animal model	[76]
		Anti-inflammatory	Polymethoxyflavones extracts from *Ageratum conyzoides* significantly reduced paw edema and nocifensive response.		[77]

(*Continued*)

Table 1 (Continued).

Herbal medicines	Bioactive compound	Pharmacology activity	Result	Experimental testing	References
Artocarpus altilis	GABA	Antidiabetic	GABA and *Artocarpus altilis* leaves target the pancreas as antidiabetic agents.	Animal model	[78]
		Antiviral	DCM extracts of *Artocarpus altilis* and *Artocarpus camansi* showed moderate anti-HCV activity.		[79]
		Anti-inflammatory	*Artocarpus altilis* extract inhibited edema.		[80]
Centella asiatica	Triterpenoid, steroid, and saponin	Antidiabetic and anti-inflammatory	*Centella asiatica* reduced renal MDA (33%), TNF-α (78%), and IFN-γ (42%) as well as brain MDA (37%), TNF-α (30%), and IFN-γ (37%) in diabetic rats. Additionally, it boosted antioxidant status in the renal and brain tissues of obese diabetic rats.	Animal model	[64]
Momordica charantia	Cucurbitane-type triterpenoids	Antidiabetic	Oral *Momordica charantia* fruit extract significantly lowered blood glucose in STZ-induced diabetic rats.	Animal model	[81]
		Anti-inflammatory	It modulates inflammasome genes and gut-adipose inflammation in HFD-fed mice.		[82]
		Antiviral	*Momordica charantia* antiviral protein inhibits multiple influenza subtypes.		[83]
Persea gratissima	Avocatin	Antiviral	*Persea americana* fruit extract inhibits dengue virus replication.	Animal model	[83]
		Anti-inflammatory	*Persea gratissima* reduces oxidative stress, boosts SOD activity, and prevents ulcers and histological damage caused by indomethacin.		[84]
		Antidiabetic	Avocatin B inhibits fatty acid oxidation boosts glucose oxidation, and reduces mitochondrial ROS, enhancing insulin sensitivity.		[85]
Phyllanthus urinaria	Excoecarianin,[86] gallic acid, corilagin, and macatannin B[87]	Antiviral	Excoecarianin from *Phyllanthus urinaria* protected vero cells from HSV-2 with an IC50 of 1.4 ± 0.1 μM	Animal model	[88]
		Antidiabetic	*Phyllanthus urinaria* inhibit porcine pancreatic amylase activity.		[87]

(*Continued*)

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Table 1 (Continued).

Herbal medicines	Bioactive compound	Pharmacology activity	Result	Experimental testing	References
Physalis angulata	Withanolides,	Anti-inflammatory	Withanolides from *Physalis angulata* showed antiproliferative, anti-inflammatory and NO inhibition effects.	Animal model	[89]
		Antidiabetic	Methanol extract of *Physalis angulata* significantly reduced blood glucose, kidney weights, fructosamine, HbA1c, MDA, creatinine and BUN in alloxan-induced diabetic rats.		[90]
Stevia Rebaudiana	Stevioside, steviol compounds, flavonoids, quinic acid, caffeic acid	Antidiabetic	*Stevia Rebaudiana* extract significantly lowers blood glucose.	Animal model	[91,92]
		Anti-Inflammatory	Stevia inhibits iNOS, pro-inflammatory cytokines, and PGE2 production.	In-Vitro	[93]
Tinospora cordifolia	Alkaloids (Magnoflorine, Palmetine, Jatrorrhizin), tannins, cardiac glycosides, flavonoids, and saponins	Anti-Inflammatory	*Tinospora cordifolia* extract has strong analgesic, anti-inflammatory and antipyretic effects.	Animal model	[94]
		Antidiabetic	*Tinospora cordifolia* stems improve glucose uptake in 3T3-L1 adipocytes and regulate glucose metabolism in diabetic rats.		[95]
Zingiber zerumbet	Kaempferol, kaempferol-3-O-methylether, zerumbone	Antidiabetic	Kaempferol and kaempferol-3-O-methylether effectively inhibit α-glucosidase, aldose reductase and glycation, key targets for DM treatment.	In-Vitro	[96]
		Anti-inflammatory	*Zingiber zerumbet* extract reduced pro-inflammatory mediators, COX-2 expression and downregulated pro-inflammatory markers mRNA.		[97]
Fibraurea tinctoria	Berberine	Antidiabetic	Berberine lowered blood glucose without affecting the weight of the heart, liver or kidney.	Animal model	[98]
Allium cepa and *Allium sativum*	NAC	Antidiabetic	NAC improved hyperglycemia and hypo-insulinemia, reduced ALT, urea, and hepatic triglycerides, lowered oxidative stress and boosted hepatic antioxidant enzymes.	Animal model	[99]

Abbreviations: LDL, Low Density Lipoprotein; NF-kB, Nuclear Factor Kappa-B; TNF-α, Tumor Necrosis Factor Alpha; IL-6, Interleukin 6; MIP-2, Macrophage Inflammatory Protein 2; NO, Nitric Oxide; gaba, Gamma-Aminobutyric Acid; DCM, Dichloromethane; HCV, Hepatitis C; MDA, Malondialdehyde; IFN-γ, Interferon Gamma; STZ, Streptozotocin; HFD, High-Fat Diet; SOD, Superoxide Dismutase; ROS, Reactive Oxygen Species; IC50, Inhibition Concentration 50%; HbA1C, hemoglobin A1c; BUN, Blood Urea Nitrogen; iNOS, inducible nitric oxide synthase; PGE2, Prostaglandin E2; COX2, Cyclooxygenase-2; mRNA, messenger Ribonucleic Acid; NAC, N-acetyl- cysteine; ALT, Alanine Aminotransferase.

Our study is limited to in vitro and in vivo models, which, while providing valuable insights, may not fully translate to humans due to physiological and metabolic differences. These differences can impact drug dosage, bioavailability, and effectiveness in human applications. Recent human studies on certain herbal products, such as curcumin and propolis, show promise against COVID-19 and diabetes (DM), but data remain limited.[21] Observational studies on other herbs, including *Echinacea purpurea*, turmeric (*Curcuma longa), Nigella sativa*, and *Zingiber officinale*, suggest potential as adjuvant therapies for COVID-19.[100] Therefore, further human studies—specifically clinical trials—are needed to confirm the efficacy, optimal dosages, and safety of these herbal treatments. This study could serve as preliminary research for future human investigations.

Conclusion

In conclusion, the limited efficacy of available allopathic medicines against COVID-19 highlights the need for alternative or complementary approaches. Current literature provides substantial evidence that herbal medicines may serve as potential adjunct therapies for managing complications in diabetes mellitus (DM) patients with COVID-19. Promising candidates include *Andrographis paniculata, Ageratum conyzoides, Artocarpus altilis, Centella asiatica, Momordica charantia, Persea gratissima, Phyllanthus urinaria, Physalis angulata, Tinospora cordifolia, Zingiber zerumbet, Fibraurea tinctoria, Allium cepa*, and *Allium sativum*. These herbal medicines may play a role as complementary preventive and adjunct therapies. To translate these findings into clinical practice, further experimental validation and clinical trials are essential to establish their efficacy and safety in COVID-19 patients with DM. Additionally, exploring their mechanisms of action, optimal dosing, and potential interactions with standard treatments would provide critical insights for integrating herbal medicines into comprehensive therapeutic strategies. This research direction could significantly enhance patient outcomes and broaden the scope of integrative medicine in managing COVID-19 and its complications.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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