Brief Report

Effect of *Ficus pumila* L. on Improving Insulin Secretory Capacity and Resistance in Patients Who Develop Diabetes After COVID-19 Infection

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Effect of *Ficus pumila L.* on Improving Insulin Secretory Capacity and Resistance in Patients who Develop Diabetes after COVID-19 Infection

Kenji Gonda [1,2,3,*], Takeshi Hai[4], Kouichi Suzuki [3,4], Akihiko Ozaki [1,2], Takashi Shibusa [5], Seiichi Takenoshita [6], Yuko Maejima [3] and Kenjyu Shimomura [3]

1 Department of Breast and Thyroid Surgery, Jyoban Hospital of Tokiwa Foundation, Iwaki City, Fukushima, Japan, 972-8322, gondake@fmu.ac.jp, ozakiakihiko@gmail.com
2 Department of Gastrointestinal Tract Surgery, Fukushima Medical University, 1 Hikarigaoka, Fukushima City, Fukushima, Japan 960-1295, gondake@fmu.ac.jp, ozakiakihiko@gmail.com
3 Department of Bioregulation and Pharmacological Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima, Japan 960-1295, suzukou8931@gmail.com, maejimay@fmu.ac.jp, shimomur@fmu.ac.jp
4 Department of Internal Medicine Daido Central Hospital, 1-1-37 Asato, Naha City, Okinawa, Japan 902-0067, 81takeshi@gmail.com
5 Department of Internal Medicine, Jyoban Hospital of Tokiwa Foundation, Iwaki City, Fukushima, Japan 972-8322, takashi-shibusa@tokiwa.or.jp
6 Department of Drug Research for Astatine-221 Targeted Alfa Therapy, Fukushima Medical University, 1 Hikarigaoka, Fukushima City, Fukushima, Japan 960-1295, akiko-t@fmu.ac.jp
* Correspondence: gondake@fmu.ac.jp; Tel.: +81-246-81-5522

Abstract: (1) Background: It has been reported that people affected by COVID-19, an infectious disease caused by SARS-CoV-2, suffer from various diseases, after infection. One of the most serious problems is the increased risk of developing diabetes after COVID-19 infection. However, a treatment for post-COVID 19 infection diabetes has not yet been established. In this study, we investigated the effects of *Ficus pumila L.* extract, which has traditionally been used to reduce blood glucose level in Okinawa, on patients who developed diabetes after COVID-19 infection.; (2) Methods: Sixty-two rehabilitation patients who developed diabetes after COVID-19 infection were included. The HOMA−β (Homeostatic model assessment of β-cell function) and HOMA-IR (Homeostatic model assessment of insulin resistance) was assessed to evaluate the glucose tolerance.; (3) Results: The HOMA-β was decreased and also HOMA-IR was increased in patient who developed after diabetes after COVID-19 infection. Subsequently, 28 patients were given *Ficus pumila L.* extract and their HOMA-β and HOMA-IR improved after ingestion. On the other hand, the control group of patients who did not consume *Ficus pumila L.* showed no improvement in both HOMA-β and HOMA-IR. (4) Conclusions: *Ficus pumila L.* extract, ingested by patients who developed diabetes after COVID-19 infection, stimulated insulin secretion capacity and improved insulin resistance.

Keywords: *Ficus pumila L.*; diabetes mellitus; COVID-19; HOMA-β; HOMA-IR

1. Introduction

A large study based on approximately 200,000 people found that patients infected with COVID-19 by SARS-CoV-2 have an increased risk of developing diabetes within a year, unrelated to the severity of symptoms upon infection [1,2].

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It has been reported that patients with no previous risk factors for diabetes are also more likely to develop diabetes after infection. Patients who develop diabetes after infection resemble type 2 diabetes mellitus, and have been reported to have both impaired insulin secretion and increased insulin resistance, which are two major causes of type 2 diabetes mellitus.

Ficus pumila L. is native to East Asia (China, Japan, and Vietnam) and belongs to the mulberry family (Figure 1a, b). In Japan, Ficus pumila is found only in Okinawa, where internationally recognized area as outstanding longevity. The extracts of *Ficus pumila L.* have been traditionally consumed in Okinawa for more than 500 years to promote their health [3] (Figure 1c, d). The bioactive compounds of *Ficus pumila L.* and the latest knowledge on treatments were reported in detail. Flavonoids (Rutin), flavones (Apigenin) and flavonols (Kaempferol) have so far been extracted from *Ficus pumila L.* leaves, stems and fruits, and these bioactive compounds exhibit multiple therapeutic activities [4] (Figure 1e). However, it is now consumed only in certain areas of the main island, and its existence is unknown even to the islanders.

In the present study, we examined whether extracts from *Ficus pumila L.* is effective in improving hyperglycemia of diabetic patients after COVID-19 infection.

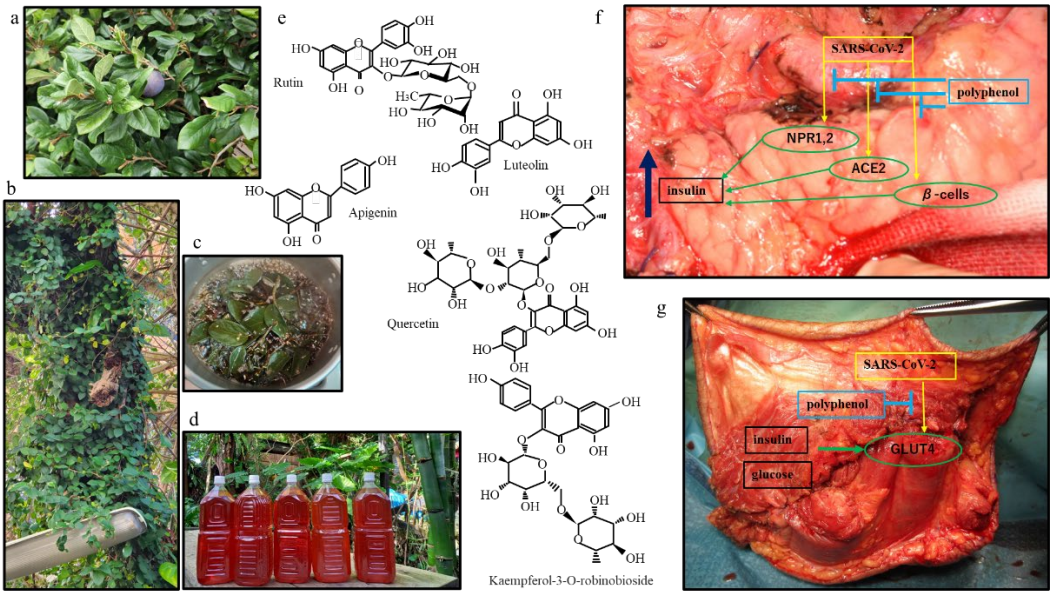

Figure 1. Close-up of the leaves, The extracts of *Ficus pumila*, Bioactive polyphenol compounds, Pancreas head and body, Axial of femoral muscle.**a.** Leaves, stems, and fruits of *Ficus pumila L. Ficus pumila L.* was named by the botanist Carl von Linne. **b.** *Ficus pumila L.* commonly known as the creeping fig or climbing fig, is a species of flowering plant in the mulberry family. **c.** With Motobu water Boiling 200 g of cleanly washed leaves and stems of *Ficus pumila L.* in 2 L of water at 100°C for 10 minutes. **d.** In Okinawa, people drank tea made from the extraction of *Ficus pumila L.* plants for their health more than 500 years. Now, the tea is extremely rare. *Ficus pumila L.* in the Motobu area of Okinawa Prefecture was carefully made into amber-colored Ficus pumila tea. **e.** Rutin, Apigenin, Luteolin, Quercetin and Kaempferol have been extracted from *Ficus pumila L.* leaves and stems. **f.** Pancreas. Polyphenols protected the function of β-cells and inhibited Neuropilin 1, 2 (NPR1,2) and recombinant human ACE2 activity in pancreatic tissue infected covid-19. **g.** Quadriceps femoris. Polyphenols stimulate GLUT4 expression, which decreased by SARS-CoV-2 infection. Insulin and glucose bind to GLUT4 and are taken up by muscle cells. Insulin and Glucose bind to GLUT4 and are taken up by muscle cells.

2. Materials and Methods

One hundred and thirteen rehabilitation patients undergoing treatment at the main hospital who developed diabetes within 1 year after COVID-19 infection were included (Jun-Sept, 2022). Of the 62 patients who were still diabetic after 6 months, 28 (15 women and 13 men, mean age: 78 years) who

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had taken *Ficus pumila L.* extract (drinking 300 ml per day of the extract obtained by boiling 200 g of leaves and branches of *Ficus pumila L.* in 2 L of water) for at least 3 months after developing diabetes. The HOMA-β and HOMA-IR were measured in 28 subjects (15 women and 13 men, mean age 78 years). HOMA-β and HOMA-IR were also measured in a control group of 34 subjects (15 women and 19 men, mean age 79 years) who had not taken the extract. Blood samples were collected at 07:30 A.M. after overnight fasting to measure fasting plasma glucose and fasting insulin levels. Values were calculated using a HOMA calculator, which was available on the Diabetes Trials Unit website (http://www.dtu.ox.ac.uk). All the values were expressed as average + SD. Normal range of the HOMA-β is over 50% and that of HOMA-IR is 2.5.

3. Results

HOMA-β value was significantly decreased after COVID-19 infection in the 28 subjects, (before; 48.3±12.7 and after: 21.5±18.9 $p<0.05$, Figure 2a). However, HOMA-β significantly improved to 55.6±16.4 after 3 months of *Ficus pumila L.* extract intake ($p<0.05$, Figure 2a). The HOMA-IR before and after COVID-19 infection were 1.23±0.37 and 4.21±0.35 ($p<0.05$, Figure 2b), respectively. The HOMA-IR value of the *Ficus pumila L.* extract ingested group was also significantly improved to 1.51±0.65 after 3 months ($p<0.05$, Figure 2b). On the other hand, the pre- and post-infection HOMA-β values of the 34 control subjects without *Ficus pumila L.* extract ingestion was 51.7±14.2 and 24.2±19.3 ($p<0.05$, Figure 2c), respectively. The value further decreased to 17.9±11.4 (Figure 2c). The HOMA-IR before and after infection were 1.19±0.45 and 3.37±0.66 ($p<0.05$, Figure 2d), respectively. The value further increased to 3.61±0.95 (Figure 2d).

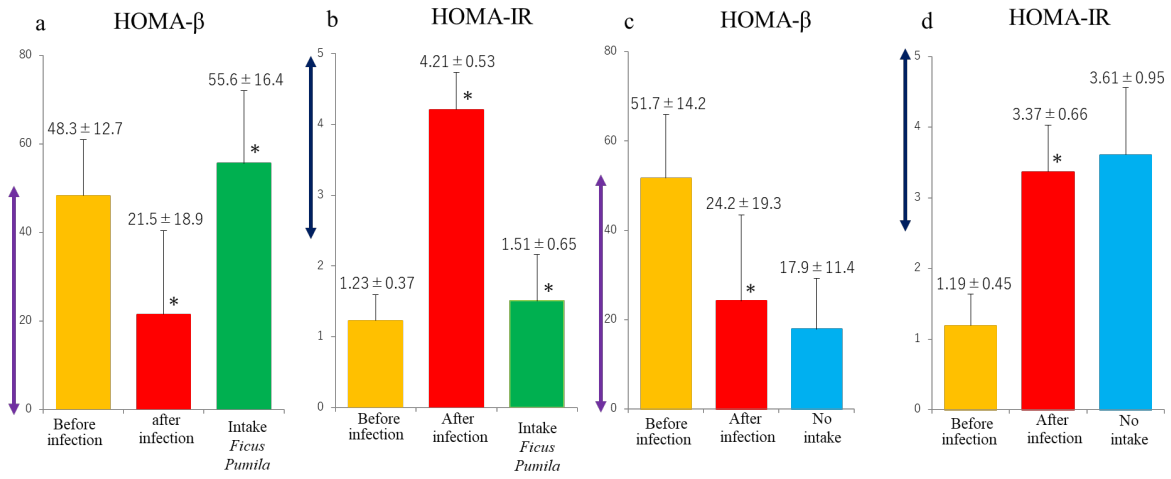

Figure 2. Results of HOMA-β and HOMA-IR evaluation. **a.** Before corona virus infection, HOMA-β levels are within normal range. (orange box) HOMA-β levels decreased after infection (red box), but increased after consumption of *Ficus pumila L.* (green box). **b.** Before corona virus infection, HOMA-IR levels are within normal range. (orange box) HOMA-IR evaluation after infection increased (red box), but decreased after ingestion of *Ficus pumila L.* (green box). **c.** Before corona virus infection, HOMA-β levels are within normal range. (orange box) Post-infection HOMA-β levels decreased (red box) but continued to decrease. (blue box). **d.** Before corona virus infection, HOMA-IR levels are within normal range. (orange box) Post-infection HOMA-IR levels increased (red box), but remained elevated. (blue box) Data are presented as average ± SD. * shows $p<0.05$. HOMA-β levels: Decreased insulin secretion capacity at 50% or less. (violet two-way arrow) HOMA-IR levels: Insulin resistance is higher than 2.5. (purple two-way arrow).

4. Discussion

In the present study, *Ficus pumila L.* extract, ingested by patients who developed diabetes after COVID-19 infection, stimulated insulin secretion capacity and improved insulin resistance.

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Inhibition of Neuropilin 1 (NRP1), which is expressed in pancreatic tissue, has been reported to improve glucose tolerance in type 2 diabetes as well as in glucose intolerance after SARS-CoV2 infection. [5–7]. Although many mechanisms associated with Angiotensin I-converting enzyme type 2 (ACE2) can lead to increased SARS-CoV-2 virulence in diabetes, proteins such as ACE2 co-receptors Neuropilin 2 (NRP2), may also be responsible for worsening the COVID-19 course [8]. The SARS-CoV-2 proteins interact with targets such as ACE2 receptor. In addition, SARS-CoV-2 can stimulate pathological intracellular signaling pathways by triggering NRP1 which play important roles in the progression of neurodegenerative diseases. Several compounds such as polyphenols, could inhibit these interactions [9]. The effectiveness of Alchemilla viridiflora Rothm (Rosaceae) methanol extract to prevent contact between virus spike (S)-glycoprotein and ACE2 and NRP1 receptors was investigated. In vitro results revealed that the flavonoid compounds inhibited 50% of virus-receptor binding interactions for NRP1 and ACE2, respectively. Molecular docking studies revealed that the compounds from A. viridiflora ellagitannins class had a higher affinity for binding with S-glycoprotein whilst flavonoid compounds more significantly interacted with the NRP1 receptor. Quercetin and pentagalloyl glucose were two compounds with the highest exhibited interfering potential for selected target receptors [10]. Polyphenol is a known NRP1,2 inhibitor, and since *Ficus pumila L.* also contains polyphenols, it is possible that the action of polyphenol in *Ficus pumila L.* may have normalized insulin secretory capacity in patients presented in this study.

ACE2 may also be involved in reduced insulin secretion after SARS-CoV-2 infection. Consistently, high ACE2 expression in the islets of Type 2 diabetes patients is reported to increase their susceptibility to SARS-CoV-2 infection, leading to impaired glucose metabolism [11]. Polyphenols, which is also ingredient of *Ficus pumila L.*, inhibit recombinant human ACE2 activity, which may prevent the development of Type 2 diabetes. Phytoestrogen genistein, a type of polyphenols, has also been reported to prevent autoimmune-induced pancreatic destruction [12]. The S-glycoprotein (Spike) of the SARS-CoV-2 forms a complex with the human transmembrane protein ACE2 during infection. Molecular docking and simulations of these molecules targeting the ACE2-Spike complex were performed. Rutin DAB10 and Swertiapuniside were obtained as the top-scored drugs as per the docking protocol [13]. ACE2 is a host receptor for SARS-CoV-2. Inhibiting the interaction between the envelope Spike of SARS-CoV-2 and ACE2 is a potential antiviral therapeutic approach, but little is known about how dietary compounds interact with ACE2. The objective of this study was to determine if flavonoids and other polyphenols with B-ring 3',4'-hydroxylation inhibit recombinant human (rh)ACE2 activity. Polyphenols reduced rhACE2 activity. Rutin and quercetin inhibited rhACE2 activity. Quercetin was the most potent rhACE2 inhibitor among the polyphenols tested. Thus, quercetin, its metabolites, and polyphenols with 3',4'-hydroxylation inhibited rhACE2 activity at physiologically relevant concentrations in vitro [14]. Different bioactive natural products against respiratory viruses with a focus on influenza A, SARS-CoV, MERS, and COVID-19 was investigated, since phytochemicals play an essential role in complementary therapies for viral infections. Based on current literature, 130 compounds have antiviral potential, and of these, 94 metabolites demonstrated bioactivity against coronaviruses. Interestingly, these are classified in different groups of natural products, including alkaloids, flavonoids, terpenoids, and others. Most of these compounds comprise flavonoid skeletons. Quercetin and rutin had remarkable antiviral potential against different viral infections. Among these compounds, Quercetin exhibited antiviral activities against influenza A, SARS-CoV, and COVID-19 and this seems to be a highly promising compound [15]. Phytocompounds have a therapeutic potential for the treatment of anti-SARS-CoV-2 may base on multi-target effects or cocktail formulation for blocking viral infection through invasion/activation, transcription/reproduction, and posttranslational cleavage to battle COVID-19 pandemic [16]. Rutin, hesperidin, and nelfinavir are clinically approved antiviral drugs with high binding affinity to proteins SARS-CoV-2, SARS-CoV, and SARS-CoV-2 spike protein [17]. Kaempferol prevents SARS-CoV-2 infection by blocking membrane fusion and possesses a broad-spectrum anti-fusion ability [18]. Propolis has shown a few key mechanisms of anti-SARS-CoV-2 action such as: the inhibition of the interaction of the S1 spike protein and ACE-2 protein; decreasing the replication of viruses by diminishing the synthesis of RNA transcripts in cells; decreasing the

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particles of coronaviruses. The anti-viral effect is observed with the single biologically active compounds found in propolis (e.g., apigenin, kaempferol, quercetin) [19]. The attachment of SARS-CoV-2 spike to ACE-2 leads the cell fusion process, so spike blockade may be a promising therapy combating COVID-19. Bioflavonoids with intrinsic bioactivities are of outmost importance to block SARS-CoV-2-ACE-2 interaction. Kaempferol 3-neohesperidoside, quercetin and luteolin showed the lowest binding affinity [20]. To cure this virus, the human ACE2 receptor, the SARS-CoV-2 main protease (Mpro), and spike proteins were found to be likely candidates for the synthesis of novel therapeutic drug. Assessing the intermolecular forces of phytochemicals with the targets of the SARS-CoV-2 Mpro spike protein resulted in the recognition of a compound, Kaempferol, as the most potent binding ligand [21]. It has been reported that SARS-CoV-2 infection decreases insulin expression in β-cells and further induces apoptosis of β-cells, resulting in decreased insulin secretory capacity [22]. Polyphenols are also thought to have protective effects on pancreatic β-cells [23] (Figure 1f).

In this study, *Ficus pumila L.* consumption also improved insulin resistance as indicated by HOMA-IR. Insulin resistance is closely related to the expression of glucose transport (GLUT) receptors on the cell surface of peripheral organs such as skeletal muscle. In particular, there is a correlation between the expression of GLUT4 and the level of insulin-resistant [24]. Reduced GLUT4 expression is one of a cause for developing insulin resistance in Type 2 diabetes [25]. It has been reported that ACE2 expression, a SARS-CoV-2 receptor, decreases with infection in peripheral tissues and this may lead to a decrease in GLUT4 expression which ultimately develop insulin resistance [26,27]. SARS-CoV-2 also binds to ACE2 expressed in skeletal muscle tissue and induces inflammatory effects, cytokinesis, and muscle catabolism, damaging the musculoskeletal system [28]. Injury of skeletal muscle fibers by SARS-CoV-2 infection has also been reported to decrease expression of GLUT4 [29]. However, polyphenols stimulate GLUT4 expression and translocation. Molecular studies revealed that these plant-derived molecules, quercetin and rutin are promising phytocompounds that showed great activity against diabetes and diabetes complications in vitro and in vivo, induced glucose uptake via increasing GLUT-4 expression and/or translocation through insulin signaling pathway, AMPK pathway, PTP1B activity inhibition or acting as partial PPARγ agonists [30]. Western blot analysis of rutin-treated showed phosphorylation of AMPK, upregulated expression of GLUT4, rutin significantly improves glucose uptake through regulating PPAR-γ and AMPK signaling pathways [31]. Flavonoids are the major phytoconstituents that display antidiabetic activity by interacting with key protein molecules related to the MAPK and PI3K-AKT signaling pathways, thereby aiding in the treatment of type 2 diabetes mellitus [32]. The luteolin, apigenin, and kaempferol increased the expressions of PPARγ, GLUT4, PPARα, and FATP, and it induced GLUT4 translocation [33]. Treatment with Kaempferol 3-O-rutinoside resulted in upregulation of insulin-dependent p-IRS, AKT and AMPK signaling molecules, and stimulation of the GLUT4 translocation, which ultimately enhanced the glucose uptake in insulin resistant skeletal muscle myotubes [34]. GLUT4, AKT2 and AMPK were docked with Kaempferol, Quercetin. Hyperglycaemia and insulin sensitivity via activation of AKT2 and AMPK was ameliorated, and the expression of GLUT4, AKT2, AMPK whose levels are reduced under diabetic condition was increased [35]. Phytochemicals, phenolic and flavonoid increased mRNA expressions of GLUT4 in pancreas and demonstrates a good anti-diabetic profile by improving insulin sensitivity and GLUT-4 translocation [36]. (Figure 1g).

The pathological mechanism of developing diabetes, after COVID-19 infection, is still unclear [37,38]. Due to the limited number of cases of diabetes caused by COVID-19, opinions are still divided [39]. However, the results of this study suggest that at least the point of action of *Ficus pumila L.* may be involved in the development of diabetes after COVID-19 infection, and the results may contain important insights not only into the mechanism of diabetes development after COVID-19 infection, but also for the treatment.

5. Conclusions

Ficus pumila L. extract can improve insulin secretory capacity and insulin resistance in post-COVID-19 infection induced diabetes.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board Ethics Review Board of Daido Central Hospital (no.20) approved the study. All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation at Fukushima Medical University.

Informed Consent Statement:
Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: MDPI Research Data Policies" at https://www.mdpi.com/ethics.

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Conflicts of Interest: The authors declare no conflicts of interest.

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