Pharmacy Education (2024) 24(3) 406 - 411
https://doi.org/10.46542/pe.2024.243.406411

IGSCPS SPECIAL EDITION

RESEARCH ARTICLE

In vitro and in silico activities of *Solanum melongena* and *Physalis angulata* in DPP-IV inhibition in Diabetes mellitus

Diana Holidah, Sahdah Faizah, Eka Rahmawati, Fifteen Aprila Fajrin, Fransiska Maria Christanty, Ika Puspita Dewi

Faculty of Pharmacy, Universitas Jember, East Java, Indonesia

Keywords
Diabetes mellitus
DPP-IV
Physalis angulata
Solanum melongena

Correspondence
Ika Puspita Dewi
Faculty of Pharmacy
Universitas Jember
East Java
Indonesia
ikapdewi@unej.ac.id

Abstract

Background: Impaired insulin secretion causes type 2 diabetes mellitus. The DPP-IV affects the secretion of insulin. DPP-IV inhibition is a potential therapeutic approach because it ensures optimal insulin secretion. Solanaceae family plants have the potential to inhibit the DPP-IV because of their phytochemicals, such as flavonoids and phenolic. **Objective:** This study aimed to evaluate the DPP-IV inhibitory activity of *Solanum melongena* and *Physalis angulata*. **Method:** The fruits were crushed and extracted. Phytochemical screening and total flavonoids and phenol contents of the extracts were determined. The DPP-IV inhibition assay was done via molecular docking, and the in vitro study was conducted to measure the percentage of inhibition. **Result:** *S. melongena* had a higher content of total flavonoids and phenolics. In the docking study, ferulic acid and withangulatin A showed the best binding activity with DPP-IV compared to other compounds. *P. angulata* had a higher DPP-IV inhibition percentage than *S. melongena*. **Conclusion:** *S. melongena* and *P. angulata* had DPP-IV inhibitory activity.

Introduction

Diabetes mellitus (DM) is a chronic condition brought on by insufficient insulin production by the pancreas or inefficient insulin utilisation by the body, therefore leading to hyperglycemia (WHO, 2022). The therapeutic management of DM must be carefully selected. Type 2 DM drugs have various targets, including the glucagon-like peptides-1 (GLP-1) receptor (Luo *et al.*, 2016).

GLP-1 is an incretin hormone that plays a role in stimulating insulin secretion in pancreatic beta cells and is rapidly degraded by the enzyme dipeptidyl peptidase-IV (DPP-IV) (Luo *et al.*, 2016)—inhibition of the DPP-IV results in an increased level of GLP-1. Examples of DPP-IV inhibitors used clinically are sitagliptin, saxagliptin, and linagliptin (Chhabria *et al.*, 2022). Treatment using DPP-IV inhibitors inhibits glucagon release and increases incretin levels, leading to increased insulin secretion, decreased gastric emptying, and lowered blood glucose levels (Gallwitz, 2019). DPP-IV inhibitors are safe because they have minimal risk of hypoglycemia, do not affect body weight, have cardiovascular protection, and are safe for patients with kidney complications (Deacon, 2019). Nonetheless, this class of drugs has several side effects, such as pancreatitis, nasopharyngitis, and skin lesions (Gallwitz, 2019). It is less able to lower HbA1c levels and is relatively more expensive than other drugs (Ministry of Health, Republic of Indonesia, 2020). Some phytochemicals such as flavonoids, phenolic acids, alkaloids, glycosides, polysaccharides, peptidoglycan, glycopeptides, and steroids work as DPP-IV inhibitors (Singh *et al.*, 2021).

Several plants belonging to the Solanaceae family are known as traditional medicines to treat DM (Kandimalla *et al.*, 2015). Antidiabetic properties of the purple eggplant (*Solanum melongena*) have been investigated through *in vivo* and *in vitro* methods where it has been shown that *S. melongena* works through the inhibition

of α-glucosidase, α-amylase, and aldose reductase enzymes (Egwim *et al*., 2013; Nwanna, 2013; Wu *et al*., 2015). *Physalis angulata* L*.,* another member of the Solanaceae family, is known as an antidiabetic that works by lowering blood sugar levels in diabetic rats and inhibiting the activity of the α-glucosidase and α-amylase enzymes in *vitro* tests (Abo & Lawal, 2013; Raju & Mamidala, 2015). *S. melongena* and *P. angulata* contain flavonoids that are thought to have antidiabetic activity (Singh *et al*., 2021). Phytochemical compounds generally contained in the Solanaceae family plants include alkaloids, flavonoids, tannins, and saponins (Wu *et al*., 2015). These phytochemicals play a role in inhibiting the DPP-IV enzyme (Yaribeygi *et al*., 2019). *Solanum incanum*, which belongs to the Solanaceae family, is known to inhibit the DPP-IV with an inhibition percentage of 68.1% (Singh *et al*., 2021).

According to Shaikh *et al.* (2021) and Pan *et al.* (2022), the highly effective compounds that inhibit DPP-IV are resveratrol, quercetin, and coumarins, which belong to the phenolic and flavonoid groups. Research has not been conducted to investigate these compounds from S. *melongena* and P. *angulata* fruits to inhibit DPP-IV. Therefore, this study aimed to investigate the DPP-IV inhibitory potential of both fruits. This study is focused on exploring the

Methods

Plant extraction

S. melongena and *P. angulata* fruits from East Java, Indonesia, were confirmed as their species by Botani Laboratory Universitas Jember (No. 047/2022 and 048/2022). The fruits were dried, cut, and then ground into powder. Exactly 200 grams of each fruit powder was soaked in 70% ethanol (ratio 1:10) for 24 hours and stirred occasionally. Afterwards, the filtrate was collected. The remaining dregs were macerated with the same solvent for 24 hours. A rotary evaporator was used for the collection, and the filtrate concentration was produced during the maceration.

Phytochemistry screening

Phytochemical screening using qualitative methods was used to determine the phytochemical composition of both extracts.

Determination of the total phenolic and flavonoid

Spectrophotometry was used to calculate the total phenolic and total flavonoids. The Folin-Ciocalteu method assessed the total phenolic, and an aluminium chloride ($AlCl_3$) assay measured total flavonoids.

Molecular docking of DPP-IV

Molegro Virtual Docker (http://molexus.io/molegro-virtual-docker/) was used to perform molecular docking. The native ligand of DPP-IV (code 4J3J) was collected from Protein Data Bank (https://www.rcsb.org/structure/4J3J). The previously identified flavonoid and phenolic compounds in both samples and two steroid compounds in P. angulata were docked to the DPP-IV protein (Maršić *et al*., 2014; Medina-Medrano *et al*., 2015; Niño-Medina *et al*., 2017; Wu *et al*., 2020). Sitagliptin and diprotin were used as controls. The structure of the ligands was obtained from PubChem, and some were drawn by ChemBioDraw Ultra 12.0. The outcome was displayed as a rerank score, a root mean square deviation (RMSD) score, and hydrogen bond strength (Nisa *et al*., 2022; Rahmayanti *et al*., 2022).

DPP-IV in vitro inhibition assay

The inhibitory activity of the DPP-IV was investigated based on the procedure from the DPP-IV enzyme inhibitor screening kit (MAK203, Sigma-Aldrich, USA). A 360 nm excitation wavelength and a 460 nm emission wavelength were used to measure the fluorescence (Sigma Aldrich, 2014). Sitagliptin was used as a control positive. Each extract was tested using three concentrations (50, 100, and 200 µg/mL), and each test sample was examined in triplicate.

Statistical analysis

A one-way ANOVA was used to examine the percentage of inhibition against DPP-IV, followed by the LSD post hoc test. The SPSS version 27.0 programme was used for all statistical analysis.

Results

Table I shows the phytochemistry screening results. The result showed that both extracts have the same phytochemicals. The total flavonoids and phenolics measurement results revealed that *S. melongena* had a higher content of both phytochemicals than *P. angulate* (Table II). The molecular docking result indicated ferulic acid from *S. melongena* and withangulatin A from *P. angulata* showed better rerank scores than the other compounds. However, the control and native ligands scored better than those two, as shown in Table III. The DPP-IV inhibition assay showed that the 200 µg/mL concentration had the best percentage inhibition value for both extracts (Table IV). However, the value was significantly lower than the value obtained for sitagliptin.

Table I: Phytochemistry screening

Phytochemical	Method	Result	
		Solanum melongena	***Physalis angulata***
Flavonoids	Bate-Smith dan Metcalf Wilstater	+	+
Alkaloids	Mayer Wagner	+	+
Saponins	Froth test	+	+
Steroid	Salkowski	+	+
Anthraquinone	Borntrager's test	-	-
Polyphenol	$FeCl_3$	+	+
Tannin	Gelatin	-	-

The plus (+) mark indicates the presence of the chemical compound, while the negative (-) mark indicates the absence of the compound.

Table II: Total phenolic and total flavonoid

Plant extract	Total phenolic (mg GAE/g)	Total flavonoid (mg QE/g)
Solanum melongena	473.764 ± 15.631	80.143 ± 1.943
Physalis angulata	312.426 ± 2.471	65.191 ± 0.989

Table III: Molecular docking of DPP-IV

Compound	Source	Rerank score	RMSD	HBond Value
Native ligand	-	-83.1137	7.92464	-0.413749
Sitagliptin	Control	-75.3611	5.28017	0
Diprotin A	Control	-67.717	15.1442	-4.81924
Quercetin	*S. melongena, P. angulata*	-63.5451	16.4038	-10.1075
Kaempferol	*P. angulata*	-68.389	14.055	-7.00335
Caffeic acid	*S. melongena, P. angulata*	-64.96999	12.6183	-6.17194
p-coumaric acid	*S. melongena, P. angulata*	-56.7254	13.2571	-7.5
Chlorogenic acid	*S. melongena, P. angulata*	-45.1525	13.5246	-16.4558
Ferulic acid	*S. melongena*	-68.0926	16.3071	-3.5112
Delfinidine	*S. melongena*	-64.1757	9.07056	-9.28354
Solanoflavone	*S. melongena*	-23.9389	18.7542	-13.6577
Withangulatin A	*P. angulata*	-75.1037	14.3445	-7.09826
Physagulin F	*P. angulata*	-60.43	13.4102	-9.0217

Table IV: DPP-IV *in vitro* inhibition assay

Sample	Concentration (µg/mL)	Percent inhibition (%)
Sitagliptin*	10	89.389 ± 0.259^{a}
Solanum melongena	50	17.785 ± 2.575^{b}
	100	20.141 ± 1.143^{bc}
	200	23.537 ± 1.224^{cd}
Physalis angulata	50	18.747 ± 1.540^{b}
	100	24.536 ± 4.803^{d}
	200	29.471 ± 3.553^{e}

[a] $p < 0.01$ compared to Sitagliptin; [b] $p < 0.01$ compared to all samples, except *S. melongena* 50 and 200 µg/mL, *P. angulata* 100 and 200 µg/mL; [c] $p < 0.01$ compared to other samples, except *S. melongena* 100 and 200 µg/mL; [d] $p < 0.01$ compared to all samples except *S. melongena* 200 µg/mL and *P. angulata* 100 µg/mL; [e] $p < 0.01$ compared to *P. angulata* 200 µg/mL. Significant discrepancies in the percentage inhibition values are shown by different superscript letters. ($p < 0.05$) between treatment groups using the One-way ANOVA test and the LSD Post Hoc

Discussion

Flavonoids and phenolics are essential in the inhibition of DPP-IV (Pan *et al.*, 2022). Quercetin, a flavonoid, is known to inhibit the DPP-IV enzyme based on the results of virtual docking (Singh *et al.*, 2021). Some phytochemicals, such as curcumin, resveratrol, luteolin, apigenin, and flavone, were discovered to have a strong affinity to DPP IV enzymes (Huang *et al.*, 2019; Singla *et al.*, 2019).

Solanaceae family plants contain phytochemical compounds, including flavonoids, saponins, alkaloids, and tannins, responsible for inhibiting the DPP-IV enzyme (Yaribeygi *et al.*, 2019). *S. melongena* has flavonoids, such as quercetin, anthocyanin, catechin, and solanoflavone (Niño-Medina *et al.*, 2017; Wu *et al.*, 2020). Some phenolic compounds found in *S. melongena* include chlorogenic acid, caffeic acid, ferulic acid, hydroxycinnamic, caffeoylquinic acid, coumaric acid, and phenolic acids (Maršić *et al.*, 2014; Niño-Medina *et al.*, 2017). Meanwhile, *P. angulata* contains flavonoids, such as kaempferol, quercetin, and dihydroflavonol (Medina-Medrano *et al.*, 2015). *P. angulata* also contains phenolics such as chlorogenic, caffeic, and *p*-coumaric (Nguyen *et al.*, 2021). Quercetin has DPP-IV inhibitory activity with inhibitory activity of 46% at a concentration of 200 µg/mL (Proencą *et al.*, 2019). Caffeic acid DPP IV inhibitory action was demonstrated with an IC_{50} value of 3.37 µM (Gao *et al.*, 2015).

Based on the rerank score, this study indicated that ferulic acid from *S. melongena* and withangulatin A from *P. angulata* strongly bonded with DPP-IV. However, the native ligand and the control scores were lower than those. Lower values indicate more stable binding to the active site (Nisa *et al.*, 2022). According to Tuersuntuoheti *et al.* (2022), quercetin and chlorogenic showed lower binding affinity than Sitagliptin in molecular docking. The use of a different software causes this distinction. The binding energy greatly depends on the docking programme used and the type of target protein (Ivanova & Karelson, 2022). Quercetin and chlorogenic acid revealed formed hydrogen and hydrophobic bonds with the active amino acid residues of DPP-IV, altering the protein structure of DPP-IV and rendering its enzymatic activity inactive (Tuersuntuoheti *et al.*, 2022).

Furthermore, the *in vitro* study showed both extracts' potential to inhibit DPP-IV. The percentage inhibition values of both extracts were higher than that of the *P. angulata* leaf extract (13.94 ± 4.08 %) at the same concentration of 100 µg/mL (Riyanti *et al.*, 2016). However, the percentage inhibition values of these extracts were lower than that of *Solanum incanum* (68.1%) (Saidu *et al.*, 2017). The inhibitory activity of both extracts is thought to be mediated by flavonoid and phenolic compounds in the extracts. The finding shows that the per cent inhibition value for both extracts is lower than the control. However, both extracts can still be developed as antidiabetics with other mechanisms, such as inhibitors of α-glucosidase and α-amylase enzymes or other mechanisms (Raju & Mamidala, 2015; Wu *et al.*, 2015). Flavonoids and phenolics can interact with hydrophobic amino acid residues near enzyme active sites, potentially inhibiting glucosidases (Li *et al.*, 2018). Flavonoids non-competitively inhibit α-amylase activity by generating complexes forming hydrophobic and hydrogen bonds, thus reducing the enzyme's binding affinities (Takahama & Hirota, 2018).

Conclusion

S. melongena and P. angulata have DPP-IV inhibitory activity. However, the value is lower than Sitagliptin. Flavonoids and phenolics in both extracts are crucial in this activity. Based on this phytochemical content, the two extracts have the potential to be developed as antidiabetics.

Acknowledgement

The authors thank Universitas Jember Research Institute and Community Service and Advanced Pharmaceutical Laboratory Universitas Gadjah Mada Yogyakarta, Indonesia.

Source of funding

This study was supported financially by Hibah KERIS Universitas Jember Research Institute and Community Service (no. 7575/UN25/KP/2023).

References

Abo, K., & Lawal, I. (2013). Antidiabetic activity of *Physalis angulata* extracts and fractions in alloxan-induced diabetic rats. *Journal of Advanced Scientific Research*, **4**(3), 32–36. https://www.sciensage.info/index.php/JASR/article/view/167

Chhabria, S., Mathur, S., Vadakan, S., Sahoo, D., Mishra, P., & Paital, B. (2022). A review on phytochemical and pharmacological facets of tropical ethnomedicinal plants as reformed DPP-IV inhibitors to regulate incretin activity. *Frontiers in Endocrinology*, **13**, 1–24. https://doi.org/10.3389/fendo.2022.1027237

Deacon, C. (2019). Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes. *Frontiers in Endocrinology*, **10**, 1–14. https://doi.org/10.3389/fendo.2019.00080

Egwim, E., Hamzah, R., & Erukainure, O. (2013). Hypoglycemic potency of selected medicinal plants in Nigeria. *Croatian Journal of Food Technology, Biotechnology and Nutrition*, **8**(3–4), 111–114. https://hrcak.srce.hr/115927

Gallwitz, B. (2019). Clinical use of DPP-4 inhibitors. *Frontiers in Endocrinology*, **10**, 1–10. https://doi.org/10.3389/fendo.2019.00389

Gao, Y., Zhu, J., Li, Z., Zhu, W., Shi, J., Jia, Q., & Li, Y. (2015). Recent progress in natural products such as DPP-4 inhibitors. *Future Medicinal Chemistry*, **7**(8), 1079–1089. https://doi.org/10.4155/fmc.15.49

Huang, P., Lin, S., Chang, C., Tsai, M., Lee, D., & Weng, C. (2019). Natural phenolic compounds potentiate hypoglycemia via inhibition of dipeptidyl peptidase IV. *Scientific Reports*, **9**(1), 1–11. https://doi.org/10.1038/s41598-019-52088-7

Ivanova, L., & Karelson, M. (2022). The impact of software used and the type of target protein on molecular docking accuracy. *Molecules*, **27**(24). https://doi.org/10.3390/molecules27249041

Kandimalla, R., Kalita, S., Choudhury, B., & Kotoky, J. (2015). A review of the antidiabetic potential of the genus *Solanum* (Solanaceae). *Journal of Drug Delivery and Therapeutics*, **5**(1), 24–27. https://doi.org/10.22270/jddt.v5i1.1026

Li, K., Yao, F., Xue, Q., Fan, H., Yang, L., Li, X., Sun, L., & Liu, Y. (2018). Inhibitory effects against α-glucosidase and α-amylase of the flavonoids-rich extract from *Scutellaria baicalensis* shoots and interpretation of the structure-activity relationship of its eight flavonoids by a refined assign-score method. *Chemistry Central Journal*, **12**(1), 1–11. https://doi.org/10.1186/s13065-018-0445-y

Luo, G., Liu, H., & Lu, H. (2016). Glucagon-like peptide-1(GLP-1) receptor agonists: Potential to reduce fracture risk in diabetic patients? *British Journal of Clinical Pharmacology*, **81**(1), 78–88. https://doi.org/10.1111/bcp.12777

Maršić, N., Mikulič-Petkovšek, M., & Štampar, F. (2014). Grafting influences the phenolic profile and carpometric traits of fruits of greenhouse-grown eggplant (*Solanum melongena* L.). *Journal of Agricultural and Food Chemistry*, **62**, 10504–10514. https://doi.org/10.1021/jf503338m

Medina-Medrano, J., Almaraz-Abarca, N., González-Elizondo, M., Uribe-Soto, J., González-Valdez, L., & Herrera-Arrieta, Y. (2015). Phenolic constituents and antioxidant properties of five wild species of *Physalis* (Solanaceae). *Botanical Studies*, **56**(24), 1–13. https://doi.org/10.1186/s40529-015-0101-y

Ministry of Health, Republic of Indonesia. (2020). *Decree of the minister of health of the Republic of Indonesia number KK.01.07/Menkes/603/2020 concerning national guidelines for medical services for the management of type 2 diabetes mellitus for adults*. https://yankes.kemkes.go.id/unduhan/fileunduhan_1610340996_61925.pdf

Nguyen, K., Nguyen, N., & Kim, K. (2021). Determination of phenolic acids and flavonoids in leaves, calyces, and fruits of *Physalis angulata* L. in Viet Nam. *Pharmacia*, **68**(2), 501–509. https://doi.org/10.3897/PHARMACIA.68.E66044

Niño-Medina, G., Urías-Orona, V., Muy-Rangel, M., & Heredia, J. (2017). Structure and content of phenolics in eggplant (*Solanum melongena*) - A review. *South African Journal of Botany,* **111**, 161–169. https://doi.org/10.1016/j.sajb.2017.03.016

Nisa, P., Adzani, A., Amalia, S., Maulidian, R., Yuniar, E., Mufidah, F., & Fajrin, F. (2022). Theobroma cacao L. (cocoa) pod husk as a new therapy for transient receptor protein vanilloid-1 (TRPV1)-targeted diabetic neuropathy: An *in-silico* study. *Pharmacy Education*, **22**(2), 104–108. https://doi.org/10.46542/pe.2022.222.104108

Nwanna, E. (2013). Inhibitory effects of methanolic extracts of two eggplant species from South-western Nigeria on starch hydrolysing enzymes linked to type-2 diabetes. *African Journal of Pharmacy and Pharmacology*, **7**(23), 1575–1584. https://doi.org/10.5897/ajpp2013.3606

Pan, J., Zhang, Q., Zhang, C., Yang, W., Liu, H., Lv, Z., Liu, J., & Jiao, Z. (2022). Inhibition of dipeptidyl peptidase-4 by flavonoids: Structure–activity relationship, kinetics and interaction mechanism. *Frontiers in Nutrition*, **9**, 1–17. https://doi.org/10.3389/fnut.2022.892426

Proencą, C., Freitas, M., Ribeiro, D., Tomé, S., Araújo, A., Silva, A., Fernandes, P., & Fernandes, E. (2019). The dipeptidyl peptidase-4 inhibitory effect of flavonoids is hindered in protein rich environments. *Food and Function*, **10**(9), 5718–5731. https://doi.org/10.1039/c9fo00722a

Rahmayanti, F., Pratoko, D., & Fajrin, F. (2022). The binding prediction of 6-paradol and its derivatives on TRPV1 agonist as a new compound for treating painful diabetic neuropathy. *Jurnal Ilmu Dasar*, **23**(2), 127. https://doi.org/10.19184/jid.v23i2.23030

Raju, P., & Mamidala, E. (2015). Anti-diabetic activity of compound isolated from *Physalis angulata* fruit extracts in alloxan induced diabetic rats. *The American Journal of Science and Medical Research*, **1**(1), 40–43. https://doi.org/10.17812/ajsmr2015111

Riyanti, S., Suganda, A., & Sukandar, E. (2016). Dipeptidyl peptidase-IV inhibitory activity of some Indonesian medicinal plants. *Asian Journal of Pharmaceutical and Clinical Research*, **9**(2), 375–377. https://journals.innovareacademics.in

Saidu, Y., Muhammad, S., Abbas, A., Onu, A., Tsado, I., & Muhammad, L. (2017). In vitro screening for protein tyrosine phosphatase 1B and dipeptidyl peptidase IV inhibitors from selected Nigerian medicinal plants. *Journal of Intercultural Ethnopharmacology*, **6**(2), 154–157. https://doi.org/10.5455/jice.20161219011346

Shaikh, S., Lee, E., Ahmad, K., Ahmad, S., Lim, H., & Choi, I. (2021). A comprehensive review and perspective on natural sources as dipeptidyl peptidase-4 inhibitors for the management of diabetes. Pharmaceuticals, **14**(6). https://doi.org/10.3390/ph14060591

Sigma Aldrich. (2014). Product information DPP4 activity assay kit. https://www.sigmaaldrich.cn/

Singh, A., Yadav, D., Sharma, N., & Jin, J. (2021). Dipeptidyl peptidase (DPP)-iv inhibitors with antioxidant potential isolated from natural sources: A novel approach for the management of diabetes. *Pharmaceuticals*, **14**(6). https://doi.org/10.3390/ph14060586

Singla, R., Kumar, R., Khan, S., Mohit, Kumari, K., & Garg, A. (2019). Natural products: Potential source of DPP-IV Inhibitors. *Current Protein & Peptide Science*, **20**(12), 1218–1225. https://doi.org/10.2174/1389203720666190502154129

Takahama, U., & Hirota, S. (2018). Interactions of flavonoids with α-amylase and starch slow down its digestion. *Food and Function*, **9**(2), 677–687. https://doi.org/10.1039/c7fo01539a

Tuersuntuoheti, T., Pan, F., Zhang, M., Wang, Z., Han, J., Sun, Z., & Song, W. (2022). Prediction of DPP-IV inhibitory potentials of polyphenols existed in Qingke barley fresh noodles: *in vitro* and *in silico* analyses. *Journal of Food Processing and Preservation*, **46**(10). https://doi.org/10.1111/jfpp.16808

WHO. (2022). *Diabetes*. https://www.who.int/news-room/fact-sheets/detail/diabetes

Wu, T., Luo, J., & Xu, B. (2015). In vitro antidiabetic effects of selected fruits and vegetables against glycosidase and aldose reductase. *Food Science and Nutrition*, **3**(6), 495–505. https://doi.org/10.1002/fsn3.243

Wu, X., Zhang, S., Liu, X., Shang, J., Zhang, A., Zhu, Z., & Zha, D. (2020). Chalcone synthase (CHS) family members analysis from eggplant (*Solanum melongena* L.) in the flavonoid biosynthetic pathway and expression patterns in response to heat stress. *PLoS ONE*, **15**(4), 1–18. https://doi.org/10.1371/journal.pone.0226537

Yaribeygi, H., Atkin, S., & Sahebkar, A. (2019). Natural compounds with DPP-4 inhibitory effects: Implications for the treatment of diabetes. *Journal of Cellular Biochemistry*, **120**(7), 10909–10913. https://doi.org/10.1002/jcb.28467