

## The Use of DLBS3233 Bioactive Fraction in Type 2 Diabetes Mellitus Management in Indonesia: A Cost-Effectiveness Analysis of Real-World Evidence

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### ABSTRACT

Diabetes has a significant clinical and economic impact on society. DLBS3233 bioactive fraction is a phytopharmaceutical derived from two native Indonesian herbs, *Cinnamomum burmanii* and *Lagerstroemia speciosa*, and is indicated for type-2-diabetes-mellitus (T2DM), where it can be used as an additional therapy for maintenance purposes. Therefore, a Cost-Effectiveness Analysis (CEA) of the DLBS3233 bioactive fraction needs to be conducted to provide an overview of its potential. This study aimed to define the cost-effectiveness of phytopharmaceuticals on T2DM management in Indonesia. This study was performed using societal perspectives and observational cost-effectiveness analysis. The clinical and economic data were retrospectively collected (2007-2022) from a total of 137 participants, of whom 66 were in the DLBS3233 bioactive fraction group and 71 were in the Non-DLBS3233 Group. The instrument used in this study was the EQ-5D-5L. The clinical data consisted of HbA1c levels, effectiveness, utility, and Visual Analogue Score (VAS), while the economic data consisted of Direct Medical Cost, Direct non-medical cost, and Indirect Cost. The incremental cost-effectiveness ratio (ICER) per quality-adjusted life years (QALYs) gained was estimated to determine the cost-effectiveness. A deterministic sensitivity analysis was conducted to assess the impact of parameter uncertainty. In the base case scenario, the DLBS3233 bioactive fraction provided a more economical and more effective treatment than the non-DLBS3233 group, with a total cost of IDR 6,837,195 (USD 434.42) compared to IDR 7,870,056 (USD 500.17) and a total QALYs of 0.490 versus 0.464. The ICER of IDR 39,535,349 (USD 25,259.62) was considered cost-effective according to the willingness to pay threshold (2021:3x Indonesian GDP = Rp.201,504,163 or USD 12,813.45). The most influential drivers of cost-effectiveness in the deterministic sensitivity analysis were changes in the total cost of the DLBS3233 bioactive fraction, the price of medicine in the non-DLBS3233 group, and the direct medical cost in the DLBS3233 group. Based on the current price in Indonesia, the DLBS3233 bioactive fraction can be considered a cost-effective option, although this remains heavily dependent on the willingness to pay threshold. Further Markov Modelling studies on DLBS3233 bioactive fraction are needed to inform the decision-making process.

**Keywords:** Cost-Effectiveness Analysis, Diabetes, DLBS3233 bioactive fraction, Incremental Cost-Effectiveness Ratio, Quality-Adjusted Life Year

## INTRODUCTION

Diabetes is a degenerative disease that has a significant clinical and economic impact (Adamjee & Harerimana, 2022; Butt et al., 2022). Diabetes is linked to a significant number of clinical complications such as retinopathy, cardiovascular diseases, and nephropathy (Alzaid et al., 2020a), as well as a global economic burden, with type 2 diabetes (T2D) accounting for more than 90% of cases (IDF, 2021). Direct medical costs were up to nine times higher in patients with T2D-related complications compared to those without (Alzaid et al., 2020b). The economic burden of diabetes in Korea was estimated at USD 18,293 million, with a per capita cost of USD 4,090 in 2019 (Oh et al., 2021). The estimated total annual cost of diabetes was approximately USD 600 million in Malaysia (Ganasegeran et al., 2020) and more than USD 6,000 million in some countries, including Brazil and Mexico (South and Central America), and the United Kingdom (UK) (Hex et al., 2024; Magliano & Boyko, 2022; Williams et al., 2020).

The economic burden of diabetes among households in Indonesia was estimated at USD 790 billion in out-of-pocket (OOP) and indirect costs (Patty et al., 2021). Medication expenses and general practitioner visits were the primary contributors to diabetes treatment costs in Indonesia. The average annual patient cost in Indonesia was US\$1207.8, with medication accounting for the Largest direct cost (87.95%), followed by general practitioner consultations (Kristina et al., 2020). A vast number of therapies have been developed, such as Insulin (Rocha et al., 2022), Sulfonylureas (Hume et al., 2022), Biguanides (Karagiannis et al., 2022; Pratama et al., 2022), Glinides (Lv et al., 2020), Thiazolidinediones (Julie S. Eggleton, 2020), Dipeptidyl Peptidase (DPP-IV) Inhibitors (Gilbert & Pratley, 2020; Singh et al., 2021), Sodium-Glucose Sotransporter (SGLT-2) Inhibitors (Klen & Dolžan, 2021) Glucagon Like Peptide-1 (GLP-1) Analogues (Gilbert & Pratley, 2020; Kabahizi et al., 2021), etc. However, a study by Fiagbe et al. reported that the prevalence of controlled diabetes patients remains low (13.6%), while 86.4% of patients still experience uncontrolled blood glucose levels (Masilela et al., 2020). Research also found that uncontrolled diabetes mellitus (DM) increases with age, ranging from 11.1% in young adults (15–24 years old) to 52.7% in older adults (65–74 years old) (Najafipour et al., 2021). Additionally, the prevalence of type 2 diabetes mellitus among

children and adolescents has risen globally over the past 2 decades (Rochmah et al., 2022).

Several factors contribute to uncontrolled diabetes patients, including medication adherence (Syahid, 2021a), drug availability (Bukhari et al., 2023; Hakim et al., 2022a; Nguyen et al., 2022), accessibility (Lin et al., 2022), and the side effects of long-term diabetes medication use (Padhi et al., 2020). Non-adherence to diabetes medication is associated with poor glycemic control and suboptimal medication benefits, which can lead to worsening medical conditions, the development of comorbidities, lower quality of life, higher healthcare costs, and increased mortality (Alharbi et al., 2024; Syahid, 2021b). According to Ewen et al.'s analysis of 30 surveys, public sector access to diabetes medication varied by economic classification: low-income countries (16.7%), lower-middle-income countries (20.8%), and upper-middle-income countries (45.5%) (Hakim et al., 2022b). Although diabetes treatments are widely used, their safety remains a concern. Previous studies found that diabetic drug rosiglitazone increased the risk of myocardial infarction and cardiovascular death. Long-term drug use had many detrimental effects (Serowik & Pantalone, 2024) (Wallach et al., 2020).

The DLBS3233 bioactive fraction is a phytopharmaceutical derived from two native Indonesian herbs, *Cinnamomum burmanii*, and *Lagerstroemia speciosa*, used as a maintenance therapy for T2DM (Hidayat et al., 2023a). A dosage of 50–100 mg once daily was found to be well-tolerated and potentially effective in improving insulin sensitivity and preserving  $\beta$ -cell function in subjects with impaired glucose tolerance (IGT) (Nugroho et al., 2024; Manaf et al., 2016). DLBS3233 bioactive fraction, a phytopharmaceutical, has been studied in formal Randomised Clinical Trials (RCTs) and is approved for use in Indonesian healthcare. Previous studies have shown that DLBS3233 bioactive fraction had no significant adverse effects on liver or kidney function. DLBS3233 bioactive fraction is safe, well-tolerated, and seldom causes hypoglycemia (Hidayat et al., 2023a). A study by Tjokroprawiro et al. reported that DLBS3233 bioactive fraction assisted T2DM patients improved their glycemic control, insulin sensitivity, lipid profile, and adiponectin level by adding 100 mg once a day to their oral diabetic treatment (Nugroho et al., 2024; Tjokroprawiro et al., 2016). In type 2 diabetes patients, DLBS3233 bioactive fraction

plus other oral anti-diabetic medications proved safe and tolerated. It has also been studied for its potential use in polycystic ovary syndrome associated with insulin resistance (Hestiantoro et al., 2024). In general, phytopharmaceuticals like the DLBS3233 bioactive fraction can help strengthen the national medicinal raw material resilience. Currently, most pharmaceutical raw materials in Indonesia are imported, raising concerns for the Indonesian government. To further support its potential benefits, an economic evaluation of the DLBS3233 bioactive fraction is necessary to provide additional evidence of its clinical and economic benefits and to explore its role within Indonesia's healthcare system. This study aimed to define the cost-effectiveness of phytopharmaceuticals for T2DM management in Indonesia.

## MATERIALS AND METHODS

### Design and Sample

The design of this study was cross-sectional. This health economic study was analyzed from a societal perspective. The clinical and economic data were collected retrospectively from 2007 to 2022 at SS Diabetes Care, Jakarta; Muhammadiyah Mardhatillah Hospital, Pemalang, Central of Java; Grha Husada Gresik Hospital, Gersik East of Java; and RSIA Soerya Sidoarjo, Sidoarjo, East of Java.

A total of 137 patients were collected based on the inclusion of patients diagnosed with uncontrolled T2DM (HbA1C > 6.5%) (Emily Eyth; Roopa Naik, 2022), and undergoing antidiabetics for at least 3 months. Patients with incomplete medical records, missing treatment cost data, and those who refused to participate were excluded. The ethical approval for this study was obtained from the Health Research Ethics Commission, Universitas Muhammadiyah Purwokerto (Number: KEPK/UMP/04/IV/2022). The participants were divided into two non-randomized groups: DLBS3233 Bioactive Fraction Group: Patients receiving DLBS3233 bioactive fraction (marketed as *Inlacin™*) either alone or in combination with insulin, metformin, glibenclamide, glimepiride, acarbose, or gliclazide. Non-DLBS3233 Group: Patients receiving antidiabetic medications excluding DLBS3233 bioactive fraction, including insulin, metformin, glimepiride, and acarbose.

### Outcome and Cost Measurement

The time horizon of this study was 2022-2023. Both patient characteristics, such as gender, age, smoking status/history, and the patient's

clinical status, including the complications of hypertension, hyper cholesterol, gout, liver, thyroid, Cardiovascular Diseases (CVD), neuropathy, and Chronic Kidney Diseases (CKD), HbA1c (before and after the treatment) were extracted from the medical record and laboratory report. Furthermore, utility score and Visual Analogue Scale (VAS) data were collected through interviews. Effectiveness was assessed by analyzing HbA1c patterns. Over time, the change in HbA1c levels was measured using the slope and R-value from linear regression. The drug was called effective if the score of Slope was negative and the number of R remained consistent ( $R > 414$ , mean of  $R = 414$ ).

Utility data was measured using the Euro Quality of Life-5 Dimension 5 Levels (EQ-5D-5L) instrument, a multi-attribute instrument for measuring preferences related to health states in individuals (Tripathy et al., 2015). The instrument consists of a descriptive system with five dimensions (mobility, self-care, usual activity, pain/discomfort, anxiety, and depression) and five levels (no problem "1", slight problem "2", moderate problem "3", severe problem "4", and extreme problem "5") and VAS of diabetes patient with 100 on the top representing the "best imaginable health state" and 0 at the bottom representing the "worst imaginable health state." Health utility scores were calculated using the value set developed by Xie et al. (Tsui et al., 2024) and their recommended model. The health utilities elicited ranged from -0.148 for the worst (55555) to 0.949 for the best (11111) EQ-5D-5L health states. Indeed, since health utility scores were calculated with a linear model, worst and best states were different than 0 and 1 (Poder & Carrier, 2021). The EQ-5D-5L has been translated and validated in Indonesian with a significant value of <0.001 for each question item and declared valid with a correlation value between  $\geq 0.60$ -0.80. The reliability test obtained a Cronbach Alpha value of 0.799, confirming the instrument's validity and reliability (Tondok et al., 2021).

The economic data included direct medical costs, direct non-medical costs, and indirect costs. Direct medical costs (consultation, medicine, and laboratory) were obtained from the clinic and hospital billing records. Direct non-medical cost (gasoline, food, internet data, toll, and parking cost) and indirect cost (productivity loss and companion's productivity loss) were gathered through interview. Cost calculation were based on economic data collected per one patient visit in a month.

Table I. Characteristics of Respondents among type-2 Diabetes Mellitus Patients

Variable	Total (N=137)		DLBS3233 (N=66)		Non DLBS3233 (N=71)		p Value
	N	%	N	%	N	%	
<b>Gender</b>							0.258
Male	67	48.91	28	42.42	39	54.93	
Female	70	51.09	38	57.58	32	45.07	
<b>Age*</b>							0.009
Mean ( $\pm$ SD)	64.57 ( $\pm$ 11.69)		67.55 ( $\pm$ 9.95)		61.85 ( $\pm$ 12.55)		
Median (min:max)	65 (30:97)		67 (45:91)		60 (30:97)		
<b>Smoking*</b>							0.001
Active Smoker	8	5.84	3	4.55	5	7.04	
History Smoker	39	28.47	21	31.82	18	25.35	
Never	90	65.69	42	63.64	48	67.61	
<b>Hypertension</b>							-
No	135	98.54	64	96.97	71	100	
Yes	2	1.46	2	3.03	0	0	
<b>Hyper cholesterol</b>							0.610
No	28	20.44	12	18.18	16	22.54	
Yes	109	79.56	54	81.82	55	77.46	
<b>Gout</b>							0.610
No	110	80.29	54	81.82	56	78.87	
Yes	27	19.71	12	18.18	15	21.13	
<b>Liver diseases</b>							0.681
No	130	94.89	64	96.97	66	92.96	
Yes	7	5.11	2	3.03	5	7.04	
<b>Thyroid</b>							-
No	135	98.54	64	96.97	71	100	
Yes	2	1.46	2	3.03	0	0	
<b>CVD</b>							0.412
No	123	89.79	62	93.94	61	85.92	
Yes	14	10.22	4	6.06	10	14.08	
<b>Neuropathy</b>							0.200
No	119	86.86	49	74.24	70	98.59	
Yes	18	13.14	17	25.76	1	1.41	
<b>CKD</b>							0.064
No	125	91.24	60	90.91	65	91.55	
Yes	12	8.76	6	9.09	6	8.45	

Continuous variables are presented as the mean  $\pm$  standard deviation or median, and categorical variables are presented as percentages. Categorical data were analyzed using chi-square, and continuous data were analyzed using a t-test. \*Significantly different at the *p*-value of < 0.05

Table II. HbA1c Condition among Diabetes Patients

Variable	Total (N=134)	DLBS3233 (N=64)	Non DLBS3233 (N=70)	P Value
<b>Initial HbA1c condition</b>				0.995
Mean ( $\pm$ SD)	9.58 ( $\pm$ 2.28)	9.58 ( $\pm$ 1.86)	9.58 ( $\pm$ 2.62)	
Median (min: max)	9.10 (6.50:20.50)	9.60 (6.50:14.90)	8.85 (6.50:20.50)	
<b>Final HbA1c condition</b>				0.935
Mean ( $\pm$ SD)	8.09 ( $\pm$ 1.72)	8.10 ( $\pm$ 1.50)	8.08 ( $\pm$ 1.91)	
Median (min: max)	7.80 (5.00:14.10)	7.90 (5.00:11.90)	7.70 (5.40:14.10)	

Data were analyzed by t-test; \*Significantly different at the *p* < 0.05

### Data Analysis

A statistical comparison test was used to analyze the respondents' characteristics, with a chi-square test applied for categorical data, and a t-test for continuous data. To estimate the cost-effectiveness of DLBS3233 bioactive fraction Group compared to the Non-DLBS3233 Group, the incremental cost-effectiveness ratio (ICER) was calculated using cost-utility analysis (CUA) and compared with the cost-effectiveness threshold, which was set at three times the gross domestic product (GDP) per capita for the year of 2021 (3x Indonesia's 2021 GDP: Rp.201,504,163 = USD 12,813.45).

A deterministic one-way sensitivity analysis was performed to assess how sensitive the ICER is to the changes in input parameters. Key parameters were varied within a Standard Deviation (SD) range, including direct medical cost, direct non-medical cost, indirect cost, and utility values.

## RESULTS AND DISCUSSION

### Participants Characteristics

A total of 137 participants were included in the study, with 66 in the DLBS3233 Group and 71 in the Non-DLBS3233 Group. The mean age of participants was 64.57( $\pm 11.69$ ). Most of them were female (51.09%) and had hypercholesterolemia status (79.56%).

However, the differences in age ( $p = 0.09$ ) and smoking history ( $p = 0,001$ ) between the two groups were not statistically significant, indicating that the DLBS3233 Group and Non-DLBS3233 Group had comparable characteristics (Table I).

The initial HbA1c level in both Groups was similarly high ( $9.58\% \pm 1.86$  vs  $9.58\% \pm 2.62$ ;  $p = 0.995$ ) (Table II). After treatment, the final HbA1c levels of the DLBS3233 Group were higher than in the Non-DLBS3233 Group, but the difference was not statistically significant ( $8.10\% \pm 1.50$  vs  $8.08\% \pm 1.91$ ;  $p = 0.935$ ).

In this study, the effectiveness of the treatment was defined as the consistency of HbA1c reduction evaluated through the pattern of HbA1c levels over time. A linear regression model was developed to analyze HbA1c levels over time. The treatment was considered effective if the score of Slope was negative and the number of R-values remained consistent ( $R > 414$ , mean of  $R = 414$ ).

This study showed that the addition of the DLBS3233 bioactive fraction was considerably less effective in consistently reducing HbA1c level than the non-DLBS3233 group (Table III). However, this difference is considered not statistically different

(26.23% vs 43.28%,  $p = 0.841$ ). On the other hand, both the utility value and VAS score for DLBS3233 patients were higher than those of patients in the non-DLBS3233 group ( $0.490 \pm 0.157$  vs  $0.464 \pm 0.141$ ; and  $60.714 \pm 15.534$  vs  $58.571 \pm 14.828$ ). (Table III).

This study revealed that the total cost required for diabetic patients to maintain the treatment using DLBS3233 bioactive fraction was lower than patients without DLBS3233 bioactive fraction ( $358.98 \pm 167.95$  vs  $398.66 \pm 263.83$ ). It was mainly because the direct medical cost among DLBS3233 patients was lower than that among non-DLBS3233 patients ( $256.52 \pm 154.41$  vs  $325.12 \pm 246.37$ ). Furthermore, the direct non-medical cost between DLBS3233 and Non-DLBS3233 patients was comparable with the value of  $55.44 \pm 26.28$  and  $55.84 \pm 17.15$ , respectively. Finally, the values of indirect cost among the two groups were considerably comparable (Table IV).

The addition of DLBS3233 bioactive fraction to the current maintenance treatment of type-2 diabetes Mellitus patients in Indonesia resulted in lower maintenance costs and higher QALYs. Therefore, the addition of DLBS3233 bioactive fraction was considered a cost-saving strategy (ICER of USD.  $-1.519,043$  /QALYs) (Table V).

The univariate sensitivity analysis showed that the ICER value was mainly influenced by the changes in the total cost of DLBS3233 bioactive fraction, the price of medicine in the non-DLBS3233 group, and the direct medical cost of the non-DLBS3233 group. However, the influence of all input parameters on the potential changes in the decision was low or even negligible (Figure 1).

The frequency of women was higher in the DLBS3233 group, which might have influenced the results of this study, especially since previous research found that men showed significantly higher reductions in HbA1c after simple lifestyle treatment and metformin (Kautzky-Willer et al., 2023; Mauvais-Jarvis et al., 2021). The DLBS3233 Group consisted of respondents who used DLBS3233 bioactive fraction as one of their diabetes medications. Meanwhile, the non-DLBS3233 group was a group of respondents who did not use DLBS3233 bioactive fraction at all as a diabetes treatment. The result found that the characteristics of respondents between the DLBS3233 and Non-DLBS3233 Group were similar.

Table III. Outcomes of Respondents among type-2 Diabetes Mellitus Patients

Variable	Total		DLBS3233		Non DLBS3233		P Value
	N	%	N	%	N	%	
<b>Effectiveness</b>	128		61		67		0.841
No	83	64.84	45	73.77	38	56.72	
Yes	45	35.16	16	26.23	29	43.28	
<b>Utility</b>	99		57		42		0.384
Mean ( $\pm$ SD)	0.479 ( $\pm$ 0.150)		0.490 ( $\pm$ 0.157)		0.464 ( $\pm$ 0.141)		
Median (min: max)	0.449 (0.18: 0.84)		0.450 (0.26: 0.84)		0.440 (0.18: 0.78)		
<b>VAS</b>	99		57		42		0.474
Mean ( $\pm$ SD)	59.796 ( $\pm$ 15.195)		60.714 ( $\pm$ 15.534)		58.571 ( $\pm$ 14.828)		
Median (min: max)	55 (30: 90)		57.5 (40: 90)		55 (30: 90)		

Continuous variables are presented as the mean  $\pm$  standard deviation or median, while categorical variables are presented as percentages. Categorical data were analyzed using chi-square, and continuous data were analyzed using the t-test. \*Significantly different at the  $p < 0.05$

Table IV. Cost of Treatment among type-2 Diabetes Mellitus Patients

Parameter	Total		DLBS3233		Non DLBS3233	
	Mean (USD)	SD	Mean (USD)	SD	Mean (USD)	SD
Consultation	53.85	9.38	54.13	9.63	53.59	9.20
Medicine	203.83	207.43	172.74	138.61	232.72	252.97
Laboratories	51.85	24.50	48.14	23.58	55.30	24.99
<b>Direct Medical Cost</b>	292.07	209.33	256.52	154.41	325.12	246.37
Gasoline	16.92	8.39	17.92	10.25	15.52	4.47
Food	25.02	10.46	23.34	10.72	27.37	9.73
Internet/Pulsa	3.20	5.13	3.71	6.63	2.52	1.60
Tol	17.72	13.22	18.39	14.42	16.84	11.68
Parking	0.29	0.16	0.30	0.16	0.28	0.16
<b>Direct non-Medical Cost</b>	55.60	22.82	55.44	26.28	55.84	17.15
Patient's Productivity Loss	50.14	32.85	45.61	33.03	55.72	32.18
Companion's Productivity Loss	46.60	46.25	50.63	55.41	40.76	28.62
<b>Indirect Cost</b>	67.81	52.53	64.17	57.61	72.88	44.72
<b>Total Cost</b>	379.55	222.95	358.98	167.95	398.66	263.83

Using the USD currency exchange rate (Rp 15,720.7)

Table V. The Incremental Cost-Effectiveness Ratio (ICER) of DLBS3233 and Non-DLBS3233 Group among type-2 Diabetes Mellitus Patients

	Cost	QALYs	Different		ICER
			Cost	QALYs	
<b>Non DLBS3233</b>	398.66	0.46	Referensi	Referensi	-1.519.043
<b>DLBS3233</b>	358.98	0.49	-39.68	0.03	

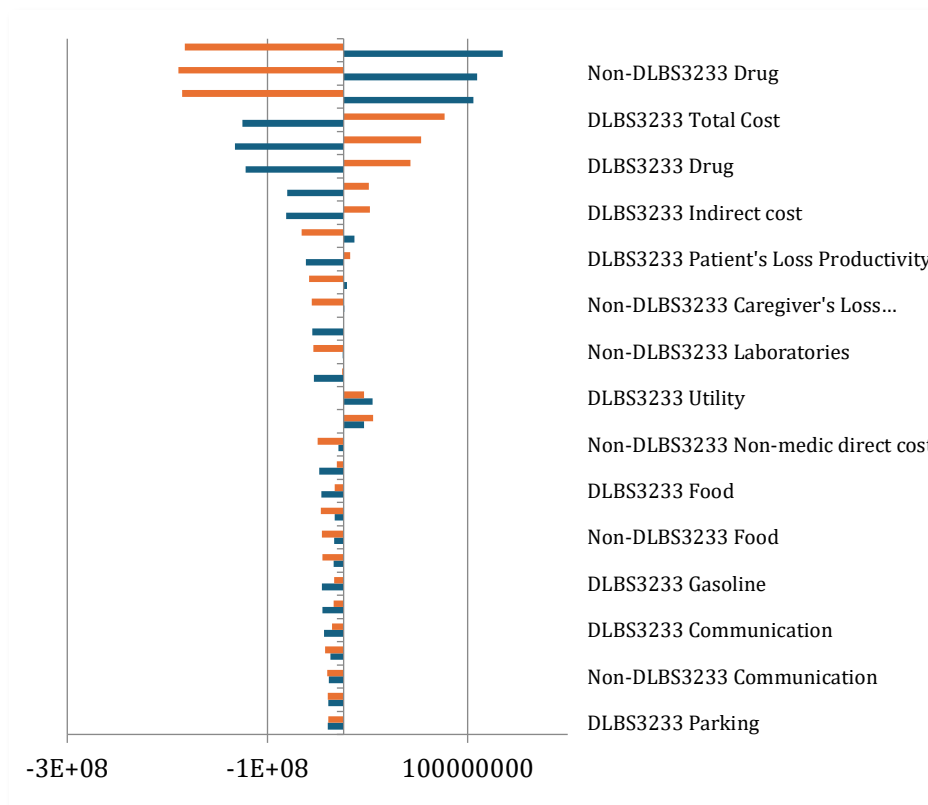


Figure 1. Univariate Sensitivity Analysis

In this cost-utility analysis, the addition of phytopharmaceutical (DLBS3233 bioactive fraction) for T2DM patients as a maintenance therapy showed a cost-saving result (ICER of USD – 1.519,043 per QALYs) since it provided a lower cost of treatment and higher QALYs compared to the current treatment (without DLBS3233 bioactive fraction). Although there were inconsistent results when we considered the clinical outcome in this study, including HbA1c at the end of the observation and the consistency of the HbA1c-reduction effect among anti-diabetics, the QALYs represent a more comprehensive view of the patients, as it describes the patient’s condition from their perspective. Furthermore, the QALYs outcome has been officially recommended by the National Health Technology Assessment (HTA) body in Indonesia as the standard outcome in health economic evaluation of new health technologies.

The main result of this analysis is considered robust, as although several input parameters significantly changed the ICER, none of the adjusted ICER values altered the interpretation that the addition of DLBS3233 bioactive fraction to the

current practice of T2DM management was cost-effective according to the currently available threshold of 3x Indonesia GDP (2021 3x Indonesian GDP is Rp.201,504,163 = USD 12,813.45).

Another finding in this analysis was the lower cost of the DLBS3233 group was primarily driven by the direct medical cost, more specifically, the medicine cost (more than Rp. 1 million difference = USD 63.59). This finding is interesting since the price of DLBS3233 bioactive fraction is generally higher than most older oral antidiabetic drugs (OAD) available in Indonesia. One possible explanation for this finding is that phytopharmaceuticals possibly possess fewer side effects, so there would be less additional medication required (Alam et al., 2022) (Haq et al., 2021). This theory could plausibly explain that although the DLBS3233 group had slightly less effective clinical outcome (comparable final HbA1c level but less consistency in lowering HbA1c level) compared to the non-DLBS3233 group, patients using the DLBS3233 bioactive fraction experienced more convenient daily condition, as represented by their higher QALYs. However, further studies are needed to support this hypothesis.

One of the advantages of this study is that all the data were collected from real-world practice in both clinics and hospitals in Indonesia. This real-world data enhances the external validity or applicability of the results to the Indonesian health system. This advantage can also promote the use of phytopharmaceuticals in Indonesia. In fact, although DLBS3233 bioactive fraction already showed valid efficacy and safety results from its RCTs (Al-Snafi, 2019; Dok et al., 2023; Hidayat et al., 2023b; Nugroho et al., 2024) and is allowed to be prescribed by formal medical doctors, the actual utilization of phytopharmaceuticals in Indonesia health system is considerably low. It is likely due to several reasons, such as the beliefs among medical doctors that phytopharmaceuticals lack scientific evidence compared to conventional therapies or a general mistrust of natural products. A study found that the more positive the health worker's perception of the quality of phytopharmaceuticals, the greater the intention to recommend phytopharmaceutical products (Jalil et al., 2022; O. Nwankwo & E. Aghahowa, 2022; Wada et al., 2019; Harjanti et al., 2014).

A high variation of T2DM medications used among the respondents was one of the limitations of this study. The guideline for maintenance therapy using phytopharmaceuticals does not exist yet. Therefore, the use of phytopharmaceuticals varies among physicians in Indonesia. However, our study included all of the clinical and economic data from real-world practices, which helped reduce bias due to this limitation. Nonetheless, further analysis, especially with more patient data, is required to evaluate the possible confounding factors influencing the outcomes.

The use of phytopharmaceuticals in Indonesia could be a strategic solution for enhancing national resilience in medicinal raw materials. T2DM treatment is among the top 10 significant annual spending categories by Badan Pengelola Jaminan Sosial (BPJS) Kesehatan. According to the main finding of this study, the use of DLBS3233 bioactive fraction or phytopharmaceuticals in Indonesia's national health security (NHS) could not only reduce the treatment cost and improve the quality of life of diabetic patients but also reduce the number of imported oral anti-diabetic medications.

## CONCLUSION

This cost-utility analysis revealed that although the addition of DLBS3233 bioactive fraction to the conventional anti-diabetes therapy

did not provide higher effectiveness in consistently improving the HbA1c level of the type-2 diabetes mellitus patients, the addition of DLBS3233 bioactive fraction was still cost-saving compared to the conventional therapy. Based on the current price in Indonesia, DLBS3233 bioactive fraction can be considered a cost-effective option, although it depends heavily on the willingness-to-pay threshold. Further Markov Modelling studies with DLBS3233 bioactive fraction are needed to inform the decision-making process.

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## CONFLICT OF INTEREST

RRT is the staff of Dexa Laboratories of Biomolecular Sciences (DLBS), a research-based organization for the discovery, development, and production of pharmaceuticals, biopharmaceuticals, and nutraceuticals under Dexa Medica, the marketing authorization holder of DLBS3233 bioactive fraction. Dexa Medica does not interfere with professional judgment or action regarding the study processes and outcomes. The interpretation and reporting of data in this study are the sole responsibility of the authors.

## REFERENCES

- Adamjee, E., & Harerimana, J. de D. (2022). Estimating the economic burden of diabetes mellitus in Kenya: a cost of illness study. *European Scientific Journal, ESJ*, 18(22), 104. <https://doi.org/10.19044/esj.2022.v18n22.p104>
- Alam, S., Sarker, M. M. R., Sultana, T. N., Chowdhury, M. N. R., Rashid, M. A., Chaity, N. I., Zhao, C., Xiao, J., Hafez, E. E., Khan, S. A., & Mohamed, I. N. (2022). Antidiabetic phytochemicals from medicinal plants: prospective candidates for new drug discovery and development. *Frontiers in Endocrinology*, 13(February). <https://doi.org/10.3389/fendo.2022.800714>
- Alharbi, S., Alhofaian, A., & Alaamri, M. M. (2024). Correlation between illness perception and medication adherence among adult patients

- with type 2 diabetes mellitus in Saudi Arabia. *Saudi Journal of Medicine and Medical Sciences*, 12(3), 244–251. [https://doi.org/10.4103/sjmms.sjmms\\_511\\_23](https://doi.org/10.4103/sjmms.sjmms_511_23)
- Al-Snafi, A. E. (2019). Medicinal value of *Lagerstroemia speciosa*: An updated review. *International Journal of Current Pharmaceutical Research*, 11(5), 18–26.
- Alzaid, A., Ladrón de Guevara, P., Beillat, M., Lehner Martin, V., & Atanasov, P. (2020a). Burden of disease and costs associated with type 2 diabetes in emerging and established markets: systematic review analyses. *Expert Review of Pharmacoeconomics and Outcomes Research*, 21(4), 1–14. <https://doi.org/10.1080/14737167.2020.1782748>
- Alzaid, A., Ladrón de Guevara, P., Beillat, M., Lehner Martin, V., & Atanasov, P. (2020b). Burden of disease and costs associated with type 2 diabetes in emerging and established markets: systematic review analyses. *Expert Review of Pharmacoeconomics and Outcomes Research*, 21(4), 1–14. <https://doi.org/10.1080/14737167.2020.1782748>
- Bukhari, I., Utami, E. F., Purmafritiah, E., & Rahmawati, S. (2023). Profile of Management and Availability of Oral Anti-Diabetic Drugs at Madapangga Public Health Centre In 2022. *Pharmaceutical and Traditional Medicine*, 7(1), 17–28. <https://doi.org/10.33651/ptm.v7i1.639>
- Butt, M. D., Ong, S. C., Wahab, M. U., Rasool, M. F., Saleem, F., Hashmi, A., Sajjad, A., Chaudhry, F. A., & Babar, Z. U. D. (2022). Cost of illness analysis of type 2 diabetes mellitus: the findings from a lower-middle income country. *International Journal of Environmental Research and Public Health*, 19(19). <https://doi.org/10.3390/ijerph191912611>
- Dok, K., Tan, S., Tjandrawinata, R. R., & Prasasty, V. D. (2023). Molecular Mechanism of DLBS3233 Bioactive Fraction in Type-2 Diabetes Mellitus: Network Pharmacology and Docking Study. *Sains Malaysiana*, 52(12), 3497–3509.
- Emily Eyth; Roopa Naik. (2022). *Hemoglobin A1C - statpearls - NCBI bookshelf* (pp. 1–5).
- Ganasegeran, K., Hor, C. P., Jamil, M. F. A., Loh, H. C., Noor, J. M., Hamid, N. A., Suppiah, P. D., Manaf, M. R. A., Ch'ng, A. S. H., & Looi, I. (2020). A systematic review of the economic burden of type 2 diabetes in Malaysia. *International Journal of Environmental Research and Public Health*, 17(16), 1–23. <https://doi.org/10.3390/ijerph17165723>
- Gilbert, M. P., & Pratley, R. E. (2020). GLP-1 analogs and DPP-4 inhibitors in type 2 diabetes therapy: review of head-to-head clinical trials. *Frontiers in Endocrinology*, 11(April), 1–13. <https://doi.org/10.3389/fendo.2020.00178>
- Hakim, S., Chowdhury, M. A. B., Ahmed, N. U., & Uddin, M. J. (2022a). The availability of essential medicines for diabetes at health facilities in Bangladesh: evidence from 2014 and 2017 national surveys. *BMC Health Services Research*, 22(1), 1–11. <https://doi.org/10.1186/s12913-022-07738-4>
- Hakim, S., Chowdhury, M. A. B., Ahmed, N. U., & Uddin, M. J. (2022b). The availability of essential medicines for diabetes at health facilities in Bangladesh: evidence from 2014 and 2017 national surveys. *BMC Health Services Research*, 22(1), 1–11. <https://doi.org/10.1186/s12913-022-07738-4>
- Haq, F. U., Siraj, A., Ameer, M. A., Hamid, T., Rahman, M., Khan, S., Khan, S., & Masud, S. (2021). Comparative review of drugs used in diabetes mellitus—new and old. *Journal of Diabetes Mellitus*, 11(04), 115–131.
- Harjanti, K., Nogosari, A. R., & Hertiani, T. (2014). Knowledge, Perceived Quality, And Intention to Recommend The Use Of Phytopharmaca. *Jurnal Manajemen Dan Pelayanan Farmasi*, 4(3).
- Hestiantoro, A., Permadi, W., Tjandrawinata, R. R., Wiweko, B., Ritonga, M. A., Ferrina, A. I., Sumapraja, K., Muharam, R., & Djuwantono, T. (2024). The Efficacy and Safety of DLBS3233, A Combined Bioactive Fraction of *Cinnamomum burmannii* and *Lagerstroemia speciosa* Plants on The Endocrine-Metabolic Profile of Women with Polycystic Ovary Syndrome: A Randomized Clinical Trial. *International Journal of Fertility and Sterility*, 18, 35–47. <https://doi.org/10.22074/ijfs.2023.551350.1283>
- Hex, N., MacDonald, R., Pocock, J., Uzdzińska, B., Taylor, M., Atkin, M., Wild, S. H., Beba, H., & Jones, R. (2024). Estimation of the direct health and indirect societal costs of diabetes

- in the UK using a cost of illness model. *Diabetic Medicine: A Journal of the British Diabetic Association*, 41(9), e15326. <https://doi.org/10.1111/dme.15326>
- Hidayat, S. T., Mulyantoro, I., Damas, S., & Tjandrawinata, R. R. (2023a). The Effect and Safety Assessment of Metformin and DLBS3233 (A Bioactive Fraction of *Lagerstroemia speciosa* and *Cinnamomum burmannii*) on Improving Metabolic Parameters in Women with Polycystic Ovary Syndrome. *International Journal of Women's Health*, 15, 971–985. <https://doi.org/10.2147/IJWH.S409685>
- Hume, A. L., Osundolire, S., Mbrah, A. K., Nunes, A. P., & Lapane, K. L. (2022). Antihyperglycemic drug use in long-stay nursing home residents with diabetes mellitus. *HHS Public Access*, 8, 10–19.
- IDF. (2021). International Diabetes Federation Diabetes Atlas 10th edition. In *International Diabetes Federation: Vol. 10th editi.* <https://doi.org/10.1016/j.diabres.2013.10.013>
- Jalil, B., Naser, A. Y., M Prieto, J., & Heinrich, M. (2022). Herbal supplements in Jordan: a cross-sectional survey of pharmacists' perspectives and knowledge. *BMJ Open*, 12(7), e057405. <https://doi.org/10.1136/bmjopen-2021-057405>
- Julie S. Eggleton, I. Jialal. (2020). Thiazolidinediones. In *NCBI Bookshelf*. StatPearls Publishing LLC.
- Kabahizi, A., Wallace, B., Lieu, L., Chau, D., Dong, Y., Hwang, E.-S., & Williams, K. W. (2021). *Glucagon-like peptide-1 (GLP-1) signalling in the brain: From neural circuits and metabolism to therapeutics.* <https://doi.org/10.1111/bph.v179.4/issue/oc>
- Karagiannis, T., Avgerinos, I., Liakos, A., Del Prato, S., Matthews, D. R., Tsapas, A., & Bekiari, E. (2022). Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. *Diabetologia*, 65(8), 1251–1261. <https://doi.org/10.1007/s00125-022-05715-4>
- Kautzky-Willer, A., Leutner, M., & Harreiter, J. (2023). Sex differences in type 2 diabetes. *Diabetologia*, 66, 986–1002. <https://doi.org/10.1007/s00125-023-05891-x/Published>
- Klen, J., & Dolžan, V. (2021). Treatment response to sglT2 inhibitors: From clinical characteristics to genetic variations. In *International Journal of Molecular Sciences* (Vol. 22, Issue 18). MDPI. <https://doi.org/10.3390/ijms22189800>
- Kristina, S. A. R. I., Endarti, D. W. I., Andayani, T. R. I. M., & Widayanti, A. W. (2020). Direct and indirect cost of diabetes mellitus in Indonesia: a prevalence based study with human capital approach. *International Journal of Pharmaceutical Research*, 13(01). <https://doi.org/10.31838/ijpr/2021.13.01.331>
- Lin, Y. K., Richardson, C., Dobrin, I., Pop-Busui, R., Piatt, G., & Piette, J. (2022). Accessibility and openness to diabetes management support with mobile phones: survey study of people with type 1 diabetes using advanced diabetes technologies. *JMIR Diabetes*, 7(2), 1–10. <https://doi.org/10.2196/36140>
- Lv, W., Wang, X., Xu, Q., & Lu, W. (2020). Mechanisms and Characteristics of Sulfonylureas and Glinides. *Current Topics in Medicinal Chemistry*, 20(1), 37–56. <https://doi.org/10.2174/1568026620666191224141617>
- Magliano, D. J., & Boyko, E. J. (2022). *IDF diabetes atlas.*
- Manaf, A., Tjandrawinata, R. R., & Malinda, D. (2016). Insulin sensitizer in prediabetes: a clinical study with DLBS3233, a combined bioactive fraction of *Cinnamomum burmannii* and *Lagerstroemia speciosa*. *Dovepress*, 10, 1279–1289.
- Masilela, C., Pearce, B., Ongole, J. J., Adeniyi, O. V., & Benjeddou, M. (2020). Factors associated with glycemic control among South African adult residents of Mkhondo municipality living with diabetes mellitus. *Medicine (United States)*, 99(48), E23467. <https://doi.org/10.1097/MD.00000000000023467>
- Mauvais-Jarvis, F., Berthold, H. K., Campesi, I., Carrero, J. J., Dakal, S., Franconi, F., Gouni-Berthold, I., Heiman, M. L., Kautzky-Willer, A., Klein, S. L., Murphy, A., Regitz-Zagrosek, V., Reue, K., & Rubin, J. B. (2021). Sex-and gender-based pharmacological response to drugs. *Pharmacological Reviews*, 73(2), 730–762. <https://doi.org/10.1124/pharmrev.120.00206>

- Najafipour, H., Farjami, M., Sanjari, M., Amirzadeh, R., Shadkam Farokhi, M., & Mirzazadeh, A. (2021). Prevalence and incidence rate of diabetes, pre-diabetes, uncontrolled diabetes, and their predictors in the adult population in southeastern Iran: findings from KERCADR study. *Frontiers in Public Health*, 9(November), 1–12. <https://doi.org/10.3389/fpubh.2021.611652>
- Nguyen, T. N., Yusuf, S., & Chow, C. K. (2022). Availability and affordability of medicines for diabetes and cardiovascular disease across countries: Information learned from the prospective urban rural epidemiological study. *Diabetology*, 3(1), 236–245. <https://doi.org/10.3390/diabetology3010014>
- Nugroho, H., Nurmilawati, N., Novitasari, D., Rombeallo, L., Effendi, R. F., Reski, R., Surayya, I., Daryanto, N. A., Putera, S., & Tjandrawinata, R. R. (2024). Effectiveness and safety of DLBS3233 in newly diagnosed type 2 diabetes mellitus: A 12-week clinical trial. *Acta Medica Indonesiana*, 56(3), 291–301. <https://www.ncbi.nlm.nih.gov/pubmed/39463112>
- Nwankwo, L. O., & Aghahowa, S. E. (2022). Pharmacists' perception on herbal-orthodox medicine interactions in some communities of south-eastern Nigeria. *The Nigerian Journal of Pharmacy*, 56(1), 79–89. <https://doi.org/10.51412/psnnjp.2022.9>
- Oh, S. H., Ku, H., & Park, K. S. (2021). Prevalence and socioeconomic burden of diabetes mellitus in South Korean adults: a population-based study using administrative data. *BMC Public Health*, 21(1), 1–13. <https://doi.org/10.1186/s12889-021-10450-3>
- Padhi, S., Nayak, A. K., & Behera, A. (2020). Type II diabetes mellitus: a review on recent drug based therapeutics. In *Biomedicine and Pharmacotherapy* (Vol. 131). Elsevier Masson SAS. <https://doi.org/10.1016/j.biopha.2020.110708>
- Patty, Y. F. P. P., Mufarrihah, & Nita, Y. (2021). Cost of illness of diabetes mellitus in Indonesia: a systematic review. *Journal of Basic and Clinical Physiology and Pharmacology*, 32(4), 285–295.
- Poder, T. G., & Carrier, N. (2021). Predicting EQ-5D-5L utility scores from the Oswestry Disability Index and Roland-Morris Disability Questionnaire for low back pain. *Expert Review of Pharmacoeconomics and Outcomes Research*, 21(1), 105–110. <https://doi.org/10.1080/14737167.2020.1755261>
- Pratama, S., Lauren, B. C., & Wisnu, W. (2022). The efficacy of vitamin B12 supplementation for treating vitamin B12 deficiency and peripheral neuropathy in metformin-treated type 2 diabetes mellitus patients: a systematic review. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, 16(10), 102634. <https://doi.org/10.1016/j.dsx.2022.102634>
- Rocha, L. V., Macdonald, I., Alsema, M., & Færch, K. (2022). The use and effectiveness of selected alternative markers for insulin sensitivity and secretion compared with gold standard markers in dietary intervention studies in individuals without diabetes: results of a systematic review. *Nutrients*, 14(10). <https://doi.org/10.3390/nu14102036>
- Rochmah, N., Faizi, M., Hisbiyah, Y., Perwitasari, R. K., Kalishah, J., Aina, Q., & Nuzula, T. M. (2022). Distribution of body mass index and random plasma glucose as early detection of diabetes mellitus in Indonesian students. *International Journal of Scientific Advances*, 3(5). <https://doi.org/10.51542/ijscia.v3i5.13>
- Serowik, T. C., & Pantalone, K. M. (2024). The evolution of type 2 diabetes management: glycemic control and beyond with SGLT-2 inhibitors and GLP-1 receptor agonists. In *Journal of Osteopathic Medicine* (Vol. 124, Issue 3, pp. 127–135). Walter de Gruyter GmbH. <https://doi.org/10.1515/jom-2023-0179>
- Singh, A. K., Yadav, D., Sharma, N., & Jin, J. O. (2021). Dipeptidyl peptidase (Dpp)-iv inhibitors with antioxidant potential isolated from natural sources: A novel approach for the management of diabetes. In *Pharmaceuticals* (Vol. 14, Issue 6). MDPI AG. <https://doi.org/10.3390/ph14060586>
- Syahid, Z. M. (2021). Faktor yang berhubungan dengan kepatuhan pengobatan diabetes mellitus. *Jurnal Ilmiah Kesehatan Sandi Husada*, 10(1), 147–155. <https://doi.org/10.35816/jiskh.v10i1.546>

- Tjokroprawiro, A., Murtiwi, S., & Tjandrawinata, R. R. (2016). DLBS3233, a combined bioactive fraction of *Cinnamomum burmanii* and *Lagerstroemia speciosa*, in type-2 diabetes mellitus patients inadequately controlled by metformin and other oral antidiabetic agents. *Journal of Complementary and Integrative Medicine*, 13(4), 413–420. <https://doi.org/10.1515/jcim-2016-0031>
- Tondok, S. B., Watu, E., & Wahyuni, W. (2021). Validitas instrumen european quality of life (EQ-5D-5L) versi Indonesia untuk menilai kualitas hidup penderita tuberkulosis. *Holistik Jurnal Kesehatan*, 15(2), 267–273. <https://doi.org/10.33024/hjk.v15i2.4759>
- Tripathy, S., Hansda, U., Seth, N., Rath, S., Rao, P. B., Mishra, T. S., Subba, S. H., Das, R., Nayak, S., & Kar, N. (2015). Validation of the euroqol five-dimensions - Three-level quality of life instrument in a classical Indian language (Odia) and its use to assess quality of life and health status of cancer patients in eastern India. In *Indian Journal of Palliative Care* (Vol. 21, Issue 3, pp. 282–288). <https://doi.org/10.4103/0973-1075.164896>
- Tsui, T. C. O., Chan, K. K. W., Xie, F., & Pullenayegum, E. M. (2024). Creating a multiply imputed value set for the EQ-5D-5L in Canada: State-level misspecification terms are needed to characterize parameter uncertainty correctly. *Medical Decision Making*, 44(4), 405–414. <https://doi.org/10.1177/0272989X241241328>
- Wada, A. S., Jatau, A. I., Bala, A. A., Haruna, A., Isa, A. M., Safiyya, A. S., & Sha'aban, A. (2019). Use of traditional medicines among pharmacists in Nigeria. *Complementary Therapies in Clinical Practice*, 35, 53–56. <https://doi.org/https://doi.org/10.1016/j.ctcp.2019.01.014>
- Wallach, J. D., Wang, K., Zhang, A. D., Cheng, D., Grossetta Nardini, H. K., Lin, H., Bracken, M. B., Desai, M., Krumholz, H. M., & Ross, J. S. (2020). Updating insights into rosiglitazone and cardiovascular risk through shared data: individual patient and summary level meta-analyses. *BMJ*, 368, 17078. <https://doi.org/10.1136/bmj.l7078>
- Williams, R., Karuranga, S., Malanda, B., Saeedi, P., Basit, A., Besançon, S., Bommer, C., Esteghamati, A., Ogurtsova, K., Zhang, P., & Colagiuri, S. (2020). Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, 162, 108072. <https://doi.org/https://doi.org/10.1016/j.diabres.2020.108072>