Evaluation of Spexin Level in Patients with Type 2 Diabetes: A Meta-analysis

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Abstract

Objective: The neuropeptide Spexin (SPX) plays a critical role in energy homeostasis. Type 2 Diabetes (T2D) is a globally prevalent metabolic disorder associated with obesity and insulin resistance. Therefore, this meta-analysis evaluates the association between SPX levels and insulin resistance in individuals with and without T2D.

Materials and methods: Data from PubMed, Embase, Scopus, Web of Science, SpringerLink, ScienceDirect, and Google Scholar were searched up to Dec 30/ 2024 using precise terms and predefined eligibility criteria. Statistical analyses were conducted using SPSS version 29. Fixed-effect models were used to calculate the pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) for SPX levels, insulin levels, and homeostatic model assessment for insulin resistance (HOMA2-IR) associated with T2D. Heterogeneity was assessed using the I^2 statistic.

Results: Our analysis revealed that SPX blood levels are significantly reduced in T2D patients compared to controls. The SMD for SPX levels was -1.31 (95% CI: -1.45 to -1.18, $p < 0.001$, $I^2 = 99\%$). Insulin resistance was significantly higher in T2D patients compared to controls (SMD: 1.24, 95% CI: 1.10 to 1.37, $p < 0.001$), alongside increased body mass index (BMI) (SMD: 0.55, 95% CI: 0.40 to 0.70, $p < 0.001$). Despite significant findings, high heterogeneity was observed across studies.

Conclusions: Our findings reveal that SPX levels are significantly lower in individuals with T2D, while insulin resistance and BMI are markedly higher. This meta-analysis highlights the potential of SPX as a biomarker for metabolic dysfunction in T2D

Keywords: Spexin, Type 2 Diabetes, meta-analysis, Forest Plot. Insulin, BMI

Introduction

Spexin (SPX), known as neuropeptide Q, is a recently identified 14-amino acid neuropeptide encoded by the *SPX* gene and was first discovered in 2007 through bioinformatics tools.[1] As a highly conserved peptide across vertebrate species, SPX is integral to various physiological processes, particularly its regulatory roles in metabolism.[2] Its interaction with galanin receptors (GALR2 and GALR3) forms the basis of its metabolic regulatory activity, modulating glucose metabolism, lipid utilization, and overall energy balance.[3] Experimental studies have demonstrated that SPX exerts profound effects on peripheral tissues by enhancing glucose uptake and inhibiting lipogenesis, thereby promoting metabolic equilibrium.[4] To further investigate its functions, Gu *et al.* analysed SPX localisation in various human endocrine tissues. Their findings revealed SPX expression in the adrenal glands, pancreas, visceral fat, and thyroid, with the highest levels observed in the adrenal glands, followed by the pancreas.[5] In addition to its metabolic functions, SPX has gained attention as a potential biomarker for insulin resistance and obesity, both of which are closely linked to the development of type 2 diabetes (T2D). Emerging evidence suggests that SPX plays a significant role in modulating key processes involved in metabolic dysfunction associated with T2D. Specifically, it facilitates insulin secretion and β-cell proliferation, critical processes

for maintaining glucose homeostasis.[6] Moreover, SPX enhances glucose uptake in peripheral tissues while suppressing lipogenesis, further emphasising its role in regulating glucose metabolism and preserving metabolic balance.[7]

The relationship between SPX levels and T2D has been explored in a limited number of studies. Evidence indicates that individuals with T2D exhibit significantly lower serum SPX levels compared to healthy controls, suggesting a potential association between SPX deficiency and the pathophysiology of T2D.[8] Similarly, plasma SPX levels have been reported to be markedly reduced in obese individuals, regardless of T2D status, when compared to normal-weight participants.[9] Although these findings are encouraging, discrepancies persist within the existing literature. Differences in study populations, methodological approaches, and assay techniques have contributed to conflicting results regarding SPX's role in T2D. Thus, a thorough meta-analysis is essential to synthesize current evidence, address gaps in knowledge, and clarify the relationship between SPX and T2D. This meta-analysis seeks to assess the relationship between SPX levels and T2D by quantifying the differences in circulating SPX levels between T2D patients and healthy controls, with a particular focus on its potential as a biomarker. Clarifying this relationship may open new avenues for diagnostic and therapeutic approaches. Given the global prevalence of T2D, these insights underscore the urgent need for innovative approaches to early diagnosis, monitoring, and treatment.

Methods

This meta-analysis was conducted to investigate the relationship between circulating SPX levels and T2D. The study was designed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, replicability, and methodological consistency (Supplemental Table 1).

A comprehensive search was conducted across multiple electronic databases, including PubMed, Embase, Scopus, Web of Science, SpringerLink, ScienceDirect, and Google Scholar, to identify relevant studies published up to Dec 30/2024. The search strategy was developed using Medical Subject Headings (MeSH) terms and free-text keywords such as "SPX," "Type 2 Diabetes," "Serum SPX," and "T2D." Boolean operators (AND, OR) were applied to optimize the search. Additionally, reference lists of included studies and relevant reviews were manually screened for further eligible articles.

A comprehensive set of eligibility criteria was developed to identify studies for inclusion. Eligible studies were those investigating SPX levels in human participants diagnosed with T2D. Only articles written in English, employing cohort, case-control, or comparative study designs, and involving adult populations with T2D were considered. Studies were excluded if they were non-English, conducted on animal subjects, included children or adolescents, lacked relevance to T2D or SPX, or did not meet the required study design criteria.

Data was independently extracted by two reviewers (AA and DA) and was confirmed by a third one (MA) using a standardized data extraction form to ensure consistency and accuracy. The following variables were systematically recorded: study characteristics, including surname of the first author, publication year, country, and study design; population characteristics, such as sample size, mean age, sex distribution, and body mass index (BMI); exposure details, including SPX levels (mean, standard deviation, or median); outcomes, which focused on the associations of SPX with insulin and insulin resistance.

The primary exposure of interest was circulating SPX, measured quantitatively in serum using enzyme-linked immunosorbent assays (ELISA). Studies were required to report mean SPX levels with standard deviations. All the selected studies reported SPX levels as mean ± SD except for Dai *et al.,* which was reported as median (interquartile range (IQR)), so we used the Meta-Analysis Accelerator website (https://meta-converter.com/) to convert all median (IQR) data into mean ± SD. Also, the same website was used to combine all different subgroups for each group (T2D or control) so we can compare the levels in general between T2D patients and control.[10]

Outcomes of interest included correlations between SPX levels and glycemic control measures, such as insulin and homeostatic model assessment for insulin resistance (HOMA2-IR). Additional outcomes included associations with metabolic health parameters, such as body mass index (BMI).

Data analysis was conducted using SPSS IBM 29.[11] A p-value of less than 0.05 was considered statistically significant. Effect sizes were expressed as standardized mean differences (SMD) with 95% confidence intervals (CIs) for continuous variables. Data synthesis accounted for heterogeneity among studies by grouping them according to their relevance to T2D outcomes and SPX levels. Statistical analyses were performed using fixed-effects meta-analysis models when heterogeneity was identified. Heterogeneity was assessed using the I^2 statistic, which quantifies the percentage of total variation between studies that is due to heterogeneity rather than chance. Typically, an I^2 value >50% indicates significant heterogeneity.[12]

The presence of reporting bias was assessed using Egger's tests where applicable using the meta-analysis online tool https://metaanalysisonline.com. These methods provided additional reliability to the conclusions drawn from the analysis.

Results

A total of 1,226 articles were identified from seven databases, including PubMed, Google Scholar, Science Direct, SpringerLink, Web of Science, EBSCO, and Scopus. After removing duplicates (n = 498) and records ineligible by automation tools (n = 36), 692 articles were screened. Of these, 680 were excluded due to irrelevance, non-English language, non-human studies, reviews or meta-analyses, pre-2018 publications, non-peer-reviewed studies, insufficient data on SPX, redundancy, poor quality, or animal studies. Nine reports were assessed for eligibility, but three were excluded because SPX results were only presented as figures or due to duplicate datasets. Ultimately, six studies were included in the meta-analysis (Figure 1) (Table 1).

This meta-analysis, incorporating data from six studies, identified significant differences in SPX levels between individuals with T2D and control groups. The overall SMD was -1.31, with a 95% CI of -1.45 to -1.18, indicating a statistically significant reduction in SPX levels among individuals with T2D ($p < 0.001$). For example, studies by Dai *et al.*[13] and Gowdu *et al.*[14] reported markedly negative effect sizes (SMD: -0.94, 95% CI: -1.16 to 0.72; SMD: -2.91, 95% CI: -3.22 to -2.59, respectively). In contrast, Amirpour *et al.* reported a positive mean difference (SMD: 0.29; 95% CI: -0.02 to 0.59),[15] which was statistically significant. These findings suggest significantly reduced SPX levels in T2D patients compared to controls, with no substantial heterogeneity across studies (I^2 = 99%) (Figure 2).

Furthermore, insulin levels were significantly elevated in T2D patients (SMD: 0.26, 95% CI: 0.12 to 0.40, $p < 0.001$), consistent with the early-stage hyperinsulinemia commonly seen in T2D as a compensatory response to insulin resistance (Figure 3). The levels of insulin resistance were also significantly higher in T2D patients (SMD: 1.24, 95% CI: 1.10 to 1.37, $p < 0.001$), underscoring its critical role in the disease's pathophysiology (Figure 4). In addition, body mass index (BMI) was significantly greater in T2D patients (SMD: 0.55, 95% CI: 0.40 to 0.70, $p < 0.001$), highlighting the well-established association between obesity and T2D as both a risk factor and a contributor to disease progression (Figure 5). However, the substantial heterogeneity observed across the data for SPX, insulin, insulin resistance, and BMI emphasizes the variability between studies, which should be taken into account when interpreting these results.

Table 1: Characteristics of included studies.

First author (publication year)	Country-study Design	Type of participants group	Sample size	Sex male/female	Age (mean±SD) year	SPX (mean±SD) ng/mL	BMI (mean±SD) kg/m^2	Insulin (mean±SD) µIU/mL	HOMA2-IR (mean±SD)
Al-fatlawiy et al. (2022),[16]	Iraq-case-control	Control	30	20/10	48.27 ± 6.336	578.72 ± 15.71	23.756 ± 0.77	5.05±1.14	1.16±0.25
		T2D	60	40/20	49.87 ± 8.090	357.67 ± 24.99	29.766 ± 3.225	7.23±1.26	2.65±0.77
Amirpour et al. (2021)[15]	Iran-case-control	Control	84	35/49	45.07 ± 10.34	2489.46 ± 1623.80	28.79 ± 5.57	17.42 ± 8.11	NA
		T2D	84	51/33	53.89 ± 8.12	2974.69 ± 1737.74	28.84 ± 5.22	12.47 ± 8.07	NA
Dai et al. (2023)[13]	China-case-control	Control	161	57/104	48.72 ± 6.32	0.23 ± 0.09	24.50 ± 3.20	7.22 ± 4.17	0.83 ± 0.48
		T2D	186	106/80	57.69 ± 9.43	0.15 ± 0.08	25.69±3.18	8.84±6.34	1.64±0.92
Gowdu, et al. (2021)[14]	India-cross-sectional study	Control	110	NA	45.5±10.0	0.79±0.03	NA	NA	7.03±0.1
		T2D	220	NA	52.85 ± 7.16	0.57 ± 0.09	NA	NA	9.32 ± 1.82
Gu et al. (2022)[17]	China-cross-sectional study	Control	41	20/21	51.8±6.2	3.17 ± 0.56	23.0±0.6	4.5±2.0	1.04±0.55
		T2D	323	235/88	47.34 ± 11.90	1.97 ± 0.56	26.33 ± 3.41	5.83 ± 5.52	2.12 ± 1.97
Mashaal et al. (2022)[18]	Egypt-case-control	Control	42	11/31	44.72 ± 8.71	1.25 ± 0.74	NA	3.71 ± 1.70	0.85 ± 0.46
		T2D	44	8/36	44.50 ± 10.46	0.64 ± 0.047	NA	5.85 ± 3.30	2.99±1.88

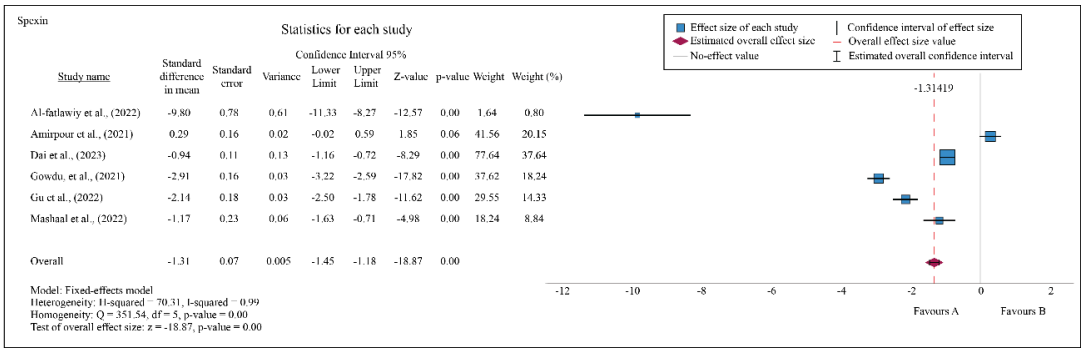

Figure 2: Forest Plot of Standardized Mean Difference (SMD) Comparing SPX Levels Between Control Participants and Individuals with T2D

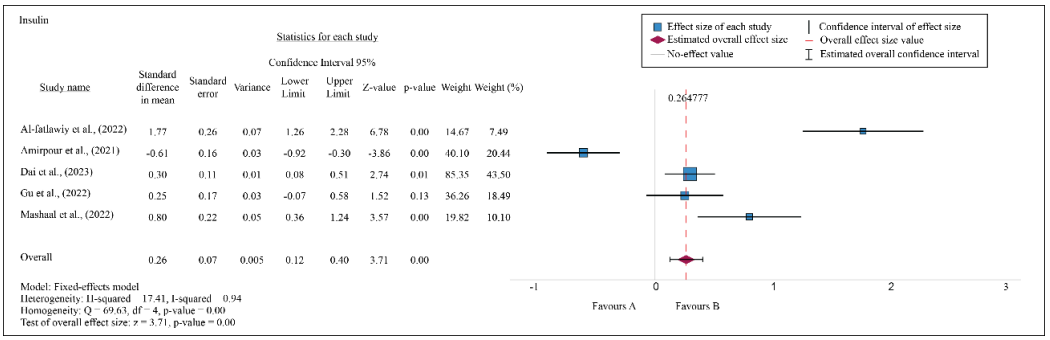

Figure 3: Forest Plot of Standardized Mean Difference (SMD) Comparing Insulin Levels Between Control Participants and Individuals with T2D

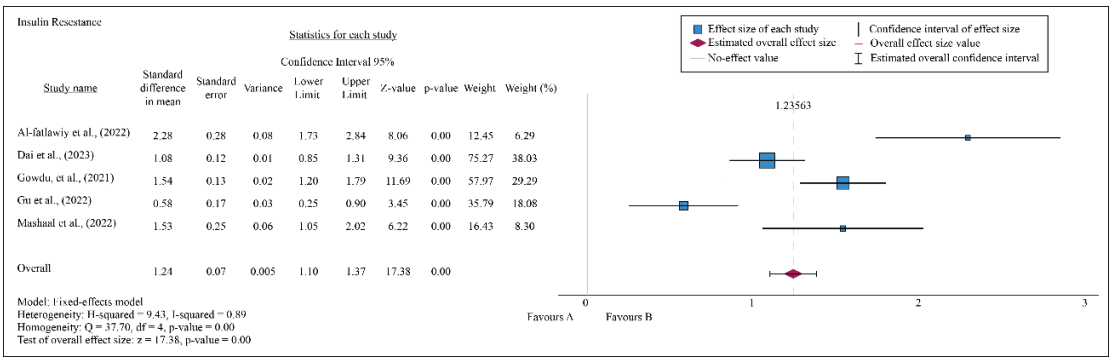

Figure 4: Forest Plot of Standardized Mean Difference (SMD) Comparing Insulin Resistance Levels Between Control Participants and Individuals with T2D

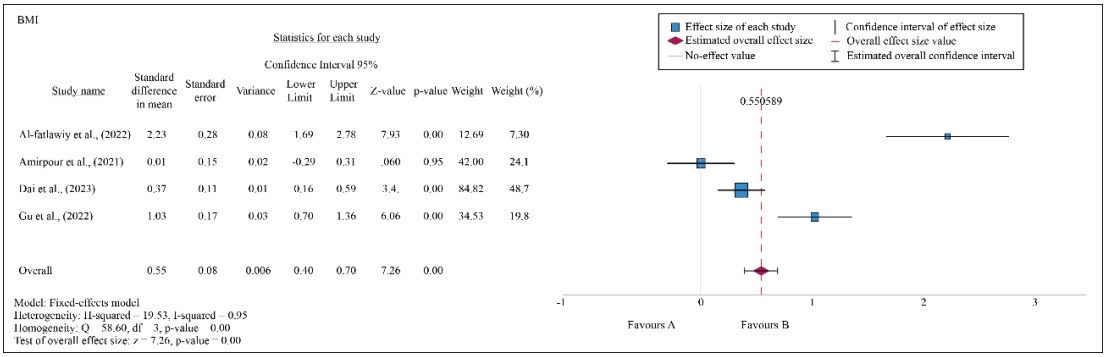

Figure 5: Forest Plot of Standardized Mean Difference (SMD) Comparing BMI Resistance Levels Between Control Participants and Individuals with T2D

To ensure a comprehensive evaluation of the methodological rigor and reliability of the included studies, the Joanna Briggs Institute (JBI) critical appraisal checklists were employed to provide a robust and transparent assessment framework.

Table 2. Quality assessment of the included cross-sectional studies based on the Joanna Briggs Institute (JBI) critical appraisal checklist

No.	Study ID	Questions assessing included cross-sectional studies								Yes (%)
		1	2	3	4	5	6	7	8	
1	Gowdu *et al.* (2021) [14]	Y	Y	Y	Y	Y	Y	Y	Y	100
2	Gu *et al.* (2022) [17]	Y	Y	Y	Y	Y	N	Y	Y	87.5

Questions: 1. Were the criteria for inclusion in the sample clearly defined? 2. Were the study subjects and the setting described in detail? 3. Was the exposure measured in a valid and reliable way? 4. Were objective, standard criteria used for measurement of the condition? 5. Were confounding factors identified? 6. Were strategies to deal with confounding factors stated? 7. Were the outcomes measured in a valid and reliable way? 8. Was appropriate statistical analysis used? Y=Yes; N=No; U=Unclear.

Table 3. Quality assessment of the included case-control studies based on the Joanna Briggs Institute (JBI) critical appraisal checklist

No.	Study ID	Questions assessing included case-control studies										Yes (%)
		1	2	3	4	5	6	7	8	9	10	
1	Al-fatlawiy *et al.* (2022) [16]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
2	Amirpour *et al.* (2021) [15]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	90
3	Dai *et al.* (2023) [13]	Y	U	U	U	U	U	U	Y	U	Y	20
4	Mashaal *et al.* (2022) [18]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	90

Questions: 1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls? 2. Were cases and controls matched appropriately? 3. Were the same criteria used for the identification of cases and controls? 4. Was exposure measured in a standard, valid, and reliable way? 5. Was exposure measured in the same way for cases and controls? 6. Were confounding factors identified? 7. Were strategies to deal with confounding factors stated? 8. Were outcomes assessed in a standard, valid, and reliable way for cases and controls? 9. Was the exposure period of interest long enough to be meaningful? 10. Was appropriate statistical analysis used? Y=Yes; N=No; U=Unclear.

Discussion

Insulin resistance is the primary underlying etiology of T2D, and obesity. Notably, one of the key features of T2D and obesity is dysregulation of adipokine secretion from visceral adiposity. Spexin is an adipokine that is adversely correlated with energy storage and is secreted by a variety of tissues, including the glandular stomach and white adipocytes. This peptide regulates a variety of metabolic processes, such as inflammation, lipolysis, energy expenditure, and eating behavior, by acting on GALR2/3 receptors. Spexin has the ability to penetrate the hypothalamus and control the hypothalamic melanocortin system, which in turn maintains a balance between food intake and energy expenditure.[19]

Spexin behavior has been examined in several animal models. Subcutaneous spexin injection (35 g/kg/day) decreased hunger and caused a 32 % reduction in caloric intake in high fat diet-induced obese rats.[20] Moreover, spexin intraperitoneal injections decreased mice food consumed during the night.[21] Body weight was significantly decreased in diet-induced obese mice following spexin intraperitoneal injection for 30 days, reduces lipid content and improves insulin sensitivity.[22] Zeng et al reported,[23] that after 12 weeks of SPX treatment, body weight and serum lipid levels decreased significantly, while insulin sensitivity in high fat diet in obese mice was improved. They also found that SPX promote oxygen consumption, increased mitochondrial content and the expression of brown-specific markers in white adipose tissue of high fat diet mice. Intracerebroventricular injection of spexin interact with NPY, GalR2 and GalR3 receptors and decrease food intake in broiler chickens.[24] When spexin was knocked out of zebrafish, the resulting spexin-2 mutant zebrafish showed a favorable metabolic phenotype, increased food intake, and elevated Agrp mRNA levels.[25,26]

Adeghate et al found that spexin co-localizes with insulin in pancreatic islet cells of normal and diabetic rats, suggesting spexin role in the regulation of pancreatic endocrine function.[27] Spexin alleviates insulin resistance and inhibits hepatic gluconeogenesis via the FoxO1/PGC-1α pathway in high fat diet induced rats and insulin resistant cells.[28] Additionally, spexin alleviates hypertension, hyperuricaemia, dyslipidemia and insulin resistance in high fructose diet induced metabolic syndrome in rats via enhancing PPAR-ɣ and AMPK and inhibiting IL-6 and TNF-α.[29]

This meta-analysis revealed a significant reduction in SPX levels among individuals with T2D. Additionally, a negative correlation was observed between BMI, insulin levels, and insulin resistance in comparison to control groups across six independent studies. Decrease in circulating SPX level was observed in obese individuals was linked to insulin resistance and metabolic dysfunction.[30,31] The mechanisms underlying the regulation of insulin resistance and energy metabolism are not yet fully understood, various hypotheses have been proposed to clarify SPX's role in metabolic syndrome-related conditions, including T2D.[32] These primarily emphasize its involvement in glucose, insulin, lipid metabolism, and energy metabolism, which are significantly disrupted in T2D, suggesting a potential role for SPX in T2D pathogenesis.

These findings are consistent with several studies that showed decreased levels of SPX in T2D and insulin resistance. Serum SPX level was significantly decreased in obese children and negatively correlated with insulin resistance and pancreatic β cell function indicators. Therefore, SPX may play a protective role in the process of glucose homeostasis and is closely related to β cell function.[33] Another study by Dai et al. who reported that SPX levels were lower in newly diagnosed T2D and even lower in established T2D, with significant negative correlations to fasting plasma glucose (FPG), HbA1c, and HOMA2-IR, alongside a positive correlation with HOMA2-β.[34] In line with these findings, Al-Fatlawiy et al. reported that circulating SPX levels were lower in diabetic patients compared to controls 16. Furthermore, Gowdu et al. identified SPX as a negatively associated biomarker linked to glucose levels, insulin resistance, liver enzymes, and inflammation in diabetes and hypertension 14. Gu et al. found that SPX levels were significantly lower in diabetes with obesity (DM-OB) group compared to diabetes with overweight (DM-OV) and diabetes with normal weight (DM-NW) groups, showing a strong negative correlation with measures of adiposity 17. After one year of standardized metabolic management, the DM-OB group exhibited the greatest increase in SPX levels and the most significant reduction in BMI, reinforcing SPX's potential as a biomarker for metabolic improvements in T2D with obesity. This association was also repored by Amirpour et al. 15. Moreover, Hodges et al. examined SPX levels in adolescents categorized by normal weight, obesity with normal glucose tolerance, and obesity with T2D.[35] Their findings indicated no significant differences in SPX levels across the three groups at 30 and 120 minutes. Despite these findings, future research must consider the complexity of confounding factors, such as age and obesity, to ensure more comprehensive and reliable results.

Obesity, a key risk factor for the development of T2D, is associated with metabolic dysfunction and chronic low-grade inflammation, which is mediated by pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[36] SPX exerts anti-inflammatory effects by reducing the concentration of these inflammatory cytokines in both liver tissue and serum of T2D animals.[37] Moreover, Decreased SPX levels have been associated with impaired lipid metabolism, facilitating the development and progression of non-alcoholic fatty liver disease , a frequent comorbidity in T2D.[38,39] Restoring SPX levels could offer significant therapeutic benefits, including enhanced insulin sensitivity, improved regulation of lipid metabolism, and mitigation of inflammation, which highlights SPX as a promising target for the treatment of T2D and associated metabolic disorders.

While this meta-analysis provides valuable insights, certain limitations should be acknowledged. First, access restrictions prevented the inclusion of certain relevant studies, which may have introduced selection bias. Second, inconsistencies in data reporting required statistical standardization. While most studies reported Spexin (SPX) levels as mean ± standard deviation (SD), one study used median with interquartile range (IQR). These values were converted into mean ± SD using a validated tool, and subgroup data were aggregated for comparability. Though these adjustments enhance interpretability, they introduce minor approximation errors. Lastly, substantial heterogeneity across studies, likely due to differences in study design and measurement methods, underscores the need for future research with standardized methodologies and broader data access.

Conclusion

In conclusion, this meta-analysis highlights a significant disparity in SPX levels between T2D patients and healthy controls, with consistently lower levels observed in the T2D population. The inverse relationship between insulin resistance and BMI suggests that SPX could play a role in modulating these metabolic disturbances, which are central to T2D development. However, the considerable heterogeneity among studies underscores the need for cautious interpretation and further research to explore potential sources of variability.

Disclosure

No conflict between the authors

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