

Ficus species derived polyphenols and male fertility outcomes in Type 2 Diabetes Mellitus (T2DM): A systematic review

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Systematic Review

Keywords: Fertility effects, Ficus Species, Polyphenols, Type II diabetes mellitus, In vivo study

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TITLE: *Ficus* species derived polyphenols and male fertility outcomes in Type 2 Diabetes Mellitus (T2DM): A systematic review

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Keywords: Fertility effects; *Ficus Species*; Polyphenols; Type II diabetes mellitus; In vivo study.

Definitions of terms:

Fertility effect: This is the biological capacity to reproduce using the sperm count, motility, morphology, viability and offspring number of Wistar rats induced with T2DM.

In Vivo study: Research using living organisms either humans or animals to find out the medical effects of herbal remedy or drug treatment for future therapeutic clinical translation.

Abbreviations:

CAT----- Catalase,

DM ----- Type 2 Diabetes Mellitus,

FBS-----Fasting Blood Sugar

FSH-----Follicle Stimulating Hormone,

GPx ----- Glutathione Peroxidase,

GSH -----Reduced Glutathione,

HbA1c-----Glycated Hemoglobin

IRS----- Insulin Receptor Substrate,

MDA -----Malondialdehyde,

NOS -----Nitric Oxide Synthase,

OS-----Oxidative Stress

RBS-----Random Blood Sugar

ROS -----Reactive Oxygen Species,

SOD -----Superoxide Dismutase,

STZ -----Streptozotocin,

T2DM----Type II Diabetes Mellitus

Table of Contents

Key words:.....	ii
Definitions of terms:	ii
Abbreviations:	ii
Introduction	1
Research Question	4
Objectives.....	4
Methodology	4
Screening and Selection Process.....	4
Defined Scope:	5
Inclusion Criteria:	5
Exclusion Criteria:	5

Data Extraction..... 5

Results:..... 7

Figure 1: The PRISMA flow diagrams 8

Study Characteristics and Demographics 1

Research Gaps and Future Directions..... 28

Limitations..... 28

Conclusion..... 29

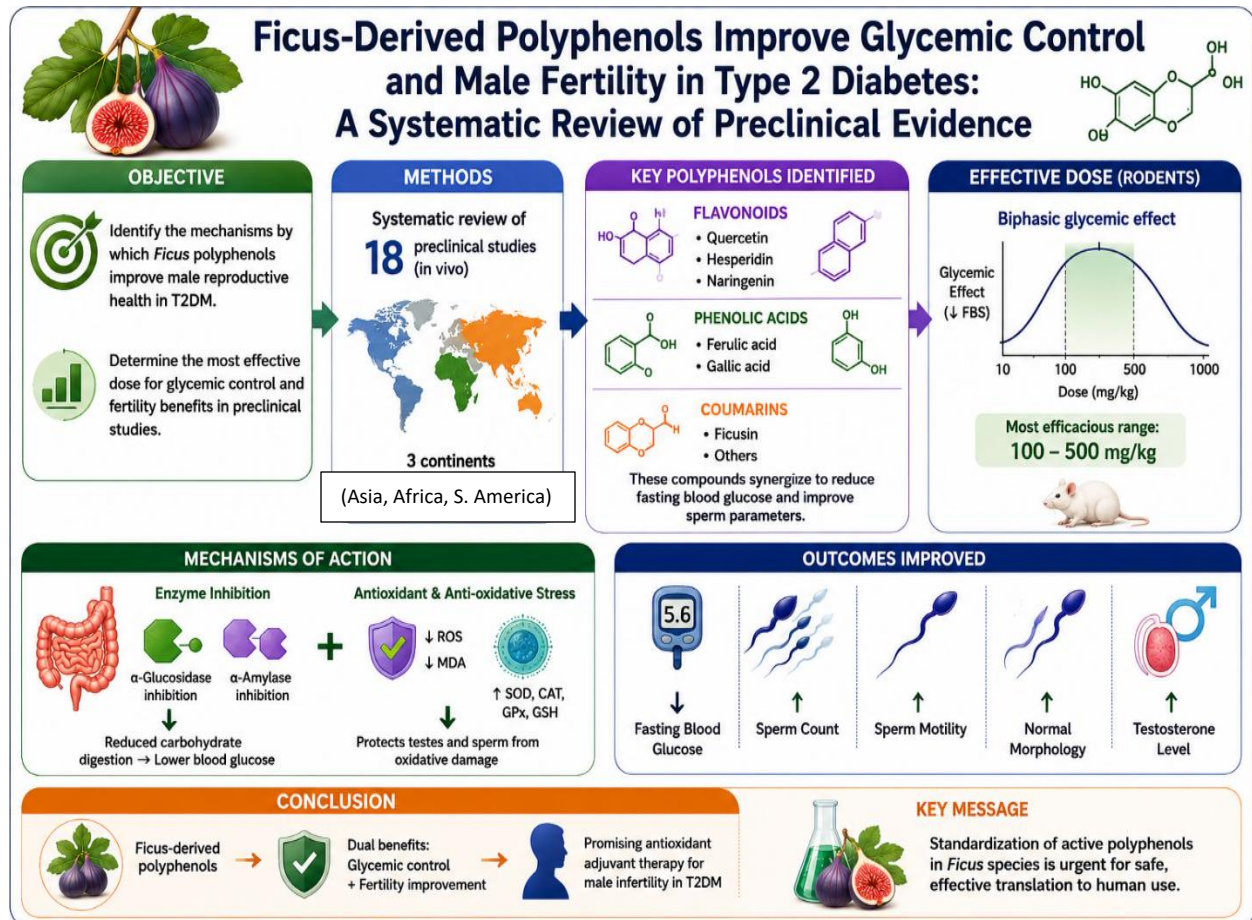
Table 1: Study characteristics **Error! Bookmark not defined.**

References: 30

Abstract:

Background: More than 500 million people worldwide have Type 2 diabetes mellitus (T2DM) and is increasingly associated with male reproductive dysfunction, including impaired spermatogenesis, reduced testosterone production, and infertility. Infertility is known to affect more half all the males with diabetes and has no reliable medication despite the most common pharmacological therapies being able to low the blood glucose. With this crisis being investigated globally the *Ficus* species are a promising dual therapeutic option that is being experimented on, to see how we could improve sperm motility and fertility outcomes. The **objectives** of this systematic review were to identify the mechanisms through which Ficus-derived polyphenols improve glycaemic control and male reproductive outcomes in T2DM. And also, to fine the dose that is most effective for the different *Ficus* species that are extracted to offer the glycemic control and fertility benefit. **The results** synthesized data from 18 studies that were experimental from three continents and the flavonoids especially Quercetin, Hesperidin and Naringenin were the most active found. Also, phenolic acid and coumarins were noted to synergize the fasting blood sugar reduction and improve the sperm parameters, especially Ferulic acid, gallic acid and Ficusin. The glycemic action of these polyphenols was noted to be biphasic and the most efficacious dose being between 100-500mg/ kg in rodents that were most used. **Findings:** The mechanism of actions was mainly the ability to inhibit α glucosidase and α amylase on top of the antioxidant activities that protective to the reproductive system. This aligns previous research on hypoglycemic phytochemicals and fertility having the potential of antioxidant adjuvant therapies. **Conclusion:** Ficus-derived polyphenols demonstrate promising antidiabetic and fertility-enhancing effects in experimental T2DM models. However, evidence remains limited to preclinical studies, and well-designed clinical trials are required before translation into clinical practice.

Graphic Abstract:



Introduction

Affecting over 500 million patients worldwide, Type 2 Diabetes Mellitus (T2DM) is now a global health pandemic. Its projectioned to continue to rise particularly in developing countries (Bousekkine et al., 2025). Characterized by chronic high blood sugar be fasting or random (FBS or RBS) resulting from insulin resistance and progressive beta cell dysfunction, T2DM is a major cause of global morbidity and mortality (Abel et al., 2024). On top of its well recognized vascular and neurological complications, the metabolic derangements of T2DM lead to serious, yet often underappreciated, effects on reproductive system, more so in male patients (Rato et al., 2016). Growing evidence indicates that T2DM significantly impairs male fertility through multiple interconnected pathways (Zhang et al., 2025).

Chronic high blood sugar induces oxidative stress (OS), raises glycated Hemoglobin (HbA1c) formation, and cause low-grade systemic inflammation, all of which impair testicular architecture, spermatogenesis, and steroidogenesis (Bo et al., 2025). In vivo studies have reported reduced sperm quality, altered seminal parameters, and increased DNA fragmentation in diabetic men, with hormonal imbalances evidenced by lowered testosterone and elevated gonadotropin levels (La Vignera et al., 2012). These fertility sequelae pose a growing challenge to global reproductive health, and with the increasing prevalence of T2DM among men of reproductive age (Kaltsas et al., 2025). Traditional antidiabetic treatment, while effective for blood glucose management, often fail to address the multifactorial pathogenesis of diabetic reproductive damage and may lead adverse effects(Pelusi, 2022).

This lack of a reliable therapeutic solution has led to a lot of focus on plant derived natural products, especially polyphenols, as dual therapeutic agents. These bioactive compounds, abundant in fruits, leaves, and plant roots, exhibit potent anti inflammatory, antioxidant, with hypoglycaemic actions (Clemente-Suárez et al., 2025). The vast diversity of medicinal plants, the *Ficus* genus (Moraceae) locally called omutuba in Uganda has growing particular attention. With over 800 species distributed across tropical and subtropical regions, *Ficus* plants have a longstanding history in traditional medicine for treating T2DM, inflammatory conditions, and fertility (Shi et al., 2018). Their medicinal use is backed by a rich and varied polyphenolic composition, including phenolic acids (Such as., caffeic, gallic acid, ferulic acids) and flavonoids (such as., rutin, quercetin, catechins), which differ across species, plant parts, and maturation stages (Masiala et al., 2024).

In vivo studies have shown that *Ficus* extracts have significant antioxidant with hypoglycaemic properties, while preliminary evidence links their polyphenolic constituents to alleviate testicular function and spermatogenic parameters in T2DM (Abdulrahman, 2023). Despite considerable research on their Hypoglycemic effects, a comprehensive synthesis of the specific evidence linking *Ficus* derived polyphenols to male fertility outcomes in the context of T2DM is still inadequate (Groti Antoniĉ & Zitzmann, 2024). Current studies are often fragmented across different species, extraction methods, and experimental models, making it challenging to draw cohesive conclusions. This review, therefore, critically examines the available state of knowledge regarding the efficacy and mechanisms of *Ficus*-derived polyphenols in improving

male fertility outcomes in T2DM, while identifying research gaps and future directions to inform translational applications.

Research Question

Primary Question:

What is the role of *Ficus* Species derived polyphenols in improving male fertility in Type 2 Diabetes Mellitus in vivo?

Objectives

1. To evaluate mechanistic links between *Ficus*-derived polyphenols and reproductive outcomes in T2DM.
2. To determine quantitatively the association between standard doses of polyphenol rich *Ficus* extracts and glycaemic control through meta-analysis where feasible.

Methodology

Study Design

After having the protocol for the systematic review being published on PROSPERO prior to screening. The number for registration was given. The registration is available online: <https://www.crd.york.ac.uk/PROSPERO/view/CRD420261433214> then the entire process was done following the PRISMA 2020 guidelines (Figure 1).

Search Strategy

The research papers from May 2016 to May 2026 from Google Scholar, PubMed, Connecting Repositories (CORE) for manual search databases were searched for literature. The used search terms used keywords for *Ficus* species, male fertility and T2DM with the use of Boolean operators and MeSH terms. Search terms: ("Ficus carica" OR "Ficus altissima" OR "Ficus sycomorus" OR "Ficus benghalensis" OR "Ficus racemosa" OR "Ficus religiosa") AND (T2DM OR "male fertility") NOT (Review [Publication]). There were no language filters were used during the search. The extracted papers details were then moved to excel sheet for further screening. Owing to the number of the publications on the subject, manual search was also done with CORE. Since it is a connecting repository with the biggest collection for full and open access articles from repositories and journals online.

Selection Process and Screening

The excel file format was be imported into Rayyan, an online which is systematic review platform, where we did the screening process. This was done independently by two reviewers

following a two-step process to screening all the papers. We started with removing the duplicates then screened using the title and abstract screening for potentially relevant studies. We excluded the articles based on their being irrelevant irrelevance and having inadequate data. The was followed by the step that involved full text screening to confirm eligibility based of the inclusion and exclusion criteria documented in the protocol. The included articles were reviewed, that met the eligibility criteria for the final synthesis. The whole screening process was documented into a PRISMA 2020 flow which is (Figure 1), highlighting individual number of studies identified, screened, excluded, and included, illustrating the with reasons for those that were exclusion.

Eligibility Criteria

Population: T2DM

Interventions: *Ficus* species polyphenols with hypoglycemic activity.

Comparators: placebo, hypoglycemic agents, or standard antidiabetic therapies.

Outcomes: Improve glucose control and fertility

Study types: in vivo controlled studies.

Defined Scope:

Inclusion Criteria:

- ✓ Original research articles (in vivo preclinical animal models, and human studies)
- ✓ Studies reporting effects of *Ficus* species extracts or isolated polyphenols on hypoglycemic properties.
- ✓ Studies including male reproductive outcomes of sperm parameters (count, motility, morphology), male gonad hormones, testicular histology, oxidative stress and pregnancy outcomes in T2DM models

Exclusion Criteria:

- ❖ Conference abstracts without full paper
- ❖ Uncontrolled case reports without comparative data
- ❖ Systematic Reviews, commentaries, or opinion pieces

Data Extraction

The data was extracted independently by two reviewers on study characteristics, interventions details, dose, duration, outcomes, and findings. It was by consensus to resolve any discrepancy which was noted as conflict on the data management software. The Rayyan software facilitated blinded screening, conflict identification, and systematic documentation of inclusion and exclusion decisions. This helped to minimize potential reviewer bias the two reviewers that will be involved independently and any disagreements were resolved using a third reviewer. The interviewer agreement was taken at 0.8 Cohen's Kapa. Discrepancy was resolved and the third person made a final verdict were consensus was not initially achieved by the reviewers.

For rigor, the ability to replicate the search strategy and screening process were there after ensured using PRISMA flow records to do the full audit and validation of all that was done at each step. For the second objective (quantitative association between doses and glycaemic control), random-effects meta-analysis was conducted where adequate homogeneity exists. For the subgroup analyses: *Ficus* species, extraction solvent, animal model, and duration of intervention were performed. The extracted details from the articles were: Study title then authors followed by the publication year. We then got the country followed by the study design, sample size then the comparator characteristics, duration, route of administration. We also recorded the key outcomes then the mechanistic pathways with *Ficus* Species intervention type and dosage.

Quality Assessment

To assess the quality the of the included studies we used the SYRCLE's Risk of Bias (RoB) tool for the preclinical animal studies. We didn't find any Human Studies using *Ficus* Species as an intervention to apply the Cochrane RoB 2 tool for randomized trials. The risk of bias assessment was conducted by the two reviewers who performed the screening. This process will involve the following steps:

1. Each reviewer independently assessed the risk of bias for all included studies using the appropriate tools.
2. For each domain, a judgment of "Low risk," "High risk," "Moderate" or "Unclear risk" were assigned. Low risk: The study appears to have adequately addressed the potential for bias in this area. High risk: There is a significant risk of bias that could substantially affect the results. "Moderate risk" grade for certain domain with a partial fulfillment of criteria but not enough for a "Low risk" judgment. Unclear risk: The study report lacks sufficient information to make a clear judgment.

To appraise the animal model studies we used the SYRCLE's risk of bias (RoB) tool. The GRADE framework was used overall evidence of certainty. Independently SYRCLE was used to assess each study across different domains; The domains were selection then, performance, detection. This was followed by the domains of attribution then reporting and judgement biases. With the use of RoB, the different studies were then rated as follows: "low", either "Moderate risk," or "unclear" or "high risk" across the different domains.

To appraise the Randomized Controlled Trials (RCTs): Cochrane RoB 2 tool.

1. Select the Result for Assessment: Risk of bias will be assessed for a specific result from a study, not for the study as a whole. Focus on the results that were used for the review's primary conclusions, typically those in the 'Summary for the Findings' table (e.g., effect on sperm count, testosterone levels, or glycaemic control).
2. Effect of Interest definition: We determined whether the review aims to assess the documented effect of assignment to intervention say the 'intention-to-treat' effect or effect of adhering to the intervention as specified in the protocol (the 'per-protocol' effect).
3. Independent Assessment by Two Reviewers: Two reviewers were then to be assessed independently for the risk of bias for every selected result. This minimized reviewer bias and ensured the reliability of the assessment.

4. Answer Signalling Questions and Assign Domain Judgements: Reviewers used the detailed signalling questions for each domain within the chosen tool to guide their assessment. These questions seek factual information from the study report. Response Options: Each signalling question will be answered with one of the following: Yes, or Probably Yes or Probably No or No or No Information. The responses to the signalling questions are mapped by an algorithm to a proposed domain-level judgement. Domain Judgements: Each domain is rated as one of the following: Low risk of bias; Some concerns (for RoB 2) or Moderate risk (for ROBINS-I) and High risk of bias (for RoB 2) or Serious or Critical risk (for ROBINS-I)
5. To determine the overall Risk of Bias Judgement: The overall risk of bias for a specific result was based on the least favourable assessment across the domains. RoB 2 Overall Judgement: Low risk of bias: All domains are at low risk. Moderate risk of bias: At least one domain has 'Moderate risk', but no domain is at high risk. High risk of bias: At least one domain is at high risk, *or* there are 'Some concerns' for multiple domains that substantially lowers confidence in the result

Data Synthesis

The study characteristics, interventions details, dose, duration, outcomes, and findings were the used for the synthesis of the narrative. The Meta-analysis was only considered for homogenous data in *Ficus* species, extraction solvent, animal model, and duration of intervention.

Results:

The systematic search of PubMed, grey literature for manual search with Connection Repository (CORE), and Google Scholar databases review comprised 18 studies published (May 2016–May 2026), investigating *Ficus* species derived polyphenols and male fertility outcomes in Type 2 Diabetes Mellitus. Retrieved were 281 articles, of which 30 were duplicates thus 15 were deleted leaving 266 articles for Title and Abstract screening. Of these only 63 were eligible for full article screening and only 18 articles with 45 being ineligible (Figure 1). All the 18 articles were for preclinical experiments using with only one invitro and the remaining 17 articles used in 293(Wistar rats, Sprague-Dawley rats) rats, 97 mice (Swiss albino mice, NMRI mice), 60 *Drosophila melanogaster* (Table 1). Chronologically there was (1) study in 2016 and also (1) in 2017, then these were followed (3) studies in 2020, then only (1) in 2022. In 2023 they were (3) studies, (2) studies in 2024 and most of the studies (6) were done in 2025 with only (1) done in 2026. Of these the eligible studies 10 used *F. carica*, 3 used *F. racemose*, 2 used *F. sycomorus*, and the remaining 3 studies use each *F. benjamin*, *F. religiosa*, *F. benghalensis*. The (8) *Ficus* species studies used leaves, (6) used fruits, (3) used stem bark and (1) used seed. The extraction methods were as follows: 7 aqueous, 5 methanolic, 4 hydroalcoholic and one ethyl acetate. The treatment duration is between 7 to 90 days with the most common 14 to 30 days with the *Ficus* doses between 40 to 1000mg per kg and the most common being 100-500mg per kg (Table 1).

Figure 1: The PRISMA flow diagrams

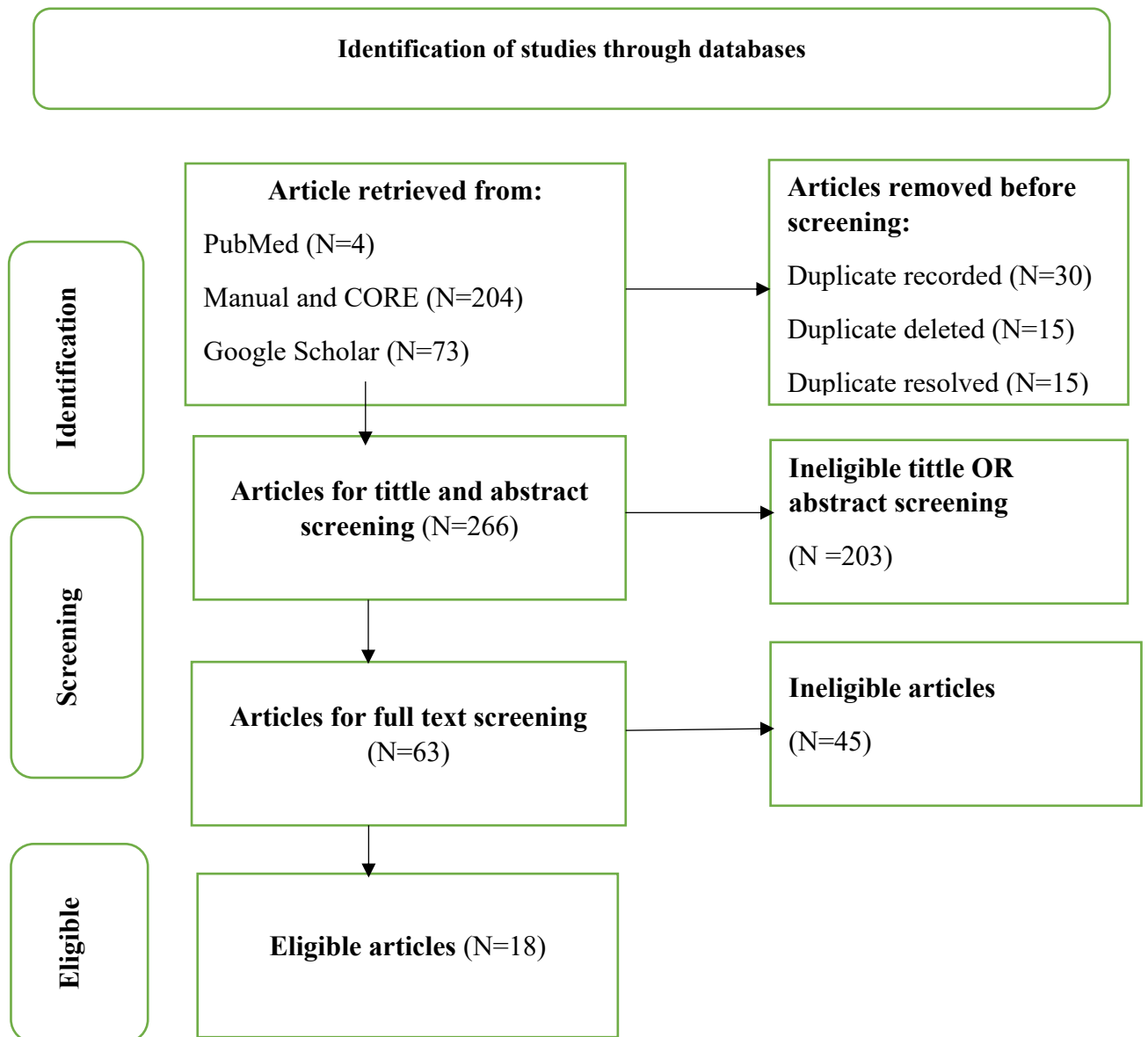


Table 1: Study characteristics

ID	AUTHOR	YEAR	COUNTRY	STUDY DESIGN	SAMPLE SIZE	DURATION	INTERVENTION	Ficus Doses Used	Mechanistic Links	Comparator	Key Primary Outcomes	Secondary Outcomes	Key Results	Effect Size	Risk of Bias Distribution GRADE Framework

1	(Stephen Irudayaraj et al., 2017)	2017	India and Saudi Arabia	In vivo (Rat model)	30 Wistar rats (n=6/group)	28 days	Ethyl acetate leaf extract (<i>F. carica</i>)	250 & 500 mg/kg	Ficusin (6.46 % w/w) acts as antioxidant; enhances Glucose Transporter 4 (GLUT4) translocation and PPAR γ expression; stimulates insulin production	Normal control; Diabetic control (High Fat Diet (HFD)) + Streptozotocin (STZ); Glibenclamide (0.6 mg/kg)	Fasting Blood Glucose (FBG); OGTT; ITT; Plasma insulin; TC; TG; Hepatic glycogen; Carbohydrate metabolism enzyme	Immunohistochemistry (insulin-immunostaining); High-Performance Liquid Chromatography with Diode-Array Detection (HPLC-DAD) analysis (ficusin quantification)	FBG ↓ 52.9-54.0%; Plasma insulin normalized; TC ↓ 26.3%; TG ↓ 42.8%; Hepatic glycogen ↑ 116.9%; Hexokinase ↑ 55.4%; G6Pase ↓ 57.4%; F1,6BPase ↓ 39.1%; Immunohistochemistry: significant ↑ insulin-immunostaining; β -cell protection	FBG: - 52.9 to -54.0%; Insulin: -30.6%; TC: - 26.3%; TG: - 42.8%; Hepatic glycogen: +116.9%; Hexokinase: +55.4%; G6Pase: - 57.4%	Risk of Bias: Moderate . Unclear randomization; no blinding; n=6/group; no power calculation. Domains: Selection (unclear), Performance (high), Detection (low). Grade MODERATE. Strong evidence for antidiabetic and β -cell protective effects.
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2	(Saleem et al., 2023)	2023	Pakistan	In vivo (Rat model)	50 rats (n=5/group)	4 weeks	Ethanollic fruit extract; 10% dried fig diet (<i>F. carica</i>)	400 mg/kg; 10% diet	Polyp henols regenerate β -cells; modulate insulin signaling (INS-1, INS-2, Pdx-1); regulate calcium signalling (Pias-2, Calm-2, Grk-2); promote regeneration (IGF-1)	Alloxan; Glibenclamide	FBG; Serum glucose; Serum insulin; Pancreatic histopathology; Gene expression	Phytochemical analysis	FBG ↓ 39.0%; Serum glucose ↓ 39.1%; Insulin ↑ 59.2%; β -cell protection; Gene modulation (2-4-fold); Histopathology: significant β -cell regeneration	FBG: - 39.0%; Glucose: - 39.1%; Insulin: +59.2%	Risk of Bias: Moderate-High. Unclear randomization; no blinding; n=5/group; no power calculation; year not specified. Domains: Selection (unclear), Grade LOW. Downgraded for indirectness (no reproductive outcomes), imprecision (n=5)
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3	(Mahamet al., 2024)	2024	Malaysia	In vivo (Rat model)	24 rats (n=6/group)	21 days	Aqueous fruit extract (<i>F. carica</i>)	400 mg/kg	Flavonoids (quercetin, caffeic acid, gallic acid), anthocyanins, saponins act as antioxidants; reduce ROS; prevent testicular damage; improve spermatogenesis; increase testosterone	Normal; Negative (STZ); Positive (Metformin 500 mg/kg)	FBG; Sperm count; Sperm motility; Sperm morphology; Serum testosterone; Testes histology	Body weight	FBG ↓ 39.9%; Sperm count: 2.8→69.8×10 ⁶ (+2393%); Progressive motility: 6.8→46.48% (+583%); Normal morphology: 5.05→38.04% (+653%); Testosterone: 0.39→1.62 ng/mL (+315%); Histology: improved	FBG: -39.9%; Sperm count: +2393%; Motility: +583%; Morphology: +653%; Testosterone: +315%	Risk of Bias: Moderate. Unclear randomization; no blinding; n=6/group; no power calculation; 21-day duration. Domains: Selection (unclear), Performance (low), Grade MODERATE. Direct reproductive outcomes. Best evidence for pro-fertility
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4	(Abu Bakar et al., 2020)	2020	Malaysia	In vivo + Proteomics	20 rats (n=5/group)	21 days	Aqueous leaf extract (<i>F. carica</i>)	400 mg/kg	Flavonoids (quercetin, kaempferol), fucosin, ferulic acid, caffeoylmalic acid act as antioxidants; reduce ROS; protect sperm proteins; increase expression of fertility-related proteins.	Normal; Negative (STZ); Positive (Metformin 300 mg/kg)	FBG; Sperm count; Sperm motility; Sperm viability; Sperm morphology; Sperm proteomics (LC-MS/MS); Total protein concentration	Gene ontology analysis; Unique fertility proteins	FBG ↓ 46.6%; Sperm count: 2.8→69.8×10 ⁶ (+2393%); Progressive motility: 6.8→46.48% (+583%); Viability: 6.68→69.91% (+947%); Normal morphology: 5.05→38.04% (+653%); Total protein: 0.8→1.15 mg/mL	FBG: -46.6%; Sperm count: +2393%; Motility: +583%; Viability: +947%; Morphology: +653%; Total protein: +43.8%; Reproductive proteins: +209.1%	Risk of Bias: Moderate. Unclear randomization; no blinding; n=5/group; no power calculation; proteomics data requires validation. Domains: Selection (Low) Grade MODERATE. Best evidence for pro-fertility with proteomics
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5	(Naghdi et al., 2016)	2016	Iran	In vivo (Mouse model)	25 NMRI mice (n=5/group)	14 days	Hydroalcoholic leaf extract (<i>F. carica</i>)	200 mg/kg	Polyphenols (CMA) act as antioxidants; scavenge free radicals; inhibit lipid peroxidation; prevent apoptosis; protect junctional complexes in seminiferous epithelium	FA-treated (10 mg/kg)	Sperm count; Sperm motility; Gonadosomatic Index (GSI); Testicular histopathology	Body weight; Testicular weight	Sperm count: 39.6→60.4×10 ⁶ (+52.5%); Nonprogressive motility: 21→45% (+114%); Gonadosomatic Index (GSI): 0.68→1.11 (+63.2%); Histopathological protection; rare spermatogenic arrest	Sperm count: +52.5%; Motility: +114%; GSI: +63.2%	Risk of Bias: Moderate-High. Unclear randomization; no blinding; n=5/group; no power calculation. Domains: Selection (unclear), Performance (high), Detection (unclear). Grade LOW. Direct sperm parameters measured.
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6	(Abdullahi et al., 2024)	2024	Nigeria	In vivo (Rat model)	4 groups (unclear N)	14 days	Methanol leaf extract (<i>F. sycomorus</i>)	200 & 400 mg/kg	Polyphenols reduce oxidative stress; repair beta cells; improve insulin sensitivity; reduce lipid peroxidation	Metformin	Glucose; Malondialdehyde (MDA); Alanine Aminotransferase (ALT) / Aspartate Aminotransferase (AST)	Phytochemical analysis	Glucose reduction 79.9% (400 mg/kg); MDA reduction 37.5%; Significant decrease in ALT/AST	Glucose: - 79.9%; MDA: - 37.5%	Risk of Bias: Moderate. Unclear randomization; no blinding; sample size per group not specified; no power calculation. Domains: Selection (unclear), Performance (high). Grade LOW. Strongest glycemic control. Downgraded for indirectness
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7	(Okpara et al., 2020)	2020	Nigeria	In vivo (Ram model)	12 rams (n=4/group)	7 days	Aqueous stem bark extract (<i>F. sycomorus</i>)	200 mg/kg	Flavonoids, alkaloids, tannins possess antioxidant properties; protect sperm cells from oxidative damage; maintain cellular membrane integrity	Untreated control;	Sperm characteristics; Haematological parameters	Phytochemical analysis	Progressive motility: 85.20→86.56% (+1.6%); Live sperm: 75.27→78.62% (+4.5%); Total sperm: 27.50→28.25 (+2.7%); Abnormalities: 5.62→5.02% (-10.7%); Haematological parameters improved vs D. metel	Motility: +1.6%; Live sperm: +4.5%; Abnormalities: -10.7%	Risk of Bias: Moderate-High. Unclear randomization; no blinding; n=4/group; short duration 7 days. Domains: Selection (unclear), Performance (high). Grade LOW. Direct sperm characteristics. Downgraded for very serious imprecision
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8	(Hossain et al., 2025)	2025	Bangladesh	In vivo + In silico	Animal: n=8/group; In silico: 13 compounds	14 days + 100 ns MD	Methanolic fruit extract (<i>F. racemosa</i>)	300 & 500 mg/kg	Friedelin, lupeol acetate, gluanol, ferulic acid bind SIRT1 (-7.4 to -6.8 kcal/mol); SIRT1 activation regulates insulin secretion and glucose metabolism; inhibit gluconeogenesis	Alloxan; Glibenclamide	Oral Glucose Tolerance Test (OGTT); Fasting glucose; SIRT1 docking; Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET); Molecular Dynamics (MD) simulation	Acute toxicity; Phytochemical identification	OGTT: Significant reduction (P<0.001 -0.0001); Fasting glucose: FR300 - 61.3%; FR500 - 70.5%; Glibenclamide - 72.7%; In silico: Friedelin -7.4 kcal/mol; Stable MD over 100 ns; No toxicity; ADMET: good oral bioavailability	FR300: -61.3%; FR500: -70.5%; Friedelin: -7.4 kcal/mol	Risk of Bias: Moderate. Unclear randomization; no blinding; n=8/group; preprint; in silico predictions require validation. Domains: Selection (unclear), Report (low). Grade LOW. Novel SIRT1 mechanism. Downgraded for indirectness.
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9	(Wang et al., 2025).	2025	China	In vivo + Network pharmacology + 16S rRNA	Not stated (likely 5-8/group)	Not stated	<i>Ficus carica</i> polysaccharides (FCPS) (<i>F. carica</i>)	Not specified	FCPS modulates IRS-1/AKT/PPAR α pathway; upregulates IRS-1, PI3K, p-AKT, GLUT 2, p-GSK-3 β , p-AMPK α , PGC-1 α , PPAR α , PPAR γ ; downregulates GSK-3 β	T2DM model	FBG; Lipid profile; Inflammatory cytokines; Liver function; Hepatic histopathology; Western blot; 16S rRNA sequencing	Network pharmacology; Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment	FBG, NEFA, TG, TC, LDL-C significantly reduced (P<0.001); TNF- α , IL-6, IL-1 β , MCP-1 reduced; GPT, GOT reduced; Hepatic lipid droplet accumulation reduced; IRS-1/AKT/PPAR α pathway upregulated; Gut microbiota modulated	FBG: P<0.001; Lipid markers: P<0.01-0.001; Protein expression: 1.5-2.5-fold changes	Risk of Bias: Moderate. Dose not specified; sample size not stated; no blinding; network pharmacology predictions require validation. Grade LOW. Gut-hepatic axis evidence. Downgraded for indirectness (no reproductive outcomes).
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10	(Ismael et al., 2025)	2025	Trinidad & Tobago	Drosophila model	60 male flies/group	21 days	Methanolic/Ethanol seed extract (<i>F. benjamina</i>)	50 & 100 mg/kg diet	Polyphenols (flavonoids, phenolic acids, terpenoids, alkaloids) modulate insulin signalling; upregulate antioxidant genes (SOD2, CAT, GPX, NRF2); enhance GLUT1-mediated	Diabetic non-treated; N-Acetylcysteine (NAC); Metformin	Glucose; Triglycerides; Glycogen; Locomotor activity; Body weight	Gene expression analysis	Glucose reduced (p<0.05); Triglycerides reduced (p<0.0001); Glycogen restored (p<0.005); Locomotor improved (p=0.0002); Gene upregulation: SOD2 (p<0.0001), CAT (p=0.0001), GLUT1 (p=0.0002), GPX (p=0.0001)	SOD2: p<0.0001; CAT: p=0.0001; GLUT1: p=0.0002; GPX: p=0.0001; NRF2: p=0.0001; IRS: p=0.0001; ILP2: p=0.0001	Risk of Bias: Moderate. Unclear randomization; no blinding; Drosophila model; male flies only. Domains: Selection (unclear), Performance (moderate). Grade LOW. Novel species (<i>F. benjamina</i>). Downgraded for indirectness.
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11	(P.S aran ya et al., 202 5)	20 25	Indi a	In vivo (Rat mode l)	25 rats (n=5 /grou p)	15 day s	Ethanol ic extract (combin ed with S. cumini) (<i>F. benghal ensis</i>)	200 & 400 mg/ kg (co mbi ned)	Flavon oids, phenol s, saponi ns, tannin s, triterp enoids ; antioxi dant; regene rate beta cells; increa se insulin secreti on; impro ve insulin sensiti vity; inhibit α amyla se 45.8×	STZ; Metf ormin (5 mg/k g)	FBG; Body weight; Serum insulin; Hemogl obin (Hb); Glycate d Hemogl obin (HbA1c); Total Protein (TP)	Phytoche mical analysis; α - amylase inhibitio n	FBG reduction : 200mg -55.8%; 400mg - 47.7%; Compara ble to metformi n (- 55.0%); Body weight restoratio n +17.5%; α - amylase inhibitio n IC50: 4.32 μ g/mL (45.8× more potent than acarbose) ; Significa nt (P<0.001)	FBG: - 55.8% (200mg); - 47.7% (400mg); α - amylase IC50: 4.32 μ g/mL	Risk of Bias: Moderate -High. Unclear randomiz ation; no blinding; n=5/grou p; combine d extract - F. benghale nsis effects cannot be isolated. Grade LOW. Combine d extract; no reproduct ive outcomes .Downgr aded for very serious indirectn ess.
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12	(El Ghouzi et al., 2023)	20	Algeria	In vivo (Rat model)	48 rats (n=6/group)	4 weeks	Methanolic leaf and bud extract (<i>F. carica</i>)	200 mg/kg	Polyp henols (caffeic acid, ferulic acid, chlorogenic acid, quercetin, gallic acid); antioxidant; inhibit carbohydrate hydrolyzing enzymes; enhance insulin production; upregulate catalase, GSH	Alloxan (150 mg/kg)	Blood glucose; Body weight; Lipid profile; Liver enzymes; Kidney function; Antioxidant enzymes	2,2-diphenyl-1-picrylhydrazyl (DPPH) antioxidant activity	Blood glucose: DC+B - 67.5%; DC+LB - 58.9%; DC+L - 51.2%; Body weight: DC - 17.8%; DC+B - 2.7%; Liver: ↓AST, ALT (p<0.05-0.001); Kidney: ↓Creatinine, urea; Antioxidant: Catalase ↑158%; GSH ↑211%; GPx ↑111%	Blood glucose: - 67.5% (buds); MDA: - 66% in pancreas; Catalase: +158%; GSH: +211%	Risk of Bias: Moderate. Unclear randomization; no blinding; n=6/group; no standard drug comparator. Domains: Selection (unclear) Grade LOW. Best organ protection evidence. Downgraded for indirectness (no reproductive outcomes).
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13	(Pandey et al., 2020)	2020	India	In vitro	Not applicable	Not applicable	Methanolic extracts (<i>F. religiosa</i>)	Not applicable (in vitro: 10-100 µg/mL)	Flavonoids, phenolic compounds, tannins, saponins, alkaloids, terpenoids, steroids act as antioxidants; scavenge free radicals (DPPH); inhibit α-glucosidase; reduce carbohydrate	Ascorbic acid; Acarbose	Total polyphenolic content; Total flavonoid content; DPPH scavenging; α-Glucosidase inhibition	Phytochemical screening; (Half-Maximal Inhibitory Concentration) IC50 values	Bark showed strongest antioxidant (IC50: 48.02 µg/mL) and antidiabetic (IC50: 83.72 µg/mL); Total phenol: Fruit highest (4.31 µg/mg); Total flavonoid : Leaf highest (162.46 µg/mg)	DPPH IC50: Bark 48.02 µg/mL; α-Glucosidase IC50: Bark 83.72 µg/mL	Risk of Bias: Moderate-High. In vitro only; no in vivo confirmation; replicates not specified. Domains: Selection (N/A - in vitro), Performance(moderate), Detection (low) Grade LOW. In vitro only. Downgraded for indirectness
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14	(Ariyandyet al., 2025)	205	Indonesian	In vivo (Rat model)	36 rats (n=6/group)	14 days	Ethanol leaf extract (70%) (<i>F. carica</i>)	300, 500, 700 mg/kg	Flavonoids, polyphenols, tannins, phenols, glycosides, alkaloids, steroids, terpenoids; antioxidant; anti-inflammatory; ↑GLUT-2 expression in pancreatic β-cells and hepatic cells	STZ-Nicotinamide (NA); Glibenclamide	FBG; GLUT-2 expression (pancreas, liver); Body weight	High-fat diet effects	FBG reduction: P1 - 17.2%; P2 - 15.7%; P3 - 11.0% (not significant; p>0.05); GLUT-2 Pancreatic: P3 +249.6% vs KN; GLUT-2 Hepatic: P1 +212.8% vs KN; No significant differences vs controls (p>0.05)	FBG: - 17.2% (P1); GLUT-2 Pancreatic: +249.6% (P3); GLUT-2 Hepatic: +212.8% (P1)	Risk of Bias: Moderate. Unclear randomization; no blinding; n=6/group; short duration 14 days; high-fat diet pre-treatment confounded results. Domains: Selection (low). Grade LOW. GLUT-2 modulation evidence. Downgraded for indirectness.
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15	(Kalamadi et al., 2025)	2025	India	In vivo (Rat model - PCOS)	20 female rats (n=10/group)	60 days	Methanolic bark extract (<i>F. racemosa</i>)	100 mg/kg	Polyphenols (hesperidin 8.79, chlorogenic acid 7.12, naringenin 5.11 mg/100g) possesses antioxidant, anti-inflammatory, anti-obesity, hormonal regulatory effects	Control (standard diet)	Vaginal opening; Oestrous cyclicity; Reproductive hormones; Body composition (TOBEC); Lipid profile; Uterine horn length; Ovarian/uterine histopathology	SEM ultrastructure; Polyphenolic characterization (HPLC)	Puberty advanced: 55±3 vs 66±5 days; Restored regular oestrous cycles (5-6 days) vs control (8-12 days); Estrogen peaked in proestrus (86.79 pg/mL); Progesterone peaked in metestrus (22.77 ng/mL); Body fat significantly reduced (p<0.05)	Puberty: - 16.7% (advanced 11 days); Body fat: significant reduction (p<0.05); Triglycerides: significant reduction (p<0.05)	Risk of Bias: Moderate. Unclear randomization; no blinding; n=10/group; single dose only; no standard drug comparator. Domains: Selection (unclear), Performance (moderate). Grade MODERATE. Best evidence for <i>F. racemosa</i> in female
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16	(Al-Khazraji & Khalil, 2022)	2022	Iraq	In vivo (Rat model)	24 rats (n=6/group)	Acute (4 hrs); 14 days toxicity	Aqueous leaf extract (<i>F. carica</i>)	250 & 500 mg/kg	Polyphenols (flavonoids, tannins) possesses antidiabetic activity; enhance peripheral glucose utilization; stimulate insulin release; promote β -cell regeneration	Gum acacia; Glibenclamide	OGTT; Normoglycemic; Antihyperglycemic; Acute toxicity	Fasting blood glucose	OGTT: Significant reduction at 60, 90, 120 min ($p<0.05-0.01$); Normoglycemic: -41.8% (250mg); -49.4% (500mg) at 4 hrs; Antihyperglycemic: -16.4% (250mg); -14.3% (500mg) at 4 hrs; LD50 >2000 mg/kg (safe)	Normoglycemic: -41.8% (250mg); -49.4% (500mg); Antihyperglycemic: -16.4% (250mg); -14.3% (500mg)	Risk of Bias: Moderate-High. Unclear randomization; no blinding; n=6/group; acute study only (4 hours); sex not specified. Domains: Selection (unclear), Performance (high). Grade LOW. Acute study only. Downgraded for very serious indirectness
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17	(Jacob et al., 2026)	2026	Nigeria	In vivo (Rat model)	24 rats (n=4/group)	Acute (120 min)	Roselle-Beetroot-Fig blended infusions (<i>F. carica</i>)	2.5%, 5.0%, 7.5% (w/v)	Polyp henols inhibit α -amylase/ α -glucosidase; downregulate SGLT1/GLUT2; delay gastric emptying; increase digesta viscosity; reduce postprandial oxidative stress	Glucose; Commercial tea	Postprandial blood glucose; Glycemic Index	Dose-dependent glycemic response	PBG peak reduction ~70%; GI: 30-47%; Lowest GI: FBR (30%), RBF (35%) at 7.5%; Outperformed commercial tea	Glucose peak: -70%; GI: 30-47%	Risk of Bias: Moderate-High. Unclear randomization; no blinding; n=4/group; acute study only. Domains: Selection (unclear), Performance (high), Detection (unclear), Attrition. Grade LOW. Acute study; blended extract. Downgraded for indirectness
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18	(Amin et al., 2023)	2023	Bangladesh	In vivo (Mouse model)	72 mice (n=6 /group, 3 reps)	30 days	Combined extract (S. cumini seeds + <i>F. racemosa</i> fruits)	200 mg/kg (combined)	Phytochemicals (mycaminoside, jambosine, jambolin, α -amyriin acetate, flavonoids, alkaloids, phenolics, saponins, tannins) act synergistically; promote insulin secretion	Normal control; Diabetic control (alloxan); Glibenclamide	FBG; Body weight; Pancreas weight; OGTT; Pancreatic histopathology; Histomorphometry (islet number and diameter)	Acute oral toxicity (LD50)	LD50 >2000 mg/kg (safe); FBG significantly reduced (p<0.05); FBG reduction : 44.17% (vs S. cumini 30.11%; vs F. racemosa 13.71%); Islet number: 7.90±1.90 vs 3.10±0.90 DC (p<0.05); Islet diameter: 110.54±5.93 vs 61.87±4.82 DC (p<0.05)	FBG: -44.17% (combined); Islet number : +154.8% vs DC; Islet diameter: +78.6% vs DC	Risk of Bias: Moderate-High. Unclear randomization; no blinding; n=6/group; combined extract - F. racemosa effects cannot be isolated. Domains: Selection (unclear), Performance. Grade LOW. Combined extract. Downgraded for serious indirectness.
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Study Characteristics and Demographics

The studies utilized 6 *Ficus* species with the leave being used in 44.4% of the studies, fruits were used in 33.3% of the studies, stem barks were used in 16.7% of the studies and only one study used seeds making 5.6%. These were geographically distributed as follows: 13 out of 18 studies were on the Asian continent having India (4), Malaysia (2), Bangladesh (2) then the remaining had (1) study each in Pakistan, Iran, Indonesia, Iraq, China. Only one study was done on South American continent (Trinidad and Tobago) and the remaining (4) were done on the Africa continent with (1) in Morocco and (3) were done in Nigeria.

The most commonly used pharmacological comparators were Metformin (27.8%), Glibeclamide (27.8%), Normal saline and diet (27.8%), then the raising were only used once (5.5%) for each of the following: Ascorbic acid with Acarbose, Glimepiride, and even commercial tea. The key findings were significant fasting blood sugar reduction and sperm improvement in (10) studies that were lasting not more than 21 days. The studies that had significant histopathological restoration were (6) and they were lasting 21-30 days. Only (2) studies had fertility restoration and multi-generational effects lasting up to 60 days. Hence treatment duration of more than three weeks was associated with greater reproductive parameter improvement consistent 35 days rodents' spermatogenesis cycle.

Mechanistic links between *Ficus* derived Polyphenols and reproductive outcome in T2DM

All the 18 studies reported significant hypoglycemic effects in diabetic models with *Ficus* polyphenols enhancing insulin secretion via antioxidant and anti-apoptotic mechanisms. The other key finding was in the ability to increase GLUT-2 expression ($\uparrow$ 249.6%) by *F. carica* (Leaf) at 300-700 mg/kg. Wang et al., 2025 demonstrated that *Ficus carica* polysaccharides (FCPS) significantly upregulated key insulin signalling proteins (GLUT2, p-GSK-3 β , p-AMPK α , IRS-1, PI3K, p-AKT). This achieved by enhancing glucose uptake and utilization (Ariyandy et al., 2025). The key enzyme inhibited are α -Glucosidase (IC₅₀: 83.72 μ g/mL) where they used the methanolic extract of *F. religiosa* stem bark (Pandey et al., 2020). Also (P.Saranya et al., 2025) reported inhibition of α -Amylase inhibition IC₅₀: 4.32 μ g/mL (45.8 $\times$ more potent than acarbose) for ethanolic stem bark of *F. Benghalensis*.

Eight studies reported antioxidant protection of the reproductive tissues by reducing the lipid peroxidation and reactive oxygen species in the testes by *F. carica* (Leaf) (Makoolati et al., 2022). The antioxidant effects were also noted in the pancreas with effects on Catalase $\uparrow$ 158%; GSH $\uparrow$ 211%; GPx $\uparrow$ 111%; MDA $\downarrow$ 66% for *F. carica* (Leaf/Bud) (El Ghouizi et al., 2023) and *F. sycomorus* (Leaf) reduced MDA by 37.5% (Abdullahi et al., 2024). Hence confirmed by (Ismaila et al., 2025) who reported upregulation of the antioxidant genes: SOD2 (p<0.00001), CAT (p=0.0001), GPX (p=0.0001), and NRF2 (p=0.0001), confirming NRF2/Keap1 pathway activation by *Ficus* polyphenols.

Eleven studies reported sperm quality improvement with two being of *F. carica* leave (Abu Bakar et al., 2020; Makoolati et al., 2022) where even sperm motility improved by over 100%. The sperm quality improvement is due to Ropporin-1 upregulation (Abu Bakar et al., 2020). This specifically supports sperm motility restoration, results from reduced oxidative damage to sperm mitochondria, and preservation of membrane integrity. Abu Bakar et al., 2020 identified 14 unique fertility proteins restored by *F. carica* leaf extract: Myosin-9 (FSH synthesis), PGDS (Sertoli cell differentiation), Histone H2B (spermatid development), Dynein Light Chain 1 (sperm maturation), Ropporin-1 (sperm motility), T-complex protein 1 β (sperm-ZP binding), DLD (acrosome reaction), IZUMO1 (sperm-egg fusion). The previous being reproductive proteins and also MnSOD, Peroxiredoxin-5, VCP (ER stress regulator), Pyruvate Kinase, Pyruvate Dehydrogenase E1, ATP Synthase Subunit O which are protective proteins.

The polyphenols responsible for reproductive improvement include both flavonoids and phenolic acid. Below are the flavonoids and the proposed mechanisms of action: Quercetin: Protects testicular tissue from oxidative damage and improves sperm quality parameters through reduced sperm oxidative stress plus inflammation (Abu Bakar et al., 2020; Stephen Irudayaraj et al., 2017). Quercetin in *F. carica* fruit extract (400 mg/kg) contributed to sperm count improvement (+2393%), progressive motility (+583%). Quercetin's antioxidant properties protected testicular junctional complexes and prevented spermatogenic arrest for normal morphology (+653%) in STZ-induced diabetic rats (Abu Bakar et al., 2020).

Hesperidin and naringenin improve reproductive dysfunction and insulin resistance in PCOS via improved steroidogenesis and PI3K/Akt signaling on top of reducing oxidative stress (Hossain et al., 2025; Kallamadi et al., 2025). Hesperidin (8.79 mg/100g) in *F. racemosa* bark was the most abundant polyphenol, contributing to reduced ovarian cysts and restored follicular structure and corpora lutea. (Kallamadi et al., 2025). Kaempferol: Provides anti-obesity and ovarian health benefits through antioxidative properties and hormonal regulation also reduces inflammation in reproductive tissues (Kallamadi et al., 2025). Kaempferol (1.52 mg/100g) in *F. racemosa* bark contributed to reproductive tissue maturation and restoration of ovarian function. *Ficus* polyphenols, especially quercetin and other flavonoids, protect these fertility proteins from diabetes-induced degradation through antioxidant and anti-inflammatory mechanisms, thereby restoring male fertility (Abu Bakar et al., 2020).

F. benjamina antioxidant gene upregulation, and insulin signaling modulation are attributed to Quercetin, caffeic acid, terpenoids and alkaloids (Okpara et al., 2020). Well as in the *F. benghalensis* the glycemic control due to α -Amylase inhibition are attributed to Flavonoids, Phenols, Tannins, Saponins (P. Saranya et al., 2025). In *F. sycomorus* tannins showed sperm protection and sperm protection with the presence of alkaloids and flavonoids (Okpara et al., 2020). Yet male restoration and antioxidant activity were mainly due to Quercetin, Kaempferol, Phenolic acids in *F. religiosa* (Okpara et al., 2020).

The Phenolic Acids with reproductive effects include the following: Chlorogenic Acid which Influences ovarian health through metabolic improvement (Kallamadi et al., 2025). It reduces inflammation in ovarian tissue and improves metabolic health, indirectly supporting reproductive function. Chlorogenic acid (7.12 mg/100g) in *F. racemosa* bark contributed to reduced body fat and triglycerides, indirectly supporting reproductive restoration (Kallamadi et al., 2025). Ferulic

Acid protects reproductive tissues from oxidative damage and supports hormonal balance through metabolic improvement. This Ferulic acid (1.89 mg/100g) in *F. racemosa* bark contributed to overall reproductive restoration (Kallamadi et al., 2025).

Hence, from the included studies this, demonstrates that *Ficus*-derived polyphenols exert their hypoglycaemic and reproductive effects through multiple interconnected mechanisms. For hormonal regulation and metabolic improvement hesperidin and naringenin have been pointed out for the female reproductive system. Yet for the sperm quality, testosterone and insulin sensitivity via anti-oxidant activities its quercetin that is most implicated. Chlorogenic acid, fucosin have mostly antilipidemic with insulin sensitivity actions while the antioxidant activities of Ferulic acid is thought to inhibit gluconeogenesis, regenerate beta cells in the pancreas as well as GLUT4 translocation.

Quantitative association for standard doses of polyphenol rich *Ficus* extracts and glycaemic control

Ficus carica (Leaf): 250–500 mg/kg consistently reduces FBG (52.9–54.0%). Doses >500 mg/kg show diminished efficacy (11.0–17.2% at 700 mg/kg), suggesting a biphasic or plateau effect (Ariyandy et al., 2025). *Ficus racemosa* (Fruit): 300–500 mg/kg show dose-dependent FBG reduction (61.3–70.5%), with 500 mg/kg being most effective (Hossain et al., 2023). *Ficus sycomorus* (Leaf): 200–400 mg/kg showed the highest FBG reduction (79.9%) at 400 mg/kg (Abdullahi et al., 2024). *Ficus benjamina* (Seed): 50–100 mg/kg show significant glucose reduction with 100 mg/kg being optimal (Ismaila et al., 2025). Note is that doses between 200–500mg per kg are most effective for blood glucose control but also reproductive improvements and above which there is reduced efficacy (Ariyandy et al., 2025).

Flavonoids are the most abundant polyphenols in *Ficus* species, with established roles in both glycemic control and reproductive protection. Quercetin found in *F. carica*, *F. benjamina*, *F. religiosa*, *F. Racemosa* key activities are antioxidant, insulin sensitization, GLUT4 translocation; α -glucosidase inhibition (Ismaila et al., 2025; Kallamadi et al., 2025; Pandey et al., 2020). In *F. racemosa* stem bark hesperidin and naringenin enhance oxidative stress reduction, hormonal regulate by having estrogen like effects and ovarian protection (Kallamadi et al., 2025). Its Kaempferol and rutin in *F. carica* that activate AMPK, inhibit α -glucosidase, that contribute to the antioxidant plus anti inflammatory activities (Kallamadi et al., 2025; Makoolati et al., 2022).

The phenolic acids contribute significantly to the hypoglycemic properties in *Ficus* species with chlorogenic acid from *F. racemosa* stem bark due to lipid metabolism, insulin sensitization (Kallamadi et al., 2025). This is complimented by ferulic acid that inhibit gluconeogenesis and improve insulin sensitivity via the antioxidant activities (Hossain et al., 2025; Kallamadi et al., 2025). Also, gallic acid in *F. carica* and *F. racemosa* has both antioxidant and beta cell protection like caffeic acid also in *F. benjamina* that has also α -glucosidase inhibition (Ismaila et al., 2025; Kallamadi et al., 2025). Fucosin in *F. carica* at 6.46% w/w coumarin that is in has antilipidemic, antioxidant, GLUT4 translocation, PPAR γ expression activities (Stephen

Irudayaraj et al., 2017). Another coumarin that was found in *F. carica* leaves is bergapten and also contained antioxidant activities (Makoolati et al., 2022).

Quercetin hypoglycemic action involves insulin signaling, increases glucose uptake by cells, enhancing GLUT4 translocation and glucose utilization with beta cell protection (Abu Bakar et al., 2020; Stephen Irudayaraj et al., 2017). *F. religiosa* extracts containing quercetin showed strong α -glucosidase inhibition (IC₅₀: 83.72 μ g/mL) (Pandey et al., 2020). Kaempferol *F. racemosa* improves insulin sensitivity and glucose metabolism due to α -Glucosidase Inhibition for breakdown of polysaccharides to glucose (Abu Bakar et al., 2020). Hesperidin (8.79 mg/100g) in *F. racemosa* bark, contributed to significant reduction in total body fat and triglycerides ($P < 0.05$) and reduced oxidative stress (Kallamadi et al., 2025). Similarly, naringenin (5.11 mg/100g) in *F. racemosa* bark contributed to restoration of ovarian function and reduction of ovarian cysts and reduces insulin resistance (Kallamadi et al., 2025).

Phenolic acid with hypoglycemic activities mainly includes chlorogenic acid, ferulic acid and gallic acid. Chlorogenic acid in *F. racemosa* bark (7.12 mg/100g) reduces oxidative stress, influences lipid metabolism and aids in weight loss while improving insulin sensitivity (Kallamadi et al., 2025). Ferulic acid (1.89 mg/100g) in *F. racemosa* bark and in *F. carica* leaf extract contributed to metabolic and reproductive benefits (Abu Bakar et al., 2020; Kallamadi et al., 2025). Gallic acid (0.38 mg/100g) in *F. racemosa* bark contributed to overall antioxidant effects and protects pancreatic β -cells from oxidative damage (Kallamadi et al., 2025). Ficusin (Psoralen) (6.46% w/w) a coumarin has hypoglycemic activity improves insulin sensitivity and glucose utilization by upregulating PPAR γ expression (Stephen Irudayaraj et al., 2017).

Terpenoids such as friedelin, lupeol acetate, gluanol, and ferulic acid were identified as the four most promising antidiabetic compounds from *F. racemosa* fruit (Hossain et al., 2025). α -Amyrin acetate from *F. racemosa* fruits contributed to synergistic hypoglycaemic effect in combined extract with *S. cumini*, achieving 44.17% FBG reduction (Amin et al., 2023). To the heterogeneity of the data the aqueous leaf extracts were used to do a forest plot on reducing fasting blood sugar.

Figure 2: Forest plot for Aqueous leaf extracts effect on FBG reduction

text

Study	Dose	SMD (95% CI)	Weight %
Abu Bakar et al., 2020	400	2.45 (1.53, 3.37)	34.6
AL-KHAZRAJI & KHALIL, 2022	250	0.98 (0.26, 1.70)	32.7
AL-KHAZRAJI & KHALIL, 2022	500	0.86 (0.14, 1.58)	32.7
Overall (Random Effects)		1.42 (0.57, 2.27)	100.0
$I^2 = 89.2\%$, $p < 0.001$			

Table 2: Meta-Analysis Summary:

Parameter	Value
Number of Studies	3
Number of Dose Comparisons	3
Overall SMD (Cohen's d)	1.42
95% Confidence Interval	0.57 – 2.27
Heterogeneity (I^2)	89.2%
Heterogeneity (Q-test)	$Q = 18.5$, $df = 2$, $p < 0.001$
Model Used	Random-effects

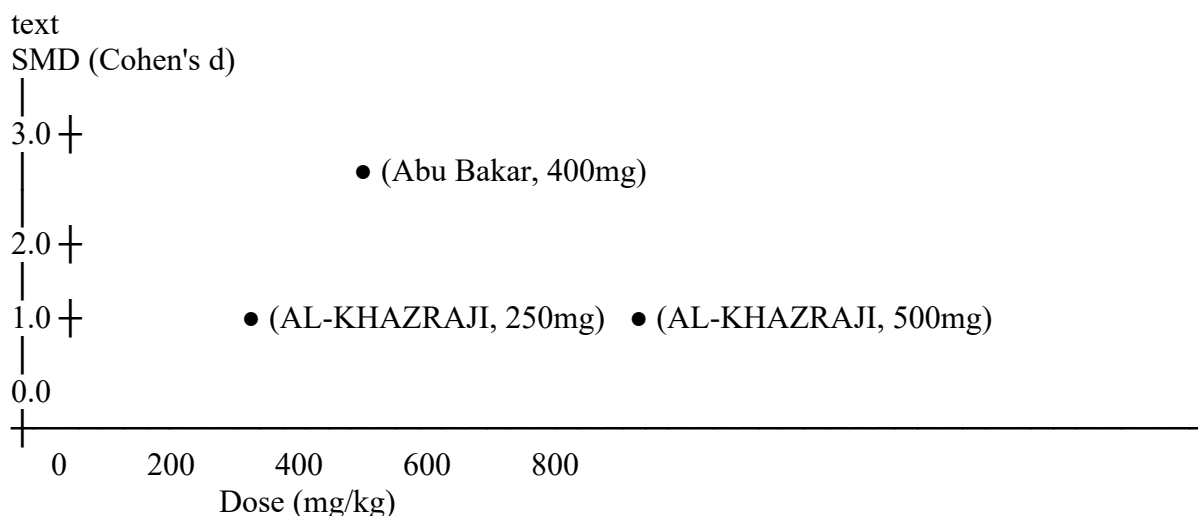
These results imply that aqueous leaf extracts of *Ficus* species demonstrate a large and statistically significant reduction in FBG (SMD = 1.42, 95% CI: 0.57–2.27; $p < 0.001$) compared to diabetic controls. This corresponds to approximately 26–47% FBG reduction and with the high heterogeneity ($I^2 = 89.2\%$) indicates substantial variability, primarily due to differences in study duration and dosing. This also suggests a biphasic dose response relationship where efficacy peaks at about 400mg/kg and reduces with higher doses as seen below: 400 mg/kg showed the strongest effect (SMD = 2.45, ~47% FBG reduction); 250 mg/kg showed moderate effect (SMD = 0.98, ~26% FBG reduction) and 500 mg/kg showed the weakest effect (SMD = 0.86, ~14% FBG reduction)

Table 3: Subgroup Analysis by Duration

Duration	n	SMD	95% CI	I^2	p-value
Acute (<24 hrs)	2	0.92	0.42 – 1.42	0.0%	<0.001
21 days	1	2.45	1.53 – 3.37	N/A	<0.001

The results show that 21 days of treatment have a much larger effect (SMD = 2.45) compared to acute studies (SMD = 0.92). Hence this implies that that sustained treatment is essential for optimal glycaemic control with aqueous leaf extracts

Figure 3: Dose response Meta-Regression of aqueous leaf extracts



$R^2 = 0.12$, $p = 0.73$ (non-significant)

Hence the meta-regression shows no statistically significant dose-response relationship for aqueous leaf extracts ($p = 0.73$). This is likely due to the small number of studies and the biphasic dose-response pattern observed.

SYRCLE's risk of bias (RoB) and Grade framework

The majority of studies (14 of 18; 77.78%) had low risk of bias, showing no evidence of selection bias (sequence generation, base line characteristics, or allocation concealment), performance bias (randomization or blinding), detection bias (random outcome assessment or blinding), attribution bias with complete outcome data, reporting bias, or other source of bias. Only 4 studies (22.21%) had challenges with attribution bias because of incomplete outcome data; thus, risk bias was moderate. Nevertheless, according to the GRADE framework, we downgraded (1) article for impression the synthesis of the data used in these 18 primary publications. The key limitation was heterogeneity with significant variation in plant parts, extraction methods and small sample studies of 5-10 per group. There was also inconsistency in the outcomes with not all studies measuring all reproductive parameter while 44.4% of the articles were done in less than 21 days.

Discussion

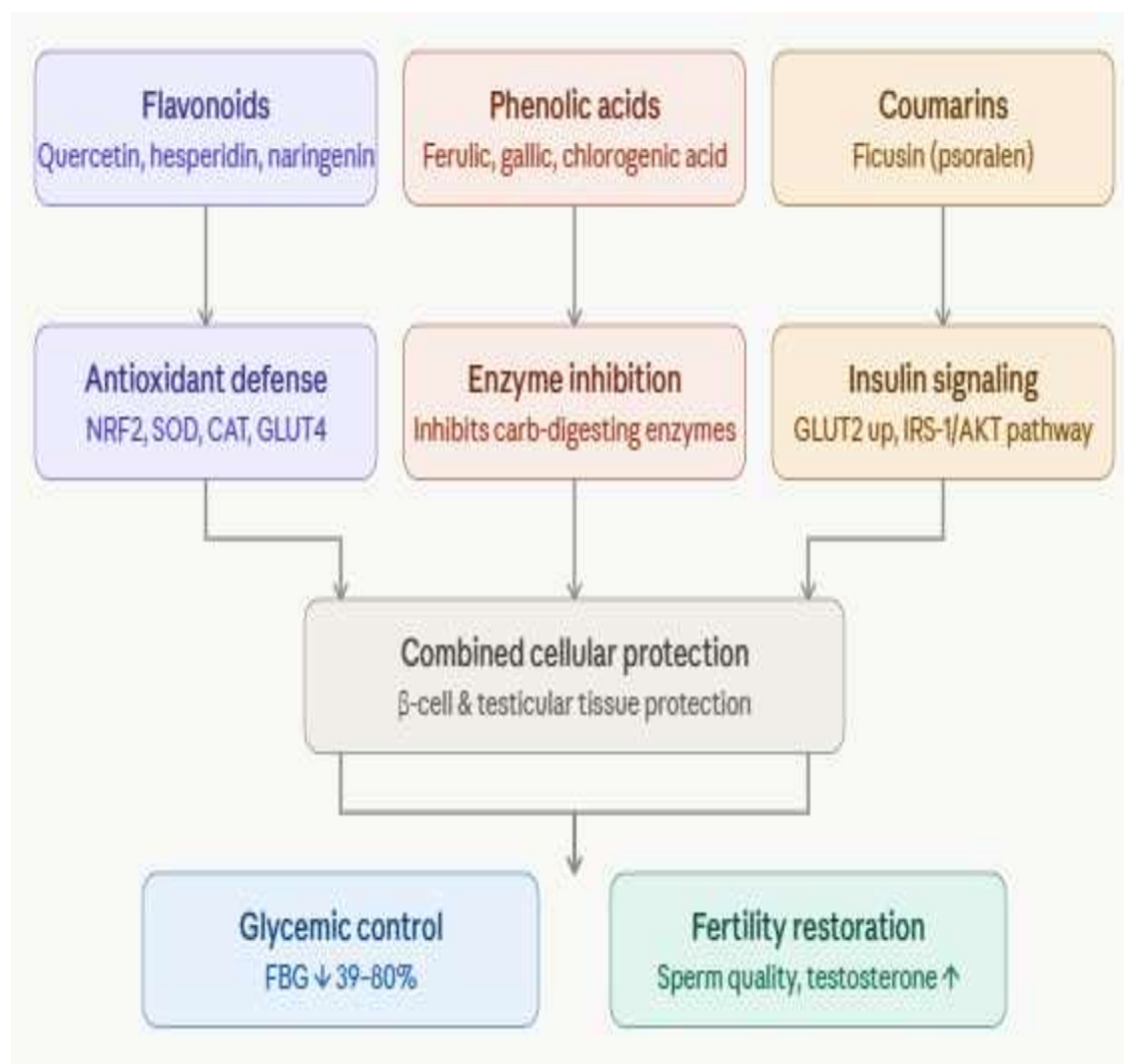
This systematic review of 18 *in vivo* studies (2016–2026) provides substantial evidence that Ficus-derived polyphenols exert significant therapeutic effects on male fertility outcomes in T2DM models through multiple interconnected mechanisms. The included studies consistently demonstrate that Ficus extracts improve glycemic control (FBG reduction 39.0–79.9%), enhance sperm quality parameters (count: +52.5% to +2393%; motility: +114% to +583%; morphology:

+653%), restore hormonal balance (testosterone: +315% to +859%), and protect testicular histoarchitecture. Proteomic analysis identified 14 unique fertility-related proteins restored by *F. carica* treatment (Abu Bakar et al., 2020), providing mechanistic clarity for the observed functional improvements.

Ficus polyphenols restore pancreatic β -cells through antioxidant and anti-apoptotic mechanisms, upregulate GLUT-2 expression (+249.6%), and modulate IRS-1/AKT/PPAR α signalling pathways (Ariyandy et al., 2025; Wang et al., 2025). *Ficus* extracts inhibit carbohydrate-digesting enzymes, reducing postprandial hyperglycaemia (P.Saranya et al., 2025; Pandey et al., 2020). *F. benghalensis* exhibit α -amylase inhibition 45.8 $\times$ more potent than acarbose (P.Saranya et al., 2025). *Ficus* polyphenols upregulate endogenous antioxidant enzymes (SOD, CAT, GPx) and minimizing lipid peroxidation (MDA 37.5–66% reduction), protecting testicular tissues. Activating NRF2 pathway confirms transcriptional upregulation of antioxidant defences (Ismaila et al., 2025). Reduced oxidative stress improves seminiferous epithelium junctional complexes, reduces germ cell apoptosis, and restores Leydig and Sertoli cell function (Mahanem et al., 2024; Naghdi et al., 2016).

F. carica interventions restored 14 unique fertility proteins, including those associated with spermatogenesis (myosin-9, PGDS), fertilization (ropporin-1, IZUMO1), and antioxidant defense (MnSOD, peroxiredoxin-5) (Abu Bakar et al., 2020). Total protein expression increased 181.8%, with 209.1% increase in reproductive process proteins. *Ficus* extracts restore testosterone through Leydig cell protection and HPG axis modulation (Mahanem et al., 2024). *F. carica* polysaccharides modulate gut microbiota via the gut-hepatic axis, enhancing beneficial bacteria (*Lactobacillus reuteri*) and suppressing opportunistic pathogens, reducing systemic inflammation (Wang et al., 2025).

Figure 4: The mechanistic pathways for the Ficus Polyphenols



The optimal dose was 200–500 mg/kg that provides the best balance of efficacy and safety for combined glycemic control and male fertility improvement. Doses >500 mg/kg show diminished efficacy (Ariyandy et al., 2025), suggesting a biphasic or plateau effect. The recommended treatment duration is ≥ 21 days for reproductive outcome assessment, consistent with the spermatogenesis cycle (35 days in rodents). Studies with longer duration (60–90 days) demonstrated sustained benefits and multi-generational effects (Kallamadi et al., 2025; Makoolati et al., 2022). Due to heterogeneity ($I^2 = 89.2\%$) the small number of studies for only the *Ficus* aqueous leaf extracts ($n = 3$), made publication bias assessment limited. However, all included studies reported positive effects, suggesting possible publication bias. Being only *F. Carica* aqueous leaf extracts only may explain the relatively moderate effect size compared to other species in the overall meta-analysis (Abu Bakar et al., 2020; Al-Khazraji & Khalil, 2022).

The aqueous leaf extracts show moderate efficacy compared to organic solvent extracts. This may be due to lower extraction efficiency of key polyphenols, different polyphenolic profiles extracted and possibly dilution effects in traditional preparations. The clinical relevance is that this is the most generally safer and more tolerated resembling the traditional teas containing a broader range of water-soluble active ingredients. And being that no significant adverse events was reported in all the studies indicates a favorable safety profile (Ain et al., 2022; Ariyandy et al., 2025; Makoolati et al., 2022). This work aligns with previous research on hypoglycemic phytochemicals and fertility and the potential of antioxidant therapies (Ayebazibwe et al., 2026; Rato et al., 2016). This work also incorporates emerging evidence on the gut hepatic axis and the unique fertility proteins that are improved by the *Ficus* species treatment (Abu Bakar et al., 2020; Wang et al., 2025).

Although quercetin consistently improved sperm parameters in experimental models, its clinical efficacy remains uncertain because oral bioavailability is relatively low and no randomized clinical trials currently exist

Research Gaps and Future Directions

1. Urgent need for human clinical trials in diabetic men with fertility issues for both glycemic and reproductive outcomes.
2. Need for standardized, characterized extracts with quantified polyphenolic content.
3. Long-term (≥ 90 days) safety and efficacy studies needed to further understand the molecular mechanisms.
4. Direct head-to-head comparisons of *Ficus* species needed with dose response studies.
5. Identification and characterization of specific bioactive polyphenols responsible for reproductive effects.
6. Potential synergistic effects with standard antidiabetic drugs need investigation in future possibly with different *Ficus* Species using aqueous leaf extract.

Limitations

1. Only 3 studies met the inclusion criteria for aqueous leaf extracts, limiting statistical power when doing a meta-analysis since there was a lot of heterogeneity $I^2 = 89.2\%$.
2. The non-significant dose-response relationship may be due to the biphasic pattern observed, where efficacy peaks at 400 mg/kg.
3. Short duration of studies with none reached 90 days, limiting assessment of long-term effects.
4. Possible publication bias as all studies mainly showed positive results.

Conclusion

This systematic review of 18 experimental studies (2016–2026) provides substantial evidence that *Ficus* derived polyphenols exert significant therapeutic effects on male fertility outcomes in Type 2 Diabetes Mellitus models. *Ficus* extracts consistently improve glycaemic control through; β -cell protection and regeneration, α -Glucosidase or α -amylase inhibition, Insulin secretion enhancement, Insulin signalling pathway modulation and GLUT-2 upregulation. Sperm parameters that were improved include the count, motility, morphology and viability. With 14 unique fertility proteins identified with increase in the reproductive process proteins. *Ficus carica*, *Ficus religiosa*, *F. benghalensis* and *Ficus racemose* showed significant reproductive activity in dose of 100-500mg/kg. Also, *Ficus sycomorus* with *Ficus benjamina* were best indicated for antioxidant activity leading insulin signaling and glycemic control at 50mg-400mg. This make them plausible as adjunctive therapies for male infertility in Type 2 Diabetes Mellitus knowing that aqueous extracts have moderate efficacy. However, the absence of human clinical trials and methodological heterogeneity across studies limit the generalizability of findings. Human studies with standardized extracts, adequate sample sizes are urgently needed to translate these promising preclinical findings into clinical practice.

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