Effects of dietary polyphenols on vasculogenic erectile dysfunction: a systematic review of pre-clinical studies.

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Abstract

Erectile dysfunction (ED) is a medical condition characterized by the inability to achieve or maintain a satisfactory erection, primarily treated with oral phosphodiesterase type 5 inhibitors. Treatment effectiveness is diminished in severe vasculogenic ED, particularly in patients with diabetes mellitus, highlighting the need for exploring alternative/complementary interventions. Among them, dietary phenolic compounds are known for their antioxidant and anti-inflammatory properties. This systematic review focuses on catechin (EGCG), quercetin, resveratrol, and curcumin, and their influence on the pathophysiology of ED. Following PRISMA 2020 guidelines (PROSPERO registration number CRD42023402016) searches across PubMed, Scopus, and Web of Science until October 2024 were conducted using relevant keywords. Inclusion criteria required original articles in English, while *in silico* studies, review articles, editorials, and original studies lacking essential polyphenol administration information were excluded. After an initial search that located 409, 445 and 285 publications on each database respectively, rigorous screening resulted in 26 publications comprising animal, *ex vivo*, and *in vitro* studies. Their quality was assessed using GRADE and SYRCLE ROB tools, revealing an overall “medium-high” or “high quality”. These polyphenols consistently demonstrated improvement in erectile function, encompassing behavioral, functional, molecular, and hormonal aspects. However, limitations were identified, such as the predominant reliance on animal models and *in vitro* trials, which may not precisely reflect human physiological responses. Hence, further clinical investigations are needed to ascertain data translational potential, standardize dosages, and establish safe and effective

prescription recommendations. Prioritizing clinical trials is essential for validating the widespread applicability and efficacy of polyphenols in managing ED.

Keywords: catechin, curcumin, diabetes mellitus, erectile dysfunction, quercetin, resveratrol

Introduction

Erectile dysfunction (ED) is a medical condition marked by the incapacity to attain or sustain an erection adequate for sexual intercourse [Ostfeld et al., 2021], which onset and progression are associated with the presence of risk factors for cardiovascular diseases (CVD), such as hypertension, hypercholesterolemia, ageing and diabetes mellitus (DM). Oral phosphodiesterase-5 inhibitors (PDE5-Is) are considered the first-line treatment for ED [Pyrgidis et al., 2021; Mazzilli, 2022]; their mechanism of action is well established. In brief, during sexual stimulation, nitric oxide (NO) is synthesized by nitric oxide synthase (NOS) and released from endothelial cells and nerve terminals to the smooth muscle cells (SMC) where it activates guanylate cyclase, an enzyme that converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). Cyclic GMP leads to the relaxation of smooth muscle in the corpus cavernosum (CC), venous dilation, increased arterial blood flow, and ultimately erection through a veno-occlusive mechanism. PDE5, an enzyme predominantly located in the SMC of the CC, breaks down cGMP into 5'-GMP. PDE5-Is competitively binds to PDE5, inhibiting the hydrolysis of cGMP, which increases cGMP levels in the SMC and extends the duration of an erection [Burnett, 2006; Huang and Lie, 2013; Kniotek and Boguska, 2017]. However, clinical trials have demonstrated that the efficacy of PDE5-Is is reduced in patients with severe vasculogenic ED and DM [Defeudis et al., 2022].

Emerging evidence points to a contribution of reactive oxygen species (ROS) and free radicals that induce oxidative stress (imbalance between pro-oxidative species and anti-oxidative defenses) to ED [Jeremy et al., 2007; Eleazu et al., 2017]. In CC, free radicals react with NO to form highly cytotoxic compounds [Zhang et al., 2011a; Eleazu et al., 2017] that lead to molecular damage, reduced levels of endothelial and neuronal-derived NO, and upregulation of pro-inflammatory cytokines [Eleazu et al., 2017; Sharifi-Rad et al., 2020]. Thus, pro-oxidative molecules and endogenous inhibitors of NOS within the CC are apparently involved in structural damage and ED [Paroni et al., 2012; Toque and Caldwell, 2014; Eleazu et al., 2017]. To mitigate oxidative damage while protecting the vascular endothelium, the use of antioxidants emerges as a promising strategy, considering that antioxidants directly prevent cellular damage caused by free radicals and ROS and therefore potentially reduce the risk or severity of ED [Olabiyi and Kayode, 2022].

Among antioxidants, polyphenolic compounds, naturally present in various food sources, have garnered significant attention in recent years. An extensive literature that recognizes catechin, quercetin, resveratrol and curcumin anti-inflammatory, anti-proliferative, and antioxidant properties and potential roles in preventing diseases, such as DM, cancer and ED could be found, which prompted their selection for this systematic review [Lin et al., 2016; Dias et al., 2022]. For other polyphenols the published studies are scarce. Epigallocatechin-gallate (EGCG) is a catechin mostly present in green tea with anti-obesity, anti-diabetic and cardiovascular-protective potential effects [Isemura, 2019]. Quercetin is a flavonol present in vegetables and fruits [Ranawat et al., 2013; Rotimi et al., 2022] with protective action against ED in diabetic rats by enhancing the availability of exogenous NO [Jiménez-Osorio et al., 2015]. Resveratrol is the most well-known

stilbene, found in grapes and red wine [Eleazu et al., 2017; Cione et al., 2020], that mitigates age-associated features and reduces ROS and inflammation, regulates metabolism, and offers therapeutic potential in DM and CVD [Pastor et al., 2019; Cione et al., 2020]. Curcumin is an anti-inflammatory curcuminoid naturally present in turmeric [Stanić, 2017] [Luiza Koop et al., 2022].

In sum, there is evidence for considering that catechin, quercetin, resveratrol and curcumin, can be used as potential mitigators of ED. The goal of this systematic review is to examine and compile all the published original studies concerning their effects on the management of ED.

Methods

This systematic review was guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (PROSPERO registration number CRD42023402016).

Search strategy

A comprehensive search was conducted on PubMed, Scopus, and Web of Science (Web of Science Core Collection), with no restrictions on publication years, up to October 2024. To assess the maximum number of published articles regarding the effect of dietary polyphenols on the onset and progression of ED, a general search was carried out using the queries "erectile dysfunction and nutrition", "erectile dysfunction and nutrient" and "erectile dysfunction and polyphenol". To avoid missing studies focusing on specific polyphenols in ED, additional searches were performed using more specific MeSH terms, including "erectile dysfunction and catechin", "erectile dysfunction and curcumin",

115 “erectile dysfunction and quercetin" and “erectile dysfunction and resveratrol". The final
116 search equation was: “(erectile AND dysfunction) AND (nutrition OR nutrient OR
117 polyphenol OR catechin OR curcumin OR quercetin OR resveratrol).
118
119 ***Eligibility criteria***
120 Inclusion and exclusion criteria were established to identify peer-reviewed studies
121 investigating the effects of the four specific polyphenols on the pathophysiology of ED.
122 The aim was to collect comprehensive data on the molecular effects of dietary
123 polyphenols.
124 The inclusion criteria were as follows: 1. Studies providing experimental data
125 (human studies, animal models and cellular models); 2. Studies analyzing the effects of
126 curcumin, quercetin, resveratrol or catechins on ED; 3. Full-text articles written in
127 English. The inclusion of studies was limited to those reported in English due to language
128 barriers, considerations of time efficiency, and the impracticality of translation costs. The
129 exclusion criteria for journal articles included: 1. *In silico* studies, review articles,
130 including systematic reviews and meta-analysis, editorials, book chapters, meeting
131 abstracts, case studies or proceeding articles; 2. Original studies that combined the
132 administration of drugs or other compounds with polyphenols or omitted crucial
133 information about dose, administration route and treatment duration.
134
135 ***Study selection***
136 The study selection process began with an initial phase in which two independent
137 reviewers, RG and CC, conducted searches in the three databases. Searches were initially
138 based on general inclusion criteria and later on more specific criteria. Based on the title

and abstract, each reviewer identified studies with potential eligibility for inclusion and those for exclusion. Subsequently, the lists were merged and a third independent reviewer, DN, conducted a final assessment to resolve any discrepancies and make the ultimate decisions regarding inclusion. After excluding duplicate studies and those not meeting the inclusion criteria, the full texts of the potentially eligible papers were retrieved and thoroughly reviewed. The exclusion criteria were then applied, and a consensus was reached among all reviewers regarding the final list of included studies.

Data extraction

A table (Table 1) summarizes the main information collected from the selected studies. Variables taken into account were: study design and ED characteristics (*in vitro* models - cell origin, including total number of donors and controls, age; animal studies - sample size, including controls and ED model, age, weight), dietary component and preparation (dosage, extension of intervention, route of administration) and the main results (functional tests, morphologic changes, molecular quantifications).

Methodological quality and data analysis

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria [Wei et al., 2016] were used to assess the quality of the evidence. This assessment considered five domains: risk of bias, indirectness, inconsistency, imprecision and publication bias. In animal studies, the SYRCLE ROB tool was employed to assess the risk of bias [Hooijmans et al., 2014]. For assessing the risk of bias in included *in vitro* studies, a modified version of the SYRCLE ROB tool was applied, excluding questions about animal experimentation (questions 1-6 were omitted) [Hipólito-Reis et al., 2022].

Quality assessments were independently performed by RG and CC. Any disagreements not resolved by discussion were decided by a third independent reviewer, DN. A consensus table (Table 2) was created, categorizing articles into five quality levels: low quality, medium-low quality, medium quality, medium-high quality and high quality.

Results

Search results

The flowchart illustrating the process of identifying the relevant studies is presented in Figure 1. An initial search located 409 publications from PubMed, 445 from Scopus and 285 from Web of Science Core Collection. After an accurate screening of titles and abstracts, 26, 30 and 29 publications, respectively, were selected for further evaluation. Subsequently, 50 duplicate articles were removed. Following this, the full text of 35 articles was meticulously reviewed but 9 of them did not meet the inclusion criteria. As a result, 26 papers were included in this systematic review.

Characteristics of selected studies

This systematic review evaluated the impact of four specific polyphenols, catechin (exclusively EGCG), quercetin, resveratrol, and curcumin on the pathophysiology of ED. The analysis encompassed four animal studies for EGCG; a total of four studies for quercetin, which included three animal studies and one *in vitro* study; 12 publications for resveratrol, comprising six animal studies, three *ex vivo* studies, one study combining animal and *in vitro* experiments, and two *ex vivo* studies shared with quercetin. Additionally, there were four animal studies, one *ex vivo* study and one study combining animal and *in vitro* trials specifically focused on curcumin (Table 1).

Catechin: main results

This systematic review exclusively included animal studies regarding the effects of EGCG on ED.

Animal studies

One of the studies was implemented in an animal experimental model of age-associated vasculogenic ED [Chen et al., 2017], while the other three utilized a DM-induced vasculogenic ED model, one of those in aged animals [Mostafa et al., 2013; Lombo et al., 2016; Huang et al., 2022]. In all of these studies EGCG was orally administered; in two studies by gavage at daily dosages of 10 and 100 mg/kg for 12 weeks [Chen et al., 2017] and 14 mg/kg for 14 consecutive days [Huang et al., 2022]; in the other two studies EGCG was dissolved in drinking water in a concentration of 7.6 mg/L over 8 days [Mostafa et al., 2013] and 2 g/L for 10 weeks [Lombo et al., 2016]. The administration of EGCG increased the ratio of intracavernous pressure relative to mean arterial pressure (ICP/MAP) when compared to untreated animals, with this increase being positively correlated with the EGCG dose [Chen et al., 2017]. In line, EGCG increased the frequency of mounting, intromission and ejaculation while reducing the latencies of these events [Huang et al., 2022]. EGCG treatment intervenes, as well, in the androgen secretion inducing an elevation in both serum testosterone [Mostafa et al., 2013] and LH [Huang et al., 2022] relative to the untreated groups. Structural changes, such as an improvement in the smooth muscle layer area when measured isolated or relatively to collagen, were observed in the cavernous tissue of aged rats treated with EGCG when compared with non-treated animals [Chen et al., 2017]. Furthermore, a dose-dependent

increase of cavernous levels of cGMP, endothelial NOS (eNOS), neuronal NOS (nNOS), dimethylarginine dimethylaminohydrolase (DDAH)1 and DDAH2 gene expression and of NOS and superoxide dismutase (SOD) enzymatic activity [Mostafa et al., 2013; Chen et al., 2017] were found in treated animals. EGCG treatment also resulted in a local decrease of asymmetric dimethylarginine (ADMA) [Chen et al., 2017] and malondialdehyde (MDA) content [Mostafa et al., 2013; Chen et al., 2017] and of PDE5 levels in blood [Huang et al., 2022], but did not alter the expression of vascular endothelium growth factor (VEGF) and angiopoietin 1 in the cavernous tissue [Lombo et al., 2016].

Quercetin: main results

The selected publications concerning the effects of quercetin on the pathophysiology of ED explored its intervention in different molecular pathways.

Animal studies

Two of the studies employed an animal experimental model of hypertension-induced vasculogenic ED [Olabiyi et al., 2021; Olabiyi et al., 2022] treated with orally administrated quercetin for 30 days at two different concentrations: 25 or 50 mg/kg/day. The other study implemented a DM-induced vasculogenic ED model [Zhang et al., 2011b] treated with intraperitoneally (IP) injected 5, 20 or 50 mg/kg/day quercetin for 8 weeks. Quercetin treatment demonstrated a dose-dependent increase in ICP [Zhang et al., 2011b], as well as, in mounting, intromission and ejaculation frequency while decreasing the latency of these processes [Olabiyi et al., 2021]. Furthermore, a dose-dependent rise in eNOS gene expression, in NO and derivative NOx levels, and in catalase and SOD activity in the cavernous tissue of quercetin-treated hypertensive and diabetic animals,

when compared to untreated groups, was found [Zhang et al., 2011b; Olabiyi et al., 2022]. The administration of quercetin also resulted in a local decrease in adenosine deaminase (ADA), acetylcholinesterase (AChE) and arginase activity [Olabiyi et al., 2022], as well as, in a reduction in thiobarbituric acid-reacting substance (TBARS), compared to untread groups [Zhang et al., 2011b].

Ex vivo study

Two *ex vivo* studies were included in this review, in which the penile strips from healthy rats were exposed to quercetin at concentrations ranging from 10 to 100 μM for 15 min [Boydens et al., 2015; Boydens et al., 2016]. The results revealed that quercetin does not cause concentration-dependent relaxation [Boydens et al., 2015; Boydens et al., 2016] or either influence acetylcholine (Ach)-, sodium nitroprusside (SNP)-, or electrical field stimulation (EFS) mediated relaxations of CC [Boydens et al., 2015]. However, quercetin significantly attenuated high glucose (HG) and methylglyoxal (MGO)-induced deficits in Ach- and EFS-responses in CC at a concentration of 30 μM [Boydens et al., 2016].

In vitro study

Supplementation of quercetin, within the concentration range of 10^{-4} to 10^{-7} M, induced a concentration-dependent relaxation of rabbit penile CC smooth muscle (PCCSM) cells, with a corresponding rise in cGMP levels in the perfusate. Quercetin also enhanced the relaxation of PCCSM cells induced by PDE5 inhibitors. However, the presence of N-Nitro-L-arginine methyl ester hydrochloride (L-NAME) or 1H-[1,2,4] Oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) significantly attenuated the relaxation response to quercetin [Choi et al., 2017].

Resveratrol: main results

In alignment with the studies addressing catechin and quercetin, the impact of resveratrol on the molecular mechanisms associated with ED was documented.

Animal studies

Of the animal studies investigating resveratrol as a treatment, four of them utilized a DM-induced vasculogenic ED rat model, one of those in aged diabetic animals [Fukuhara et al., 2011; Yu et al., 2013; Bai and An, 2015; Yu et al., 2022]. In all of these studies, resveratrol was administered via oral gavage at a dose of 5 mg/kg/day for either 4 weeks [Fukuhara et al., 2011] or 8 weeks [Yu et al., 2013; Yu et al., 2022], or a dose of 25 mg/kg/day for 8 weeks [Bai and An, 2015]. Two other studies adopted a rabbit experimental model of hypercholesterolemia-induced vasculogenic ED [Bozkurt et al., 2016; Murat et al., 2016] and in both, animals were treated with orally administrated resveratrol for 6 weeks, in a dose of 4 mg/kg/day [Bozkurt et al., 2016] or of 8 mg/kg/day [Murat et al., 2016]. One additional study implemented a chronic mild stress model of ED in rats [Yazir et al., 2018a], wherein resveratrol was IP injected at a dose of 20 mg/kg/day for 8 weeks. The results demonstrated that resveratrol treatment led to an increase in the ICP/MAP ratio [Fukuhara et al., 2011; Yu et al., 2013; Bai and An, 2015], endothelium-dependent relaxation response [Murat et al., 2016], cGMP [Bai and An, 2015; Yu et al., 2022] and NO levels [Yu et al., 2022] when compared to untreated animals. Furthermore, an increase in eNOS activation [Bai and An, 2015; Bozkurt et al., 2016; Yazir et al., 2018a] (although not significant in [Bozkurt et al., 2016]) was demonstrated by an increase in p(S1177)-eNOS and decrease of p(T495)-eNOS [Murat et al., 2016]. As well, increment in nNOS [Bai and An, 2015; Yazir et al., 2018a] and Sirt-

1 gene expression [Yu et al., 2013; Yu et al., 2022] and SOD activity [Yu et al., 2013; Yu et al., 2022] was observed in animals treated with resveratrol. Resveratrol also led to a rise in the smooth muscle to collagen ratio [Yu et al., 2013] as well as in the content of smooth muscle and endothelium when compared to untreated animals [Yu et al., 2022], which aligns with the reduction in apoptosis within corporal tissue [Yu et al., 2013] ensuing the decrease in forkhead transcription factor O 3a (FOXO3a) and p53 gene expression found in the cavernous tissue of both young and aged animals [Yu et al., 2013; Yu et al., 2022]. Resveratrol treatment led to the regularization of blood LDL and total cholesterol levels in the hypercholesterolemia-induced model of ED [Bozkurt et al., 2016] but, concerning glucose levels in blood, whilst Bai and An et al. verified a decrease, Fukuhara et al. failed to observe variation in DM-induced ED resveratrol-treated animals [Fukuhara et al. 2011; Bai and An et al. 2015]. Interestingly, the depressive-like behaviors and the serum levels of corticosterone and testosterone were attenuated by treatment in rats exposed to chronic mild stress [Yazir et al., 2018a]. In addition, resveratrol resulted in a cavernous reduction of PDE5, ROS and superoxide anion levels [Bai and An, 2015], MDA activity [Yu et al., 2013; Yu et al., 2022], and local and circulating levels of proinflammatory factors, such as tumor necrosis factor alfa (TNF-α), interleukin (IL) 1 beta (IL-1β), IL-6, C-reactive protein (CRP), intercellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractant protein 1 (MCP1) [Yazir et al., 2018a].

Ex vivo studies

Five *ex vivo* studies were included in this review. In two of them, penile strips from healthy rats were exposed to resveratrol at concentrations ranging from 10^{-4} to 10^{-6} [Dalaklioglu and Ozbey, 2013; 2014] and in the other two studies penile strips from mice

were exposed to concentrations ranging from 10 to 100 μM for 15 min [Boydens et al., 2015; Boydens et al., 2016]. In the fifth study, the penile tissue was excised from rabbits subjected to a chronic mild stress model of ED, and the treatment involved a dosage of 20 m/kg/day over 12 weeks, administered via IP injection to animals [Yazir et al., 2018b]. In the phenylephrine (Phe) pre-contracted endothelium-intact tissues, the addition of resveratrol induced a potent relaxation response in a concentration-dependent manner [Dalaklioglu and Ozbey, 2013; 2014; Boydens et al., 2016]. The same result occurs in tissues pre-contracted with norepinephrine (NOR) [Boydens et al., 2015]. However, this relaxation response was partially attenuated by the removal of endothelium from CC and in the presence of L-NAME (only at a concentration of 10 μM in [Boydens et al., 2015]) and ODQ (but not cyclooxygenase inhibitor indomethacin (INDO)) [Dalaklioglu and Ozbey, 2013], or in KCl (80 mM)- contracted tissues [Dalaklioglu and Ozbey, 2013]. In this condition, the contraction response of the CC induced by the addition of $CaCl_2$ to Ca^{2+}- deprived high KCl solution was significantly inhibited by resveratrol (1M) incubation [Dalaklioglu and Ozbey, 2013]. In line, pre-treatment of CC strips with tetraethylammonium (TEA) [Dalaklioglu and Ozbey, 2013; 2014], glibenclamide and $BaCl_2$ [Dalaklioglu and Ozbey, 2014] resulted in a significant reduction in the relaxation response to resveratrol, while no differences were observed with voltage-dependent potassium (Kv), 4-aminopyridin (4-AP) and iberiotoxin (IbTX) [Dalaklioglu and Ozbey, 2014]. Nonetheless, relaxant responses to resveratrol were not significantly affected by the combination of selective inhibitors of small and intermediate conductance calcium-activated potassium (BK_{Ca}) channels [Dalaklioglu and Ozbey, 2014]. Resveratrol was also able to significantly reverse palmitic acid (PA)-induced decrease of EFS-relaxation [Boydens et al., 2015] and significantly attenuated HG and MGO-induced deficits in Ach-

and EFS-responses in CC at a concentration of 30 μM [Boydens et al., 2016]. In the unique ex-vivo study employing CC strips from resveratrol-treated rabbits, an increased response to EFS-induced neurogenic and carbachol-induced endothelium-dependent relaxation was identified. Resveratrol did not affect the responses to Phe and KCl-induced contractions, nor to papaverine and SNP-mediated relaxation responses [Yazir et al., 2018b].

In vitro studies

Treatment of cultured human CC smooth muscle cells with 10 to 100 mM of resveratrol resulted in a concentration-dependent increase in cGMP levels. However, this effect was attenuated by the administration of L-NAME or sirtinol [Fukuhara et al., 2011].

Curcumin: main results

Curcumin targets equivalent molecular mechanisms affected by the other polyphenols.

Animal studies

All the included animal studies devoted to the study of curcumin employed an experimental model of DM-induced vasculogenic ED [Abdel Aziz et al., 2012; Abdel Aziz et al., 2015; Zaahkouk et al., 2015; Draganski et al., 2018; Jiang et al., 2023]. In these experiments, the oral administration of 10 mg/kg/day of curcumin for a single dose or over 12 weeks, 30 mg/kg/day for 8 weeks and 2 mg/kg of novel water-soluble curcumin-protein conjugates in a single dose [Abdel Aziz et al., 2012; Abdel Aziz et al., 2015; Zaahkouk et al., 2015; Jiang et al., 2023] or the application of curcumin-nanoparticles for 2 weeks [Draganski et al., 2018], to diabetic animals led not only to the increase in the ICP/MAP ratio but also on the levels of heme oxygenase (HO)-1 gene

355 expression and of HO activity. Additionally, when orally administered curcumin resulted
356 in higher levels of cavernous cGMP in comparison with the untreated diabetic group, with
357 these effects persisting for up to 1 week and approaching the values of the control group
358 (without DM). Furthermore, there was an enhancement in local eNOS and nNOS gene
359 expression and enzymatic activity in curcumin-treated groups when compared to diabetic
360 untreated groups. In addition, data demonstrated a rise in nuclear transcription factor-
361 erythroid 2-related factor 2 (Nrf2) gene expression in diabetic rat groups treated with
362 curcumin compared with untreated diabetic rats [Abdel Aziz et al., 2012; Zaahkouk et al.,
363 2015; Jiang et al., 2023]. Administration of curcumin also increased the content of CC
364 endothelial cells as well as glutathione peroxidase 4 (GPX4) and cysteine/glutamate
365 antiporter Xc− system (xCT) expression levels [Jiang et al., 2023], while decreased gene
366 expression of inducible NOS (iNOS), factor nuclear kappa B (NF-Kβ) (or NF-κB-
367 activating protein (Nkap)) and p-38 and MDA and 4-hydroxynonenal (4HNE) levels,
368 when compared with the untreated diabetic group [Abdel Aziz et al., 2012; Abdel Aziz et
369 al., 2015; Zaahkouk et al., 2015; Jiang et al., 2023].
370
371 ***Ex vivo study***
372 A unique study utilized the penile tissue from rats with DM-induced vasculogenic ED,
373 treated with orally administered curcumin in a dosage of 200 mg/kg/day over 8 weeks
374 [Khimmaktong et al., 2019]. Curcumin reversed the DM-associated damage in the penile
375 microvasculature, considering that treatment increases the diameter of the tunica media
376 of dorsal arteries (DA) and deep dorsal vein (DV) in the penile tissue of diabetic rats.
377 Furthermore, curcumin induces a decrease in the thickness of collagen fibers within the
378 trabeculae, as well as a decrease in the diameter and thickness of DA and DV, resembling

the results observed in the control group. The administration of curcumin also led to an increase in the diameter of the venous sinuses of the glans of the penis and a decrease in the diameter of the venous sinuses of the CC when compared to the untreated diabetic animals.

In vitro study

Treatment with 30 μM of curcumin of CC endothelial cells led to an increase in cell viability as well as in GPX4, xCT, Nrf2 and HO-1 gene expression. It also resulted in a decrease in MDA levels and oxidative stress [Jiang et al., 2023].

Risk of bias

The studies included in this review generally exhibited good quality, according to GRADE criteria, with a medium to low risk of bias, as seen in Table 2. Especially, in terms of bias risk assessment, the majority of the studies indicated a “medium-low risk.” Globally, there was found a low risk of bias associated with the domains of baseline characteristics, random housing, selective outcome reporting or other sources of bias, whereas sequence generation, allocation concealment, blinding of investigators, random outcome assessment and some incomplete outcome data emerged as a common challenge.

Discussion

This systematic review compiles data from experimental studies focusing on the influence of catechin, quercetin, resveratrol, and curcumin in vasculogenic ED. These compounds, naturally present in foods, exhibit low toxicity and may be used concurrently with medications or as alternative in ED treatment with a minimum risk. The careful analysis

of the publications included in this study evidenced that these four polyphenols share action mechanisms that encompassed molecular and functional parameters, behavioral and hormonal modulation, structural improvements in the CC, and antioxidant and anti-inflammatory properties, that overall led to favorable conditions to improve erectile function. This evidence constitutes a major strength of this study.

All studied polyphenols exhibited consistent positive outcomes across different animal models of vasculogenic ED. Treatment with catechin/EGCG, quercetin, resveratrol, or curcumin, increases the ICP/MAP, which is a valuable indicator of erectile function supporting the direct effect of those compounds in the control of the disease [Fukuhara et al., 2011; Zhang et al., 2011b; Abdel Aziz et al., 2012; Yu et al., 2013; Abdel Aziz et al., 2015; Bai and An, 2015; Zaahkouk et al., 2015; Chen et al., 2017; Draganski et al., 2018; Yu et al., 2022; Jiang et al., 2023]. In agreement with animal data, *ex vivo* and *in vitro* studies evidenced resveratrol and quercetin vasorelaxant properties [Dalaklioglu and Ozbey, 2013; 2014; Boydens et al., 2015; Boydens et al., 2016; Choi et al., 2017], respectively. In particular, quercetin induced a concentration-dependent relaxation of PCCSM cells, accompanied by increased cGMP levels and a synergistic effect when used in association with PDE-Is through increment of the relaxation response previously attenuated by L-NAME or ODQ [Choi et al., 2017], highlighting the involvement of NO-dependent pathways in quercetin's mechanism of action. Quercetin, however, did not induce concentration-dependent relaxation in *ex vivo* experiments with tissues from healthy animals [Boydens et al., 2015; Boydens et al., 2016] although it significantly attenuated deficits in Ach- and EFS-mediated responses induced by HG and MGO, molecules abundant in DM-related environment [Boydens et al., 2016]. These findings

reinforce that quercetin alone, or in association with established ED medications can be used to mitigate ED-related abnormalities arising from DM.

Both EGCG and quercetin improve behavioral changes, such as increased frequencies of mounting, intromission, and ejaculation [Olabiyi et al., 2021; Huang et al., 2022], further supporting these compounds' efficacy. Interestingly, one of the included studies not only evaluated the sexual behavior effects of quercetin treatment but also explored its role in purinergic pathways in the brain, where the signal stimulus activates a molecular cascade leading to penile erection [Olabiyi et al., 2021]. It was demonstrated that besides enhancing sexual behavior, the modulation of ectonucleotidases, ADA activity and NO levels in the hypothalamus were improved by treatment, suggesting that quercetin presents a more comprehensive impact in the organism and may indeed be a promising tool for managing ED [Olabiyi et al., 2021]. EGCG treatment also incremented androgen and LH secretion [Mostafa et al., 2013; Huang et al., 2022], while IP- administrated resveratrol caused a decrease in serum testosterone comparatively with controls [Yazir et al., 2018a]. Although testosterone deficiency itself is not a direct barrier to erectile function, androgens play a vital role in male sexual health, influencing aspects beyond erectile function, including libido, sperm production, and overall reproductive organ health [Corona and Maggi, 2022]. Its influence is indeed linked to the maintenance of the function of penile tissues, including vascular endothelium and erectile tissue. However, it did not seem probable that the decrease of testosterone observed in those resveratrol-treated rats is enough to impact the cavernous tissue of those animals [Yazir et al., 2018a], considering that fluctuations of testosterone levels, including age-related decrease, do not immediately influence the erectile function or the cavernous cellular viability. In fact, other selected studies demonstrated resveratrol vascular and corporal protective effects

complemented by a favorable shift in smooth muscle-to-collagen ratio and a decrease in apoptosis [Yu et al., 2013; Yu et al., 2022]. In line, EGCG and resveratrol promoted structural improvements in the CC, the former in the enhancement in the smooth muscle layer area [Lombo et al., 2016; Yu et al., 2022], which is a very relevant feature since the loss of smooth muscle content or the loss of muscle relaxation capacity underlies the ED associated with age and DM [Ferrer et al., 2010; Wei et al., 2012] and the last throughout the restorative effect on the penile microvasculature and the preventive effect on cavernous fibrosis [Khimmaktong et al., 2019].

Molecular analyses also support the beneficial effect of EGCG, quercetin, resveratrol, and curcumin in ED. All studied polyphenols increase levels of molecules that directly intervene in erectile mechanism, such as eNOS gene expression that is upregulated in cavernous tissue by every polyphenol, but also in mitigation of oxidative stress and inflammation; EGCG dose-dependently increases cavernous levels of cGMP, nNOS, DDAH1 and DDAH2 gene expression and of NOS and SOD enzymatic activity. EGCG also led to a reduction in blood PDE5 levels [Huang et al., 2022] and a local reduction in ADMA and MDA content [Mostafa et al., 2013; Chen et al., 2017]; quercetin dose-dependently upregulates NO levels, and antioxidative enzyme activity within the CC [Zhang et al., 2011b; Olabiyi et al., 2022] and exhibited additional direct and indirect antioxidative properties by decreasing ADA, AChE, and arginase activity [Olabiyi et al., 2022], coupled with a decrease in TBARS [Zhang et al., 2011b]; resveratrol increases cavernous and *in vitro* cGMP and NO levels [Fukuhara et al., 2011; Bai and An, 2015; Yu et al., 2022] and upregulates nNOS, and Sirt-1 gene expression [Yu et al., 2013; Bai and An, 2015; Yu et al., 2022] while decreases levels of pro-inflammatory and pro-oxidative molecules [Yazir et al., 2018a], such as ROS, and superoxide anion and PDE5 [Bai and

An, 2015]. *In vitro* upregulation of cGMP was attenuated by the administration of L-NAME or sirtinol, evidencing a dependency on NO and Sirt pathways; curcumin increments cavernous cGMP levels and nNOS gene expression [Abdel Aziz et al., 2012; Zaahkouk et al., 2015; Jiang et al., 2023] and respective enzymatic activity [Abdel Aziz et al., 2012; Abdel Aziz et al., 2015; Zaahkouk et al., 2015] and exhibited antioxidative and ferroptosis properties, as reflected in the elevated HO-1 gene expression, HO activity [Abdel Aziz et al., 2012; Abdel Aziz et al., 2015; Zaahkouk et al., 2015; Draganski et al., 2018; Jiang et al., 2023] and GPX4 and xCT levels [Jiang et al., 2023], and anti-inflammatory effects by reducing iNOS, NF-kβ, and p-38 gene expression [Abdel Aziz et al., 2012; Abdel Aziz et al., 2015; Zaahkouk et al., 2015].

Insights into the impact of polyphenols on ED are predominantly drawn from animal studies, *ex vivo*, and *in vitro* experiments, given the scarcity of clinical trials. While the chosen experimental models effectively recapitulate normal causes of ED, such as DM, ageing, hypertension, and hyperlipidemia, allowing for the extrapolation of results to humans, the obtained findings may not precisely reflect the complex physiological responses in humans, particularly those that depend on behavioral stimulus, which constitutes a limitation. Among the animal studies, two of them used a chronic mild stress model instead of a model of vasculogenic ED, making it challenging to extrapolate results to humans when compared to data from vasculogenic ED models. The scarcity of clinical trials in patients limits the generalizability of the results to diverse populations experiencing ED, which raises questions about the relevance of the observed effects to real-world scenarios. Another limitation is the methodological diversity across studies, including variations in dosages and treatment duration, which makes it challenging to establish a standardized approach for potential clinical applications, with putative

497 indication of doses and prescription patterns. In addition, in three of the animal studies
498 the polyphenols were administered by IP injection [Zhang et al., 2011b; Yazir et al.,
499 2018a; Yazir et al., 2018b] and in one by skin absorption of nanoparticles [Draganski et
500 al., 2018], which does not precisely replicate what occurs in humans, as these compounds
501 are typically ingested through foods or isolated for oral administration. Furthermore, none
502 of the included animal studies specified the method used to generate the allocation
503 sequence, whether investigators or caregivers were blinded, or how blinding was
504 implemented. Selection criteria for animals included in the analyses were often unclear,
505 with one study reporting fewer number, compared to the number of initial animals, in
506 some analyses without explanation [Yazir et al., 2018a], factors that may impact the risk
507 of bias of their findings. In sum, while the experimental evidence suggests positive
508 alterations in behavioral, functional, molecular, and hormonal aspects, the translation of
509 these findings to human populations remains speculative. Notwithstanding, observational
510 studies suggest that the intake of these dietary components could prevent ED [Cassidy et
511 al., 2016]. Therefore, further clinical investigations are essential to elucidate the true
512 translational potential of catechin, quercetin, resveratrol, and curcumin in managing ED
513 and ensuring their safe and effective use in diverse patient populations.

514

515 **Conclusion**

516 In conclusion, this systematic review underscores the significant positive impacts of
517 catechin, quercetin, resveratrol and curcumin on ED as demonstrated in experimental
518 studies. These compounds are prevalent in diet, specifically found in legumes, fruits,
519 vegetables, cereals and beverages. Considering the limitations associated with ED

520 treatments, these compounds emerge as potential dietary agents for the prevention or
521 management of ED. The observed beneficial effects on behavioral, functional, molecular,
522 and hormonal aspects in various experimental models suggest their potential clinical
523 relevance. However, the translation of these findings into effective therapeutic strategies
524 for human ED requires further searching through comprehensive clinical trials. Future
525 research efforts should focus on evaluating the true efficacy and safety profile of these
526 polyphenols in diverse human populations with ED, aiming to establish their role as
527 viable dietary interventions for improving erectile function.
528

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Legends of figures

Figure 1- Flowchart of the process of selection of the articles.

723 Table 1 - Summary of the main information extracted from the selected studies.

Polyphenol treatment	Study design and characteristics (sample size; age)	Erectile dysfunction model	Dietary component and preparation (dosage; intervention duration)	Administration route	Main results	Authors, publication date
EGCG	Animal study Sprague-Dawley male rats 12-week-old weighing 280–300 g; controls n=10; 18-month-old weighing 620–680 g; controls n=10; EGCG-treated n=20	Age-associated vasculogenic ED	EGCG: 10 mg/Kg/day and 100 mg/kg/day (aged group) 12 weeks	Oral gavage (saline solution)	⊕ ICP/MAP ⊕ Cavernous levels of cGMP ⊕ SOD, DDAH and NOS activities and DDAH1, DDAH2, eNOS and nNOS gene expression in penile tissue ⊕ Smooth muscle/collagen ratio ⊖ ADMA and MDA content and PRMT1 gene expression in penile tissue	[Chen et al., 2017]
EGCG	Animal study Aged albino male rats 2 years old; non and diabetic controls n=25/group; EGCG-treated n=25	Diabetes-induced vasculogenic ED, by IP injection of STZ	EGCG: 7.6 mg/L 8 weeks	Oral administration (drinking water)	⊕ Cavernous levels of cGMP and eNOS gene expression ⊕ Serum testosterone levels ⊖ Cavernous MDA content	[Mostafa et al., 2013]
EGCG	Animal study Wistar male rats weighing 250–300 g; non and diabetic controls n=8/group; EGCG-treated n=8	Diabetes-induced vasculogenic ED, by IP injection of STZ	EGCG: 2 g/L 10 weeks	Oral administration (drinking water)	⊕ Smooth muscle area in the CC ● No differences in expression of VEGF and its receptors, angiopoietin/Tie-2system	[Lombo et al., 2016]
EGCG	Animal study Long-Evans male rats	Diabetes-induced vasculogenic	EGCG: 40 mg/Kg/day 14 consecutive days	Oral gavage	⊕ Mounting, intromission and ejaculation frequencies ⊕ Serum LH levels	[Huang et al., 2022]

	7–8 weeks old; non and diabetic controls n=8/group; EGCG-treated n=9	ED, by IP injection of STZ			⊖ Blood glucose and PDE5 levels ⊖ Mounting, intromission and ejaculation latencies	
Quercetin	Animal study Wistar male rats weighing 200–250 g; non and hypertensive controls n=6/group; quercetin-treated n=6	Hypertension-induced vasculogenic ED	Quercetin: 25 mg/Kg/day and 50 mg/kg/day 30 days	Oral gavage (25 % ethanol solution)	⊕ Copulatory behaviour (increased mounting, intromission and ejaculation frequencies) ⊕ Activity of E-NTPDase and NO levels in the hypothalamus ⊖ Mount, intromission and ejaculation latencies ⊖ ADA activity in the hypothalamus ● No difference in 5´nucleotidase activity in the hypothalamus	[Olabiyi et al., 2021]
Quercetin	Animal study Wistar male rats weighing 200–250 g; non and hypertensive controls n=6/group; quercetin-treated n=6	Hypertension-induced vasculogenic ED	Quercetin: 25 mg/Kg/day and 50 mg/kg/day 30 days	Oral gavage (25 % ethanol solution)	⊕ Antioxidant status (catalase and SOD activities) and NO levels in CC ⊖ Activity of arginase, AChE, and ADA in CC	[Olabiyi et al., 2022]
Quercetin	Animal study Sprague-Dawley male rats; non and diabetic controls n=8/group; quercetin-treated n=8	Diabetes-induced vasculogenic ED, by IP injection of STZ	Quercetin: 5, 20, and 50 mg/Kg/day 8 weeks	IP injection	⊕ ICP ⊕ Cavernous SOD activity, NO and derivative NOx levels and eNOS gene expression ⊖ TBARS levels in CC ● No difference in body weight and blood glucose	[Zhang et al., 2011]

Quercetin	*Ex vivo* study Adult Swiss male rats 8–12 weeks old; controls n=7–8; quercetin-treated n=7-8	Penile CC tissue from healthy mice	Quercetin: 10-100 µM, 15 min		● No concentration-dependent relaxation or influence on Ach-, SNP- or EFS-mediated relaxations of CC	[Boydens et al., 2015]
Quercetin	*Ex vivo* study Swiss male rats 8–12 weeks old; controls n=5–6; quercetin-treated n=5-6	Penile CC tissue from healthy mice	Quercetin: 1-100 µM, 15 min		⊖ HG and MGO-induced deficits in Ach- and EFS-responses in CC (30 µM)	[Boydens et al., 2016]
Quercetin	*In vitro* study Male New Zealand white rabbits weighing 2500–3000 g; controls n=4/group; quercetin-treated n=4/group	PCCSM of healthy rabbits	Quercetin: 10^{-4}, 10^{-5}, 10^{-6} and 10^{-7} M		⊕ Relaxation of PCCSM cells induced by PDE5 inhibitors, attenuated by the presence of L-NAME and ODQ ⊕ cGMP in the perfusate	[Choi et al., 2017]
Resveratrol	*In vitro* study Human cells Animal study Sprague-Dawley male rats 8-week-old weighing 250–350 g; non and diabetic controls n=4/group; resveratrol-treated n=4	CC smooth muscle cells from patients undergoing penectomy Diabetes-induced vasculogenic ED, by IP injection of STZ	Resveratrol: 10 mM, 30 mM, or 100 mM, 5 h Resveratrol: 5 mg/Kg/day 4 weeks	Intragastric administration	⊕ cGMP levels (*In vitro*) ⊕ICP/MAP (*In vivo*) ● No difference in body weight and blood glucose (*In vivo*)	[Fukuhara et al., 2011]
Resveratrol	Animal study Sprague-Dawley male rats	Diabetes-induced vasculogenic	Resveratrol: 5 mg/Kg/day 8 weeks	Intragastric administration	⊕ ICP/MAP ⊕ Gene expression of Sirt1; SOD activity and smooth muscle/collagen ratio in CC	[Yu et al., 2013]

	12-week-old weighting 250–300 g; non and diabetic controls n=17/12 per group; resveratrol-treated n=17	ED, by IP injection of STZ			⊖ Gene expression of p53 and Fox03a and apoptosis in CC ⊖ MDA activity in CC	
Resveratrol	Animal study Sprague–Dawley male rats weighing 200-250 g; non and diabetic controls n=12/group; resveratrol-treated n=12	Diabetes-induced vasculogenic ED, by IP injection of STZ	Resveratrol: 25 mg/kg/day 8 weeks	Oral gavage (3 % hydroxyethyl starch solution)	⊕ ICP/MAP ⊕ Cavernous nNOS and eNOS gene expression and levels and cGMP levels ⊖ Blood glucose, body weight, superoxide anion and ROS levels in CC ⊖ PDE-5 gene expression	[Bai and An, 2015]
Resveratrol	Animal study Sprague-Dawley male rats 20-month-old weighting 700-750 g; non and diabetic controls n=17/group; resveratrol-treated n=17	Diabetes-induced vasculogenic ED	Resveratrol: 5 mg/Kg/day 8 weeks	Intragastric administration	⊕ ICP/MAP ⊕ Smooth muscle and endothelium content, NO and cGMP levels and SOD activity ⊕Sirt1 expression ⊖ Cell apoptosis, MDA activity and p53 and FOX03a l gene expression in the CC	[Yu et al., 2022]
Resveratrol	Animal study New Zealand white male rabbits 3-month-old weighting 2600-3200 g; non and hypercholesterolemic controls n=7/group; resveratrol-treated n=10	Hypercholesterolemia-induced vasculogenic ED	Resveratrol: 4 mg/Kg/day 6 weeks	Oral administration (drinking water)	⊕ eNOS gene expression levels (not significantly) ⊖ Total and LDL cholesterol levels ● No difference in LOX-1 mRNA expression levels	[Bozkurt et al., 2016]

Resveratrol	Animal study Adult New Zealand male rabbits weighting 2500–3000 g; non and hypercholesterolemic controls n=7/group; resveratrol-treated n=6/7	Hypercholesterolemia-induced vasculogenic ED	Resveratrol: 8 mg/Kg/day 6 weeks	Oral administration (drinking water)	⊕ Endothelium-dependent relaxation responses in CC ⊕ Activatory-phosphorylation (S1177) of eNOS and activated phosphovasodilator-stimulated phosphoprotein levels in CC ⊖ Phosphorylation (T495) of eNOS and NADPH oxidase activity in CC	[Murat et al., 2016]
Resveratrol	Animal study Wistar albino male rats weighting 220–250 g; non and stress controls n=8/group; resveratrol-treated n=8	Chronic mild stress model of vasculogenic ED	Resveratrol: 20 mg/Kg/day 8 weeks	IP injection	⊕ Body weight; penile nNOS, eNOS and MCP gene expressions ⊖ Depressive-like behaviors (decreased immobility time and increased sucrose consumption and preference) ⊖ TNF-α, IL-1β, and CRP-1 gene expressions ⊖ Serum and penile levels of inflammatory markers (TNF-α, IL-1β, IL-6, CRP, ICAM-1, MCP-1) and serum corticosterone, and testosterone	[Yazir, Demirtaş Şahin, et al., 2018a]
Resveratrol	*Ex vivo* study Wistar male rats weighing 250-300 g; control n=6–8/group; resveratrol-treated n=6-8	Penile CC strips of healthy rats	Resveratrol: 10^{-4}, 10^{-5} and 10^{-6} M		⊕ Relaxation in a concentration-dependent manner in endothelium-intact tissues (pre-contracted with Phe), but partially abolished by the removal of endothelium and the presence of L-NAME and ODQ	[Dalaklioglu and Ozbey, 2013]

				⊕ Relaxation responses in the presence of KCl ⊖ Relaxation responses in pre-treatment of CC strips with TEA ⊖ Contraction response of CC induced by stepwise addition of $CaCl_2$ to high KCl with no Ca^{2+} solution	
Resveratrol	*Ex vivo* study Male Wistar rats weighing 250–300 g; control n=5-7/group	Penile CC strips of healthy rats	Resveratrol: 10^{-4}, 10^{-5} and 10^{-6} M	⊕ Relaxation in a concentration-dependent manner in endothelium-intact tissues (pre-contracted with Phe) ⊖ Relaxation responses in pre-treatment of CC strips with TEA, glibenclamide and $BaCl_2$, but not in presence of Apa plus charybdo, 4-AP and IbTX	[Dalaklioglu and Ozbey, 2014]
Resveratrol	*Ex vivo* study Swiss male mice 8–12 weeks old; controls n=7-8/group; resveratrol-treated n=7–8	Penile CC tissue from healthy mice	Resveratrol: 10-100 μM, 15 min	⊕ Concentration-dependent relaxation in CC ●L-NAME reduced the resveratrol-induced relaxation at a concentration of 10 μM ● No influence in Ach-, SNP- or EFS-mediated relaxations in CC ● Reverse PA-induced decrease of EFS-relaxation	[Boydens et al., 2015]
Resveratrol	*Ex vivo* study Adult Swiss male mice	Penile CC tissue from healthy mice	Resveratrol: 1-100 μM, 15 min	⊕ Concentration-dependent relaxation in CC	[Boydens et al., 2016]

	8–12 weeks old; controls n=5–6/group; resveratrol-treated n=5–6				⊖ HG and MGO-induced deficits in Ach- and EFS-responses in CC (30 μM)	
Resveratrol	*Ex vivo* study New Zealand male rabbits weighing 2500–3000 g; non and stress controls n=6/group; resveratrol-treated n=6	Penile CC strips of chronic mild stress model of ED	Resveratrol: 20 mg/Kg/day 12 weeks	IP injection	⊕ EFS-induced neurogenic and carbachol-induced endothelium-dependent relaxation	[Yazir, Demirtaş Şahin, et al., 2018b]
Curcumin	Animal study Albino male rats weighing 180-200 g; non and diabetic controls n=12/group; curcumin-treated n=12	Diabetes-induced vasculogenic ED, by IP injection of STZ	Curcumin: 10 mg/kg (one single dose) or daily Water soluble curcumin: 2 mg/kg (one single dose) or daily 12 weeks	Oral administration	⊕ ICP/MAP ⊕ cGMP levels, HO and NOS enzyme activity, eNOS, nNOS, HO-1, Nrf2 gene expression in CC ⊖ NF-kβ, p38, and iNOS gene expression in CC	[Abdel Aziz et al., 2012]
Curcumin	Animal study Albino male rats weighing 180–200 g; non and diabetic controls n=10/group; curcumin-treated n=10	Diabetes-induced vasculogenic ED, by IP injection of STZ	Curcumin: 10mg/kg Novel curcumin derivative: 2 mg/kg (one single dose) 12 weeks	Oral administration	⊕ ICP/MAP ⊕ HO-1 and Nrf2 gene expression, and cGMP levels in CC ⊕ HO and NOS enzyme activity in CC ⊖ NF-Kβ and p38 gene expression in CC	[Abdel Aziz et al., 2015]
Curcumin	Animal study Albino male rats weighting 180–200 g; non and diabetic controls n=10; curcumin-treated n=10	Diabetes-induced vasculogenic ED, by IP injection of STZ	Curcumin: 10 mg/Kg (one single dose) Novel curcumin derivative: 2 mg/Kg (one single dose) 12 weeks	Oral administration	⊕ ICP/MAP ⊕ cGMP levels; HO and NOS enzyme activity; HO-1 and Nrf2 gene expression in CC ⊖ NF-kβ and p38 gene expression in CC	[Zaahkouk et al., 2015]

Curcumin	Animal study Zucker male rats 20 weeks old; controls n=5/group; curcumin-treated n=5	Diabetes-induced vasculogenic ED	Curcumin: 10 mg/Kg, 6 applications 2 weeks	Skin absorption	⊕ ICP/MAP ⊕ HO-1 gene expression in CC ⊖ nKAP gene expression in CC	[Draganski et al., 2018]
	In vitro study Rat cells	CC endothelial cells	Curcumin: 30 μM for 24 h		⊕ Cell viability (*in vitro*) ⊕ GPX4 and xCT proteinexpression (*in vitro*) ⊖ MDA levels and oxidative stress (*in vitro*) ⊕ Nrf2 and HO-1 gene and protein expression (*in vitro*)	
Curcumin	Animal study Sprague-Dawley male rats 8-week-old weighting 250-300g; non and diabetic controls n=4/group; curcumin-treated n=4	Diabetes-induced vasculogenic ED, by IP injection of STZ	Curcumin: 30 mg/Kg/day 8 weeks	Oral gavage	⊕ ICP/MAP ratio (*in vivo*) ⊕ Content of endothelial cells, and cavernous eNOS, GPX4, xCT, Nrf2 and HO-1 protein expression (*in vivo*) ⊖ Cavernous MDA and 4HNE levels (*in vivo*) ⊕ Cavernous GPX4 gene expression (*in vivo*)	[Jiang et al., 2023]
Curcumin	*Ex vivo* study Wistar male rats weighting 200–250 g; non and diabetic controls n=10/group; curcumin-treated n=10	Penile CC from diabetes-induced vasculogenic ED, by IP injection of STZ	Curcumin: 200 mg/Kg/day 8 weeks	Oral gavage	⊕ Diameter of tunica media of DA and DV in the penile tissue ⊕ Diameter of the venous sinuses of the glans of the penis ⊖ Thickness of collagen fibers within trabeculae and diameter	[Khimmaktong et al., 2019]

		and thickness of DA and DV of the penis ⊖ Diameter of venous sinuses in CC

*Abbreviations: 4-AP, 4-aminopyridin. Ach, acetylcholine. AChE, acetylcholinesterase. ADA, adenosine deaminase. ADMA, asymmetrical dimethylarginine. CC, corpus cavernosum. cGMP, cyclic guanosine monophosphate. CRP, C-reactive protein. DA, dorsal arteries. DDAH, dimethylarginine dimethylaminohydrolase. DV, deep dorsal veins. ED, erectile dysfunction. EFS, electrical field stimulation. eNOS, endothelial nitric oxide synthase. E-NTPDase, ecto-nucleoside triphosphate diphosphohydrolase family. Fox03a, forkhead transcription factor O 3a. GPX4, glutathione peroxidase 4. HG, high glucose. 4HNE, 4-hydroxynonenal. HO-1, heme oxygenase-1. ICAM-1, intercellular adhesion molecule-1. ICP, intracavernous pressure. iNOS, inducible NOS. IP, intraperitoneal. L – NAME, N-Nitro-L- arginine methyl ester hydrochloride. lbTX, iberiotoxin. LDL, low-density lipoprotein. LH, luteinizing hormone. LOX – 1, lectin-like oxidized LDL receptor-1. MAP, mean arterial pressure. MCP, monocyte chemoattractant protein. MDA, malondialdehyde. MGO, methylglyoxal. PCCSM, penile CC smooth muscle. NADPH, nicotinamide adenine dinucleotide phosphate. NF–Kβ, nuclear factor kappa B. nKAP, NF–Kβ-activating protein. nNOS, neuronal NOS. NOS, nitric oxide synthase. NOx, nitrite and nitrate. Nrf2, nuclear transcription factor-erythroid 2-related factor 2. ODQ, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one. PA, palmitic acid. PDE5, phosphodiesterase 5. PRMT1, protein arginine methyltransferases 1. ROS, reactive oxygen species. sGC, soluble guanylyl cyclase. Sirt1, sirtuin1. SNP, sodium nitroprusside. SOD, Superoxide dismutase. STZ, streptozotocin. TBARS, thiobarbituric acid-reacting substance. TEA, tetraethylammonium. TNF – α, tumor necrosis factor alfa. VEGF, vascular endothelial growth factor. xCT, cysteine/glutamate antiporter. Xc− system. α–SMA, alpha smooth muscle actin. ⊕, Increase. ⊖, Decrease.

738 Table 2- Quality of the selected studies according to the SYRCLE´s ROB tool and GRADE criteria.

		SYRCLE´s ROB tool											GRADE				
Authors, publication date	**Study design**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Risk of bias ***	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Conclusion**
EGCG																	
Chen et al., 2017	Animal	U	Y	U	Y	U	U	Y	Y	Y	Y	Low risk	Medium risk	Low risk	Low risk	Low risk	Medium-high quality
Mostafa et al., 2013	Animal	U	U	U	Y	U	U	Y	U	Y	Y	Medium-low risk	Low risk	Low risk	Low risk	Medium risk	Medium-high quality
Lombo et al., 2016	Animal	U	Y	U	Y	U	U	Y	Y	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Huang et al., 2022	Animal	U	Y	U	Y	U	U	Y	Y	Y	Y	Low risk	Medium risk	Low risk	Low risk	Low risk	High quality
Quercetin																	
Olabiyi et al., 2021	Animal	U	Y	U	Y	U	U	Y	Y	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Olabiyi et al., 2022	Animal	U	Y	U	Y	U	U	Y	Y	Y	Y	low risk	Low risk	Low risk	Low risk	Low risk	High quality
Zhang et al., 2011	Animal	U	U	U	Y	U	U	Y	Y	Y	Y	Medium-low risk	Medium risk	Low risk	Low risk	Low risk	Medium-high quality
Boydens et al., 2015	*Ex vivo*							Y	U	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Boydens et al., 2016	*Ex vivo*							Y	U	Y	Y	Medium-low risk	Low risk	Low risk	Low risk	Low risk	High quality
Choi et al., 2017	*In vitro*							Y	U	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Resveratrol																	
Fukuhara et al., 2011	Animal	U	Y	U	Y	U	U	Y	U	Y	Y	Medium-low risk	Medium risk	Low risk	Low risk	Low risk	Medium-high quality

Fukuhara et al., 2011	*In vitro*							Y	Y	Y	U	Low risk	Medium risk	Low risk	Low risk	Low risk	Medium-high quality
Yu et al., 2013	Animal	U	Y	U	Y	U	U	Y	Y	Y	U	Medium-low risk	Medium risk	Low risk	Low risk	Low risk	Medium-high quality
Bai and An, 2015	Animal	U	Y	U	Y	U	U	Y	Y	Y	Y	Medium-low risk	Medium risk	Low risk	Low risk	Low risk	Medium-high quality
Yu et al., 2022	Animal	U	Y	U	Y	U	U	Y	U	Y	Y	Medium-low risk	Medium risk	Low risk	Low risk	Low risk	Medium-high quality
Bozkurt et al., 2016	Animal	U	Y	U	Y	U	U	Y	Y	Y	U	Medium-low risk	Low risk	Low risk	Low risk	Low risk	High quality
Murat et al., 2016	Animal	U	Y	U	U	U	U	Y	Y	Y	Y	Medium-low risk	Low risk	Low risk	Low risk	Low risk	High quality
Yazir, Demirtaş Şahin, et al., 2018a	Animal	U	Y	U	U	U	U	Y	Y	U	Y	Medium-low risk	Medium risk	Medium risk	Medium risk	Low risk	Medium quality
Dalaklioglu and Ozbey, 2013	*Ex vivo*							Y	U	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Dalaklioglu and Ozbey, 2014	*Ex vivo*							Y	U	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Boydens et al., 2015	*Ex vivo*							Y	U	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Boydens et al., 2016	*Ex vivo*							Y	U	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Yazir, Demirtaş Şahin, et al., 2018b	*Ex vivo*	U	Y	U	Y	U	U	Y	Y	Y	Y	Low risk	Medium risk	Low risk	Medium risk	Low risk	Medium-high quality
Curcumin																	

Abdel Aziz et al., 2012	Animal	U	Y	U	U	U	U	Y	U	Y	Y	Medium risk	Low risk	Low risk	Low risk	Medium risk	Medium quality
Abdel Aziz et al., 2015	Animal	U	Y	U	U	U	U	Y	U	Y	Y	Medium risk	Low risk	Low risk	Low risk	Medium risk	Medium quality
Zaahkouk et al., 2015	Animal	U	Y	U	U	U	U	Y	Y	Y	Y	Medium-low risk	Low risk	Low risk	High risk	Medium risk	Medium quality
Draganski et al., 2018	Animal	U	Y	U	U	U	U	Y	Y	Y	Y	Medium-low risk	Medium risk	Medium risk	Medium risk	Medium risk	Medium quality
Jiang et al., 2023	Animal	U	Y	U	Y	U	U	Y	U	Y	Y	Medium-low risk	Medium risk	Low risk	Low risk	Low risk	Medium-high quality
Jiang et al., 2023	*In vitro*							Y	U	Y	Y	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Khimmaktong et al., 2019	E*x vivo*	U	Y	U	Y	U	U	Y	U	Y	Y	Medium-low risk	Low risk	Low risk	Low risk	Low risk	High quality

* For the animal studies, the SYRCLE ROB tool was used to help the assessment of the risk of bias. For *in vitro* studies, the SYRCLE ROB tool was adapted. Questions from SYRCLE´s ROB tool (Q1-Q10): Q1: Was the allocation sequence adequately generated and applied?; Q2: Were the groups similar at baseline or adjusted for confounders in the analyses?; Q3: Was the allocation to the different groups adequately concealed during?; Q4: Were the animals randomly housed during the experiment?; Q5: Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?; Q6: Were animals selected at random for outcome assessment?; Q7: Was the outcome assessor blinded?; Q8: Were incomplete outcome data adequately addressed?; Q9: Are reports of the study free of selective outcome reporting?; Q10: Was the study apparently free of other problems that could result in high risk of bias?
Response codes to Q1-Q10: Y:Yes; N: No; U:Unclear.

Data Availability Statement

Data openly available in a public repository that issues datasets with DOIs.

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Author contributions

RG, CC, EP, MWV and DN have made major contributions to (i) the conception or design of the study, RG, CC and DN to (ii) the acquisition, analysis, or interpretation of the data; and RG (iii) wrote the draft of the manuscript. RG, CC, EP, MWV and DN read and approved the final manuscript.

Declaration of interest

The authors have no conflicts of interest related to the publication of this paper.