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The potential protective effects of curcumin on the diabetic ovary: Experimental and molecular approaches

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Summary. Diabetes mellitus (DM) causes numerous systemic diseases in animals and humans. This may also lead to reproductive problems among individuals of reproductive age. Detrimental effects such as apoptosis in ovarian granulosa cells, degradation of communication proteins, decreased oocyte quality, delayed meiotic maturation, and atrophy are among the increasing evidence that chronic hyperglycemia causes reproductive problems. Numerous studies have reported that the antidiabetic properties of the antioxidant curcumin may be due to its inhibition of oxidative stress, inflammation, and insulin resistance. There are also data indicating that curcumin reduces the risk of DM and its associated symptoms. This review discusses the protective or curative properties of curcumin in the treatment of DM-related problems in the ovary and seeks to elucidate potential underlying mechanisms. While the use of curcumin as a supportive/therapeutic agent has been introduced for the reduction of reproductive problems that may be caused by uncontrolled DM, more studies on this subject are needed.

Key words: Curcumin, Diabetes mellitus, Ovary, Female fertility

Introduction

Hereditary and environmental factors are implicated in developing diabetes mellitus (DM), a metabolic disorder that leads to high blood sugar levels (Herman, 2007). There are estimated to be 451 million individuals with DM worldwide. This is predicted to rise to 693 million by 2045. It is also estimated that 49.7% of all individuals with DM have not been diagnosed. Studies have also estimated that 21.3 million newborns are affected by hyperglycemia during pregnancy and that the number of patients with impaired glucose tolerance will reach 374 million (Cho et al., 2018).

DM not only raises blood sugar levels, it can also result in retinopathy, nephropathy, neuropathy, cardiovascular disease, and reproductive issues (Forbes and Cooper, 2013). The disease is spreading rapidly worldwide due to lifestyle-related factors and entails a high risk of mortality and morbidity. Therefore, research aimed at mitigating DM-associated issues is crucial to (Forbes and Cooper, 2013).

Type 1 diabetes mellitus (T1DM) is a condition that develops when certain environmental factors (bacterial, chemical, and diet-related) trigger an autoimmune response in genetically susceptible individuals. These cells are usually destroyed by antibodies developed against beta cells in the pancreas. Minimal or no endogenous insulin secretion is a hallmark of T1DM. Glucose metabolism is compromised by damaged insulin secretion or resistance in its receptors in the tissue in type 2 diabetes mellitus (T2DM), (Kharroubi, 2015).

Deleterious effects of DM on women's reproductive activities have been reported (Wu et al., 2017). Women with DM are exposed to an increased risk of irregular menstruation compared with non-DM women of similar age and often experience delayed menarche (Strotmeyer et al., 2003). Before the first use of insulin in the clinical treatment of T1DM in 1922, girls with DM were reported to rarely experience menarche, and only 2% of women with the condition achieved successful pregnancy (Livshits and Seidman, 2009). Insulin treatment causes menstrual bleeding to begin in many female diabetics but is not sufficient to eliminate menstrual irregularity. During their reproductive years, a third of women with DM experience issues such as oligomenorrhea, polymenorrhagia, and amenorrhea. This is roughly twice the prevalence of menstrual abnormalities among women without DM (Yeshaya et al., 1995). Additionally, women with DM have been observed to enter menopause earlier than other women (Snell-Bergeon et al., 2008). Patients with T1DM

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experience several reproductive issues that call for specialized diagnosis and treatment, even with advances in insulin therapy.

Although there are many theories concerning DM, the idea that DM-related problems are caused by increased free radicals represents the most logical potential mechanism from a pathophysiological and symptomatic perspective (Volpe et al., 2018). Research findings indicate that people with DM are vulnerable to oxidative stress (OS), and that elevated blood glucose levels are linked to free radical-mediated lipid peroxidation. Additionally, researchers have noted that DM lowers the activity of intracellular antioxidant enzymes (Kowluru et al., 2001).

The purpose of therapeutic research in this context is to reduce and postpone DM-related problems. The roots of the plant turmeric contain a phenolic substance known as curcumin, which is beneficial in the treatment of several chronic disease states that are linked to OS and inflammation (Soleimani et al., 2018). Curcumin has attracted considerable interest as a potential therapeutic agent in experimental DM and in the management of complications in DM patients because it effectively lowers hyperglycemia and hyperlipidemia (Zhang et al., 2013b).

In one of our previous studies, we examined how curcumin treatment affects the ovaries at various times in experimental DM animals. Fifty-six Wistar rats aged 12 weeks and weighing 250-300 g were used in that research. The study groups were designated as control (Cont), sham (Sham), diabetic (DM), and diabetic animals treated with curcumin classified as early (DC1), late (DC2), or simultaneous (DC3) curcumin-exposed groups, and a curcumin only (Cur) group. Animals in the DC1, DC2, and DC3 groups were treated with curcumin after induction of DM for seven or 21 days or simultaneously with DM induction, respectively. The study objective was to determine the effects of early, late, and simultaneous administration of curcumin on DM ovarian tissue (Tufekci and Kaplan, 2023). Qualitative evaluations of ovarian structures from that study are summarized below (Figs. 1-3).

The current review study was planned to discuss the data obtained from scientific studies on the effects of DM-related complications in the ovary, particularly considering the antioxidant properties of curcumin, its use as a potential treatment, and the underlying mechanisms.

General effects of diabetes on the ovary

A literature search reveals abundant evidence of the deleterious effects of DM on the female reproductive system in humans and animals. Examination of the reproductive cycle of experimental DM female rats shows that anovulation, hyperandrogenism, oocyte maturation, delays in the meiosis stage, and polycystic ovary syndrome (PCOS) are frequently encountered. In addition, apoptotic processes can be triggered in follicles and granulosa cells in DM rats. Oligomenorrhea, together with disorders in the estrous cycle, oocyte-granulosa communication, and follicle development, are other common DM effects on the reproductive system (Gaete et al., 2010; Codner et al., 2012). Similarly, menstrual irregularities, poor quality oocytes and numbers (due to an increased atresia rate), disorders in ovarian function, delayed menarche, and dysmenorrhea have also been reported (Solomon et al., 2002; Arrais and Dib, 2006) (Fig. 4).

Insulin can increase Kiss1/kisspeptin expression by directly influencing gonadotropin-releasing hormone (GnRH) neurons, stimulating the gonadotropic axis' secretive behavior (Salvi et al., 2006; Pralong, 2010). Suppression of Kiss1 expression in the hypothalamic tissue of female and male rats because of streptozotocin (STZ)-induced DM (Castellano et al., 2006, 2009). Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion decrease in line with decreased GnRH production in women with DM (Codner and Escobar-Morreale, 2007; Hassan et al., 2023).

Insulin can stimulate androgen secretion in theca cells. Simultaneous exposure of cells to both LH and insulin considerably increases the effect of insulin. This can be considered the principal finding that insulin functions as a common co-gonadotropin (Poretsky et al., 1992). Insulin binds to insulin and insulin-like growth factor-I (IGF-I) receptors in theca, granulosa cells, and stromal cells via tyrosine kinase signaling. This is the mechanism by which insulin exerts its effect on the ovary (Codner and Escobar-Morreale, 2007). Since insulin potentiates FSH-stimulated steroid release, it stimulates estrogen release in granulosa cells exposed to insulin and FSH (Willis et al., 1996).

It is essential to compensate for insulin resistance and hyperinsulinemia during ovarian stimulation in DM women. Previous studies have shown that insulin-resistant infertile women require greater FSH doses to induce follicle formation and exhibit lower estradiol concentrations during ovarian stimulation than women with normal insulin sensitivity (Pasquali et al., 2003; Wellons et al., 2017). Insulin is capable of stimulating the growth of preovulatory follicles, inhibiting ovarian follicle apoptosis and atresia, controlling follicle maturation, and ultimately suppressing ovarian expansion and cyst formation because of its gonadotropic impact (Kezele et al., 2002). A disorder in the secretion or activity of insulin may, therefore, adversely affect ovarian activity.

Cholesterol metabolism, the primary precursor molecule in synthesizing steroid hormones, is known to change profoundly in DM (O'Meara et al., 1990). Numerous investigations have demonstrated that ovarian steroid metabolism alterations are linked to DM (Colton et al., 2002). Estradiol and progesterone synthesis in rat granulosa cells decrease due to high glucose levels (Arrais and Dib, 2006; Chabrolle et al., 2008). Impaired hypothalamic-pituitary function has been reported in DM animals, with the response to GnRH stimulation and

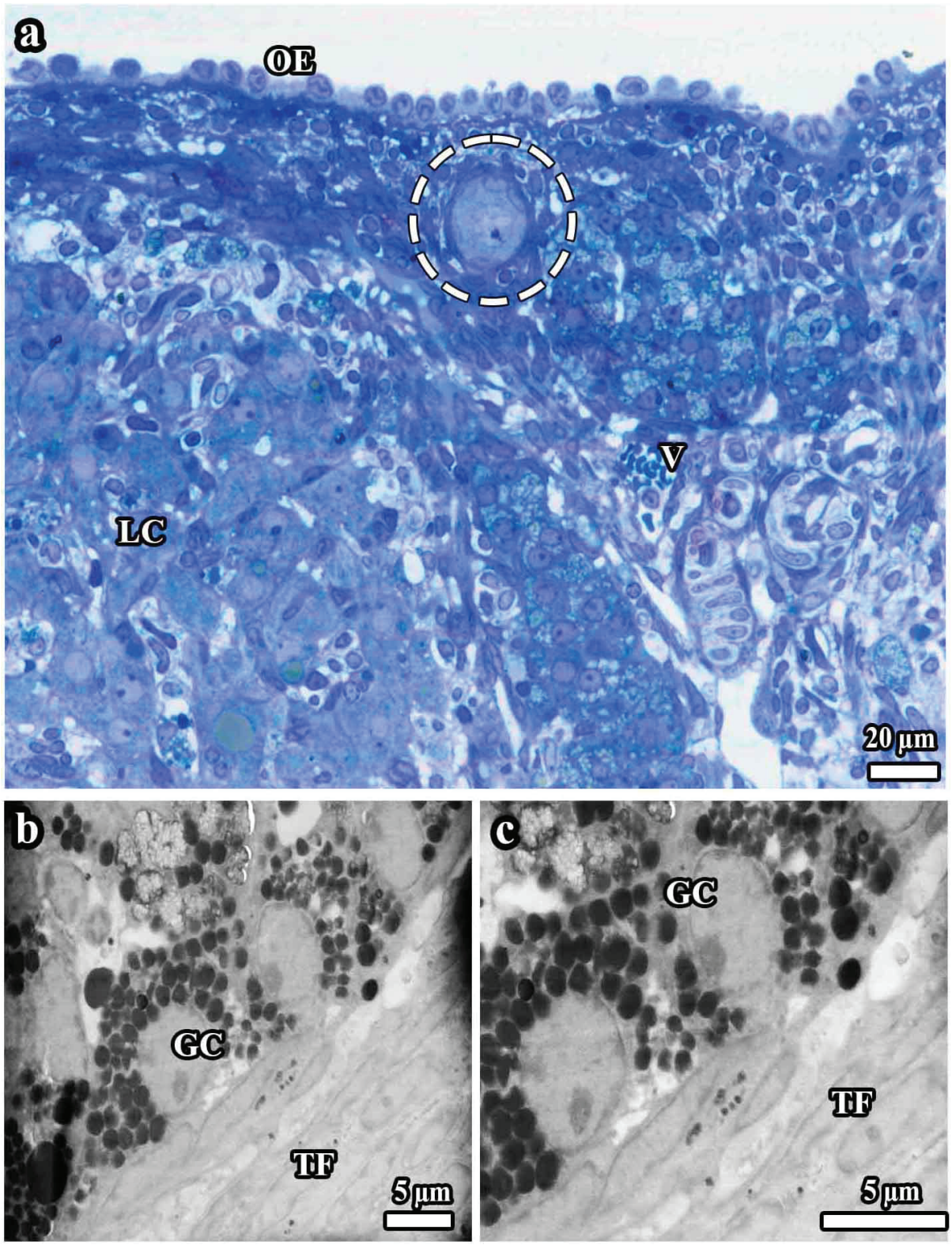

Fig. 1. a. A light microscope image of an ovary from the control group, displaying a single-layered cuboidal ovarian epithelium (OE) covering the ovarian surface with normal structural integrity. The nucleus of a primordial follicle located in the cortex, surrounded by flattened cells, is enclosed within well-defined boundaries (dashed circle). The blood vessels (V) exhibit well-preserved structures. The luteal cells (LC) of the corpus luteum are filled with secretion granules, and their structures are normal. Resin section, toluidine blue staining. **b, c.** Electron microscope images of ovaries from the control group showing granulosa cells (GC) in the wall of a follicle. The cell cytoplasm, particularly the lipid droplets, nucleus, and nucleoli, possesses well-defined boundaries. The theca folliculi (TF) also exhibit a normal structure.

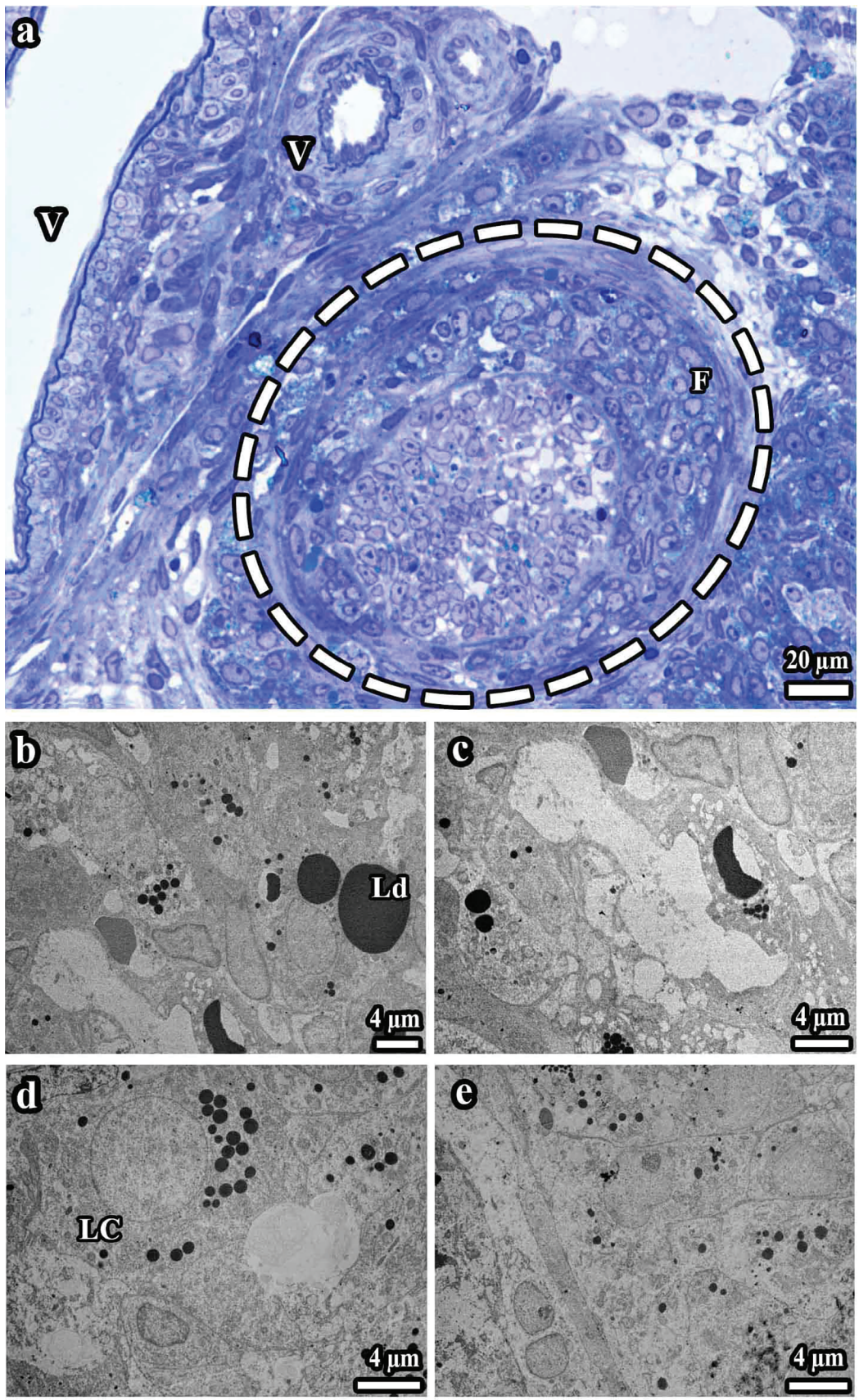

Fig. 2. a. General view of the ovarium from the Sham group. An intact ovarian structure and a remnant of a follicle (F) (dashed circle) are visible. This follicle in the cortex is organized with theca and granulosa cells, forming the corpus luteum. A longitudinal and cross-sectional view of a blood vessel located in the cortex of the ovary can be seen (V). The muscle cells and lumen of the vessel wall are clearly distinguishable. Resin section, toluidine blue staining. **b-e.** Electron microscope images of ovarian tissue from the Sham group show that the boundaries of luteal cells (LC) and lipid droplets (Ld) are normal in appearance.

both FSH and LH levels decreasing (Johnson and Sidman, 1979). Low prolactin levels have been linked to T1DM in women (Arrais and Dib, 2006). At the same time, a decrease in testosterone and androstenedione levels has been observed in women of reproductive age with kenotic diabetes due to suppression of the hypothalamic-pituitary system (Gluud et al., 1982). In addition, DM has been reported to alter the ovary's gonadotropin response, resulting in ovarian failure (Liu et al., 1972).

There is growing evidence that persistently high blood sugar levels cause detrimental effects on follicular development, resulting in reproductive problems. The main cause of DM-related complications is apoptosis resulting from damage to DNA structure, increased OS, and endoplasmic reticulum (ER) stress. Maternal DM results in dynamic changes in the ER during embryonic development and early stages of mouse oocyte maturation (Zhang et al., 2013a).

An increase in apoptotic markers, including caspase 3, Bax, and annexin V, has been shown in DM ovaries, proving that DM increases apoptosis (Lin et al., 2010). Research involving experimentally induced DM in mice has reported high concentrations of lipid droplets in granulosa cells and atretic follicles, together with atrophy and lipid loss in ovarian stromal cells. Researchers have suggested that these structural alterations may interfere with oocyte maturation (Tatewaki et al., 1989) and reduce the likelihood of pregnancy (Ratchford et al., 2008).

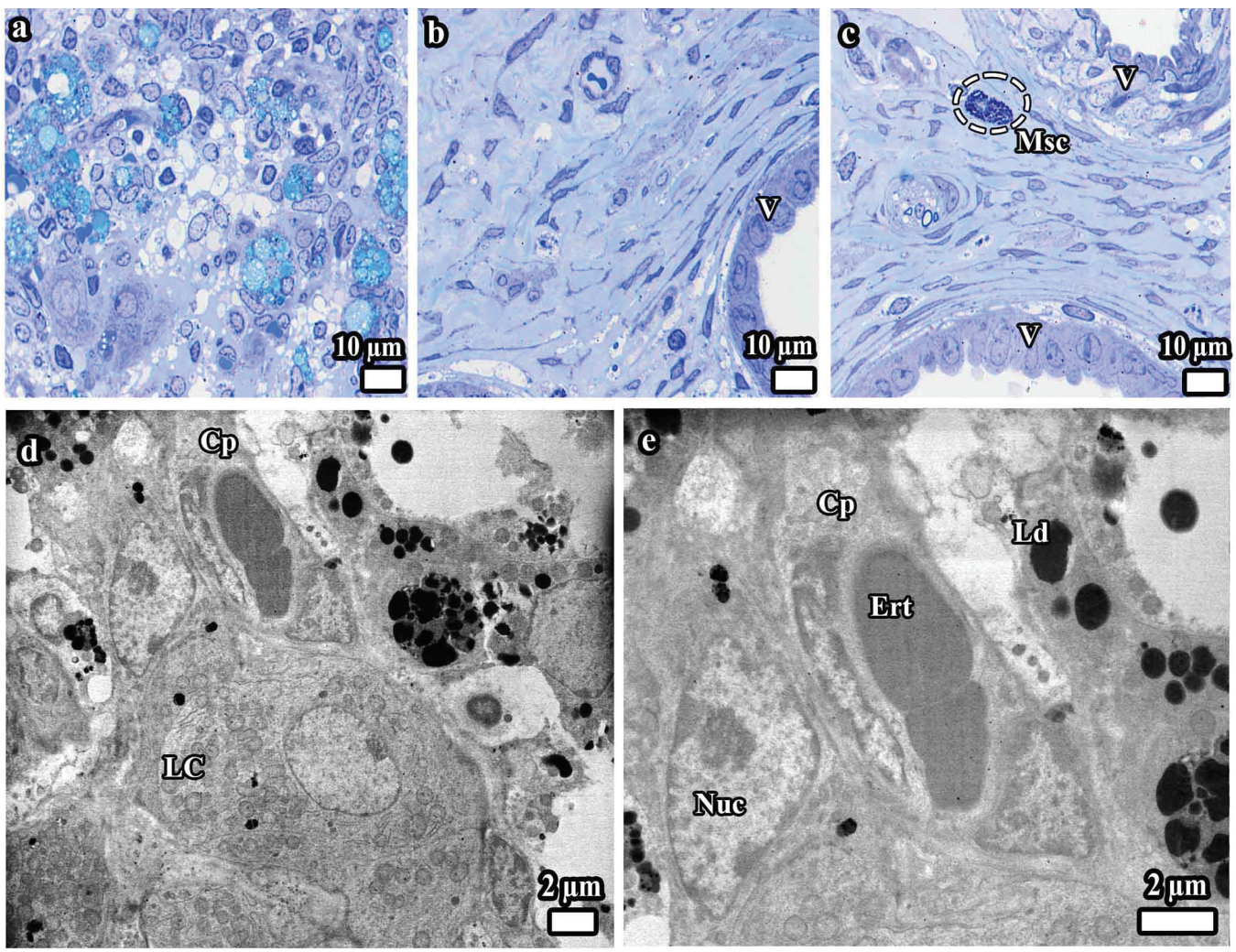

Fig. 3. a. Numerous spindle-shaped fibroblasts and oval nuclei of cells in the connective tissue are apparent in ovarian tissue from the Curcumin group. Numerous small-diameter spaces can also be seen between these cells. **b, c.** The presence of vessels in the loose connective tissue in the medulla of the organ is clearly evident. The morphology of the blood vessels is well-preserved; a mast cell (Msc) can be seen near the vessel. Resin section, toluidine blue staining. **d, e.** Luteal cells (LC) can be seen in ovarian electron microscopy images from the Curcumin group. The cytoplasm and nucleus (Nuc) of the cells in the tissue appear to exhibit normal morphology. In addition, the blood vessels (Cp) of the tissue are healthy in appearance. Ert, erythrocyte; Ld, lipid droplet.

Research into DM indicates that the effects of hyperglycemia on oocyte maturation that induce or suppress meiosis are mediated via gap junction connections (Downs, 2000). Decreased connections between oocytes and cumulus cells have been shown in cumulus-surrounded oocytes in DM animals. This finding is corroborated by another investigation, which found that diabetic cumulus cells exhibited substantially lower expression of two gap junction proteins, known as Cx43 and Cx26, compared with control cells (Ratchford et al., 2007, 2008). Reduced gap junction connections hinder the energy substrates that cumulus cells transmit to the oocyte, which lowers the quality of the oocyte and prevents it from maturing (Carabatsos et al., 2000; Ratchford et al., 2007). In another experimental DM study involving STZ, oocytes of DM mice were found to possess developmental abnormalities, decreased size, delays in meiotic maturation, decrease in gap junction proteins, and death in granulosa/cumulus cells (Chang et al., 2005).

According to another study, DM mouse oocytes exhibited reduced levels of germinal vesicle disintegration, a sign of oocyte meiotic maturity (Diamond et al., 1989). DM mice oocytes have been shown to progress to metaphase II less quickly following ovulation stimulation in comparison with controls (Colton et al., 2002). Several studies conducted after that research confirmed the findings reported therein (Kim et al., 2007; Ratchford et al., 2008). High levels of spindle fiber abnormalities, such as chromosome misalignment during meiosis, have also been detected in DM mice oocytes, and this has been reported to lead to a higher rate of aneuploidy in ovulating oocytes (Wang et al., 2009).

Cumulus-surrounded oocytes from DM mice have been shown to exhibit abnormalities in the activation of AMP-activated kinase (AMPK) activity, glutamic pyruvate transaminase, hydroxyacyl-CoA dehydrogenase, and glucose, purine, and cAMP metabolism (Ratchford et al., 2007). Impaired prostaglandin (PGE2) production has also been shown in cumulus-surrounded oocytes in rat ovaries obtained from DM models (Jawerbaum et al., 1999). Oocytes from DM animals are thought to exhibit decreased meiotic activity due to all these factors.

According to reports, DM also impairs the structural and functional properties of mitochondria, the most prevalent organelle in mammalian oocytes that influences oocyte quality and assists embryonic development and fertilization (Van Blerkom, 2004; May-Panloup et al., 2007). DM mouse oocytes possess a higher concentration of mitochondrial DNA and exhibit a greater degree of mitochondrial gene transcription than non-DM mouse oocytes. The lower ovulation rates and oocyte maturation in DM mice compared with controls have been attributed to compromised mitochondrial function (Ma et al., 2012; Wang et al., 2012).

In a study involving transmission electron microscopy, Wang et al. (2009) observed evident structural defects in the mitochondria of DM oocytes. These ultrastructural changes suggest mitochondria-dependent apoptosis in the somatic cells (Senoo-Matsuda et al., 2005). Variations in ATP concentrations may affect the development of embryos, the implantation process, and the quality of oocytes. Studies have provided evidence of decreased ATP content in cumulus-surrounded oocytes and preovulatory oocytes from DM mice (Ratchford et al., 2007). Additionally, abnormal mitochondria in the oocyte in maternal DM can be transferred to the embryo and subsequently proliferate, causing problems during embryogenesis and fetal development (Wang and Moley, 2010).

One of the most important markers of ovarian reserve is anti-Mullerian hormone (AMH), secreted from the granulosa cells of preantral and antral follicles (Feyereisen et al., 2006). Research has shown lower AMH levels in women with T1DM than non-DM women. Similarly, research has reported relatively low ovarian reserve in DM rats (Erbas et al., 2014; Nayki et al., 2016). Significantly lower thyroid stimulating hormone (TSH) levels have also been reported in amenorrheic women compared with non-DM women with normal menstrual cycles (Arrais and Dib, 2006). According to research, 30-40% of women with T1DM also have PCOS, a condition characterized by enlarged ovaries and anomalies in ovarian morphology (Codner and Escobar-Morreale, 2007).

Insulin receptors are found in various tissue components in the ovary, including the granulosa, stromal, and thecal compartments. However, hyperinsulinemia reduces the expression of insulin receptors in target tissues (Nandi et al., 2004). While *in vivo* hyperinsulinemia is linked to decreased insulin binding in the ovary, high insulin doses *in vitro* eliminate specific insulin binding in stromal ovarian tissue. Insulin resistance, therefore, raises reactive oxygen species (ROS) levels in oocytes, causing cell dysfunction (Ou et al., 2012). Insulin also increases the growth and production of ovarian cysts induced by human chorionic gonadotropin in experimental animals (Benito, 2011).

Normal follicular development, ovulation, and corpus luteum development depend on angiogenesis (Abulafia and Sherer, 2000). Dominant and developing follicles possess greater vascularity, which increases the amount of nutrients that mature follicles receive. In addition, vascular support is highly important for functional and phenotypic changes in granular cells. (Ramakrishnan et al., 2005). Inhibiting the HIF1A-VEGF pathway suppresses ovarian angiogenesis, one of the potential molecular processes behind aberrant ovarian functioning caused by DM. Researchers have also reported that thickenings occur in the basement membranes of the blood vessels in the ovaries in a DM model induced using alloxan in rabbits, and that these vascular changes may adversely affect ovarian function (Liebhart and Szamborski, 1975) (Fig. 4).

Numerous studies have indicated that OS plays a crucial role in the outcomes and development of DM.

DM patients have higher levels of serum malondialdehyde (MDA) and erythrocyte membrane lipid peroxidation (Kumawat et al., 2013; Erbas et al., 2014). In contrast, plasma levels of SOD, CAT, and glutathione peroxidase (GPX) decrease in DM patients (Indran et al., 2004). One important intracellular antioxidant is glutathione (GSH). This and other thiols protect against oxidative damage and maintain cellular redox equilibrium. GSH levels have been observed to decrease in individuals with DM (Erbas et al., 2014).

Curcumin

The hydrophobic polyphenol curcumin obtained from the rhizomes of *Curcuma longa* (Turmeric) is an important plant in the field of traditional medicine (Mirzaei et al., 2016). Curcuminoid has a 2-9% turmeric content (Priyadarsini, 2014). Curcumin is recognized and used in different forms various purposes in numerous countries (Hewlings and Kalman, 2017).

Considerable research has been conducted on curcumin, including human and animal studies (Tülüce et al., 2024). The conclusion is that curcumin is an agent with a wide range of pharmacological and biological properties. The most important of these are anti-inflammatory, antimicrobial, anticarcinogenic, antihyperglycemic, and neuroprotective activities (Forbes and Cooper, 2013; Momtazi et al., 2016). Additionally, this molecule exhibits a range of therapeutic actions against several illnesses, including non-alcoholic cancer, fatty liver disease, anxiety, metabolic syndrome, osteoarthritis, and ulcers (Sahebkar, 2014; Momtazi and Sahebkar, 2016). Curcumin is used even at high doses because it is a

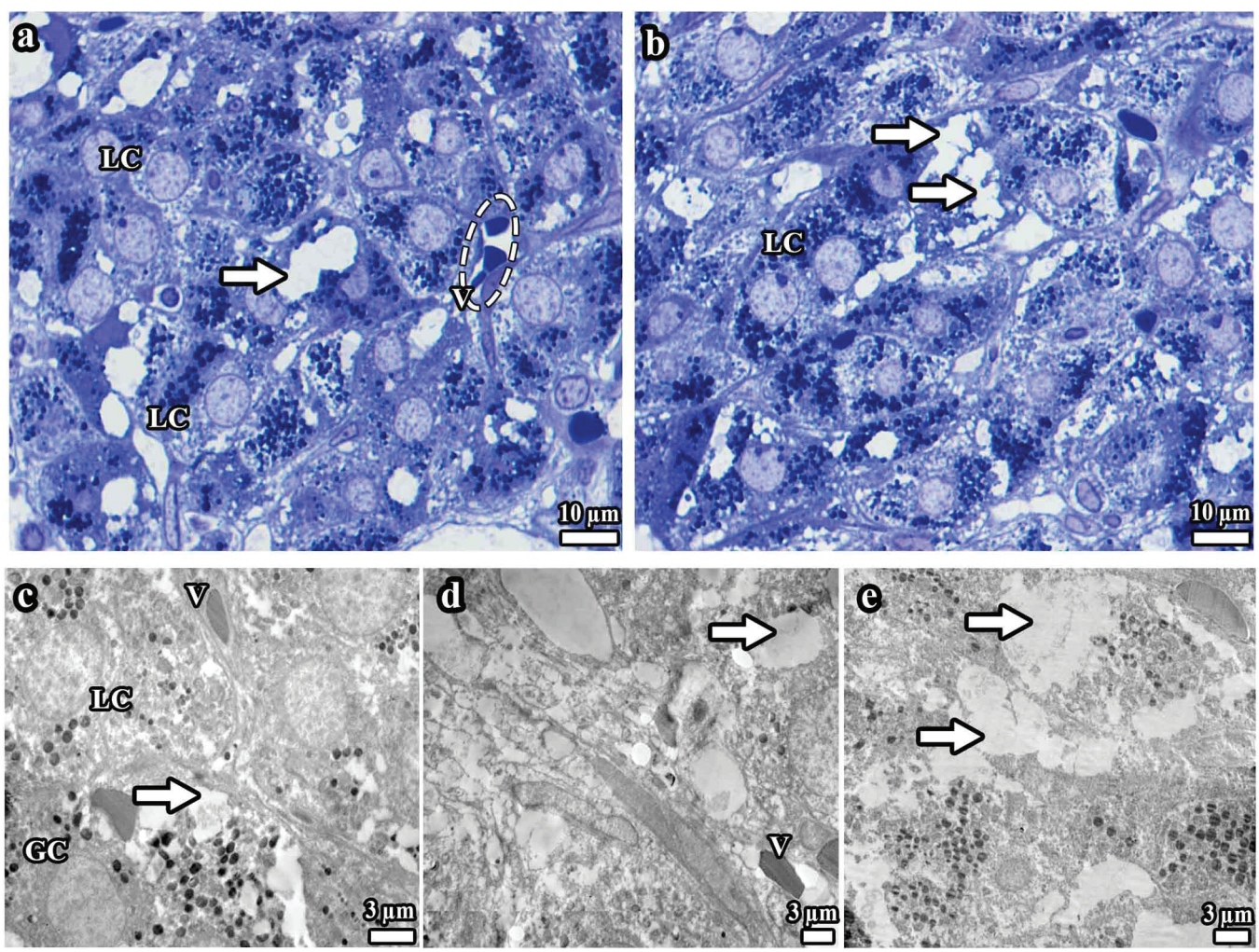

Fig. 4. Light microscope images of the DM ovary. **a, b.** The general structure of the corpus luteum in the DM group after ovulation. A noteworthy increase in spaces can be seen between both luteal cells and capillaries (arrow). Blood cells can be seen adhering to the wall of the capillary (dashed circle). Resin section, toluidine blue staining. **c-e.** Electron microscope images of ovaries from the DM group reveal an increase in spaces between granulosa cells (GC) and luteal cells (arrows), showing disrupted cell integrity. Thinning of blood vessel walls (V) is also noticeable.

biologically safe agent, according to several human and animal studies (Lao et al., 2006).

Is curcumin a potent therapeutic option for diabetes?

Therapeutic agents targeting glycemic management have recently emerged in the prevention and treatment of DM, a condition that is reaching pandemic proportions (Pivari et al., 2019). In this context, studies have discussed using medicinal plants to treat and prevent DM (Suksomboon et al., 2011; Demmers et al., 2017). Curcumin (*Curcuma longa*) is one of the most popular of these (Pivari et al., 2019). Since it has various pharmacological effects and is safe at all doses, the therapeutic use of curcumin is increasing (Kunnumakkara et al., 2017; Pivari et al., 2019). These effects are closely related to the fact that curcumin triggers different dose-dependent molecular mechanisms (Pivari et al., 2019). OS at the cellular level due to T2DM plays a significant role in the pathogenesis of various diseases. In addition to oxidative stress, apoptosis and intracellular calcium levels also play important roles in the pathophysiology of diabetic ovary. Hyperglycemia-induced reactive oxygen species (ROS) leads to excessive production of ROS, disrupting the redox balance and causing cellular damage. This oxidative environment activates apoptotic pathways, leading to granulosa cell apoptosis and follicular atresia, which compromises ovarian function. In addition, hyperglycemia alters intracellular calcium homeostasis, and high calcium levels contribute to mitochondrial dysfunction and further increase ROS and apoptosis. These interconnected mechanisms highlight the fundamental role of oxidative stress and calcium dysregulation in regulating ovarian dysfunction in diabetes (Tola et al., 2013). Due to its antioxidant properties, curcumin reduces lipid peroxidation by keeping antioxidant enzyme levels at normal values (Jiménez-Flores et al., 2014). Inflammation is a common mechanism in T2DM complications. Some studies have shown that curcumin leads to a decrease in inflammatory markers such as tumor necrosis factor-α (TNF-α) in serum (Jain et al., 2009; Zheng et al., 2018). Curcumin has also been reported to perform a regulatory function in lipid metabolism in the DM liver (Pivari et al., 2019). It also regulates transcription factors in hepatic lipogenesis gene expression (Seo et al., 2008) (Fig. 5).

Curcumin reduces inflammation by regulating and inhibiting several different biological processes. It exerts its effect on inflammation through the regulation and inhibition of various molecular pathways. In this context, it has been reported to suppress the activation of nuclear factor-kappa B (NF-κB) and the cyclo-oxygenase-2 (COX-2) enzyme (Sivani et al., 2022). Studies have also suggested that curcumin reduces plasma levels of interleukin-6 (IL-6), TNF-α, and monocyte chemotactic protein-1 during DM treatment (Jain et al., 2009) (Fig. 6).

The primary characteristic of the curcumin molecule that makes it a therapeutic option for patients with DM is its multi-targeting ability (Quispe et al., 2022). Despite its versatile activity, curcumin's pharmacokinetic qualities, such as low absorption, chemical stability, and bioavailability, limit its therapeutic application. The therapeutic effectiveness of curcumin depends on the dose and chemical options enhanced by different chemical modifications. Modifications of curcumin integrated into nanoparticles may enhance its therapeutic efficacy. Additionally, potential side effects may increase when high doses of curcumin are used (Pivari et al., 2019; Oliveira et al., 2020). The authors of an experimental study reported that curcumin and metformin treatment in DM rats led to a synergistic effect against dyslipidemia and OS (Roxo et al., 2019). In a further investigation, curcumin-loaded silver nanoparticles applied to eliminate the restrictive properties of curcumin yielded an improvement by enhancing the effect of metformin (Hassan et al., 2023). Curcumin-loaded nanoparticles stimulate insulin sensitivity and produce an anti-glycemic effect (Saratale et al., 2018; Das et al., 2019). Inflammatory mediators such as TNF-α are the main target for demonstrating the antidiabetic effect of curcumin since they play a role in inducing various DM complications. Curcuminoids are

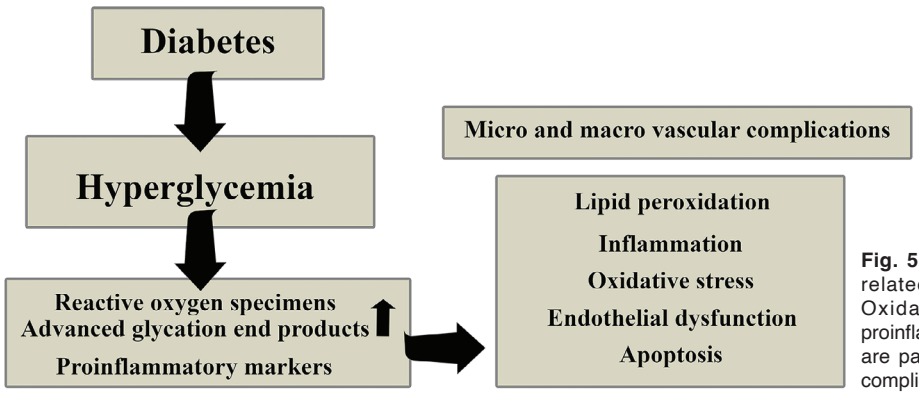

Fig. 5. Hyperglycemia caused by DM triggers DM-related macro- and microvascular complications. Oxidative stress, apoptosis, and changes in proinflammatory markers resulting from hyperglycemia are particularly important in the emergence of these complications. Modified from (Marton et al., 2021).

very effective and safe in reducing c-reactive protein (CRP) levels. Significant results have been achieved in treating DM because curcumin targets inflammatory mediators (Hussain et al., 2022). Studies have shown that curcumin exerts a significant protective and therapeutic effect on DM because it has multiple molecular targets. The effectiveness of curcumin on possible mechanisms in DM may vary depending on the dose and method of administration.

The healing effect of curcumin in the diabetic ovarium

Curcumin exhibits phytoestrogen effects and can, therefore, interact with the endocrine system and be used to treat disorders, thereby affecting the hypothalamic-pituitary-ovarian (HPO) axis (Bachmeier et al., 2010; Sirotkin and Harrath, 2014). Its administration has been found to normalize decreased progesterone and estradiol levels in PCOS, a condition closely related to T2DM (Reddy et al., 2016a), and also to reduce the frequency of pyknotic granulosa cells (Reddy et al., 2016a). Curcumin acts through anti-angiogenic and anti-tumorigenic pathways in ovarian cancer types and is mediated by VEGF, NF-κB, IL-6, and matrix metalloproteinases (Lin et al., 2007). Investigation of the beneficial effects of curcumin on fertility has shown that it changes how the ovaries respond to gonadotropin and how ovarian hormones are released, raising oocyte growth and production in rabbits and the number of offspring produced by them. Curcumin has also been shown to exhibit pro-necrotic, pro-apoptotic, and antiproliferative effects in response to stress caused by a decrease in FSH receptors on mouse ovarian cells (Tiwari-Pandey and Ram Sairam, 2009).

Curcumin protects the ovaries during folliculogenesis and oogenesis (Figs. 7-9). Research into the effect of curcumin on ovarian follicles observed that the width and numbers of primary, secondary, and tertiary follicles increased. In addition, researchers have suggested that curcumin exerts an inhibitory effect against the stress effects occurring in the zona pellucida around the oocyte and thus reduces the nuclear maturation of mouse oocytes (Tiwari-Pandey and Ram Sairam, 2009; Voznesens'ka et al., 2010).

An experimental study reported that high doses of curcumin resulted in less testosterone and more progesterone secretion in rabbit ovaries (Sirotkin, 2014). Another study found that curcumin increased LH in the plasma of rats exposed to γ-irradiation (Inano et al., 2000). Another study suggested that LH affects leptin release and regulates ovarian function in rabbits and showed that LH mediates the action of curcumin on the ovary (Sirotkin et al., 2017). Additionally, LH has been found to suppress ovarian leptin release in control animals but to promote it in curcumin-fed groups. (Sirotkin et al., 2017).

Research has demonstrated that OS reduces the number of oocytes and follicles (Miyamoto et al., 2010). In a study evaluating the effects of curcumin on reproduction activity, insulin, and glucose intolerance in mothers with DM, 100 mg/kg of curcumin was reported to decrease thiobarbituric acid reactive substance expression while increasing the expression of some antioxidant enzymes (SOD, CAT, and GSH). Researchers have shown that curcumin can modify reproductive processes by reducing OS and represents a potential option in the treatment of DM during pregnancy (Lu et al., 2019). An experimental study reported increased MDA levels in a DM group, while CAT and SOD activities decreased. The authors also reported that these antioxidant enzyme activities were at normal levels in DM rats given 80 mg/kg of curcumin for seven weeks (Hussein and Abu-Zinada, 2010). In

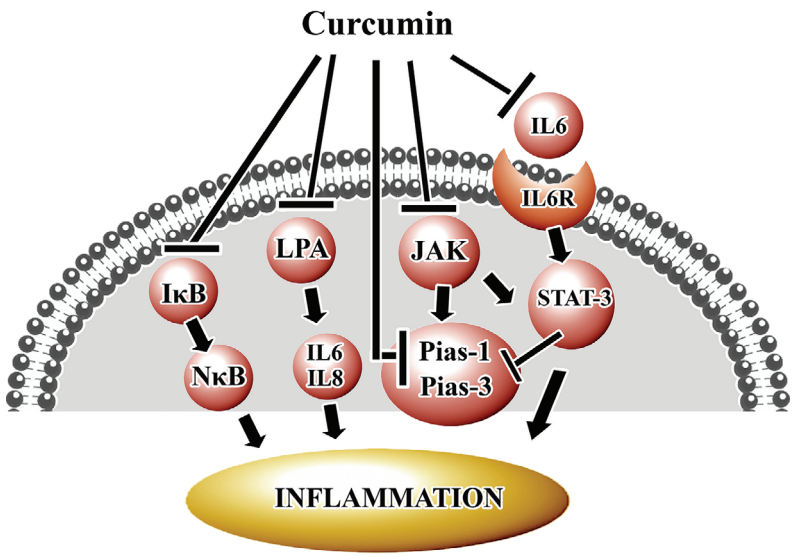

Fig. 6. Possible gene mechanisms underlying the anti-inflammatory properties of curcumin. Suppression of lysophosphatidic acid (LPA), Janus kinase (JAK), κB (IκB), and IL-6 inhibitors is the mechanism involved in the anti-inflammatory effect of curcumin. IL-8: Interleukin 8, NF-κB: Nuclear factor kappa, Pias-1, -3: Protein inhibitor of activation, STAT 3: Signal transducer and activator of transcription. Modified from (Sivani et al., 2022)].

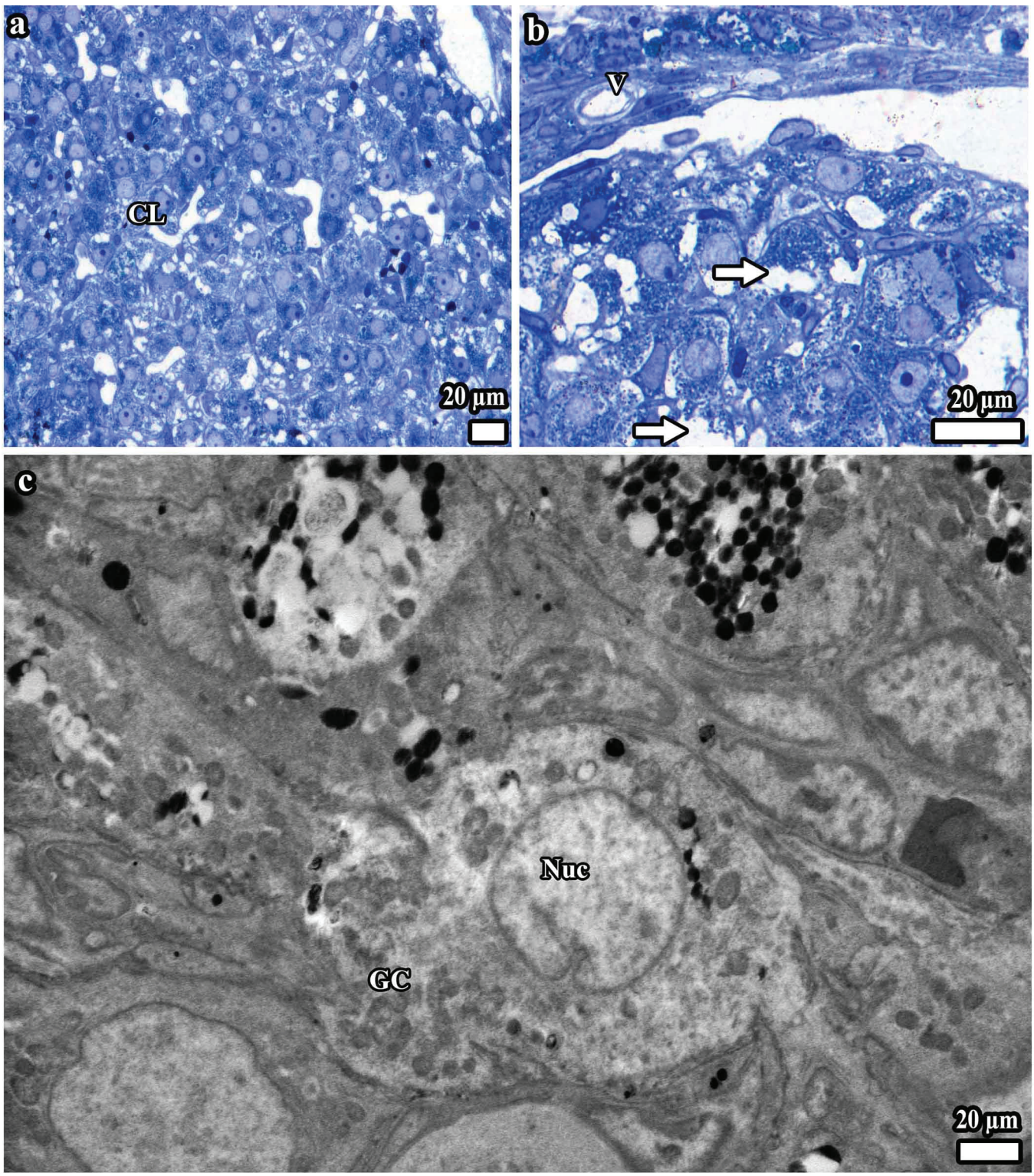

Fig. 7. The protective effect of curcumin on DM ovaries in light and electron microscope images. **a, b.** Light microscope images obtained from semi-thin sections of the corpus luteum (CL) part of the ovarian tissue from the DC1 group. Although the luteal cells of the CL can be easily distinguished, the spaces between the cells are also noticeable (arrow). The blood vessel (v) has a well-organized endothelium with open lumens. Resin section, toluidine staining. **c.** A granulosa cell (GC) containing lipid droplets can be seen in the electron microscope image as a well-preserved cell structure with no spacing between them. The integrity of the nuclear envelope surrounding the nucleus (Nuc) is well-maintained, with a distinct boundary. The distances between granulosa cells are typical.

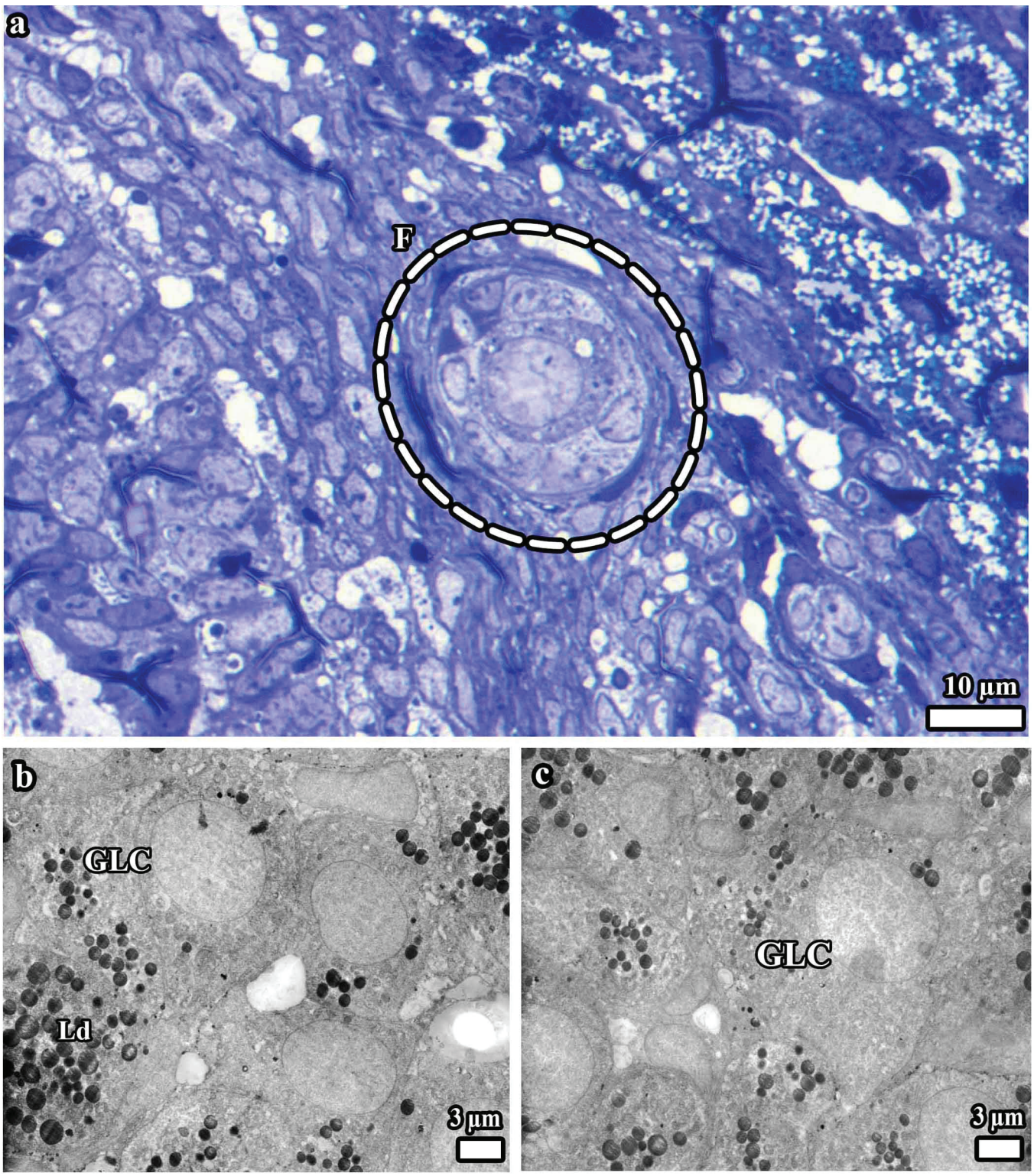

Fig. 8. Light and electron microscope images showing curcumin's healing and protective effects in the ovary against DM in the DC2 group. **a.** A developing follicle (F) structure (dashed circle) can be seen in an ovarian cortex from this group. The follicle structure is well-preserved, with a noticeable and distinct nuclear boundary and follicular cells. Resin section, toluidine blue staining. **b, c.** The ovary's granulosa lutein cells (GLC) can be seen in the electron microscope images. The cytoplasm, nuclei, and the gaps between the cells all appear normal. The boundaries of the lipid granules (Ld) in the cells are clear, and the structure of the membranes surrounding the organelles is healthy.

conclusion, the present research shows that curcumin enhances cellular antioxidant defense and protects against lipid peroxidation thanks to its antioxidant properties. Its antioxidant activity helps prevent STZ-triggered oxidative damage in DM.

Curcumin is thought to stimulate numerous mechanisms in the preventive or curative treatment of DM. One of the leading mechanisms involves the increase in levels of intracellular antioxidants such as CAT and GPX in DM. The antioxidant effect of curcumin that occurs in this way aims to prevent ovarian toxicity. Animals with experimentally induced PCOS have been shown to possess lower endogenous antioxidant levels and higher OS indicators in their ovaries. The significant decrease in CAT, GSH, and SOD activity in animals with PCOS was attributed to curcumin therapy (Reddy et al., 2016b). Research has suggested that curcumin plays a protective role by inhibiting DM-induced OS (Suckow and Suckow, 2006), and it is thought that these effects can be mediated through the suppression of superoxide anion free radicals and ROS (Sikora et al., 2010). Although

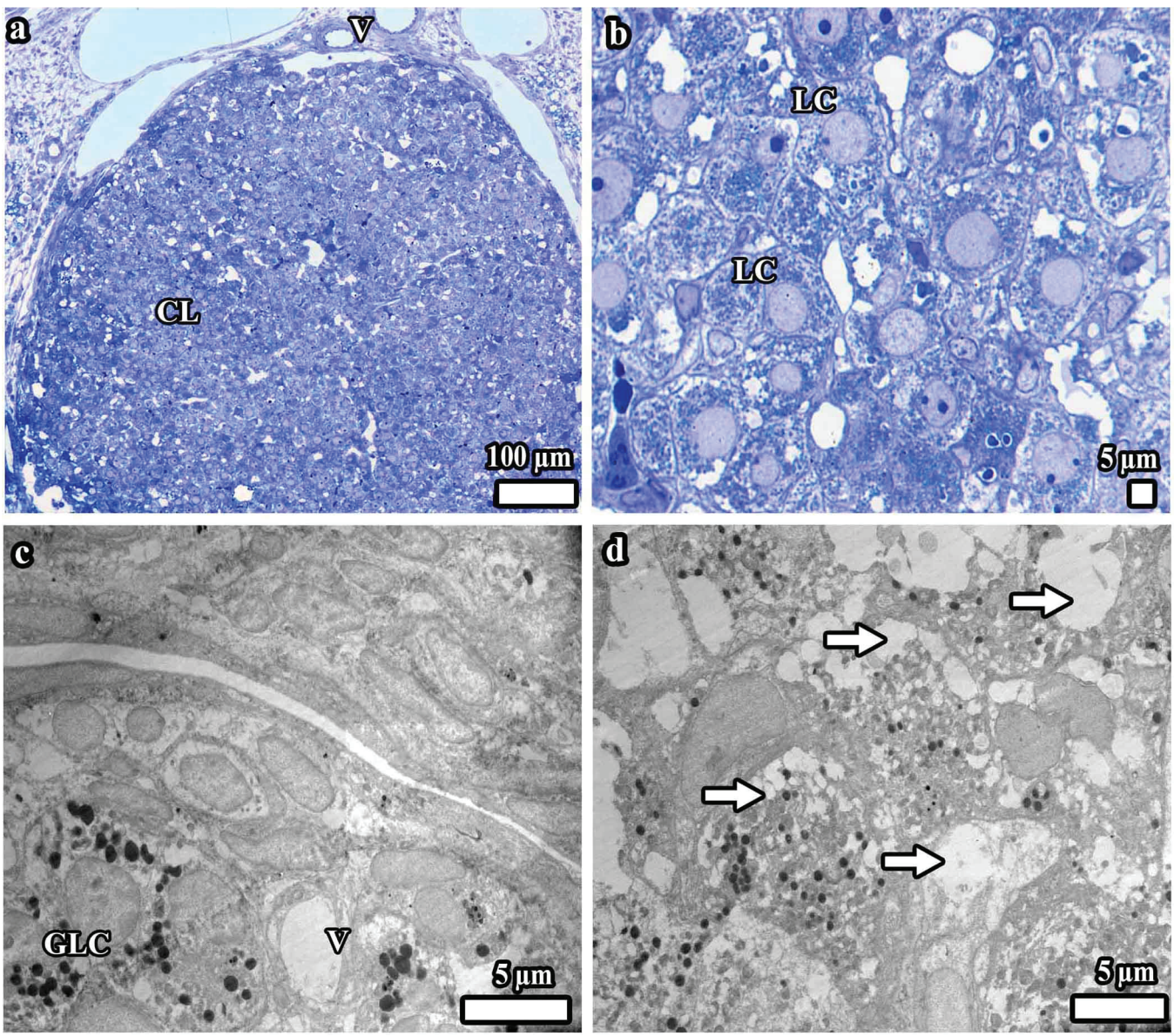

Fig. 9. a. A general image of the corpus luteum (CL) formed post-ovulation in ovaries from the DC3 group. **b.** Luteal cells and capillaries remain intact; however, an increase in spaces between the cells is noticeable. Resin section, toluidine blue staining. **c, d.** In the electron microscope image, granulosa lutein cells (GLC) containing many lipid droplets are observed. The spaces between the cells (arrow) are markedly widened. V, vessel; LC, luteal cell.

curcumin exhibits pro-apoptotic effects in malignant cells, it exerts protective effects on reproductive organ activity because of its antioxidant and anti-apoptotic properties (Mohebbati et al., 2017). Inano et al. (2000) demonstrated the anticancer properties of curcumin and suggested that it suppresses cell proliferation and promotes epithelial cancer cell apoptosis (Terlikowska et al., 2014). Researchers found that curcumin prevents apoptosis and OS in granulosa cells, leading to a significant increase in the number of primordial follicles in a group taking the supplement compared with a group experiencing premature ovarian failure (Yan et al., 2018). Another study investigated the proliferative and antiapoptotic effects of curcumin on mouse ovarian follicles exposed to ionizing radiation. According to that research, ovarian follicles exposed to radiation do not undergo follicular atresia when mice are given curcumin (100 mg/kg) for 10 days (Aktas et al., 2012).

Possible apoptotic and autophagic pathways used by curcumin in ovarian cells

Regulation of impaired OS and inflammation can be considered an important therapeutic target in recovery from PCOS. Curcumin represents a powerful option in the treatment of PCOS by reducing levels of mediators, such as TNF-α and IL-6, and increasing those of antioxidant enzymes, such as SOD. In addition, experimental evidence has indicated that curcumin improves hormonal and metabolic irregularities in PCOS. High-dose applications of curcumin and modulations thereof aimed at increasing bioavailability have become increasingly important in treating PCOS in recent years (Shojaei-Zarghani et al., 2022). Curcumin's primary target mechanism in treating hormonal disorders in PCOS is the PI3K/Akt and Nrf2/ HO^{-1} pathway, which suppresses apoptosis in granulosa cells, OS, and inflammation. Additionally, curcumin reduces ovarian androgen receptor levels (Shi et al., 2009; Choi et al., 2010; Yan et al., 2018; Shojaei-Zarghani et al., 2022).

One of the main mechanisms involved in the therapeutic efficacy of curcumin in PCOS is the upregulation of PPAR-γ, and this factor plays a vital role in regulating energy metabolism, insulin sensitivity, and lipid metabolism. Follicle development, enhanced granulosa cell steroid hormone synthesis, and regulation of oocyte maturation are all achieved by the activation of this factor (Vitti et al., 2016; Shojaei-Zarghani et al., 2022).

Autophagic and apoptotic processes play a crucial function in the cell in case of stress caused by toxicity. Activated by the apoptotic process, autophagy is a mechanism that protects the cell exposed to stress against that stress (Lin et al., 2022). Several studies examining curcumin activity in apoptotic and autophagic processes have reported results, including cytotoxic effects (Bielak-Zmijewska et al., 2010; Chen et al., 2010; Huang et al., 2013). Curcumin upregulates key proteins of apoptosis and autophagy processes, such as caspase-3 and beclin-1, in granulosa cells (Lin et al., 2018). Cytotoxicity caused by high doses of curcumin may lead to various side effects in the female reproductive system (Moreira-Pinto et al., 2020). Regarding the proteins targeted by curcumin, it exhibits various effects on potential apoptotic and autophagic mechanisms. Curcumin activates the apoptotic process in cancer cells by stimulating the mitogen-activated protein kinase (MAPK) cascade (Mehta et al., 2018). It also activates autophagy and inhibits the apoptotic process by activating the ERK1/2 signaling pathway in chondrocyte cells (Li et al., 2017). Curcumin also produces anti-apoptotic and pro-apoptotic effects in the cell, depending on the dose (Lin et al., 2022).

In the autophagic process, cytoplasmic proteins and organelles are taken up into vesicles and combined with lysosomes to form autophagic lysosomes. Autophagy resolves intracellular dysfunction by breaking down non-essential components. Autophagic reactions that occur during cellular stress can cause cell damage as they also affect normal components. Under conditions of OS, reactive oxygen radicals accumulate in the ovary and induce excessive autophagy and apoptosis, because of which low-quality oocytes are formed (Duan et al., 2024). One of the primary mechanisms controlling autophagy and ovarian function is the mTOR/AMPK pathway (Liu et al., 2020; Kumariya et al., 2021; Duan et al., 2024). Curcumin has been reported to inhibit apoptosis and excessive autophagy in the ovary. Research has suggested that curcumin protects granulosa cells exposed to OS from apoptosis by regulating autophagy. It has also been suggested that curcumin activates AMPK and inhibits mTOR when regulating the autophagic process (Duan et al., 2024). The dose-related effects of curcumin, as well as its bioavailability, solubility, and stability, should be considered in the context of such regulation. When treating the female reproductive system with curcumin, this antioxidant agent needs to be encapsulated with lipid-based carriers, since high doses may be required to achieve optimal results. Previous studies have provided evidence that curcumin exhibits a protective effect on granular cells when applied at low doses and causes granular cell damage at high doses (Moballegh Nasery et al., 2020; Moreira-Pinto et al., 2020).

Curcumin induces the apoptotic process and suppresses growth in human ovarian cancer. According to reports, curcumin leads to increased *p53* gene expression, which is both an apoptosis-inducer and tumor-suppressor (Mohebbati et al., 2017). Cancer cells tend to escape from apoptotic processes, and apoptosis is closely related to tumor formation and metastasis. Curcumin administration reduces Bcl-2 expression and stimulates the MAPK pathway against ovarian cancer. Apoptotic processes are thus induced in cancer cells. The administration of curcumin together with Apo2L/TRAIL, a tumor necrosis factor-related apoptosis-inducing ligand, prevents resistance to chemotherapy drugs and induces apoptosis (Liu et al.,

2023).

In cases of physiological and pathological problems, ER stress occurs with the accumulation of misfolded and unfolded proteins in the ER lumen. Cell death is activated if ER stress cannot be repaired (Liu et al., 2023). Regarding the pathogenesis of PCOS, apoptosis occurs in granulosa cells due to ER stress. Curcumin protects granulosa cells from apoptosis in PCOS pathogenesis by activation of the phosphatidylinositol 3-kinase (PI3K/AKT) pathway and inhibition of the inositol-requiring transmembrane kinase endoribonuclease-1α/X-box binding protein 1 (IRE1α-XBP1) pathway associated with ER stress (Zhang et al., 2022). The PI3K/AKT cascade, a cellular regulator of events, such as differentiation, apoptosis, proliferation, and cellular homeostasis, also has a function in the apoptotic process in ovarian granulosa cells (Zheng et al., 2022) (Fig. 10). Due to curcumin's antioxidant and anti-inflammatory capacity, its reducing effect on TNF-α, IL-6, and CRP concentrations improves the morphology that is impaired by PCOS (Saifi et al., 2022).

However, curcumin reduces inflammation by inducing apoptosis to improve glucose homeostasis in damaged pancreatic tissue (Ganugula et al., 2017). Additionally, an *in vitro* study suggested that curcumin reduces the viability of granulosa cells by inducing apoptosis and activating autophagic pathways. The dose-dependent effects of curcumin on the female reproductive organs should, therefore, not be ignored when using curcumin for therapeutic purposes (Lin et al., 2022; Saifi et al., 2022).

The pro-apoptotic, anti-apoptotic, and autophagic effects of curcumin in different doses and application methods need to be investigated to eliminate these side effects. One of the disadvantages of curcumin treatment is that 40% of it is excreted in stool, a phenomenon closely related to the rapid metabolism and absorption of curcumin. Different application methods, such as using nanoparticles and liposome encapsulation in curcumin treatment, can, therefore, be employed to enhance its bioavailability. Additionally, encapsulation of this agent with liposome inhibits cancer cells by inducing apoptosis (Kamal et al., 2021).

New insights into the effectiveness of curcumin in the diabetic ovary

Female reproductive abnormalities, especially PCOS, are frequently seen in patients with T1DM. Since T1DM also occurs in childhood and adolescence, disorders in the reproductive system also develop at early ages. Although T2DM has a shorter disease duration than T1DM, the risk of reproductive disorders is similar (Thong et al., 2020). PCOS, which is generally seen in women of reproductive age and has multisystemic effects, causes insulin resistance, pancreatic beta-cell dysfunction, and hyperinsulinemia. It is, therefore, treated as a disease that leads to DM (Agrawal et al., 2023). PCOS is an endocrine condition that occurs in many women. Insulin resistance and irregular menstrual cycles are associated with this syndrome. The risk of T2DM may also be higher in women with PCOS (Zehravi et al., 2021). Although there is known to be a strong association between PCOS and T2DM, the mechanisms involved in dysglycemia in PCOS have not yet been fully elucidated (Livadas et al., 2022).

A decrease in insulin sensitivity and an increase in the incidence of T2DM have been determined in premenopausal women in comparison with men in the same period of life. The abnormal glucose homeostasis observed in the menopausal period is thought to be related to the decrease in 17β-estradiol levels in women. Estrogen deficiency or disorders in estrogen signaling are closely related to insulin resistance. Estrogen, which performs a crucial function in reproductive development, can be regulated by different gene groups (Yan et al., 2019). 17β-estradiol is regulated by hepatic FoxO1 gene-

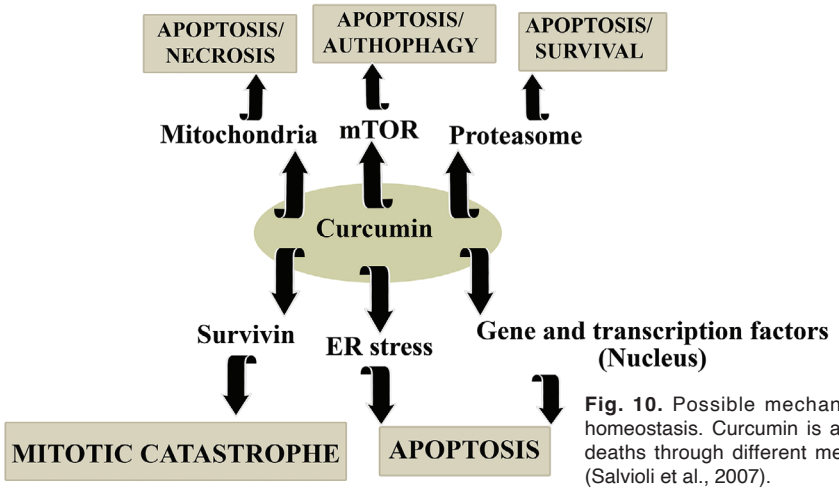

Fig. 10. Possible mechanisms involved in the effect of curcumin on cellular homeostasis. Curcumin is a multi-target therapeutic agent that causes various cell deaths through different mechanisms to maintain cell homeostasis. Modified from (Salvioli et al., 2007).

mediated gluconeogenesis. Additionally, 17β-estradiol reduces body weight in ovariectomized females, which occurs independently of the FoxO1 gene (Xu et al., 2011; Yan et al., 2019).

Tüfekci and Kaplan (2023) investigated how DM affects ovarian morphology and provided evidence that the condition lowers the volume and number of follicles (Figs. 7-9) (Tufekci and Kaplan, 2023). According to a study on the impact of maternal DM, female children born to DM mothers have fewer main and preantral follicles in their ovaries. At the same time, the diameters of these follicles decreased (Khaksar et al., 2013). Pregnancy increases mortality in DM women and also the risk of congenital anomaly development. Additionally, the risk of T2DM and obesity increases in offspring exposed to DM during the prenatal period. Gestational DM, defined as glucose intolerance, is a metabolic disorder frequently encountered in patients with PCOS (Choudhury and Devi Rajeswari, 2021). Aktun et al. reported that hyperinsulinemia and insulin resistance may be considered the underlying mechanisms of PCOS (Aktun et al., 2016). Hyperinsulinemia and insulin resistance resulting from T1DM and T2DM lead to functional impairment in the ovary. In T2DM, granulosa cells are stimulated due to hyperinsulinemia, and the number of small follicles increase. This increases the prevalence of PCOS due to diabetes (Thong et al., 2020; Choudhury and Devi Rajeswari, 2021). In addition, hyperinsulinemia and hyperandrogenism induce dysregulation of growth hormones and premature granulosa cell luteinization. Irregularities in growth hormones also disrupt oocytes at the cellular level (Choudhury and Devi Rajeswari, 2021).

The pathogenesis of polycystic ovary and T2DM appear to be similar; for this reason, agents that involve the same mechanisms are used for treating the two conditions. Recent studies have focused on the intestinal microbiota. These approaches aimed at improving or protecting the intestinal microbiota may be employed effectively in the treatment of cases in which PCOS and diabetes are co-present (Duan et al., 2021). Various mechanisms related to insulin resistance are proposed as underlying gonadal steroid disorders in PCOS. These include a variety of genetic mechanisms, and insulin-resistance disorders are frequently regarded as specific genetic abnormalities. Decreased insulin activity is associated with abnormalities in the autophosphorylation of the insulin receptor substrate and insulin receptors during insulin signaling (Bloomgarden, 2003). The development of insulin receptors in the pituitary, brain, ovary, and uterus can be considered evidence for the significance of insulin activity in reproductive system diseases. Insulin is known to stimulate follicular development via insulin receptors on granulosa cells.

Insulin also binds to receptors in the ovary, activating the tyrosine kinase signaling pathway and ensuring androgen secretion through taka cells (Codner et al., 2012). Anovulation and hyperandrogenism are intimately associated with hyperinsulinemia and insulin resistance. PCOS can also trigger the risk of T2DM. Therapeutic targets involving diabetic mechanisms should, therefore, be investigated when treating polycystic ovaries (Carreau and Baillargeon, 2015).

Conclusions

Recent studies have confirmed that the antioxidant curcumin is highly important in the prevention and treatment of diabetes and related diseases. Due to its antioxidant properties, curcumin can change how ovarian hormones are released, and how the ovaries react to gonadotropin. It can also exert cytoprotective effects on the ovary. This review article discusses possible mechanisms and the various effects of diabetes and curcumin on the structure of the ovary and the components thereof. Limitations of this review include the lack of data from long-term studies, insufficient information about the safety of different doses of curcumin, and insufficient data due to a lack of studies involving pregnant women. In light of the literature, it can be concluded that curcumin may potentially play a cytoprotective role in the DM ovary. However, human and animal research involving different doses is now required to determine the potential of curcumin in limiting adverse diabetic conditions in the ovary.

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