products such as malondialdehyde (MDA), Hydrogen Peroxide (H2O2) and Hydroxyl Radicals (35). These intermediates may be responsible for destroys the structure plasma membranes of sperm and makes it more fragile as a result of the breakdown of unsaturated fatty acids and are very sensitive to the ROS , and it is associated with sperm cluster and its non-motility, decrease in the percentage of live sperms and increased percentage of dead sperms , morphologically abnormal sperms and impairment of spermatogenesis , which leads to infertility (36 ; 37) . ROS that cause oxidation of group (-SH) in proteins and DNA that alter the sperm production and function and increase the Its susceptibility to attack by means of attachments (38), suggested study by Said (39) that abnormal sperm morphology combined with elevated ROS production may serve as a useful indicator of potential damage to sperm DNA . Oxidative stress has been implicated as a factor that contributes to various forms of cell death, including as a specific inducer of apoptosis by activating caspase-8, which reflects the effect on spermatogenesis (7). Many of Etoposide dose-limiting toxicities occur due to its generation of toxic oxygen species, resulting in oxidative stress, which negatively affects the cell division leading to death and then weakness fertility or infertility (40).. Shown studies (7, 41) findings the testicular alterations and germ cell damage caused by etoposide could be partially mediated by Sertoli cells which can provoke serious harm to spermatogenesis . The suggested mechanism is that etoposide up-regulates certain caspases, important regulators of the cell cycle, and this leads to induction of apoptosis in affected cells (42) .

In our study showed decrease in test fertility because decrease of testosterone , LH and FSH in the current study, which are the main responsible for the composition spermatogenesis and development of sperm (Bieber *et al.,* 2006) , or may be due to the damage caused to DNA germ cells can be caused oxidative stress by the treatment as spermatogonia and up to the premeiotic differentiation but not during the post-meiotic steps , this may be explained with the high frequency of cells with the features of programmed death due to inhibition of Topomearse II , causing damage in the sperm cell DNA, which forces the cells to commit suicide in the process of death the programmed cell apoptosis led to decreased spermatogenesis , and possibly the damage to this DNA can be passed on to generations of treated animals, and can lead to death in births (10) . This is the conclusion of our current study, Bieber et al. (34) reported that the exposure of rats to platinum -cis for 9 weeks caused an increase in the number of deaths and congenital malformations of the fetus , The current study agreed with previous studies (7, 34,10) .

Treatment with quercetin and/or Hesperidin improved the current study parameters , may be due to of Flavonoid compound help to normalize the affected testicular functions and the hormonal axis (43 , 44) . Led treatment with quercetin, the results show there is a significant increase in gene expression for CYP11A1, LHr and LH subunit gene as well as Testosterone and LH and FSH ,These results are in agreement with earlier reports (43 ;45). flavonoids that reported the protective potentials in improving the testicular and pituitary functions and maintaining the cellular components of DNA, RNA, nucleic acids and lipid in the membranes through the reduction of lipid peroxidation and increased antioxidants in the tissues (46,47). Also (48) is mentioned in the ability of flavonoids to protect the biopolymers from the effect of free oxygen-free radicals that cause damage to DNA , Miyake *et al.,* (49) mention that Hesperidin improved the levels of GSH, CAT in diabetic rats and inhibited oxidative stress free radicals, and reduced oxidase 8-hydroxy-2' -deoxyguanosine (8-OHdG) derived from deoxyguanosine , an indicator of DNA oxidation , Hesperidin and Quercetin have improver effect on plasma gonadotropin concentration (50, 51) , Also quercetin have effect on testis by other sex organs through stimulating the testis and epididymis or hypothalamic-pituitary-testis axis through stimulating testosterone hormone secretion (47). In this study the reproductive hormones have cooperative effect on sperms and testis cells. LH stimulate leydig's cells to synthesis of testosterone hormone, and then come the role of FSH which is stimulate sertoli cells to production of androgen binding protein(ABP) , which transport of testosterone to the target site in the spermatogonia and epididymis for development and maturation of sperms (52). Quercetin also stimulates the enzymes responsible for the carry of cholesterol to Leydig cells for the synthesis of testosterone (53). Quercetin also influence the enzymes that convert cholesterol into pregnonolone, the first step in the synthesis of steroids (52) . Khaki (54) noted that Quercetin caused an increase in hormones (Testosterone, LH, FSH) in diabetic rats with streptozotocin . Indicate study of (55) clearly demonstrated that hesperidin have attenuated the harmful effects on reproductive system toxicity of cisplatin-induced in male rats . Hozayen *et al.,* (56), showed pretreatment hesperidin improved (testosterone, LH and FSH) level in serum in rats, improvement testicular toxicity caused by doxorubicin – induced .

In the present study, administration of QE (20 mg/kg bw) and/or HES (25 mg/kg bw) /rat for 2 months significantly increased sperm motility , count , activity , viability and normal morphology in both experimental groups as compared with the Etoposide-treated group could be due to the protective effect of flavonoids (QE , HES) administration , which have been reported to scavenge H2O2, hydroxyl radical , nitric oxide , superoxide anion . Thus, in inhibiting the cellular DNA damage (57, 58). Several studies have reported the inhibitory effects of catechin, quercetin, and other flavonoids on in vitro lipid peroxidation. Beside, these productive effects are reflected by the decrease of malonaldehyde level and increase in total antioxidants capacity in according with these results, ElMazoudy *et al.,* (59) Showed the positive effect of quercetin (10 and 20 mg/kg) on sperm characteristics was observed as indicated by the increment in SOD and CAT activities because is ability of quercetin, via two aromatic rings in its structure, can penetrate the phospholipid membranes and upregulation of

antioxidant (60). Besides, it decreased the total abnormal sperm number in experimental groups . Similarly, Taepongsorat *et al.,* (61) observed that Quercetin improved the sperm motility, concentration and viability in rats . This finding is consistent with previous reports which indicated that quercetin increased the antioxidant activities of SOD and CAT (62), In study Trivedi *et al.,* (63) showed Hesperidin protects testicular toxicity of doxorubicin in male rat, prevention of oxidative stress, DNA damage and the cellular toxicity and protection against doxorubicin-induced germ cell toxicity was further evident from the sperm count and sperm head morphological evaluation. was confirmed (63) role of nuclear factor-kappa B, p38 and caspase-3 on hesperetin-mediated protection against doxorubicin-induced testicular toxicity.

In addition, the effect of Quercetin as an antioxidant and its ability to improve the function of mitochondria and cell movement and activity in general is likely to be achieved by maintaining the balance of calcium inside and outside the cell (64) , as explained by Ikizler *et al.,* (65) reported that Quercetin stimulates the increase in ATP production, which is the main source of energy and the important mediator of many vital pathways in the cell, activating the sperm movement. study of (55) was observed that hesperidin was orally administered (50 mg/kg) for 14 days have attenuated the harmful effects on sperm characteristics of cisplatin-induced reproductive system toxicity . Reported (66) that Hesperidin has proven ameliorative effects in BaP-induced testicular toxicity by increase sperm count, motility, and daily sperm production and this protection resides, at least in part, on its antioxidant properties.

Showed our study improved in fertility parameters , This may be due to the role of flavonoids(Hesperidin , Quercetin) in providing protection against oxidative stress and damage caused by free radicals at the tissue level and various body organs including the male reproductive system, This is consistent with the results of some studies that demonstrated the importance and efficacy of flavonoids in reducing the toxicity of anticancer cancer-induced in fertility parameters (47, 55) . It also works Quercetin to inhibit the enzyme Xanthine oxidase, which is the main enzyme in the process of lipid peroxidation and thus prevents this process and protects the cell membrane and mitochondria , This enzyme is one of the enzymes that mediate the process of generating free radicals(59) . The current results clearly indicate that Quercetin induced fertility as indicated by a marked increase in the testosterone and LH and FSH levels. Similarly, Khaki *et al.,* (54) found that Quercetin increased the serum testosterone levels and had beneficial effects on sperm parameters in streptozotocin-induced diabetic male rats. Also, Ma *et al.,* (47) reported that Quercetin can increase serum testosterone levels in male rats .

Combining antioxidants may increase their effectiveness , In (QE +HES) showed synergistic potential and significant reach all parameters in current study to control group , recently reported attempts to elucidate the mechanism of action of this Flavonoids, due to have the ability to form non-covalent bonds within the lipid layers close to the cell's plasma membrane, Which greatly enhances its antioxidant activity in this combination and regeneration of endogenous antioxidants (67). The flavonoids may interact with the polar head of phospholipids at water lipid interface, enhancing membrane rigidity and consequently protecting membranes from oxidative damage (68) , The antioxidant activity of flavonoids depends upon the arrangement of functional groups about the nuclear structure. The configuration, substitution, and total number of hydroxyl groups substantially influence several mechanisms of antioxidant activity such as radical scavenging and metal ion chelation ability (69) , Conjugation between the A (in Quercetin) and B (in Hesperidin) rings allows a resonance effect of the aromatic nucleus that provides stability to the flavonoid radical . Free radical scavenging by flavonoids is potentiated by the presence of both the elements besides other structural features (70). It is proposed that B ring OH groups form hydrogen bonds with the 3-OH, aligning the B ring with the heterocycle and A ring. Due to this intramolecular hydrogen bonding, the influence of a 3-OH is enhanced by the presence of a 3′,4′-catechol, elucidating the potent antioxidant activity of flavan-3-ols and flavon-3-ols that possess the latter feature (71,72), Flavonoid protect against oxidative damage by various mechanisms include (1) suppression of ROS formation either by inhibition of enzymes or by chelating trace elements involved in free radical generation; (2) scavenging ROS; and (3) upregulation or protection of antioxidant defenses (70) .

Some researchers have reported synergy between naturally occurring flavonoids in vitro , vivo of animals experimental . Smet *et al.,* (73) found that dietary synthetic antioxidants combined with α-tocopherol were more effective than rosemary, green tea, grape seed, or tomato extracts alone, in sparing tocopherols oxidation and in preventing oxidation of fresh frozen chicken patties . In a study by Hozayen *et al.,* (74), found that pretreatment with rutin and/ or hesperidin (synergism of Flavonoids) may improvement of testicular dysfunction caused via doxorubicin – induced, by amelioration in the levels of (testosterone, LH and FSH) in male rats . Schlachterman, *et al.,* (75) was determined that combined dietary polyphenols (Quercetin, and Catechin) led to inhibit breast cancer progression growth in a nude mouse model in vivo , indicate Zhang *et al.,* (76) were Combination of curcumin and quercetin has the potential than that of individual treatment as anti-gastric cancer drug for further development, through inhibit the phosphorylations of ERK and AKT and induce apoptosis via mitochondrial pathway .

CONCLUSION

The findings in this study showed that Flavonoids enhances testicular oxidative status through administrated (QE) and (HES) severally or in combination (synergism) prevents by improved the harmful effects of Etoposide on reproductive parameters in male rats and toward the normal values .

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