

PLANT POLYPHENOLS - POLIFENOLI VEGETALI

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Mediterranean Diet as a Shield against Male Infertility and Cancer Risk Induced by Environmental Pollutants: A Focus on Flavonoids. *Int. J. Mol. Sci.* **2022**, *23*, 1568. <https://doi.org/10.3390/ijms23031568>

The role of environmental factors in influencing health status is well documented. Heavy metals, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, dioxins, pesticides, ultrafine particles, produced by human activities put a strain on the body's entire defense system. Therefore, together with public health measures, evidence-based individual resilience measures are necessary to mitigate cancer risk under environmental stress and to prevent reproductive dysfunction and non-communicable diseases; this is especially relevant for workers occupationally exposed to pollutants and/or populations residing in highly polluted areas. The Mediterranean diet is characterized by a high intake of fruits and vegetables rich in flavonoids, that can promote the elimination of pollutants in tissues and fluids and/or mitigate their effects through different mechanisms. In this review, we collected evidence from pre-clinical and clinical studies showing that the impairment of male fertility and gonadal development, as well as cancers of reproductive system, due to the exposure of organic and inorganic pollutants, may be counteracted by flavonoids

- Ferlazzo N, Micali A, Marini HR, Freni J, Santoro G, Puzzolo D, Squadrito F, Pallio G, Navarra M, Cirimi S, Minutoli L.

A Flavonoid-Rich Extract from Bergamot Juice, Alone or in Association with Curcumin and Resveratrol, Shows Protective Effects in a Murine Model of Cadmium-Induced Testicular Injury. *Pharmaceuticals (Basel)*. 2021 Apr 21;14(5):386. doi: 10.3390/ph14050386.

It is known that cadmium damages testis structure and functionality. We examined the effects of nutraceuticals such as a flavonoid-rich extract of bergamot juice (BJe), alone or in association with curcumin (Cur) and resveratrol (Re), on mice testicular dysfunction caused by cadmium chloride (CdCl₂). Controversial data on the protective effects of Cur and Re are available, while no evidence on the possible role of BJe exists. Adult male C57 BL/6J mice were administered with CdCl₂ and treated with Cur, Re, or BJe alone or in combination for 14 days. Then, testes were removed and processed for molecular, structural, and immunohistochemical analyses. CdCl₂ increased the mRNA of IL-1 β , TNF- α , p53, and BAX while reduced that of Bcl-2 and induced tubular lesions and apoptosis of germinal cells. Cur, Re, and BJe at 40 mg/kg significantly improved all of these parameters and events, although BJe at 20 mg/kg showed a lower protective effect. The association of Cur, Re, and BJe at both doses of 50/20/20 and 100/20/40 mg/kg brought each parameter close to those of the control. Our results indicate that the nutraceuticals employed in this study and their associations exert a positive action against Cd-induced testicular injury, suggesting a possible protection of testis functionality in subjects exposed to environmental toxicants.

- Kim M, Jee SC, Kim KS, Kim HS, Yu KN, Sung JS. Quercetin and Isorhamnetin Attenuate Benzo[a]pyrene-Induced Toxicity by Modulating

Detoxification Enzymes through the AhR and NRF2 Signaling Pathways. *Antioxidants (Basel)*. 2021 May 16;10(5):787. doi: 10.3390/antiox10050787.

Benzo[a]pyrene, classified as a Group 1 carcinogen, is metabolized to B[a]P-7,8-dihydrodiol-9,10-epoxide (BPDE), causing DNA mutations and eventually cancer. Quercetin is a dietary flavonoid abundant in fruits and vegetables. After quercetin intake, quercetin's metabolites isorhamnetin and miquelianin are more highly concentrated than quercetin in the human plasma. In this study, we investigated the molecular mechanisms associated with the cytoprotective effect of quercetin and its metabolites against benzo[a]pyrene from a detoxification perspective. Quercetin and its metabolite isorhamnetin reduced benzo[a]pyrene-induced cytotoxicity, whereas the metabolite miquelianin did not mitigate benzo[a]pyrene-induced cytotoxicity.

Moreover, quercetin and isorhamnetin reduced intracellular levels of BPDE-DNA adducts. The formation and elimination of BPDE is mediated by the xenobiotic detoxification process. Quercetin and isorhamnetin increased the gene and protein expression levels of phase I, II, and III enzymes involved in xenobiotic detoxification. Furthermore, quercetin and isorhamnetin induced the translocation of aryl hydrocarbon receptor (AhR) and nuclear factor erythroid 2-related factor 2 (NRF2), which regulate the expression level of phase enzymes. Our results suggest that quercetin and isorhamnetin promote the metabolism, detoxification, and elimination of B[a]P, thereby increasing anti-genotoxic effects and protecting against B[a]P-induced cytotoxicity.

- Wang J, Zhu H, Lin S, Wang K, Wang H, Liu Z.

Protective effect of naringenin against cadmium-induced testicular toxicity in male SD rats. *J Inorg Biochem.* 2021 Jan;214:111310. doi: 10.1016/j.jinorgbio.2020.111310.

This study aimed to investigate the effect of naringenin (Nar) on cadmium (Cd)-induced testicular toxicity. Twenty-four male Sprague-Dawley (SD) rats aged 5 weeks were used. Rats were administered with 0.9% NaCl (control group), CdCl₂ (2 mg/kg b.w. intraperitoneally), Nar (50 mg/kg b.w. orally), and CdCl₂ + Nar (2 mg/kg b.w. intraperitoneally and 50 mg/kg b.w. orally, respectively) for 4 weeks. Results showed that body weight, relative testis weights, and sperm quality decreased in the Cd-treated group, and Cd accumulated in serum and testes. Pathological examination showed that Cd can cause testicular damage. Cd decreased the serum concentrations of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. It also decreased the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Moreover, exposure to Cd resulted in decreased content of reduced glutathione (GSH) and total antioxidant capacity (T-AOC) concentrations, as well as increased malondialdehyde (MDA) and hydrogen peroxide (H₂O₂) contents. Cd also provoked testis autophagy by upregulating the expression of the autophagy-related proteins P62 and LC3 II. However, the combined administration of Nar and Cd significantly attenuated the Cd-induced negative effects by increasing the body weight, relative testis weights, and sperm quality and by decreasing testicular damage. Simultaneous supplementation of Nar and Cd markedly restored the decreased levels of GnRH, FSH, LH, testosterone, GSH, and T-AOC and the activities of SOD, CAT, and GPx caused by Cd treatment. Nar further suppressed MDA and H₂O₂ production and protected the testes from Cd-induced autophagy by downregulating P62 and LC3 II expression. Therefore, Nar protected the testes from Cd-induced toxicity.

- Abarikwu SO, Simple G, Onuoha CS. Morphometric

Evaluation of the Seminiferous Tubules and the Antioxidant Protective Effects of Gallic Acid and Quercetin in the Testis and Liver of Butyl Phthalate Treated Rats. *Indian J Clin Biochem.* 2020 Jan;35(1):20-31. doi: 10.1007/s12291-018-0788-0.

The antioxidant protective effects of gallic acid (GAL) and quercetin (QUE) against oxidative stress induced by di-butyl phthalate (DnBP) in the liver and testis of rats were evaluated in this study. Adult albino Wistar rats (180-225 g) were treated with QUE or GAL (50 mg/kg) alone or in combination with DnBP (1 mL/kg) for 15 days. After treatment, tissue samples were taken for determination of glutathione and malondialdehyde levels, and superoxide dismutase and catalase activities. Serial sections of the testis and liver were stained with haematoxylin and eosin for microscopy and seminiferous tubular morphometry. As expected, DnBP induced oxidative stress was evident by increased malondialdehyde level in both organs. Co-treatment with GAL or QUE reversed the malondialdehyde by 45.42, 37.44 and 37.57%, 23.32% and catalase by 52.21, 70.15 and 85%, 38.14% in the testis and liver respectively whereas superoxide dismutase activity and glutathione level were differently modulated parallel to histopathological improvement in both tissues. The seminiferous tubular diameter, epithelial height, epithelial germ cell count and tubular length were significantly decreased by 11.09, 51.91, 40.65 and 11.10% respectively versus control values after DnBP treatments and were attenuated on co-treatment with GAL or QUE. Co-treatment with GAL afforded better protective effects in both tissues but QUE treatment alone appeared more effective than GAL on the investigated morphometric data. It seems likely that GAL or QUE prevented the tissue damage but the antioxidant profiles of the liver and testis are different in response to the oxidative stress.

- Han C, Wei Y, Geng Y, Cui Y, Li S, Bao Y, Shi W.

Bisphenol A in utero exposure induces ovary dysfunction in mice offspring and the ameliorating effects of *Cuscuta chinensis* flavonoids. Environ Sci Pollut Res Int. 2020 Sep;27(25):31357-31368. doi: 10.1007/s11356-020-09202-4.

To study the alleviating effects of flavonoids from *Cuscuta chinensis* (CCFs) on ovary injury in female offspring of pregnant mice exposed to BPA, five groups ($n = 20$) of pregnant mice were intragastrically administrated with BPA (5 mg/kg/day) and CCFs (20 mg/kg/day, 30 mg/kg/day, 40 mg/kg/day) at pregnancy days 1-18. The ovaries and serum of F1 female mice were collected at postnatal day (PND) 21 and PND 56 for the detection of related indicators. The ovarian and testicular histomorphologies were observed with hematoxylin-eosin staining (H&E). The levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and the contents of estradiol (E2), progesterone (P4), and testosterone (T) in serum were detected by radioimmunoassay. The contents of ovarian and testicular estrogen receptor alpha ($ER\alpha$) and estrogen receptor beta ($ER\beta$) were detected by enzyme-linked immunosorbent assay (ELISA). The expression of caspase-7, caspase-9, bcl-2, and bax in ovaries and testes of offspring mice were detected by Western blot, and apoptosis in ovaries and testes was detected by TUNEL. The mRNA relative transcription levels of $ER\alpha$, progesterone receptor (PgR), DNA methyltransferase1 (Dnmt1), DNA methyltransferase3A (Dnmt3A), and DNA methyltransferase3B (Dnmt3B) were detected by real-time quantitative PCR (RT-qPCR). The ovary of female offspring with PND 56 was treated with bisulfite sequence PCR (BSP). Our results showed that, compared with the BPA group, 40 mg/kg CCFs significantly reduced the ovarian index of F1 females and the ovarian cytoapoptosis ($P < 0.01$). CCFs also can alleviate the injure of the levels of serum hormone, hormone receptors, and DNMTs induced by BPA in F1 females at PND 21 and PND 56. Forty milligrams per kilogram of CCFs significantly inhibited the hypermethylation of the H19/Igf2 imprinted gene induced by BPA ($P < 0.01$). It indicated that CCFs adjusted H19/Igf2 methylation by increasing the expression of DNMTs, thereby increasing the levels of reproductive hormones and receptors along with reducing the cytoapoptosis.

Mirkov I, Stojković D, Aleksandrov AP, Ivanov M, Kostić M, Glamočlija J, Soković M. Plant Extracts and Isolated Compounds Reduce Parameters of Oxidative Stress Induced by Heavy Metals: An up-to-Date Review on Animal Studies. Curr Pharm Des. 2020;26(16):1799-1815. doi: 10.2174/1381612826666200407163408.

Background: Heavy metals are elements that are naturally found in the earth. They are used in many modern-day applications in agriculture, medicine, and industry. Heavy metal poisoning occurs when the body's soft tissues absorb too much of a particular metal. The heavy metals of interest for this review paper were cadmium, arsenic, mercury, and lead since these are the most common metals that the human body can absorb in toxic amounts. Different plant species were investigated in recent years for their effect on oxidative stress parameters after intoxication with heavy metals.

Objectives: This review paper is focused on the current update to research on heavy metals induced oxidative stress in animal models and improvement of the oxidative stress parameters upon/co-/after treatment with different plant extracts and isolated compounds.

Methods: The available literature was screened for the novel data regarding the influence of plant extracts and compounds on heavy metals induced oxidative stress. For that purposes Scopus database was used, looking for the publications in the last 5-10 years with the key terms: plant extracts, oxidative stress, in vivo, cadmium, lead, mercury and arsenic.

Results: Various parameters of oxidative stress were investigated, and their improvement with plant extracts/compounds was observed in the brain, lungs, kidneys, liver, uterus, testis, thymus, spleen, heart, skin and blood of experimental animals. Common parameters used to determine oxidative stress in animals were: superoxide dismutase; catalase; reduced glutathione; glutathione reductase; glutathione-S-transferase; glutathione peroxidase; lipid peroxidation; oxidized glutathione; malondialdehyde; xanthine oxidase; nonprotein-soluble thiol; thioredoxin reductase; total sulphhydryl group; nitric oxide; γ -glutamyl cysteine synthetase.

Conclusion: The most investigated species for antioxidant effects upon intoxication with heavy metals seem to be *Allium sp.*, *Bacopa monniera*, *Camellia sinensis*, *Moringa oleifera*, *Vitis vinifera* and *Zingiber officinale*. According to literature data, the most promising effect to alleviate symptoms of intoxication was achieved with proanthocyanidins obtained from *Vitis vinifera*.

- Mouro VGS, de Melo FCSA, Martins ALP, de Lucca Moreira Gomes M, de Oliveira JM, de Freitas MBD, Demuner AJ, Leite JPV, da Matta SLP.

Euterpe oleracea (Martius) Oil Reverses Testicular Alterations Caused after Cadmium Administration. Biol Trace Elem Res. 2020 Oct;197(2):555-570. doi: 10.1007/s12011-019-02004-x.

Cadmium (Cd) is an environmental pollutant that induces reproductive toxicity by generating reactive oxygen species, which leads to oxidative stress. *Euterpe oleracea* fruits are known for being rich in oils containing triacylglycerol and phenolic compounds. They are considered as potent antioxidants to be used to counteract Cd effects within the testis. In the present study, adult males Swiss mice were treated with CdCl₂ aqueous solution (4.28 mg/kg) by gavage for 7 days. The experimental groups were treated with *Euterpe oleracea* oil at the doses of 50, 100, and 150 mg/kg, for 42 days. The results showed that Cd intoxication led to increased tubular pathologies, such as reduction in epithelium height and area thus increasing both luminal diameter and tubule-epithelium ratio. Besides, Leydig cell's morphometry indicated reduction in nucleus and cytoplasm volumes of this cell type, which were recovered after *E. oleracea* oil intake. In addition, serum testosterone levels, testicular Mn and Zn concentrations, SOD and CAT activity, and germ cell viability increased after oil intake. Therefore, *E. oleracea* oil showed a regenerative effect in the testicular parenchyma negatively affected by Cd, mainly in the animals that received the highest oil concentration (150 mg/kg).

- Wang J, Zhu H, Wang K, Yang Z, Liu Z.

Protective effect of quercetin on rat testes against cadmium toxicity by alleviating oxidative stress and autophagy. Environ Sci Pollut Res Int. 2020 Jul;27(20):25278-25286. doi: 10.1007/s11356-020-08947-2.

Cadmium (Cd), a highly toxic heavy metal, adversely affects human and animal health. Quercetin (Que) is a kind of flavonoid that can protect many tissues from the toxic effect of heavy metals. Although many studies have explored the adverse effects of cadmium on rats and other animals, the mechanism of Cd-induced testicular autophagy and the antagonistic effect of Que on cadmium remain unclear. In this study, Sprague-Dawley rats were treated with Cd, Que or Cd, and Que supplements to explore the mechanisms of Que-alleviated testis injury caused by Cd exposure. The rat body weight and relative testicular weight were measured. Morphological changes in testes and indices of oxidative stress were also examined. The expression levels of autophagy-related genes were detected as well. Results showed that Cd decreased the rat body weight and relative testicular weight and induced pathological changes in testes. Conversely, Que alleviated these changes. We also found that Cd increased the malondialdehyde content and decreased the contents of total superoxide dismutase, glutathione peroxidase, catalase, and glutathione. Moreover, the protein expression levels of P62 and LC3-II increased under Cd exposure conditions. Conversely, Que obviously alleviated these toxic activities induced by Cd. Overall, this study showed that Cd accumulated in rat testes, leading to oxidative stress and autophagy. Que can reduce cadmium toxicity by reducing oxidative stress and inhibiting autophagy. The specific mechanism of Que antagonizing Cd toxicity can provide new insights into countering cadmium toxicity.

- Wei Y, Han C, Li S, Cui Y, Bao Y, Shi W.

Cuscuta chinensis flavonoids down-regulate the DNA methylation of the H19/Igf2 imprinted control region and estrogen receptor alpha promoter of the testis in bisphenol A exposed mouse offspring. Food Funct. 2020 Jan 29;11(1):787-798. doi: 10.1039/c9fo02770j.

Exposure to the emerging contaminant bisphenol A (BPA) is ubiquitous and associated with reproductive disorders. The BPA effect as an endocrine disruptor is widely known but other mechanisms underlying developmental disease, such as epigenetic modifications, still remain unclear. The objective of this study was to investigate whether *Cuscuta chinensis* flavonoids (CCFs) can be used as a dietary supplement to reverse BPA-induced epigenetic disorders, by analyzing the molecular processes related to BPA impairment of

testicular development. BPA and different concentrations of CCFs were administered to the dams at gestation day (GD) 0.5-17.5. The testis and serum of male mice were collected at postnatal day (PND) 21 and PND 56 for the detection of related indicators. Our results showed that compared with the BPA group, CCFs could significantly increase the serum contents of testosterone (T), estradiol (E2) in males at PND 21 and PND 56, as well as the contents and transcription levels of DNA methyltransferase 3A (Dnmt3A), Dnmt3B in males at PND 21 and that of estrogen receptor alpha (ER α) at PND 56. The expressions of Dnmt1 and ER α at PND 21 and ER β at both PND 21 and PND 56 in males were significantly decreased with the administration of different concentrations of CCFs ($P < 0.01$ or $P < 0.05$). CCFs also significantly inhibited the BPA-induced hypermethylated status of the ER α promoter and H19/Igf2 imprinting control region (ICR) in the testis at PND 56. These results indicated that CCFs could decrease the methylation levels of ER α and H19/Igf2 genes by inhibiting the expression of DNA methyltransferases (DNMTs), thereby decreasing the levels of reproductive hormones and receptors in adult males, and ultimately alleviating the negative effect of BPA on testicular development in male mice.

- Yu W, Xu Z, Gao Q, Xu Y, Wang B, Dai Y.

Protective role of wogonin against cadmium induced testicular toxicity: Involvement of antioxidant, anti-inflammatory and anti-apoptotic pathways. *Life Sci.* 2020 Oct 1;258:118192. doi: 10.1016/j.lfs.2020.118192.

The present study was conducted to identify possible health - promoting effects of wogonin (Wog) on testicular dysfunction in rats caused by cadmium. Pre-treatment of cadmium chloride (Cd: 5 mg/kg b.wt.) administered rats with wogonin (10 mg/kg b.wt) resulted in significant improvement in Cd-induced decrease in body and organ (testes and epididymides) weights. Wogonin treatment significantly improved Cd-induced reduction in sperm quality and quantity, steroidogenic gene (SFI, StAR, CYP11A1, 3 β -HSD, CYP17A1 and 17 β -HSD) and protein (SF1, StAR and CYP17A1) expressions and serum testosterone levels. Wogonin treatment provided significant protection to Cd-induced aggression in testicular oxidative (elevated levels of MDA) and anti-oxidative (diminished activities of SOD, CAT and GPx) status. Wog significantly up-regulated mRNA levels of Nrf2, NQO1 and HO-1 and down-regulation of Keap1 in cadmium treated testes. Wogonin administration significantly suppressed Cd-stimulated increase in inflammatory reactions (increase in NF- κ B p65 DNA, p-IKK β , TNF- α levels and decrease in IL-10 levels). Wogonin prevented apoptotic damage by enhanced protein distribution of caspase-9, caspase-3, and Bax due to Cd exposure. Furthermore, Wogonin presented significant protection to histo-morphometric changes resulted after Cd administration. Taken together, the findings of this study provided clear evidence of the therapeutic potential of Cd-induced testicular toxicity at least partly due to its antioxidant, anti-inflammatory and anti-apoptotic properties.

- Wei Y, Li S, Han C, Bao Y, Shi W.

Cuscuta chinensis flavonoids alleviate bisphenol A-induced apoptosis of testicular cells in male mice offspring. *Andrologia.* 2019 Dec;51(11):e13427. doi: 10.1111/and.13427..

Bisphenol A (BPA) is a widespread environmental endocrine disruptor that has multiple effects on reproductive organ development. To investigate the effect of *Cuscuta chinensis* flavonoids (CCFs) on testicular apoptosis induced by BPA in male mice offspring, pregnant mice were administered intragastrically with BPA and CCF at gestation day (GD) 0.5-17.5. The testes of male offspring (F1 males) were collected at post-natal day (PND) 21 and PND 56 for the detection of related indicators. The results showed that compared with the BPA group, the testicular index in CCF groups was significantly increased at PND 21 ($p < .01$). For the mice of different concentrations of CCF groups, the expression levels of bax, caspase-9 and caspase-7 proteins were significantly decreased at PND 21 and PND 56, while the expression level of bcl-2 protein was significantly increased, and testicular apoptotic cells were also decreased significantly ($p < .01$ or $p < .05$). Forty mg/kg CCF has no significant difference compared with the control group. The results indicated that CCF could protect the testis development of F1 male mice by alleviating the apoptosis of testicular cells induced by BPA.

- Mosbah R, Djerrou Z, Mantovani A.

Protective effect of Nigella sativa oil against acetamiprid induced reproductive toxicity in male rats. Drug Chem Toxicol. 2018 Apr;41(2):206-212. doi: 10.1080/01480545.2017.1337127.

The present study was designed to investigate the adverse reproductive effects of acetamiprid, besides the possible protective role of Nigella sativa oil (NSO), as a potential antioxidant agent. Thirty-two male Wistar rats were allocated into four equal groups of eight, control (CRL), acetamiprid (ACMP, 27 mg/kg), Nigella sativa oil (NSO, 0.5 ml/kg) and in combination (ACMP + NSO). The experimental animals were dosed by gavage (5 days per week) for 45 consecutive days. Body weight gain, reproductive organs weights, sperm characteristics, testosterone, and thiobarbituric acid-reactive substances (TBARS) levels were investigated. The obtained results showed that ACMP decreased significantly ($p < 0.001$) the body weight gain and the absolute weights of reproductive organs (testes, epididymis, and seminal vesicles). Furthermore, significant alterations at least ($p < 0.01$) in semen characteristics were noted in ACMP group as evidenced by a decline in spermatids number, sperm count, sperm motility, and testosterone level with an increase in abnormal and dead sperm and TBARS level. Treatment with NSO alone may stimulate spermatogenesis, increased significantly ($p < 0.001$) spermatids number and the weight of seminal vesicles. On the other hand, the co-administration of NSO along with ACMP can mitigate more efficiently and modulate in certain cases the adverse effects induced by ACMP on reproductive organs weights, semen quality, testosterone, and TBARS levels (at least $p < 0.001$). This obvious protective role of NSO against ACMP induced reproductive toxicity may be due to its antioxidant properties and ability to reduce TBARS levels as shown in this work.

- Quiller G, Mérida-Ortega Á, Rothenberg SJ, Cebrián ME, Gandolfi AJ, Franco-Marina F, López-Carrillo L.

Dietary flavonoids improve urinary arsenic elimination among Mexican women. Nutr Res. 2018 Jul;55:65-71. doi: 10.1016/j.nutres.2018.04.012.

Inorganic arsenic (iAs) exposure increases risk of several diseases, including cancer. Some nutrients such as flavonoids enhance glutathione activity, which in turn play a key role in iAs elimination. Our objective was to explore whether dietary non-soy flavonoids are associated with iAs metabolism. We hypothesized that the intake of flavonoids belonging to the following groups, flavan-3-ols, flavone, flavonol, flavanone, and anthocyanidin, is positively associated with urinary dimethylarsinic acid (DMA), which is the most soluble iAs metabolite excreted. We performed a cross-sectional study that included 1027 women living in an arsenic-contaminated area of northern Mexico. Flavonoid intake was estimated using a validated food frequency questionnaire. Concentration of urinary iAs and its metabolites (monomethylarsonic acid and DMA) were determined by high performance liquid chromatography ICP-MS. Results showed positive significant associations between DMA and the flavonoid groups flava-3-ols ($\beta = 0.0112$) and flavones ($\beta = 0.0144$), as well as the individual intake of apigenin ($\beta = 0.0115$), luteolin ($\beta = 0.0138$), and eriodictyol ($\beta = 0.0026$). Our findings suggest that certain non-soy flavonoids may improve iAs elimination; however, there is still very limited information available regarding the consumption of flavonoids and iAs metabolism.

- Clementino M, Shi X, Zhang Z.

Prevention of Polyphenols Against Carcinogenesis Induced by Environmental Carcinogens. J Environ Pathol Toxicol Oncol. 2017;36(1):87-98. doi: 10.1615/JEnvironPatholToxicolOncol.2017019057.

Cancer is one of the major causes of death in humans. Of all cancers, 19% are attributed to exposure to environmental chemical carcinogens. Dietary polyphenols from teas, vegetables, fruits, and many others exhibit multiple activities against cancers. Exposure to environmental carcinogens such as ultraviolet B (UVB), polycyclic aromatic hydrocarbons (PAHs), and heavy metals has been demonstrated to cause cancer in humans. In this article, we specifically select UVB, PAHs, and metals as representative of three types of environmental carcinogens: physical, organic, and inorganic, respectively. We provide a comprehensive review on the role of various dietary polyphenols against carcinogenesis induced by those three types of

carcinogens. We summarize the current knowledge of and prospects for prevention of those three groups of carcinogens induced by dietary polyphenols in vitro and in vivo.

- Elmallah MIY, Elkhadragy MF, Al-Olayan EM, Abdel Moneim AE.

Protective Effect of *Fragaria ananassa* Crude Extract on Cadmium-Induced Lipid Peroxidation, Antioxidant Enzymes Suppression, and Apoptosis in Rat Testes. Int J Mol Sci. 2017 May 5;18(5):957. doi: 10.3390/ijms18050957.

Cadmium is a deleterious environmental pollutant that threatens both animals and human health. Oxidative stress and elevated levels of reactive oxygen species (ROS) have recently been reported to be the main cause of cellular damage as a result of cadmium exposure. We investigate, here, the protective effect of strawberry crude extracts on cadmium-induced oxidative damage of testes in rats. Four groups ($n = 8$) of 32 adult male Wistar rats weighing 160-180 g were used. The control group received 0.9% saline solution all over the experimental period (5 days). Group 2 was intraperitoneally injected with 6.5 mg/kg CdCl₂. Group 3 was provided only with an oral administration of strawberry methanolic extract (SME) at a dose of 250 mg/kg. Group 4 was treated with SME before cadmium injection with the same mentioned doses. It was shown that cadmium exposure results in a significant decrease in both relative testicular weight and serum testosterone level. Analyzing the oxidative damaging effect of cadmium on the testicular tissue revealed the induction of oxidative stress markers represented in the elevated level of lipid peroxidation (LPO), nitric oxide (NO), and a decrease in the reduced glutathione (GSH) content. Considering cadmium toxicity, the level of the antioxidant enzyme activities including catalase (CAT), superoxide dismutase (SOD2), glutathione peroxidase (GPx1), and glutathione reductase (GR) were markedly decreased. Moreover, gene expression analysis indicated significant upregulation of the pro-apoptotic proteins, bcl-2-associated-X-protein (*BAX*), and tumor necrosis factor- α (*TNFA*) in response to cadmium intoxication, while significant downregulation of the anti-apoptotic, B-cell lymphoma 2 (*BCL2*) gene was detected. Immunohistochemistry of the testicular tissue possessed positive immunostaining for the increased level of TNF- α , but decreased number of proliferating cell nuclear antigen (PCNA) stained cells. Administration of SME debilitated the deleterious effect of cadmium via reduction of both LPO and NO levels followed by a significant enhancement in the gene expression level of *CAT*, *SOD2*, *GPXI*, *GR*, nuclear factor-erythroid 2-related factor 2 (*NFE2L2*), heme oxygenase-1 (*HMOX1*), Bcl-2, and PCNA. In addition, the SME treated group revealed a significant increase in the level of testosterone and GSH accompanied by a marked decrease in the gene expression level of Bax and TNF- α . In terms of the summarized results, the SME of *Fragaria ananassa* has a protective effect against cadmium-induced oxidative damage of testes.

- Li X, Jiang X, Sun J, Zhu C, Li X, Tian L, Liu L, Bai W.

Cytoprotective effects of dietary flavonoids against cadmium-induced toxicity. Ann N Y Acad Sci. 2017 Jun;1398(1):5-19. doi: 10.1111/nyas.13344.

Cadmium (Cd) damages the liver, kidney, bones, reproductive system, and other organs. Flavonoids, such as anthocyanins and flavonols, which are commonly found in plant foods, have shown protective effects against Cd-induced damage. The cytoprotective effects of flavonoids against Cd-induced diseases are mainly attributable to three mechanisms. First, flavonoids clear reactive oxygen species, thereby reducing lipid peroxide production and improving the activity of antioxidation enzymes. Second, flavonoids chelate Cd, thus reducing the accumulation of Cd and altering the levels of other essential metal ions in vivo. Third, flavonoids reduce DNA damage and inhibit apoptosis. In addition, flavonoids were found to inhibit inflammation and fibrosis and improve glycometabolism and the secretion of reproductive hormones. We introduce the daily dosage and absorption rate of flavonoids and then focus on their bioactive effects against Cd-induced toxicity and reveal the underlying metabolic pathway, which provides a basis for further study of the nutritional prevention of Cd-induced injury. In particular, a better understanding is needed of the structure-activity relationship of flavonoids against Cd toxicity, which has not yet been reported.

- Abarikwu SO, Farombi EO.

Quercetin ameliorates atrazine-induced changes in the testicular function of rats. *Toxicol Ind Health.* 2016 Jul;32(7):1278-85. doi: 10.1177/0748233714555389.

The protective effect of quercetin (QT) on atrazine (ATZ)-induced testicular damage in rats was investigated. Sexually mature male Wistar rats (weighing 220-250 g) divided into four groups with six animals in each group were given ATZ (120 mg kg⁻¹; 1/16 of the median lethal dose for an oral dose) and/or QT (10 mg kg⁻¹) daily via gavage for 16 days. By the end of day 16, rats given ATZ alone had significantly lower sperm counts, daily spermatozoa production, and sperm motility and significantly higher abnormal sperm numbers than the untreated control rats. The rats given ATZ alone also had significantly decreased 3 β -hydroxysteroid dehydrogenase (HSD) and 17 β -HSD activities than the control rats. Lactate dehydrogenase activity and malondialdehyde levels were significantly increased, whereas superoxide dismutase activity decreased but glutathione levels remain unaffected after ATZ exposure. These changes were reversed toward control values in the QT + ATZ-treated animals, though the sperm motility was 28% below the control levels but was still higher than in the ATZ-treated rats. The results indicate that QT might improve testicular function of rats exposed to ATZ, but its protective effect on sperm motility might be partial.

- Ali I, Hurmerinta T, Nurmi T, Berglund M, Rüegg J, Poutanen M, Halldin K, Mäkelä S, Damdimopoulou P.

From pure compounds to complex exposure: Effects of dietary cadmium and lignans on estrogen, epidermal growth factor receptor, and mitogen activated protein kinase signaling *in vivo*. *Toxicol Lett.* 2016 Jun 24;253:27-35. doi: 10.1016/j.toxlet.2016.04.020.

Exposure to environmental endocrine active compounds correlates with altered susceptibility to disease in human populations. Chemical risk assessment is single compound based, although exposure often takes place as heterogeneous mixtures of man-made and natural substances within complex matrices like diet. Here we studied whether the effects of cadmium and enterolactone on endocrine endpoints in dietary exposure can be predicted based on pure compound effects. Ovariectomized estrogen reporter ERE-luciferase (ERE-luc) mice were maintained on diets that intrinsically contain increasing concentrations of cadmium and enterolactone precursors for three and 21 days. The activation of the ERE-luc, epidermal growth factor receptor (EGFR), mitogen activated protein kinase (MAPK)-ERK1/2, and classical estrogen responses were measured. Interactions between the diets and endogenous hormone were evaluated by challenging the animals with 17 β -estradiol. Compared to animals on basal purified diet, mice consuming experimental diets were exposed to significantly higher levels of cadmium and enterolactone, yet the exposure remained comparable to typical human dietary intake. Surprisingly, we could not detect effects on endpoints regulated by pure enterolactone, such as ERE-luc activation. However, cadmium accumulation in the liver was accompanied with activation of EGFR and MAPK-ERK1/2 in line with our earlier CdCl₂ studies. Further, attenuation of 17 β -estradiol-induced ERE-luc response in liver by experimental diets was observed. Our findings indicate that the exposure context can have substantial effects on the activity of endocrine active compounds *in vivo*. Thus, whenever possible, a context that mimics human exposure should be tested along with pure compounds.

- Dragone R, Ermilov L, Grasso G, Maggioni S, Mantovani A, Frazzoli C.

Antioxidant power as biochemical endpoint in bread for screening and early managing quality and toxicant-related safety anomalies in food production. *Food Chem Toxicol.* 2016 Aug;94:31-8. doi: 10.1016/j.fct.2016.04.028.

Flaxseeds are both a food ingredient and a natural source of antioxidants (e.g. lignans, PUFAs) and pro-oxidant contaminants (e.g. cadmium): the variable mixture of anti- and pro-oxidant substances may impact on the redox homeostasis of flaxseed-enriched foods. The antioxidant power is studied here as biochemical activity of flaxseeds in white wheat bread and as endpoint for possible screening of anomalous variations of bioactive

mixtures (antioxidants vs. prooxidants) in food matrices. A bioprobe assay based on the superoxide dismutase (SOD) enzyme (6 channels of the multiprobe bioelectronic platform BEST) was performed on white wheat bread with and without flaxseeds. Nine BEST channels were simultaneously used for validation and monitoring of measuring conditions (temperature, pH, conductivity). Findings were compared with quantitative analysis of antioxidants and pro-oxidant contaminants. Organic and aqueous extracts of both bread types were examined in parallel. The SOD-probe detected the difference in antioxidant power given by 10% flaxseed, thus supporting the use of antioxidant power detected by bioenzymatic screening as sensitive biochemical endpoint. Mixtures of bioactive molecules in foods generate biochemical activities that can be monitored as time-effective indicators of invariability, which is pivotal in the daily control of anomalies in food production and therefore in the protection of consumers' health.

- Mérida-Ortega Á, Hernández-Alcaraz C, Hernández-Ramírez RU, García-Martínez A, Trejo-Valdivia B, Salinas-Rodríguez A, Svensson K, Cebrián ME, Franco-Marina F, López-Carrillo L.

Phthalate exposure, flavonoid consumption and breast cancer risk among Mexican women. *Environ Int.* 2016 Nov;96:167-172. doi: 10.1016/j.envint.2016.08.023

Objective: To evaluate if selected phthalate exposure and flavonoid intake interact on breast cancer (BC) risk.

Material and methods: Interviews and urine samples were obtained from 233 women with histologically confirmed BC and 221 healthy controls matched by age and place of residence, from various states of northern Mexico. Urinary metabolites concentrations of diethyl phthalate (DEP), butyl benzyl phthalate (BBzP) and dioctyl phthalate (DOP) were determined by solid-phase extraction coupled with high-performance liquid chromatography/isotope dilution/tandem mass spectrometry. Using a semiquantitative food frequency questionnaire, consumption of five types of flavonoids (anthocyanidins, flavan-3-ols, flavanones, flavones and flavonols) was estimated according to three food groups: vegetables, fruits and legumes-oil seeds.

Results: A higher intake of anthocyanidins and flavan-3-ols (from vegetables), synergistically increased the negative association between BBzP and BC. No other significant flavonoid-phthalate multiplicative interactions on the risk for BC were found.

Conclusion: The consumption of some flavonoids may interact with exposure to phthalates on the risk of BC. Epidemiological and underlying mechanisms information is still insufficient and requires further investigations.

- Mosbah R, Yousef MI, Maranghi F, Mantovani A.

Protective role of Nigella sativa oil against reproductive toxicity, hormonal alterations, and oxidative damage induced by chlorpyrifos in male rats. *Toxicol Ind Health.* 2016 Jul;32(7):1266-77. doi: 10.1177/0748233714554675.

This study is aimed at elucidating the possible protective effects of Nigella sativa oil (NSO) in alleviating the toxicity of chlorpyrifos (CPF) on reproductive performance in male rats. Animals were orally administered with NSO (1 ml/kg/day), CPF (20 mg/kg/day), and NSO + CPF every day for 4 weeks. Results showed that CPF decreased spermatid number, sperm count, daily sperm production, and sperm motility while increased dead sperm and abnormal sperm compared with the control. Also the levels of testosterone, thyroxine levels, steroidogenic enzyme 17-ketosteroid reductase, body weight, food intake, and relative weight of reproductive organs were decreased. Thiobarbituric acid reactive substances were increased, while glutathione (GSH) and antioxidant enzymes were decreased in plasma and testes of rats treated with CPF. Histopathological examination of testes showed a decrease in the number of seminiferous tubules, form shrinkage, enlargement of the connective tissue and gametogenic changes in germ cells of rats treated with CPF. NSO alone increased testosterone, semen characteristics, GSH, and antioxidant enzymes and decreased the levels of free radicals. Furthermore, the presence of NSO with CPF alleviates its toxic effects. Our results indicated that NSO can improve semen picture and moderate CPF-induced reproductive toxicity.

- Hsu YL, Hsieh CJ, Tsai EM, Hung JY, Chang WA, Hou MF, Kuo PL.

Didymin reverses phthalate ester-associated breast cancer aggravation in the breast cancer tumor microenvironment. *Oncol Lett.* 2016 Feb;11(2):1035-1042. doi: 10.3892/ol.2015.4008.

The present study demonstrated two novel findings. To the best of our knowledge, it is the first study to demonstrate that regulated upon activation, normal T-cell expressed and secreted (RANTES), produced by breast tumor-associated monocyte-derived dendritic cells (TADCs) following breast cancer cell exposure to phthalate esters, may contribute to the progression of cancer via enhancement of cancer cell proliferation, migration and invasion. Furthermore, the present study revealed that didymin, a dietary flavonoid glycoside present in citrus fruits, was able to reverse phthalate ester-mediated breast cancer aggravation. MDA-MB-231 cells were treated with butyl benzyl phthalate (BBP), di-n-butyl phthalate (DBP) or di-2-ethylhexyl phthalate (DEHP). Subsequently, the conditioned medium (CM) was harvested and cultured with monocyte-derived dendritic cells (mdDCs). Cultures of MDA-MB-231 cells with the conditioned medium of BBP-, DBP- or DEHP-MDA-MB-231 tumor-associated mdDCs (BBP-, DBP- or DEHP-MDA-TADC-CM) demonstrated enhanced proliferation, migration and invasion. Exposure of the MDA-MB-231 cells to DBP induced the MDA-TADCs to produce the inflammatory cytokine RANTES, which subsequently induced MDA-MB-231 cell proliferation, migration and invasion. Depleting RANTES reversed the effects of DBP-MDA-TADC-mediated MDA-MB-231 cell proliferation, migration and invasion. In addition, didymin was observed to suppress phthalate-mediated breast cancer cell proliferation, migration and invasion. The present study suggested that didymin was capable of preventing phthalate ester-associated cancer aggravation.

- Manzolli ES, Serpeloni JM, Grotto D, Bastos JK, Antunes LM, Barbosa Junior F, Barcelos GR.

Protective effects of the flavonoid chrysin against methylmercury-induced genotoxicity and alterations of antioxidant status, *in vivo*. *Oxid Med Cell Longev.* 2015;2015:602360. doi: 10.1155/2015/602360.

The use of phytochemicals has been widely used as inexpensive approach for prevention of diseases related to oxidative damage due to its antioxidant properties. One of dietary flavonoids is chrysin (CR), found mainly in passion fruit, honey, and propolis. Methylmercury (MeHg) is a toxic metal whose main toxic mechanism is oxidative damage. Thus, the study aimed to evaluate the antioxidant effects of CR against oxidative damage induced by MeHg in Wistar rats. Animals were treated with MeHg (30 µg/kg/bw) in presence and absence of CR (0.10, 1.0, and 10 mg/kg/bw) by gavage for 45 days. Glutathione (GSH) in blood was quantified spectrophotometrically and for monitoring of DNA damage, comet assay was used in leukocytes and hepatocytes. MeHg led to a significant increase in the formation of comets; when the animals were exposed to the metal in the presence of CR, higher concentrations of CR showed protective effects. Moreover, exposure to MeHg decreased the levels of GSH and GSH levels were restored in the animals that received CR plus MeHg. Taken together the findings of the present work indicate that consumption of flavonoids such as CR may protect humans against the adverse health effects caused by MeHg.

- Androutopoulos VP, Tsatsakis AM.

Benzo[a]pyrene sensitizes MCF7 breast cancer cells to induction of G1 arrest by the natural flavonoid eupatorin-5-methyl ether, via activation of cell signaling proteins and CYP1-mediated metabolism. *Toxicol Lett.* 2014 Oct 15;230(2):304-13. doi: 10.1016/j.toxlet.2013.08.005.

Eupatorin-5-methyl ether (E5M) is a flavone containing 4 methoxy groups that is present in plants with medicinal activity, whereas luteolin (L) is a polyhydroxylated flavone commonly encountered in dietary products. In the present study we investigated the interaction of the two flavonoids with cytochrome P450 CYP1 enzymes in breast cancer MCF7 cells. Both compounds induced a dose dependent increase in CYP1A1 and CYP1B1 mRNA levels, as well as in EROD activity, a marker of CYP1 enzyme activity. Induction of cytochrome P450 CYP1 expression by E5M was accompanied by translocation of the ligand-activated transcription factor AhR to the nucleus, as demonstrated by confocal immunofluorescence. More importantly,

although E5M was less active than L in inhibiting proliferation of MCF7 cells, when the cells were pretreated with the CYP1 inducer Benzo[a]pyrene (BaP) the potency of E5M was augmented. HPLC and LC-MS analysis revealed that E5M was metabolized to a major conversion product assigned E5M1 resulting from one step demethylation reaction in MCF7 cells whereas L metabolism by recombinant CYP1A1 did not reveal any metabolites. E5M1 production in BaP-induced MCF7 cells was attenuated in the presence of the CYP1A1 inhibitor α -naphthoflavone. E5M further induced a dose dependent increase in the cell signaling proteins p21, JNK and p-JNK in MCF7 cells. This effect was enhanced in BaP pretreated cells and was associated with G1 arrest and a small percentage of apoptosis (3.5%). E5M antiproliferative effect in BaP pretreated cells was attenuated in the presence of the CYP1A1 inhibitor α -naphthoflavone, as demonstrated by Western blotting and FACS analysis. Taken together the results demonstrate that BaP sensitizes MCF7 cells to E5M antiproliferative activity via enhanced induction of p21, JNK and p-JNK that in turn results by cytochrome P450 CYP1-mediated conversion to the metabolite E5M1.

- Arafa MH, Mohammad NS, Atteia HH.

Fenugreek seed powder mitigates cadmium-induced testicular damage and hepatotoxicity in male rats. *Exp Toxicol Pathol.* 2014 Sep;66(7):293-300. doi: 10.1016/j.etp.2014.04.001.

Cadmium is a potential environmental and industrial pollutant affecting human tissues and organs including liver and testes. The protective role of fenugreek seed powder (FSP) was investigated in male rats subjected to cadmium-induced testicular injury and hepatic dysfunction. Testicular damage and hepatotoxicity were induced by oral administration of cadmium chloride (5 mg/kg body weight, once a day) for 7 weeks. FSP was given at 5% w/w in chow diet for 8 weeks, starting 1 week before cadmium administration. FSP intake significantly increased serum testosterone level and testis weight that were reduced by cadmium. FSP also compensated deficits in hepatic and testicular antioxidant defense system, interleukin-4 and nitric oxide levels, reduced serum liver function enzyme activities and suppressed lipid peroxidation in hepatic and testicular tissues resulted from cadmium administration. Additionally, FSP attenuated the cadmium-induced elevations in hepatic and testicular tumor necrosis factor- α and transforming growth factor-beta1 levels as well as cadmium deposition and hydroxyproline content. The protective effect afforded by FSP was mainly due its antioxidant, antifibrotic and anti-inflammatory effects. In conclusion, the results of the present work indicated that FSP may represent a promising medicinal herb to protect hepatic and testicular tissues from the detrimental effects of cadmium.

- Barański M, Srednicka-Tober D, Volakakis N, Seal C, Sanderson R, Stewart GB, Benbrook C, Biavati B, Markellou E, Giotis C, Gromadzka-Ostrowska J, Rembiałkowska E, Skwarło-Sońta K, Tahvonon R, Janovská D, Niggli U, Nicot P, Leifert C.

Higher antioxidant and lower cadmium concentrations and lower incidence of pesticide residues in organically grown crops: a systematic literature review and meta-analyses. *Br J Nutr.* 2014 Sep 14;112(5):794-811. doi: 10.1017/S0007114514001366.

Demand for organic foods is partially driven by consumers' perceptions that they are more nutritious. However, scientific opinion is divided on whether there are significant nutritional differences between organic and non-organic foods, and two recent reviews have concluded that there are no differences. In the present study, we carried out meta-analyses based on 343 peer-reviewed publications that indicate statistically significant and meaningful differences in composition between organic and non-organic crops/crop-based foods. Most importantly, the concentrations of a range of antioxidants such as polyphenolics were found to be substantially higher in organic crops/crop-based foods, with those of phenolic acids, flavanones, stilbenes, flavones, flavonols and anthocyanins being an estimated 19 (95 % CI 5, 33) %, 69 (95 % CI 13, 125) %, 28 (95 % CI 12, 44) %, 26 (95 % CI 3, 48) %, 50 (95 % CI 28, 72) % and 51 (95 % CI 17, 86) % higher, respectively. Many of these compounds have previously been linked to a reduced risk of chronic diseases, including CVD and neurodegenerative diseases and certain cancers, in dietary intervention and epidemiological studies.

Additionally, the frequency of occurrence of pesticide residues was found to be four times higher in conventional crops, which also contained significantly higher concentrations of the toxic metal Cd. Significant differences were also detected for some other (e.g. minerals and vitamins) compounds. There is evidence that higher antioxidant concentrations and lower Cd concentrations are linked to specific agronomic practices (e.g. non-use of mineral N and P fertilisers, respectively) prescribed in organic farming systems. In conclusion, organic crops, on average, have higher concentrations of antioxidants, lower concentrations of Cd and a lower incidence of pesticide residues than the non-organic comparators across regions and production seasons.

- Bharti S, Misro MM, Rai U.

Quercetin supplementation restores testicular function and augments germ cell survival in the estrogenized rats. *Mol Cell Endocrinol.* 2014 Mar 5;383(1-2):10-20. doi: 10.1016/j.mce.2013.11.021.

Quercetin, as a flavonoid, has been recognized to possess dual properties of an oxidant and antioxidant as well. The role of quercetin (QC), as an antioxidant in countering estradiol-3-benzoate (EB) induced adverse effects and germ cell apoptosis in adult rat testis was presently investigated. Adult rats received EB (0.075 mg/rat/5th day) alone or EB+QC (15 mg/kg bw/alternate day) simultaneously for 30 days. Revival of spermatogenesis following QC intervention was associated with a significant restoration in serum and intra-testicular levels of testosterone. Decline in lipid peroxidation and simultaneous improvement in the activities of superoxide dismutase, catalase and glutathione s-transferase were very much evident. Identically, total antioxidant capacity and glutathione demonstrated a marked improvement. QC augmented germ cell survival leading to a decrease in cell apoptosis. Expression of downstream apoptotic markers, caspase-3 and poly-ADP-ribose polymerase (PARP) presented a significant reduction. Down regulation with respect to upstream markers, caspase-8 and -9, Fas, FasL, Bax, and p53 was similarly observed. Taken together, the above findings indicate that with the dose presently used quercetin with its antioxidant and antiestrogenic properties restored testicular function leading to revival of spermatogenesis. It also augmented germ cell survival primarily mediated through downregulation in the expressions of upstream, downstream and other markers in the pathways of metazoan apoptosis.

- Petriello MC, Newsome B, Hennig B.

Influence of nutrition in PCB-induced vascular inflammation. *Environ Sci Pollut Res Int.* 2014 May;21(10):6410-8. doi: 10.1007/s11356-013-1549-5.

The nutritional profile of an individual can influence the toxicity of persistent environmental toxicants. Polychlorinated biphenyls (PCBs), prevalent environmental pollutants, are highly lipid-soluble toxic compounds that biomagnify through trophic levels and pose cancer, neurocognitive, and atherosclerotic risk to human populations. There is a growing body of knowledge that PCBs can initiate inflammatory responses *in vivo*, and this inflammation can be either exacerbated or ameliorated by nutrition. Data indicate that diets high in certain dietary lipids such as omega-6 fatty acids can worsen PCB-induced vascular toxicity while diets enriched with bioactive food components such as polyphenols and omega-3 polyunsaturated fatty acids can improve the toxicant-induced inflammation. There is evidence that bioactive nutrients protect through multiple cell signaling pathways, but we have shown that lipid raft caveolae and the antioxidant defense controller nuclear factor (erythroid-derived 2)-like 2 (Nrf2) both play a predominant role in nutritional modulation of PCB-induced vascular toxicity. Interestingly, there appears to be an intimate cross-talk between caveolae-related proteins and cellular Nrf2, and focusing on the use of specific bioactive food components that simultaneously alter both pathways may produce a more effective and efficient cytoprotective response to toxicant exposure. The use of nutrition as a protective tool is an economically beneficial means to address the toxicity of persistent environmental toxicants and may become a sensible means to protect human populations from PCB-induced vascular inflammation and associated chronic diseases.

- Farombi EO, Abarikwu SO, Adesiyan AC, Oyejola TO.

Quercetin exacerbates the effects of subacute treatment of atrazine on reproductive tissue antioxidant defence system, lipid peroxidation and sperm quality in rats. *Andrologia*. 2013 Aug;45(4):256-65. doi: 10.1111/and.12001.

The study investigated the reproductive function and the antioxidant defence system of rats co-exposed to atrazine [ATZ, 120 mg kg⁻¹ body weight (b. wt)] and quercetin (QT, 20 mg kg⁻¹ b. wt.). ATZ had no significant effects on feed intake, body weights and reproductive organs weight except prostate weight. Sperm abnormalities were increased, whereas sperm production, sperm motility and epididymal and testicular sperm numbers were decreased with ATZ treatment. Antioxidant enzymes including superoxide dismutase, glutathione-S-transferase and glutathione peroxidase were significantly altered in the epididymis and testis resulting to lipid peroxidation. A potentiating response on glutathione-S-transferase and aspartate aminotransferase activities in the testis and on lactate dehydrogenase activity and glutathione level in the epididymis was observed in the QT + ATZ animals. Quercetin alone decreased seminal vesicle and prostate weights, increased superoxide dismutase activity in the testis and ascorbate level in the epididymis. Mild pathological changes were observed in the ATZ group, whereas considerable necrosis of seminiferous tubular cells with hypoplasia of the epithelia was observed in the QT + ATZ animals. The epididymis of these animals had multilayered and sometimes a single lining epididymal epithelium with few spermatozoa. We conclude that quercetin at the investigated dose increases the susceptibility of rat reproductive tissues to atrazine-induced oxidative damage.

- Abarikwu SO, Pant AB, Farombi EO.

Dietary antioxidant, quercetin, protects sertoli-germ cell coculture from atrazine-induced oxidative damage. *J Biochem Mol Toxicol*. 2012 Nov;26(11):477-85. doi: 10.1002/jbt.21449.

Quercetin (QT), a dietary-derived flavonoid, is ubiquitous in fruits and vegetables and plays an important role in human health by virtue of its antioxidant function. The present study was designed to examine the effects of QT on oxidative damage that was induced by the herbicide, atrazine (ATZ), in mixed cultures of Sertoli-germ cells. Results showed that treatment with QT increased cell viability and decreased catalase activity, malondialdehyde, and reactive oxygen species (ROS) levels. QT treatment also increased the mRNA expression of glutathione peroxidase (GSH-Px), glutathione reductase (GR), glutathione-S-transferase, and superoxide dismutase-1 and could not reversed to the control levels ATZ-induced steady-state mRNA levels of these antioxidant genes as well as the level of glutathione and activities of GSH-Px and GR. QT has protective effect against ATZ-induced oxidative stress through a reduction in ROS levels and lipid peroxidation.

- Farombi EO, Adedara IA, Akinrinde SA, Ojo OO, Eboh AS.

Protective effects of kolaviron and quercetin on cadmium-induced testicular damage and endocrine pathology in rats. *Andrologia*. 2012 Aug;44(4):273-84. doi: 10.1111/j.1439-0272.2012.01279.x.

This study evaluated the effects of kolaviron, a biflavonoid from *Garcinia kola* seed, and quercetin on cadmium-induced reproductive toxicity in rats. Adult male rats were administered with either cadmium (15 mg kg⁻¹) alone or in combination with kolaviron (200 mg kg⁻¹) or quercetin (10 mg kg⁻¹) daily for 5 days. Cadmium-treated rats showed ($P < 0.05$) decrease in the body weight gain, testis and epididymis weights. However, upon co-administration of kolaviron or quercetin, these changes were significantly reversed in cadmium-treated rats. Also, administration of kolaviron or quercetin significantly prevented cadmium-mediated decrease in sperm motility and epididymal sperm concentration and reversed the increased level of sperm abnormality to near control. In testes and sperm, cadmium treatment resulted in significant decrease in the activities of superoxide dismutase, catalase and glutathione peroxidase, whereas it increased glutathione S-transferase activity as well as hydrogen peroxide and malondialdehyde levels. While plasma levels of

triiodothyronine and tetraiodothyronine remained unaffected, the levels of testosterone, luteinising hormone and follicle stimulating hormone were decreased in cadmium-treated rats. Cadmium treatment caused mild congestion of interstitial vessels and oedema in the testes. Taken together, kolaviron and quercetin inhibited the adverse effects of cadmium on the antioxidant enzymes, markers of oxidative stress, endocrine and testicular structure in rats.