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ANTIOXIDANT ACTIVITY OF BIOACTIVE FLAVONOID: QUERCETIN

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ABSTRACT

Toxicant exposure and free radical generation are closely associated with number of complications due to oxidative stress. Greater free radical generation and reduced antioxidant leads to diseased condition. Endogenous antioxidant prevents free radical generated oxidative stress but fails in case greater free radical generation. In such cases, phytoconstituents including flavonoids are needed. Quercetin and other flavonoid exhibit protective potential against toxicants inducing reproductive and endocrine toxicities. The summarized data of recent investigations which emphasized upon reproductive and endocrine protective efficacy of quercetin against their abnormalities. Changes in serum hormones, biochemical reactions, histopathological structures, behavioral changes etc. are occurred by toxicants and these are neutralized with the help of quercetin supplementation. Among flavonoids, quercetin has medicinal importance and potential antioxidant properties by affecting the activity and level of generated free radicals. The present review article summarized the data obtained from PubMed, Google Scholar, Scopus which highlighted the antioxidant properties of bioactive flavonoids quercetin and its mechanism of action against free radicals and oxidative stress. The data of previous study also supporting the different kinds of toxicants inducing complications by free radical generation.

KEYWORDS: Quercetin, Oxidative stress, ROS, Endocrine system, Reproductive system.

INTRODUCTION

The production of reactive oxygen species (ROS) is because of normal cellular metabolism. At low to moderate concentration of free radicals they do not affect physiological processes, but at high concentrations, they produced adverse modifications in biological components such as lipids, proteins, and DNA.[1] The normal cellular metabolism produces free radicals having one or more unpaired electrons in their outermost shell and thus giving the reactivity to the molecule. Superoxide anion (O_2^-), hydroxyl radical (°OH^-), and hydrogen peroxide (H_2O_2) are three major ROS that have physiological significance and these all are endogenous source of oxidative stress. Other than that, the exogenous source of free radicals are cigarette smoking producing superoxide and nitric oxide[2], ozone exposure due to ozone layer depletion causing lipid peroxidation affecting pulmonary functions[3], hyperoxia producing reactive oxygen and nitrogenous species[4], in the presence of O_2 ionizing radiations like X-rays convert hydroxyl and superoxide radicals into hydrogen peroxides, which reacts with redox active metals like Fe and Cu, which induces oxidative stress[5], other than that heavy metals and chemical fertilizers are also capable to generate free radicals and oxidative stress.

Under normal condition the generated free radicals are neutralized by the antioxidant system of the body, but under stress condition antioxidant system fails to neutralize then exogenous antioxidants are required. The total antioxidant capacity of body comprises of enzymatic and non-enzymatic antioxidants. The enzymatic scavengers of antioxidant defense are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GTPx), glutathione peroxidase (GST) etc. and vitamin A, vitamin E, glutathione (GSH), and carotenoids like β-carotene are some non-enzymatic scavengers of antioxidant defense system. The accumulation of ROS results in oxidative stress and antioxidant defense system counteracts and restores the redox balance by either activating or inhibiting the genes encoding defensive enzymes, transcription factors, and structural proteins.[6]

Other than the endogenous source of antioxidants, exogenous sources are also required in case of oxidative stress. Many phytoconstituents are acts as antioxidants and develop the great interest for researchers.[7] Among the various classes of phytochemicals flavonoid also have antioxidant properties. In the variety of food and food products like fruits, vegetables, grains, bark, roots, tea, red wine etc. possess flavonoid with variable

phenolic structures and among that quercetin is also a flavonoid found in kinds of propolis.[8]

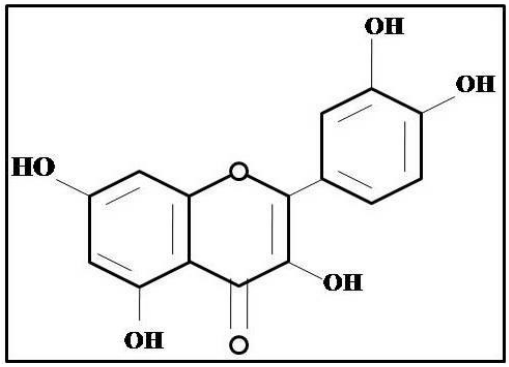

Fig. 1: the chemical structure of quercetin showing the two carbon rings joined by carbon rings with five hydroxyl groups attached.

In plants the synthesis of flavonoids is a defensive process against the UV light and environmental stress. Quercetin donates electron and acts as free radicals, which resulting in the delocalization by resonance.[9] Quercetin is an aglycone form of flavonoid glycoside with highest medicinal importance in cardiovascular disorders, anticancer, antitumor, antiulcer, antiviral, anti-inflammatory, anti-diabetic, gastroprotective, anti-hypertensive, anti-immunomodulatory and anti-infective properties.[10] Lipid peroxidation generates free radicals and molecular oxygen oxidize them, which propagate chain reaction and generates lipid peroxy radicals with the help of metal ions as catalyst. Quercetin protects the biological system from that by binding to transition metal ions and inhibiting the reaction.[11]

The antioxidant capacity of quercetin is mainly demonstrated by its effect on enzymatic activity of glutathione, signal transduction pathways, reactive oxygen, and nitrogenous species (ROS & RNS). The possible mechanism involved is to reduce the level of generated free radicals and protects the cell against oxidative stress induced damages and quercetin have potential to interfere with cellular functions including lipid peroxidation.[12] The possible mechanism involved in antioxidant activity of quercetin are as follows.

Direct effect on free radicals and ROS

Quercetin resist ROS induced oxidative damage in smokers, UV-B induced skin lesions and morphological changes in sperm by pesticide exposure. It is previously demonstrated that, quercetin stimulates 16HBE cells to repair oxidative damage after exposing to fine particulate matter by inhibiting ROS production and regulating anti-inflammatory process.[13] UV-B radiations affect cellular functions by generating ROS and imbalanced endogenous antioxidant system, quercetin protects cellular damage by resisting increased ROS level by UV-B and enhance the antioxidant system.[14] Quercetin shows hepatoprotective effect by inducing the expression of hepatic antioxidant enzymes in case of liver injury in mice.[15] All flavonoids contain hydroxyl group, which are easily oxidized by radicals by donating hydrogen atoms to radicals. This results in more stable and less stable radicals.

$$\text{Flavonoid(OH)} + \text{R}^{\bullet} \longrightarrow \text{Flavonoid(O)}^{\bullet} + \text{RH}$$

Fig. 2: Chemical reaction of flavonoid action.

Here, R° is a free radical, stabilized by accepting the H atom form OH of flavonoid results into less reactive flavonoid radical.

Nitric oxide synthase activity

Quercetin prevents from nitric oxide synthase activity induced ischemic reperfusion injury and acts as renal protective, high nitric oxide concentration causes oxidative damage in macrophages.[16, 17] Activated macrophages increases, nitric oxide and superoxide anions production which reacts with free radicals and produce peroxynitrile resulting in cell damage. Reduced free radical and peroxynitrile production by quercetin intake leads to less damage.[18]

Xanthine oxidase pathway

Xanthine oxidase pathway is also as important as nitric oxide pathway for oxidative damage to vital systems. Xanthine dehydrogenase and oxidase are involved in metabolism of xanthine to uric acid, under ischemia xanthine dehydrogenase converts into oxidase which is the source of free radicals. In reperfusion, xanthine oxidase reacts with molecular oxygen and releases superoxide radicals and from previous studies it is demonstrated that, quercetin and silibin reduce oxidative injury by inhibiting xanthine oxidase activity.[19]

Leucocyte immobilization

The immobilize leucocytes stimulates degranulation of neutrophils, which releases cytotoxic oxidants and inflammatory mediators resulting in tissue injury. Leucocyte adhesion to endothelial walls generates free radicals, which activates complement system. Dietary flavonoid intake helps in decreased immobilized leucocytes and inhibit neutrophil degranulation without affecting superoxide production.[20, 21]

Interaction with enzymatic systems-

Flavonoids retain enzymatic system interaction other than free radical scavenging activity. Iron in presence of free radicals causes lipid peroxidation and rutin, quercetin and other flavonoids inhibit lipid peroxidation by iron chelating and iron stabilizing properties.[22] Quercetin and other flavonoids have beneficial role in disease management systems. In neutrophils chetomatic compounds with lipoxygenase produce arachidonic acid, which starts inflammatory responses and previously reported that, flavonoid intake inhibits arachidonic acid production and trigger cytokines.[23]

Effect on GSH

GSH inhibits effect of free radicals by catalysed them into H_2O_2 and then H_2O by oxidizing GSH to GSSG. In liver and red blood cells GSSG reduced to GSH. Hence, GSH increase total antioxidant capacity of body and previously it is reported that, intake of quercetin and other flavonoids helps in GSH synthesis. Quercetin promotes healing by removing free radicals and up regulates endogenous antioxidant defence system and pre-treatment with quercetin prevents neuronal ischemia which proves neuroprotective efficacy of quercetin.[24]

Effect on signal transduction pathway

Quercetin regulates activating, inhibitory, up regulatory, down regulatory signal transduction pathways. Dietary quercetin improves antioxidant state, injury healing and reduce toxicity. Quercetin protects against acute spinal cord injury by promoting antioxidant activity by inhibiting p38MAPK/iNOS signalling pathway, down regulation of MDA levels and upregulation of SOD activity.[25]

Mechanism of Antioxidant action of Quercetin

Apoptosis caused by free radical induced oxidative stress by environmental factors and mitochondrial electron chain system, in such case exogenous antioxidant sources are required and quercetin and other flavonoids are frequently used because of therapeutic potential. Generated free radicals alter enzymatic and non-enzymatic antioxidant systems and regulates NRFB, AMPK and MAPK signaling pathways. Activation of signaling events like p53 mediated apoptotic pathways, NF-κB and NF-E2 factors mediated antioxidant response elements are due to these signaling pathways, which all induce oxidative stress in endocrine as well as reproductive system. The dietary intake of quercetin and other flavonoid helps in reducing free radicals generated oxidative stress by affecting enzymatic and non-enzymatic antioxidant defense systems. Quercetin intake improves antioxidant defense system and restores toxicity.[26, 27]

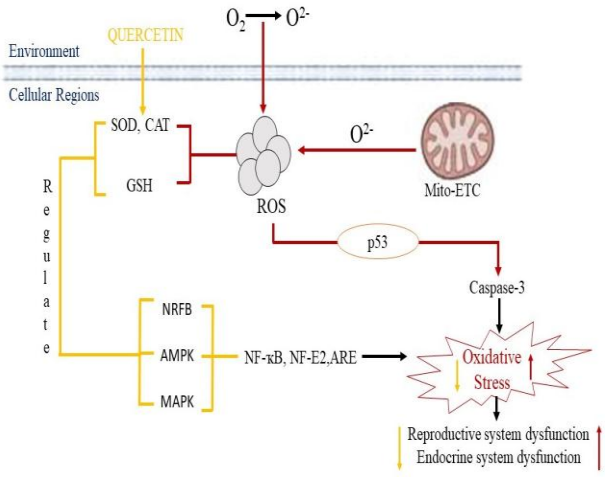

Fig. 3: Action of quercetin over generated oxidative stress.

Effect on endocrine glands

Endocrine glands and hormones secreted plays an important role in the maintenance of physiology. All hormones have their specific mechanism of action and targeted organ. Thyroid an endocrine gland found attached to trachea in neck region in mammals. Hypothalamus in brain stimulates anterior pituitary by thyrotropin releasing hormone (TRH), which then secretes thyroid stimulating hormone (TSH) and stimulates thyroid gland to release triiodothyronine (T3) and tetraiodothyronine (T4). These hormones help in regulation of growth and development, basal metabolic rate, temperature, and iodine balance of body.[28] Goiter, hyperthyroidism, hypothyroidism, and thyrotoxicosis are some common thyroid dysfunctions, which are most common among all endocrine disorders.[29] 2 gm quercetin per day in diet helps in upregulating the antioxidant defense system and disease prevention.[30] The seed extract of *Ammona squamosa* majorly contains quercetin and helps in prevention of thyrotoxicosis in hyperthyroid male mice. The intake of quercetin as dietary supplements has preventive role, which is experimentally proven that quercetin treatment to hyperthyroid mice brings to normal thyroid hormone level and decreased hepatic D1 activity.[31]

Testosterone secreted by the testes after receiving stimulation by hypothalamus and pituitary which is required for normal functioning in male reproductive system. Reproductive toxicity induced by toxicant cadmium is corrected after quercetin treatment helping in altering the testosterone, FSH and LH levels.[32] *Pseudomonas aeruginosa* rod shaped gram negative bacterium exposure leads to hypothyroidism. Repeated exposure to bacterium leads to decreased T3 and T4 levels and elevated TSH level. Bacterium exposure also cause thyrotoxicosis and oxidative stress in thyroid gland.[33]

Hyperglycemia or type II diabetes is common due to many toxicological factors leading to altered hormone secretion by pancreas. Increased oxidative stress and declined antioxidant defense mechanism leads to resistance to insulin, defective insulin secretion, and increased glucose production. All these abnormalities precede to type II diabetes.[34] Various *in vitro* and *in vivo* studies have experimentally proved that quercetin protects the pancreatic β-cells from inflammatory damages and inhibit xanthine oxidase, lipid peroxidation, cyclooxygenase, and lipoxygenase. Quercetin also reduces the activity of aldose reductase, which is responsible for sorbitol production via polyol pathway. Sorbitol induces diabetic retinopathy, neuropathy, and nephropathy. From previous reported studies it is found that quercetin protects pancreatic cells against oxidative stress by reducing aldose reductase activity.[35] Sulphasalazine (SASP) is a drug used to treat inflammatory bowel diseases like rheumatoid arthritis induces alteration in reproductive and thyroid hormones, which can be effectively treated with administration of

flavonoid quercetin and rutin. Increased serum FSH, LH and testosterone levels of SASP treated rats restores after treatment with quercetin and rutin and elevated T3 and T4 levels as compared to SASP treated rats.[36]

Effect on reproductive system

The problem of infertility is common due to environmental pollution like metal ions, pesticides, radiations, drugs, and chemicals. Nearly, 40% of cases are due to male partners because free radicals generated oxidative stress cause structural and functional damage in testis and sperm production.[37] Previously it has been reported that, quercetin plays a crucial role to cure male infertility and enhances sperm viability, motility, and level of testosterone.[38] Exposure to bisphenol cause testicular dysfunction and treatment with quercetin helps in improved quality and quantity of semen volume and histopathological changes in seminiferous tubules. Quercetin administration ameliorates chromosomal aberration in primary spermatocytes induced by bisphenol. Exposure to synthetic pyrethroids like deltamethrin and cypermethrin induce reproductive alterations including reduced testosterone level, reduced semen volume, increased sperm abnormality, histopathological damages, elevated lipid peroxidation and altered reproductive behavior are cured by administration of flavonoids curcumin and quercetin.[39] In males, fertility and reproductive behavior is maintained by testosterone and androgen from Leydig cells after stimulation by LH. From previous data, in rat cadmium exposure cause histological changes in Leydig cells leads to altered reproductive behavior and consumption of flavonoids as antioxidant shows beneficial role against various toxicants.[32, 40] From recent *in vivo* and *in vitro* studies, it is reported that, quercetin increases antioxidants capacity of ovary by upregulating the oxidative stress related gene expression.[41] Quercetin supplementation in heat stressed rabbit showed significantly improved follicular development and minimized granulosa cells apoptosis.[42] Antioxidant and anti-apoptotic activity of quercetin in cadmium chloride induced uterus and ovarian toxicity in female Wistar rats.[43] From previous study it has been reported that repeated exposure to UVB radiation induce abnormal estrous cycle in female Wistar rat, which may lead to altered female reproductive functions.[44] The constant dietary intake of quercetin enhance fertility in male and female, which is experimentally proved that dietary quercetin regulates transglutaminase-2 activity in follicular and ovarian cells of female mice responsible for fertility.[45] From previously reported data, quercetin ameliorates SASP induced reproductive toxicity in rats. Co-administration of quercetin with SASP showed increased sperm motility and viability. Increased sperm count and decreased sperm abnormality has been shown in quercetin treated rats as compared to SASP treated rats. Quercetin treatment increases cholesterol and steroidogenic enzyme activity as compared to SASP treated rats. Quercetin treatment also encounter SASP induced oxidative stress by reducing MDA level and SOD activity and increasing the GSH, GST and GPX activities in rat testes. Increased testes weight by SASP treatment restored after coadministration of quercetin.[36]

DISCUSSION

Increased pollution and distressed lifestyle are mainly responsible for free radicals and toxicity. Free radical generation and oxidative stress causes different kinds of abnormalities including neurological disorders, reproductive pathology, endocrine pathology, ageing, inflammation etc. due to xenobiotic effects of toxicants. Developmental disorders and infertility are the result of this stress and can be reduced by intake of dietary antioxidants. An antioxidant rich dietary supplement helps in free radical scavenging and decline oxidative stress. Natural antioxidants are derived from plants and synthetic antioxidants are manufactured chemically and quercetin is a chemical compound derived from plants like onion, grapes, broccoli etc. and serve medicinal properties to mankind.

Quercetin is a flavonoid abundantly found in fruits and vegetables and on the medicinal point of view, quercetin intake improves human health against variety of toxicants and reduce effect of generated free radical and oxidative stress. Quercetin treatment is effective because it influences enzymatic and non-enzymatic antioxidants. The applications of quercetin in pharmaceutical fields are limited by its low absorption because it is low soluble, comparatively little bioavailability, and poor permeability. When it forms complexes with metal ions or complex ions, its bioavailability and antioxidant effects are enhanced. In recent years, newer preparations of quercetin have emerged including nanoparticles loaded with quercetin, polymeric micelles of quercetin, quercetin loaded mucoadhesive nano emulsion, and quercetin loaded gel.[46,47] These preparations improve the solubility and bioavailability of quercetin, which enhance the medicinal value, antioxidant properties and offers new drug formulations for research and development.

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