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PHARMACOLOGICAL EFFECTS OF QUERCETIN- A MAJOR COMPONENT OF ROSE HIPS

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ABSTRACT

Quercetin is a flavanol present naturally in various plants such as rose, onions, apples etc. Quercetin has proven to exhibit anti-allergic, anti-viral, anti-cancer, anti-oxidant and anti-inflammatory properties. Quercetin supplements if taken along with the diet can also reduce the risk of many diseases. The present article is a detailed review on the pharmacological effects of quercetin on common diseases like cancer, diabetes, gastric ulcer, obesity, hypertension, neurodegenerative disorders and brain injuries, cardiovascular disorders etc.

Keywords-, Allergic Rhinitis, Anti-Cancer, Cardiac Injury, Diabetes, Gastric Ulcer, Hypertension, Neurodegenerative Diseases, Obesity, Quercetin

I. INTRODUCTION

Quercetin, a naturallyexisting phenol compound, has received considerable attention because of its overwhelming presence in foods such as berries, red onions, apples, and many other plants. It belongs to a subclass of flavonoids called flavanol.Flavonoids belong to a group of natural substances with variable phenolic structure,known for their beneficial effects on health and are responsible for imparting attractive colours to flowers, fruits and leaves, It is one of the major components of rose hips of many rose species like *Rosa canina* ,*Rosa damascena*. [1] [2]Quercetin and its sugar-bound, or glycosylatedforms represent 60-75% of flavonoid intake [3]. Quercetin has displayed the ability to prevent the oxidation of low-density lipoproteins (LDL) by scavenging free radicals and chelating transition metal ions. It is also known for its anti-inflammatory, antioxidant, antiviral and anticancer properties. [4]

II. THE HEALTH BENEFITS OF QUERCETIN

This compound provides many health promoting benefits, including improvement of cardiovascular health, eye diseases, allergic disorders, obesity, reducing risk for cancers and many more.[5] [6]

2.1 Cancer Fighting Properties

Cancer is one of the fastest growing chronic diseases today and most cancer treatments such as chemotherapy and radiation also damage the nervous system and have common side effects such as peripheral neuropathy, headaches, and chronic pain [7].

Epidemiological studies have shown that the consumption of vegetables, fruits and tea is associated with a low risk of cancer. Many natural dietary phytochemicals found in fruits, vegetables, spices and tea have been shown to be protective against cancer in various animal models. Quercetin has been shown repeatedly to have anti-carcinogenic properties that may prevent the development of certain cancers. Researchers are becoming increasingly aware of the role of flavonoids in the treatment of tumor growths. Experimental evidences show that quercetinexerts anti-proliferative and apoptotic activities and inhibits the enzymes involved in proliferation and signal transduction pathways. These activities of quercetin make it a promising candidate for treatment and prevention of various cancers. [8]

Quercetin treatment may be a possible therapeutic agent in the treatment of the following cancers:-

2.1.1 Bladder Cancer

Bladder cancer is one of the most common cancers of the urinary tract in the world. A study examined the mechanisms of quercetin on inhibition of bladder cancer.In addition to current treatments, novel therapies, such as targeted therapy which has made great progress in cancer treatment may be an important strategy for treatment of bladder cancer.

AMPK plays an important role in regulating cellular metabolism, including cell apoptosis, tumour survival and growth. Furthermore, AMPK has been considered as a potential therapeutic target for the treatment of cancer.

Two human and one murine bladder cancer cell lines were used to examine the killing effect of quercetin and the underlying mechanisms.In an experiment two different assays were used for assessment of apoptosis; Cell viability assay and clonogenic assay.In order to determine whether quercetin affected the proliferation of the bladder cancer cell lines in vitro, the effects of the quercetin was analysed on the bladder cancer cell lines using MTT approach. The cell line was grown in 10% FBS and was exposed to various concentrations ofquercetin and cell viability determined by tetrazolium-based assay after 48 hours. It was found that quercetin led to a dose-dependent inhibition on cell proliferation. Cellular apoptosis was considerably increased in the quercetin-treated groups compared to the control group.

The results of this study show the anti-proliferative potential of quercetin on tumor cells by activating AMPK signalling pathway and provides solid foundation on the clinical application of quercetin in bladder cancer treatment. [9]

2.1.2 Lung Cancer

Lung cancer is one of the most common cancers in many countries and accounts for 28% of all cancer deaths. Unfortunately, only 15% of people are diagnosed at an early, localized stage because most lung cancers begin to grow silently without any symptoms until the cancer is in an advanced stage.[27] Thus, there is an urgent need for novel diagnosis, prevention and/or treatment of lung cancer.

An experiment was performed by T.T.T.Nguyen , et al. where human A549 lung cancer cells were treated with 14.5, 29.0, 43.5 and 58.0 mM of quercetin for 24 and 48 h. Cell viability and cell growth were assessed by the MTT assay (a colorimetric assay for assessing cell metabolic activity)and BrdU incorporation, respectively. Control cells were treated with 0.1% DMSO alone. Quercetin caused a dose-dependent reduction in DNA synthesis and cell viability .Significant inhibition in BrdU incorporation was observed as early as 24 h post-treatment .50% reduction in cell viability was seen at a dose of 29.0 mM after 48 h incubation. To determine if quercetin reduced cell number by inducing apoptosis, TUNEL assay was performed. DNA fragmentation was detected in quercetin-treated cells. In cells treated with 0.1% DMSO, 14.5, 29.0, 43.5 and 58.0 mM of quercetin for 24 h, approximately 5.8% of apoptotic cells were observed. The percentage of apoptotic cells in the treatment groups compared with the control group were statistically significant at as determined by the Kruskal--Wallis test. Because apoptosis in mammalian cells has been shown to be regulated by Bax, Bcl-2, Bcl-xL, Bad, it was determined whether quercetin-induced apoptosis in A549 cells was also associated with the modulation of these proteins. To test this possibility, cell lysate from A549 cells treated with different concentrations of quercetin was examined by western blot analysis.

Quercetin induced a significant elevation in the expression of pro-apoptotic Bax and Bad. Treatment of A549 cells with 14.5, 29.0, 43.5 and 58.0 mM of quercetin for 14 h led to 1.1-, 1.1-, 2.5- and 3.5-fold increase in Bax. Similar elevations were observed in Bad levels, which increased 1.1-, 2.1-, 2.2- and 2.3-fold, respectively, in the quercetin treatment as compared with controls.It was proven that quercetin inhibited the A549 cell growth and induced apoptosis. [10]

Another experiment was performed by Zhao X .Zhang J to analyse the inhibitory effect of quercetin on the growth of lung cancer cell (A549) by MTT. The effect of quercetin on levels of MMP-9 (mRNA and protein) and TGF-β1 (protein) in A549 were also measured by RT-PCR and Western blot, respectively.

This study had similar results showing that quercetin induced the apoptosis of A549. It was a reversible competitive inhibitor of MMP-9, with the increase in quercetinconcentration, the levels of MMP-9 (mRNA and protein) and TGF-β1 (protein) were decreased, and the number of tumor cells on wear filter membrane was reduced. It was concluded that quercetin is a competitive inhibitor of MMP-9 and could downregulate the expression of MMP-9 and TGF-β1, which plays an important role in A549 apoptosis. [11]

2.1.3 BreastCancer

A study by Xiao-Hui Deng, et al aimed at observing the effects of quercetin on the proliferation of the breast cancer cell line MCF-7 and the gene expression of survivin, an inhibitor of apoptosis protein that is highly expressed in most cancers .[12]

The molecular mechanism underlying the anti-proliferative effect of quercetin was also investigated. MCF-7 breast cancer cells were treated with various concentrations of quercetin. The inhibitory effect of quercetin on proliferation was detected using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method and the inhibition rate was calculated. Cellular apoptosis was detected by immunocytochemistry and survivin mRNA expression levels were observed using reverse transcription-polymerase chain reaction (RT-PCR). Western blot analysis was used to analyse changes in the expression levels of survivin protein.

Results showed that quercetin induced the apoptosis and inhibited the proliferation of the MCF-7 breast cancer cells in a time- and concentration-dependent manner. The mRNA and protein expression levels of survivin were reduced as the concentration of quercetin increased, which may be the mechanism underlying its antitumor effect.[13]

2.2 Diabetes

Quercetin acts an enhancer when it comes to anti-diabetic tests. Kaur G et al studied the effect of curcumin with and without quercetin, which acts as an enhancer.

Curcumin is a nutraceutical obtained from the rhizomes of Curcuma longa with a significant medicinal value against numerous disorders.

The target of the study was to explore the anti-diabetic potential of combinatorial extract of curcumin with piperine and quercetin (CPQ) in streptozotocin- and nicotinamide-induced diabetic rats. Induction of Diabetes mellitus was done by single intra-peritoneal injection of streptozotocin (55 mg/kg) and nicotinamide (120 mg/kg-1). CPQ was orally administered at 100 mg kg-1 dose/day for a period of 28 days. At the end of 28 days, blood was analysed for glucose, HDL, LDL and total cholesterol level. Oral glucose tolerance test (OGTT) was also conducted at the end of 28 days.

Results showed that plasma glucose was significantly reduced by oral administration of CPQ at the dose of 100mg kg-1 at the end of 28days, as compared to diabetic control group.The reduction in the plasma glucose produced by the CPQ extract significantly more compared to curcumin alone. There was a significant improvement in the body weight with CPQ compared to diabetes control group. OGTT revealed a significantly high glucose tolerance in CPQ fed rats compared to the diabetic control as well as the rats fed with curcumin alone.Better therapeutic potential was evident when curcumin was given with quercetin than when it was given alone to treat type II diabetes. [14]

2.3 Gastric Ulcer

A study conducted by Ömer et al aimed to examine anti ulcerogen and antioxidant effects of quercetin on ethanol-induce gastric lesions in rat.

Thirty healthy inbred mat Wistar albino rats, weighing 200-250g, were divided into 3 groups A(control), B(Ethanol) and C (Ethanol+Quercetin) of 10 rats each. They were kept under standard laboratory conditions.In groups B and C, gastric ulcers were induced by administrating 100% ethanol (1 ml/200 g, intragastric).In group C, QE was given two hour prior to administrating 100% ethanol. QE was dissolved in 0.5 ml of DMSO (Merck) just before injection. The solution was kept in the dark and dose of QE was chosen on the basis of a previous study.After an hour of administration of ethanol, animals were sacrificed by cervical dislocation and the stomach of each was removed and opened and washed in physiological saline solution. The stomach was laid flat and mucosal lesions were traced on acetate paper so that measurement of the gross gastric mucosal lesions could be made. Gross mucosal lesions were recognized as haemorrhage or erosions with damage to the mucosal surface. The area of stomach and gross lesions were calculated by image analysis system.

The results were that Erythrocyte MDA, serum NO and gastric tissue MDA significantly increased and also the antioxidant levels significantly decreased in group B. QE treatment significantly decreased the elevated MDA and NO, and also increased the reduced antioxidant enzyme activities in group C.[15]

2.4 Obesity

Obesity is characterized by the rapid expansion of visceral adipose tissue, resulting in a hypoxic environment in adipose tissue which leads to change of gene expression in adipocytes. This leads to dysregulation of metabolism and adipokine secretion in adipose, which further leads to the development of inflammation and metabolic diseases.Quercetin is best known for its anti-oxidant property and anti-inflammatory properties in terms of obesity.

Human SGBS pre-adipocytes were taken and cultivated. SGBS cells were differentiated into adipocytes and cultured in FCS-free differentiation medium. After four days, this medium was replaced by differentiation medium which excluded dexamethasone, IBMX, and rosiglitazone, which was changed every 3 to 4 days. At day 12 after induction of differentiation, 25 µM quercetin, dissolved in 23 µL DMSO, was added to cell cultures (15 mL), and 23 µL DMSO without quercetin was added to control-cultures (15 mL), resulting in a 0.15% (v/v) DMSO concentration in all cell cultures. All cell cultures were cultivated for another 48 h and then exposed to hypoxia. Hypoxic environment was created when cells were placed in a MIC-101 modular incubator chamber, flushed with a mixture of 1% O_2, 5% CO_2, and 94% N_2, sealed, and incubated at 37 °C. Adipocytes were cultured in hypoxic environment for 16 h, whereas control groups were cultured under normoxic conditions (21% O_2).

When gene expression of quercetin-treated and hypoxic cultivated samples was compared to samples cultivated under normoxia and without quercetin, a significant inhibition of ANGPTL4, CFD/adipsin, PFKP, and PAI-1 was found. Each of these is assumed to be involved in the development of obesity-associated complications. [16]

2.5 Hypertension

The impact of quercetin on BP was assessed through a systematic review and meta-analysis of available randomized controlled trials.The results of the meta-analysis showed significant reductions both in systolic BP and diastolic BP following supplementation with quercetin. When the studies were categorized according to the quercetin dose, there was a significant systolic BP and diastolic BP-reducing effect in randomized controlled trials with doses ≥500 mg/day, and lack of a significant effect for doses <500 mg/day .

Further studies can be conducted to investigate the clinical relevance of these results and the possibility of Quercetin application as an add-on to anti-hypertensive therapy. [17]

2.6 BrainInjuries and Neurodegenerative Diseases

Quercetin exhibits a major role in altering the progression of brain injuries and neurodegenerative diseases by protecting against oxidative stress. Subarachnoid haemorrhage has become a serious medical problem because of its high mortality and morbidity worldwide. Morbidity is defined in terms of neurological repercussions which include intracranial hypertension, cerebral vasospasm, brainedema, cerebral infarction.Disturbances in

the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA, resulting in oxidative stress which reflects an imbalance in the normal mechanisms of cellular signalling.

A study was conducted to elucidate the positive effectsof quercetinonoxidative stress-mediated cerebral dysfunction.A pre-chiasmatic blood injection was induced in sham-operated model (SAH) treated with 0.9% saline and a dose of 10 mg/kg quercetin was administered intraperitoneally. The experimental rats were anesthetised and a 1.0-mm burr hole was drilled 7.5 mm anterior to the Bregma at the midline. A rounded tip needle with a side hole was tilted 30º in the sagittal plane and was pushed to the skull base until its tip reached 2.5 mm anterior to thechiasma. The burr hole was then sealed with bone wax. 0.3 ml of the sample of arterial blood from the right femoral artery was then injected aseptically into the pre-chiasmatic cistern using a syringe pump for about 60 sec. The rats were kept in a head-down position at 30º for 30 min to permit the blood flow around the basal arteries. After this procedure, the rats were allowed free access to food and water for 48 hours. Using a described scoring system, the neurological function of all animals were recorded. The results showed that the neurobehavioral deficits were improved, brain edema was significantly reduced on the administration of quercetin.[18]

Another study aimed to analyse the neuroprotective effects of quercetin on neurons in the cecum of diabetic rats. Experiment was carried out on twenty-four rats by preparing muscular tunic from their cecadividing into four groups namely - control, control supplemented with quercetin (200 mg/kg), diabetic and diabetic supplemented with quercetin. Immunohistochemical double staining technique was performed followed by density analysis of neuronalpopulation.

This study proves that treatment with quercetin helps to reduce the diabetes-associated dilation of the cecum in diabetic supplemented with quercetin group to 34% of the controls. Further, it exhibits a neuroprotective effect by maintaining the density of the general neuronal population but did not affect the density of the subpopulation.[19]

2.7 Ischemia-Reperfusion Injury Of The Eye

A population based case study was carried out to evaluate the intakes of the flavonoid subclasses and the risk of ophthalmological diseases. Dietary datawasgatheredandresults showed that quercetin intake is inversely associated with age relatedophthalmological risk. Higher quercetin intake is an important dietary factor in the reduction of the risk of ophthalmological diseases.[20]

An experiment was performed to analyse the effect of quercetin on retina by reducing apoptosis induced by ischemia-reperfusion injury in a rat model.Ischemia/reperfusion injury (IRI) is caused by a sudden temporary impairment of the blood flow to the particular organ(http://www.journalrip.com/PDF/JRIP-4-20.pdf) It was conducted on twenty-four rats which were divided into four equal groups by elevating the intraocular pressure above the perfusion pressure - control, ischemic, solvent, and quercetinischemia-reperfusion injury. Immediately prior to ischemia-reperfusion injury, intra-peritoneal injections of 20 mg/kg of quercetin and dimethyl sulfoxide were performed in the quercetin and solvent groups, while the retinas were allowed to be reperfused.

The thicknesses of the retinal ganglion cell layer, inner nuclear layer, inner plexiform layer, outer plexiform layer and outer nuclear layer were measured after forty-eight hours in all groups after injury.The results showed that administration of quercetinreduces the thinning of all retinal layers. The anti-apoptotic effect of quercetin was observed on the mean number of TUNEL (+) cells in inner nuclear layer in the ischemic and quercetin groups which was ($P<0.005$) while, that of caspase-3 (+) cells in inner nuclear layer of ischemic and quercetin groups was ($P<0.001$) respectively. Therefore, use of quercetin is beneficial in the treatment of retinal injury because of its anti-apoptotic effect.[21]

2.8. Allergic Rhinitis

Quercetin has been known to modify the clinical conditions of allergic diseases such as allergic rhinitis (AR) by its anti-inflammatory and anti-allergic effects.

The effect of quercetin on the development of Allergic rhinitis(AR) was analyzed by using model rats. The sensitization of rats was done with toluene 2,4-diisocyanate(TDI) by the method of intranasal instillation of a 10 % TDI in ethyl acetate in a volume of 5 µl.This was done for 5 continuous days(once in a day).After a 2-day interval this procedure was again repeated.Rats were then treated after 5 days of the second sensitizationwith various dosages of quercetin.This was done for 2 to 7 days.The initiation of Nasal allergy-like symptomswas done by bilateral application of TDIin ethyl acetate.This was determined by counting sneezing and nasal rubbingbehaviors for 10 min just after TDI nasal challenge.After TDI nasal challenge, the levels of calcitonin gene-related peptide (CGRP) and nerve growth factor (NGF) in nasal lavage fluids wereanalyzed by ELISA.The inhibition of sneezing and nasal rubbing movements was observed if quercetin was given orally for5 and 7 days but not 2 and 3 days.

The minimum dosage that caused notable inhibition was 25 mg/kg.The increase in CGRP and NGF contents in nasal lavage fluids was inhibited by oral administration of quercetin at more than 25 mg/kg for 5 days.This proves that quercetin can be a good supplementfor the management and treatment of Allergic diseases.[22]

2.9 Cardiovascular diseases

Globally, cardiovascular diseases are the number one cause of death. It is is caused by risk factors such as high blood pressure, cholesterol, overweight/obesity, tobacco use, lack of physical activity and diabetes that can be controlled, treatedormodified.[23] [24]

Flavonoids have positive effects on cardiovascular, neoplastic and neurodegenerative diseases. The most significant studies are on its antioxidant effect.

The aim of a study by CiviS , et al was to prove the effects of Quercetin in an experimental rat model of chronic constriction injury (CCI).42 adult Wistarrats were randomly assigned to different groups.Chronic constriction injury to thesciatic nerves and single dose of quercetin,morphine and gabapentinewas given to animals in control.Different dosages of quercetin were given to different groups of animals.The evaluation of mechanical hypersensitivity,thermal sensitivity, locomotor activity and anxiety for Pre-injury and post-injury wererecorded and different groups were compared.

Quercetin had more significant effects in chronic constriction injury model ascompared to morphine and gabapentine.Quercetin was more effective than Gabapentine and morphine in terms ofalleviating mechanical and thermal hypersensitivity. Also, if quercetin is given before injury for 4 days, long-term effectiveness on mechanical hypersensitivity was observed.[25]

2.10 Post-traumatic Cardiac Injury

Inflammation and oxidative stress contributes to secondary cardiac dysfunctionas they have significant roles in posttraumatic cardiomyocyte apoptosis. The protective effect of quercetin on trauma-induced secondary cardiacinjury was studied by Jing Z, et al. The evaluation of cardiomyocyte apoptosis and cardiacdysfunction in rats(IN VIVO) was done using TUNEL staining and a biological mechanic experiment system.The recognition of In vitro, cell viability, tumor necrosis factor-a (TNF-a),reactive oxygen species (ROS) and [Ca(2+)] of H9c2 cells was done using an MTT assay,ELISA, and 2',7'-dichlorofluorescindiacetate and fluo-4 acetoxymethyl ester assays respectively.Posttraumatic cardiomyocyte apoptosis and cardiac dysfunction was improved whenquercetin was given before treatment.

This tells us that quercetin switches posttraumatic cardiac dysfunction by decreasingcardiomyocyte apoptosis through the suppression of TNF-a ,ROS overproduction and Ca(2+) overload in cardiomyocytes.It illustrates a likely deterrent approachfor the treatment of secondary cardiac injury after mechanical trauma.[26]

III. CONCLUSION

After going through various studies on how quercetin can play a major role in decreasing the effect of various diseases, we can conclude that the compound quercetin has high potential in the field of medicine, for the treatment of diseases like, cancer, cardiac injury, diabetes etc. Quercetin taken in small amounts has minimal side effects. This makes it a potent natural supplement that can be included in our diet.

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