World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 7, Issue 2, 2018 ISSN: 2319-5622 USA CODEN: JPROK3

Review Article

# RUTIN: A PHARMACOLOGICAL REVIEW

**Nitin B. Ghiware [1], Akshay Rautrao [1], Pavan P. Wankhade [1], Ajay D. Kshirsagar [2], Haidarali M. Shaikh [1] ***

*[1] Center for Research in Pharmaceutical Sciences (CRPS), Nanded Pharmacy College, Op. Kasturba Matru Seva Kendra, Shyam Nagar, Nanded-431605(M.S), INDIA.*

*[2] School of Pharmacy, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded, Maharashtra 431606, INDIA.*

**Received on: 12-02-2018; Revised and Accepted on: 26-02-2018**

## *ABSTRACT*

***R**utin (quercetin 3-O rutinoside), is a flavonol glycoside between the flavonol quercetin and the disaccharide rutinose (α-L-Rhamnopyranosyl-(1→6)-β-D-glucopyranose) also known as Vitamin P. Rutin has been claimed to possess various pharmacological properties by various researchers through in-vivo and in-vitro studies. Rutin has been known to function as an anti-cancer, anti-bacterial and anti-inflammatory agent along with anti-diabetic, cardioprotective and neuroprotective agent. The molecular targets for showing various activities are found to be TNF-α, NFk-B, iNOS, EGRF, AP-, ERK1/2, JAK2 signaling, IL-1b, PARP, DNA pol β and DNA ligases, and PI3 kinase. So taking inconsideration the action of rutin on these molecular targets and correlating their roles the prediction can be made about beneficial effects of rutin in diseases such as viral infections, AIDS, multiple sclerosis, bone resorption, muscular dystrophy, incontinentia pigmenti, COPD.*

***KEYWORDS:** Rutin, Anti-Cancer, Anti-Inflammatory, Anti-Diabetic, Cardioprotective Neuroprotective agent, TNF-α.*

## INTRODUCTION

**R**utin (quercetin 3-O rutinoside), is a flavonol glycoside composed of the flavonol quercetin and the disaccharide rutinose (α-L-Rhamnopyranosyl-(1→6)-β-D-glucopyranose) [1-3]. Rutin is plenteous in a variety of commonly ingested foods. As *Ruta graveolens* contains rutin as its one of the main chemical constituents that's why it is referred as rutin. Onion, wine, grape, some of the fruits, teas and buckwheat contains rutin [2]. The buds and flowers of *Sophora japonica* contain between 15-20 % of rutin, while the leaves contains 2-8% rutin [4]. The other sources of rutin are the *Rheum* species, *Asparagus*, pagoda tree, *citrus* fruits (like orange, grapes, lemon, lime) ash tree, berries such as mulberry and cranberries. It is also found in Clingstone peaches as one of the primary flavonol. European Elder (berry), Hawthorn (*Crataegus laevigata*), Horse tail (*Equisetum arvense*), Bilberry (*Viccinium myrtilus*) [5].

Rutin has been claimed to possess various pharmacological properties by various researchers through *in-vivo* and *in-vitro* studies. Rutin has good anti-oxidant activity [6]. Rutin works as a scavenger of reactive oxygen species (ROS) by donating hydrogen atoms to peroxy radicals, superoxide anions, and singlet oxygen and hydroxyl radicals. It also functions as a terminator and chelator of metal ions that are capable of oxidizing lipid peroxidation [11].

Above more ever studies suggest that rutin alters signal transduction, causes activation of transcription factors and gene expression, and may also shelter DNA by interacting with carcinogens that have passed out the detoxification processes [11]. A handful of studies also demonstrated effectiveness of rutin in kidney protection effect in ischemia/reperfusion renal injury as well as in drug-induced nephropathy and diabetic nephropathy [12].

The renal protective effect of rutin on chronic kidney dysfunction besides diabetic nephropathy is being studied with the possible mechanisms and potential therapeutic approaches to progression of chronic kidney disease (CKD) with renal mass reduction [13, 14]. Rutin is one of the naturally derived compounds; it is usually nontoxic and manifests a diverse range of worthwhile biological activities [7].

As anti-thrombic agent the rutin gains advantages over agents like Juniferdin or Bacitracin by overcoming their limitations such as cytotoxicity or non-selectivity. Rutin is selective towards extra-cellular PDI (Extracellular protein disulfide isomerase) and is relatively non-toxic [5]. More ever the potential use of rutin in protecting cognitive deficits and for the treatment of sporadic dementia of Alzheimer type senile dementia type Alzheimer (SDAT) was studied [14]. Kamalakkannan N investigated the antihyperglycaemic and antioxidant effect of rutin [15].

By taking in conformity the importance of this natural bioconstitiuent rutin in variety of diseases mentioned above. This review is intended to piece together all the molecular aspects with reference to the mechanism of action of rutin in respective diseases and the future prospective and possibilities regarding the implementation of rutin in other ways in these diseases.

## PHARMACOLOGICAL ACTIVITIES OF RUTIN:

### 1. Antioxidant Activity:

The rutin was known to possess the strong antioxidant activity. In one of the study carried out by Jianxiong Yang *et al* by using the various in vitro antioxidant models, he concluded that rutin showed the concentration dependent antioxidant activity [16]. This antioxidant potential of rutin plays very key role in the management of various disorders like cancer, myocardial infraction etc. Free radical scavenging, antiradical and metal ion-chelating actions, along with the ability to react with superoxide ion and inhibit xanthine oxidase and lipid peroxidation of flavonoids have been reported in various model systems. Flavonoids, especially quercetin and rutin, are known to have strong scavenging ROS, chelating iron ions, which play a vital role in

***Corresponding author:**

***Haidarali M. Shaikh***

*Center for Research in Pharmaceutical Sciences (CRPS),*
*Nanded Pharmacy College,*
*Op. Kasturba Matru Seva Kendra,*
*Shyam Nagar, Nanded-431605(M.S), INDIA.*
** E-Mail: haidar26ali@gmail.com*

**DOI: https://doi.org/10.5281/zenodo.1188425**

initiating free radical reactions as well as suppressing the generation of hydroxyl radicals in the Fenton reaction. ROS plays important role in a wide range of human diseases such as atherosclerosis and cancers. Imbalance between ROS generation and antioxidants leads to oxidative damage to all cell targets (DNA, lipids, and proteins) [26-30]. The presence of one or several phenolic groups leads to the antioxidant activity thus related to their ability to act as free radical scavengers [17]. Rutin is one of the flavonol glycosides so that it is known to have the strong antioxidant, ion chelating, radical scavenging activity is directly proportional to the presence of a hydroxyl group of the C ring, in position three i.e.3-OH. Rutin possesses four hydroxyl groups: at C-5, C-7 of A ring and at C-3', C-4' of B ring also most of the flavonoids having both a C-4 carbonyl group and a C-3 or C-5 hydroxyl group same as in case of rutin known to form chelates with iron ions as well as sequester metal ions, this leads to their antiperoxidative properties by preventing the formation of free radicals [62].

**2. Anticancer Activity:**

Several studies suggest that diets rich in fruit and vegetables exert protective effects against cardiovascular disease and certain cancers [31-33]. This effect may be due to the presence of antioxidant activity. The ROS of both endogenous and exogenous sources can cause the disturbance in the pro-oxidant and antioxidant balance which may lead to cell damage.[20]One of the reasons behind the occurrence of carcinogenesis is DNA damage combined with insufficient DNA repair [21, 22].

There were various studies have been performed which confirms the anti-cancer potential of rutin. Rutin shows in vivo antitumor effects along with exerts anti angiogenic properties, lacks toxic effects on mice bearing colon tumor had been revealed during study [23]. The effectiveness of rutin in human leukemia and murine leukemia cells were reported in two different studies which shows that the differentiations of the precursors of macrophage and T cells were inhibited [23, 24]. Likewise many other studies were carried out for proving effectiveness of rutin as the potential anticancer agent. Results of one study which was carried out by Comet assay using HepG2 cells proves the effectiveness of quercetin and urosolic acid as antigenotoxic at this level but same effect not seen in case of rutin which may leads to conclusion that rutin may acts by another mechanism.[25] The Cyclin D1 protein belongs to the G1 cyclin class which plays key role in regulation of cell cycle. More ever the recent work shows that over expression of this protein may leads to the colorectal carcinogenesis. Rutin shows expression of Cyclin D1 protein so it can be correlated with its anticancer potential. Likewise rutin also possesses capacity to inhibit growth and induce differentiation of cultured glioblastoma cells; decreased levels of extracellular-signal-regulated kinases1/2 (ERK1/2) phosphorylation (P-ERK1/2) and accumulation of cells in the G2 phase of the cell cycle may be the possible reason for these effects. [34] Rutin possess the regulating effect on reactive oxygen species mediated mitochondrial dysfunction pathway which is responsible for protective effect on the intracellular GSH (glutathione) antioxidant system and prevented $H_2O_2$-induced apoptosis of HUVECs [35].

Studies shows that the upregulated levels of cyclooxigenase-2 (COX-2) are observed in cancer cells [76-78]. Eukaryotic transcription factors such as nuclear factor NF-kappa-B (NF- kB) or activator protein-1 (AP-1) responsible for the regulation of the expression of COX-2 [83], ultimately blocking of COX-2 expression due to the inhibition of AP-1 and NFkB might lead to the suppression of cell transformation [79, 80]. In the work carried out by one of the researcher found that rutin reduces B[a]PDE-induced COX-2 expression through AP-1 and NF-kB as well as inhibits the B[a]PDE-induced phosphorylation of the Raf/MEK/ERK and PI3 K/Akt pathways Therefore, rutin shows significant chemoprotective property because epidermal growth factor receptor (EGFR) and the upregulation of COX-2 have been detected in many types of cancer [84-87]. COX-2 is upregulated by activated EGFR through an EGFR-Ras-MAPKs-AP-1-COX-2 cascade [81, 82]. Rutin suppressed B[a] PDE-induced COX-2 expression by targeting epidermal EGFR [88]. Rutin acts in case of DNA damage in the form of single-strand breaks induced by hepatocarcinogens by modulation of DNA damage and repair enzymes. DNA single-strand breaks necessitate the induction of repair enzymes, particularly Poly (ADP-ribose) polymerase (PARP). At the time of maximum DNA damage, PARP activity has been observed to be highest [64]. This is to be expected since various DNA damages bring about a considerable increase in PARP activity [65-67]. Rutin decreases DNA damage ultimately the activities of PARP, DNA polymerase β and DNA ligases are also reduced [64]. The reduction in proliferation and viability of glioblastoma cells by rutin mediated through the decreased levels of ERK1/2 phosphorylation P-ERK1/2 likewise accumulation of cells in the G2 phase of the cell cycle along with the nuclear condensation and DNA fragmentation is seen [34].

**3. Effect of Rutin as Anti-Inflammatory:**

The inflammation is an essential phenomenon; it works as the alarm in many harmful conditions. This protective response helps to optimize the possible damage in such conditions. Marked inflammation and associated failure of repair process is characteristic of various autoimmune disorders. Proinflammatory molecules like tumor necrosis factors alpha (TNFα), certain interleukins, prostaglandins and even pathogenic concentration of nitric oxide are significant in such conditions. Thus we can correlate inflammatory condition to many diseases [36]. The study of rutin derived from *Ruta graveolens* L. (Rutaceae) revealed the anti-inflammatory effect of rutin by downregulation of nitric oxide synthase (iNOS) and COX-2 [37]. The anti-inflammatory effect of rutin have been revealed by using carrageenan induced rat paw oedema model, the results showed the decreased inflammatory conditions furthermore it is also observed that rutin reduced the polymorphonuclear neutrophils chemotaxis to fMet-Leu-Phe significantly in a dose-dependent manner, along with elastase exocytosis also inhibited [38]. Another study by researchers concluded the effectiveness of rutin against cisplatin-induced renal inflammation and apoptosis [40]. Rutin may be useful for the prevention and treatment of inflammatory bowel disease (IBD) and colorectal carcinogenesis via attenuation of pro-inflammatory cytokine production through regulation of interleukine-1b (IL-1b) and interleukine-16 (IL-6) gene expression. Likewise some other studies also showed that rutin has been reported to attenuate trinitrobenzenesulfonic acid (TNBS) induced colitis in rats, presumably by managing the intestinal oxidative stress. Aslike Galvez et al. also found that oral administration of rutin plays significant role in prevention of colonic damage and inflammation associated with acetic acid-induced colitisin rats [41-43]. The effectiveness of rutin was also been investigated by using the acute and chronic models of inflammation. The result of given study showed that the rutin is most effective in chronic phase of inflammation of adjuvant arthritis [44].

In case of renal fibrosis rutin may act via inhibiting the activation of transforming growth factor beta1 (TGFβ1-smad) signaling which leads to decrease in inflammatory conditions in fibrosis [3]. Up-regulation of pro-inflammatory mediators NFkB and pro-inflammatory cytokines i.e. tumor necrosis factor-alpha (TNF-α), IL-1b accompanied by dysregulated immune responses resulting in tissue damage ultimately leads to the ulcerative colitis, inflammatory bowel disease and Crohn's disease [69]. It is known that nuclear factor NFkB is being strongly activated by the expression of TNF-α which is itself up-regulated by NFkB. These two auto regulated factors known to have vital role in management of the inflammatory conditions [70, 75]. For this reason, therapeutic intervention against TNF-α or NFkB activation has been used for treatment of inflammatory bowel disease (IBD) [70, 71]. Rutin causes expression of NF-κB-dependent luciferase (NFDL) reporter gene and induction of interleukine-8 (IL-8), a target gene of NFkB mediated through TNF-α. Further it can be correlated with the attenuation of IL-8 induction which is well known neutrophil-attracting chemokine was well correlated with reduction of myeloperoxidase (MPO) activity i.e. an indicator for recruitment of neutrophil in the distal colon beneficial in colitis. [72, 73, 75]. Rutin as similar to other flavonoids interferes with the binding of p65 to DNA leads to the suppression of TNF-α –induced NFkB activation resulting in inhibition of the transcriptional activity of NFkB [74, 75].

**4. Effect of Rutin on CNS:**

Rutin also claimed for its effect on the CNS. The beneficial effects of rutin in treating CNS related disorders is one of the topic of interest for the researchers as it belongs to phytochemical constituent of plant species which claimed to posses the potential to treat various CNS related complications and known to have lesser side effects than the other medication used in treatment of CNS related disorders. One of the major clinical issues associated in the treatment of schizophrenia is tardive dyskinesia (TD), a motor disorder of the orofacial region, resulting from chronic neuroleptic treatment. In the pathophysiology of

neuroleptic-induced TD increased reactive oxygen species and oxidative are implicated [45]. The author stated that rutin appears to be particularly responsible for neuroprotective action against haloperidol-induced TD as well as in the prevention of neuroleptic-induced orofacial dyskinesia [46]. Rutin also showed the neuroprotective effect by improving levels of antioxidant enzyme along with inhibiting lipid peroxidation in 6-hydroxydopamine (6-OHDA)-induced pheochromocytoma-12 (PC-12) cells [48]. So these effects have been proven to be the major deciding factor in neurodegenerative diseases such as Parkinson's and Alzheimer's diseases [47]. M. M. Khana *et al* concluded that rutin was proven a novel approach in lowering the risk or improving the function of ischemia–reperfusion brain injury-related disorders as results showed marked reduction in infarct size, suppressed neuronal loss, reduced the neurological deficits in terms of behaviours and diminished the p53 expression in MCAO rats after rutin treatment [49]. Rutin is essential for the antidepressant activity of *Hypericum perforatum* extract, a plant which was traditionally known for its anti-depressant properties used in many countries for the treatment of mild to moderate forms of depression which was being proven by study which confirms that it possesses a synergistic effect with *Hypericum perforatum* extract in the forced swimming test [50]. Antidepressant-like effect of ethanolic extract of *Schinus molle* and its isolated constituent rutin was studied by using the tail suspension test the results of the given study confirms the antidepressant property. In this study immobility time reduced in test group but no such effect was seen in case of forced swim test. This preclinical evaluation also provides evidence for the involvement of the serotonergic and noradrenergic and/or dopaminergic systems in the mechanism of the antidepressant-like action of rutin [51].

Rutin has a direct effect on glial cells in vitro act through the activation of astrocytes and microglia, TNFα release, and iNOS induction; this may be beneficial in management of the various CNS disorders [68]. Rutin also known to have protective effect on neural crest cells via down regulation of regulation of extracellular-signal-regulated kinases1 (ERK2) and phosphatidylinositol-3-kinases (PI3 kinase) in Neural crest (NC) cell might be due to two mechanisms: (1) enhanced cell proliferation (2) decreased cell death as the extracellular-signal-regulated kinases (ERK) and phosphatidylinositol-3-kinases (PI3 kinase) signaling pathways regulate several cellular responses including apoptosis, mitosis, motility, proliferation and differentiation [89-93]. The protective effect in ischemic neural apoptosis which is being seen in after rutin treatment is by attenuating the reduction of the p53 expression leads to decreased oxidative stress [49].

**5. Effect of Rutin on CVS:**

Rutin known to have beneficial effects in improvement of CVS complication such as hypertension, hyperlipidemia and myocardial infarction [54]. Vasorelaxant and hypotensive effects of rutin were determined in normotensive anaesthetized rats, a significant non concentration-dependent relaxing effect [52]. In vitro the inhibitory effect on angiotensin-converting enzyme (ACE) activity was studied results of study showed that at concentrations of rutin, this confirms the rutin had potent antihypertensive activity [53]. In an in vivo study, the preventive role of rutin on lipoproteins, lipids and ATPases in normal and isoproterenol (ISO) induced myocardial infarction in rats. Rutin significantly lowered levels of acids (FFAs), low density lipoproteins-C (LDL-C), cholesterol, triglycerides (TGs), free fatty and very low density lipoproteins-C (VLDL-C) in serum and increased the level of high density lipoproteins-C (HDL-C) in serum in ISO-treated rats. Rutin pre-treatment showed a significant increase in the activities of Na+/K+-ATPase and Mg2+-ATPase and decrease in the activity of Ca2+-ATPase in ISO-treated rat. [55] Rutin administration showed increased levels of TC, TGL, HDL and VLDL, whereas levels of LDL have decreased [56].

The study showed that the flavonols of quercetin and rutin diminished Cu2+-oxidized LDL-induced ROS generation and mitigated endothelial apoptosis by modulating cellular apoptotic machinery via initiation of Janus kinase signal transducer and activator of transcription (JAK-STAT) signaling, leading to differential activation of mitogen-activated protein kinases (MAPK)-dependent mechanisms rutin exhibited protection against oxidized LDL through hampering MAPK dependent pathways involving the activation of JAK2 which proves beneficial in management of myocardial infarction [94]. The mechanisms of protective effects of rutin in case of the $H_2O_2$-induced cytotoxicity and apoptosis in human umbilical vein endothelial cells (HUVECs) are contributed to a combination of reactive oxygen species down-regulation, glutathione (GSH) upregulation, lastly by suppressing endothelial cell apoptosis. Since increases in oxidative stress is key factor which cusses the endothelial cell injury having vital role in cardiovascular diseases, in such cases rutin can be used in the treatment of cardiovascular diseases [35].

**6. Antidiabetic Activity:**

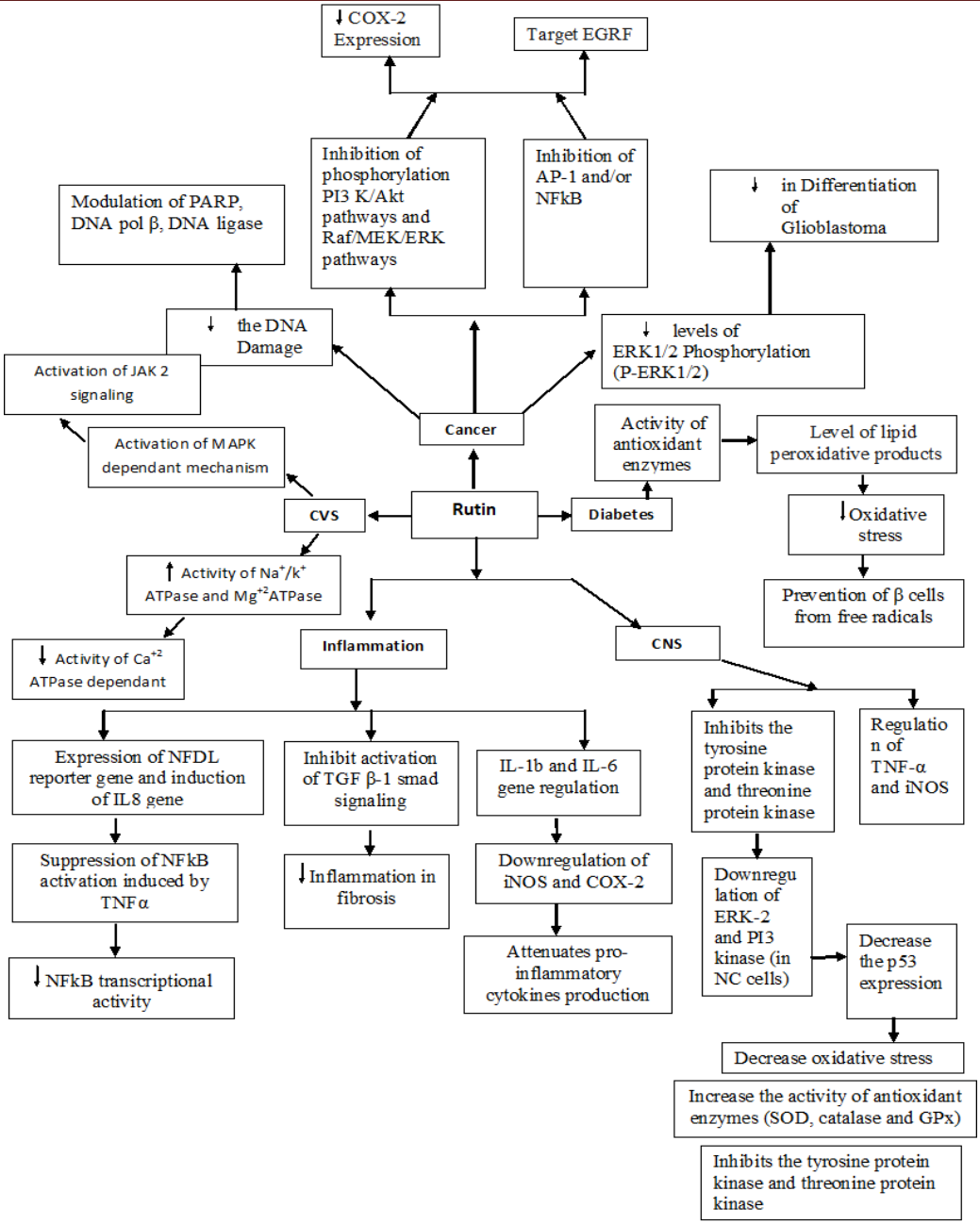
Diabetes mellitus is one of the metabolic disorders characterized by hyperglycemia. The metabolic disorders include alterations in the carbohydrate, fat, and protein metabolisms associated with absolute or relative deficiencies in insulin secretion and insulin action. Insulin secretion from pancreatic β-cells and insulin action on liver, muscle and other target tissues helps to maintain blood glucose level [63]. Rutin treatment to diabetic rats significantly reduced plasma glucose levels and increased insulin levels. As being a polyphenolic flavonoid, the intact functional β-cells to produce insulin and/or protect the functional β-cells from further deterioration could be induced by rutin so that they remain active and produce insulin [57]. Diabetic pancreas is characterized by increase in the lipid peroxidative products such as thiobarbituric acid reactive substances (TBARS) and haptoglobin (HP) and a decrease in antioxidant activity. Pancreas possesses low levels of antioxidants and is more susceptible to oxidative damage [61]. Rutin was able to increase the activities of antioxidant enzymes (SOD i.e. Superoxide dismutase, catalase, and GPx i.e. glutathione peroxidase) and decrease the concentration of lipid peroxidative products in diabetic pancreas. The capacity of flavonoids to transfer electrons, free radicals, chelates metals catalysts and activates antioxidant enzymes in biological system. After the treatment of rutin plasma of streptozotocin (STZ) diabetic rats found to have decreased lipid peroxidation and improved antioxidant status [57]. Rutin was also known to protect the functional β-cells of the islets by scavenging free radicals and restoring the antioxidant enzyme activities of the pancreas. Some researchers have pointed out that flavonoids have the ability to protect and regenerate β-cells of the islets of Langerhans [58-60].

**NEW POSSIBILITIES OF RUTIN IN DIFFERENT DISEASES:**

As seen we came to know the various targets through which rutin acts to claim its therapeutic importance.

The one of the molecular target of rutin is NF-kB [70-73, 75]. According to studies NF-kB plays important role in management of nearly dozens of diseases such as atherosclerosis [96-98], asthma [99-103], viral infections, AIDS [104-108], tumorigenesis, diabetes, muscular dystrophy[109-113], incontinentia pigmenti [114-116], rheumatoid arthritis, multiple sclerosis[117-119], bone resorption [120-124], heart diseases, Alzheimer's disease, and so on.

The Down regulation of COX-2 expression is another main characteristic of rutin, besides regulating the inflammation COX-2 also known to play important function in maintaining sound health. Studies show that kidney developed severe disruption in COX-2 null mice [126, 127]. So this can be linked to the Hepatoprotective characteristic of rutin. Induced COX-2 levels are being observed during the ovulation as it is necessary for the successful rupture of the follicle.COX-2 responsible for uterine contraction during labor [128-130]. By down regulating the COX-2 expression rutin may affect uterine contraction and proportionally prolong the pregnancy time during labor. By down regulating the function of IL-8 gene rutin may prove to be useful in chronic obstructive pulmonary disorders.




## CONCLUSION

The surplus of research which has been carried out divulge that the rutin has wide range of beneficial pharmacological properties like antioxidant, anticancer, anti-inflammatory, antidiabetic, neuroprotective and cardioprotective effects along with molecular targets in respective diseases also revealed. On basis of these molecular targets the possible beneficial effects of rutin in case of some other diseases like viral infections, AIDS, multiple sclerosis, bone resorption, muscular dystrophy, incontinentia pigmenti, COPD etc. also proposed. The main disadvantage of rutin is its poor aqueous solubility which lids to poor bioavailability and second possible reason for poor bioavailability is that before absorption rutin must be hydrolyzed into quercetin. The researchers must do work in the direction to increase the bioavailability of rutin along with the role of rutin in management of other diseases.

**ABBREVIATIONS:**

Reactive oxygen species (ROS),
Chronic kidney disease (CKD),
Extra-cellular PDI (Extracellular protein disulfide isomerase),
Sporadic dementia of Alzheimer type senile dementia type Alzheimer (SDAT),
Extracellular-signal-regulated kinases1/2 (ERK1/2),
Phosphorylation extracellular-signal-regulated kinases1/2 (P-ERK1/2),
Cyclooxigenase-2 (COX-2),
Tumor necrosis factors alpha (TNFα),
Nuclear factor NF-kappa-B (NF- kB),
Activator protein-1 (AP-1),
GSH (glutathione),
Epidermal growth factor receptor (EGFR),
Poly (ADP-ribose) polymerase (PARP),
Nitric oxide synthase (iNOS),
Inflammatory bowel disease (IBD),
Interleukine-1b (IL-1b),
Interleukine-16 (IL-6),
Trinitrobenzenesulfonic acid (TNBS),
Transforming growth factor beta1 (TGFβ1-smad),
Tumor necrosis factor-alpha (TNF-α),
NF-κB-dependent luciferase (NFDL),
Interleukine-8 (IL-8),
Myeloperoxidase (MPO),

Tardive dyskinesia (TD),
6-hydroxydopamine (6-OHDA),
Pheochromocytoma-12(PC-12),
Extracellular-signal-regulated kinases1 (ERK2),
Phosphatidylinositol-3-kinases (PI3 kinase),
Neural crest (NC) cell,
Isoproterenol (ISO),
Low density lipoproteins-C (LDL-C),
Triglycerides (TGs),
Very low density lipoproteins-C (VLDL-C) ,
High density lipoproteins-C (HDL-C),
Janus kinase signal transducer and activator of transcription (JAK-STAT) signaling,
Mitogen-activated protein kinases (MAPK),
Human umbilical vein endothelial cells (HUVECs),
Glutathione (GSH),
Thiobarbituric acid reactive substances (TBARS),
Haptoglobin (HP),
Superoxide dismutase (SOD),
Glutathione peroxidase (GPx),
Streptozotocin (STZ).

**REFERENCES:**


1. Nidhi Gupta. A bioactive Flavonoid, Handbook of Medicinal Plants and their Bioactive Compounds. Research sign post, Trivandrum **2014**;51-57.
2. Jasuja R, Passam FH, Kennedy DR., Kim SH, Hessem LV, Lin L, Bowley SR, Joshi SS, Dilks JR, Furie B, Furie BC and Flaumenhaft R. Protein disulfide isomerase inhibitors constitute a new class of antithrombotic agents. J Clin Investig **2012**;122(6):2104–13.
3. Yu Han, Jin-Shan Lu, Yong Xu, Lei Zhang, Bao-Fa Hong, Rutin ameliorates renal fibrosis and proteinuria in 5/6-nephrectomized rats by anti-oxidation and inhibiting activation of TGFβ1-smad signaling . Int J Clin Exp Pathol **2015**;8(5):4725-4734
4. Natha´ lia Lucci and Paulo Mazzafera. Distribution of rutin in fava d'anta (Dimorphandra mollis) seedlings under stress. J Plant Interact **2009**;4(3):203-208.
5. Mohammad Arif Dar, Nahida Tabassum, Rutin- potent natural thrombolytic agent. Int Cur Pharm J **2012**;1(12):431-435.
6. Salem S. Al-Rejaie, Abdulaziz M. Aleisa, Mohamed M. Sayed-Ahmed, Othman A. AL-Shabanah, Hatem M. Abuohashish, Mohammed M. Ahmed, Khaled A. Al-Hosaini and Mohamed M. Hafez. Protective effect of rutin on the antioxidant genes expression in hypercholestrolemic male Westar rat. BMC Complem and Altern Med **2013**;13:136.
7. Wenying Ren, Zhenhua Qiao, Hongwei Wang, Lei Zhu, Li Zhang, Flavonoids: Promising AnticancerAgents. Med Res Rev **2003**;23(4):519-534.
8. Kamel KM, Abd El-Raouf OM, Metwally SA, Abd El-Latif HA and El-sayed ME. Hesperidin and rutin, antioxidant citrus flavonoids, attenuate cisplatin-induced nephrotoxicity in rats. J Biochem Mol Toxicol **2014**;28:312-319.
9. Khan RA, Khan MR and Sahreen S. Protective effects of rutin against potassium bromate induced nephrotoxicity in rats. BMC Complement Altern Med **2012**;12:204.
10. Kampkotter A, Nkwonkam CG, Zurawski RF, Timpel C, Chovolou Y, Watjen W and Kahl R. Investigations of protective effects of the flavonoids quercetin and rutin on stress resistance in the model organism Caenorhabditis elegans. Toxicol **2007**;234:113-123.
11. Srinivasan M, Rukkumani R, Ram Sudheer A and Menon VP. Ferulic acid, a natural protector against carbon tetrachloride-induced toxicity. Fundam Clin Pharmacol **2005**;19:491-496.
12. Korkmaz A and Kolankaya D. Inhibiting inducible nitric oxide synthase with rutin reduces renal ischemia/reperfusion injury. Can J Surg **2013**;56:6-14.
13. Alvarez-Prats A, Hernandez-Perera O, Diaz-Herrera P, Ucero AC, Anabitarte-Prieto A, Losada-Cabrera A, Ortiz A and Rodriguez-Perez JC. Combination therapy with an angiotensin II receptor blocker and an HMG-CoA reductase inhibitor in experimental subtotal nephrectomy. Nephrol Dial Transplant **2012**;27:2720-2733.
14. H. Javed, MM. Khan, A. Ahmad, K. Vaibhav, ME. Ahmad, A. Khan, M. Ashafaq, F. Islam, MS. Siddiqui, MM. Safhi, F. Islam. Rutin prevents cognitive impairments by ameliorating oxidative stress and neuroinflammation in rat model of sporadic dementia of Alzheimer type. Neuroscience **2012**;210:340-352.
15. Kamalakkannan N, Prince PS. Antihyperglycaemic and antioxidant effect of rutin, a polyphenolic flavonoid, in streptozotocin-induced diabetic wistar rats. Basic Clin Pharmacol Toxicol **2006**;98(1):97-103.
16. Jianxiong Yanga, B. Juan Guoa, Jiangfeng Yuanb, In vitro antioxidant properties of rutin. LWT **2008**;41:1060–1066.
17. O. Benavente-Garcia, J. Castillo, J. Lorente, A. Ortuno and JA. del Rio. Antioxidant activity of phenolics extracted from Olea europaea L. leaves Food Chem **2000**;68:457.
18. G. Cao, E. Sofic and RL. Prior. Antioxidant and prooxidant behavior of flavonoids: structure-activity relationships. Free Radi Biol and Med **1997**;22(5):749–760.
19. JE. Brown, H. Khodr, RC. Hider and C. Rice-Evans. Structural dependence of flavonoid interactions with Cu2+ ions: implications for their antioxidant properties. Biochem J **1998**;330(3):1173–1178.
20. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Intera **2006**;160:1–40.
21. Olinski R, Gackowski D, Foksinski M, Rozalski R, Roszkowski K, Jaruga P. Oxidative DNA damage: assessment of the role in carcinogenesis, artherosclerosis, and acquired immunodeficiency syndrome. Free Radic Biol Med **2002**;33:192–200.
22. Klaunig JE, Kamendulis LM. The role of oxidative stress in carcinogenesis. Annu Rev Pharmacol Toxicol **2004**;44:239–267.
23. Angel Josabad Alonso-Castro, Fabiola Domınguez, Alejandro. Garcia-Carrancia Rutin Exerts Antitumor Effects. Archi Med Res **2013**;44:346-351.
24. Jing-Pin Lina, Jai-Sing Yangb, Chi-Cheng Luc, Jo-Hua Chiangc, Chang-LinWud,
Jen-Jyh Line, Hui-Lu Linf, Mei-Due Yangg, Kuo-Ching Liuh, Tsan-Hung Chiui, Jing-Gung Chungd,J. Rutin inhibits the proliferation of murine leukemia WEHI-3 cells in vivo and promotes immune response in vivo Leukemia. Res **2009**;33:823–828.
25. AA. Ramosa, CF. Limaa, ML. Pereira b, M. Fernandes-Ferreira, C. Pereira-Wilson. Antigenotoxic effects of quercetin, rutin and ursolic acid on HepG2 cells: Evaluation by the comet assay. Toxicol Lett **2008**;177:66–73.
26. IB. Afanas'ev, AI. Dorozhko, AV. Brodslui, VA. Kostyuk and AI. Potapovitch. Chelating and free radical scavenging mechanisms of inhibitory action of rutin and quercetin in lipid peroxidation. Biochem Phumcol **1989**;38:1763-1769.
27. SJ. Duthie, AR. Collins, GG. Duthie and VL. Dobson. Quercetin and myricetin protect against hydrogen peroxide-induced DNA damage(strand breaks and oxidized pyrimidines) in human lymphocytes. Mutut Res **1997**;393**:**223-23 1.
28. T. Nakayama, M. Yamada, T. Osawa and S. Kawalushi. Suppression of active oxygen-induced cytotoxicity by flavonoids. Biochem Phurmcol **1993**;265-267.
29. J. Robak and RJ. Gryglewski. Flavonoids are scavengers of superoxide anions. Biochem Phunnucol **1998**;37:837-841.
30. VA. Kostyuk and AI. Potapovich. Antiradical and chelating effects in flavonoid protection against silica-induced cell injury. Arch Biochem Biophys.1998; 355: 43-48.
31. CA. Rice-Evans and NJ. Miller. Antioxidant activities of flavonoids as bioactive components of food. Biochem Soc Truns **1996**;24:790-795.
32. G. Block. A role for antioxidants in reducing cancer risk. Nutr Rev **1992**;50:207-213.
33. PCH. Hollman, MGL. Hertog and MB. Katan. Role of dietary flavonoids in protection against cancer and coronary heart disease. Biochem Soc Truns **1996**;24:785-789.
34. BL. Santos, AR. Silva, BPS. Pitanga, CS. Sousa, MS. Grangeiro, BO. Fragomeni, PLC. Coelho, MN. Oliveira, NJ. Menezes-Filho, MFD. Costa, RS. El-Bachá, ES. Velozo, GP. Sampaio, SM. Freire, M. Tardy, SL. Costa. Antiproliferative,proapoptotic and morphogenic effects of the flavonoid rutin on human glioblastoma cells. Food Chemi **2011**;127:404–411.

35. G. Guohua, Q. Yuan, H. Wen, Z. Shu, Y. Xiaohua, L. Dan. Rutin inhibits hydrogen peroxide-induced apoptosis through regulating reactive oxygen species mediated mitochondrial dysfunction pathway in human umbilical vein endothelial cells. Eur J Pharmacol **2010**;628:27–35.
36. A. Van der Vliet, JP. Eiserich, CE. Cross. Nitric oxide: a Proinflammatory mediator in lung disease? Respi Res **2000**;1:67–72.
37. SK. Raghav, B. Gupta, C. Agrawal, K. Goswami, HR. Das. Anti-inflammatory effect of Ruta graveolens L. in murine macrophage cells. J Ethnopharmacol **2006**;104:234–239.
38. L. Selloum, H. Bouriche, C. Tigrine, and C. Boudoukha. Anti-inflammatory effect of rutin on rat paw oedema and on neutrophils chemotaxis and degranulation. Exp Toxic Pathol **2003**;54:313–318.
39. W. Lee, SK. Ku, JS. Bae. Barrier protective effects of rutin in LPS-induced inflammation in vitro and in vivo. Food Chem Tox **2012**;50:3048-3055.
40. W. Arjumand, A. Seth, S. Sultana. Rutin attenuates cisplatin induced renal inflammation and apoptosis by reducing NFkB, TNF-α and caspase-3 expression in wistar rats. Food Chem Toxi **2011**;49:2013-2021.
41. T. Cruz, J. Galvez, MA. Ocete, ME. Crespo, F. Sanchezde Medina, A. Zarzuelo. Oral administration of rutoside can ameliorate inflammatory bowel disease in rats. Life Sci **1998**;62:687–95.
42. J. Galvez, T. Cruz, E. Crespo, MA. Ocete, MD. Lorente F. Sanchezde Medina. Rutoside as mucosal protective in acetic acid-induced rat colitis. Planta Med **1997**;63:409–14.
43. KH. Kwona, A. Murakamia, T. Tanakab, H. Ohigashi. Dietary rutin, but not its aglycone quercetin, ameliorates dextran sulfate sodium-induced experimental colitis in mice:attenuation of pro-inflammatory gene expression. Biochem Pharmacol **2005**;69:395–406.
44. AE. Rotelli, T. Guardia, AO. Juárez, NE. de la Rocha, LE. Pelzer. Comparative study of flavonoids in experimental models of inflammation. Pharmacol Res **2003**;48(6):601–606.
45. OA. Andreassen, HA. Jorgensen. Neurotoxicity associated with neuroleptic induced oral dyskinesias in rat's implications for tardive dyskinesia? Prog Neurobiol **2000**;61:525–541.
46. M. Bishnoi, K. Chopra, SK. Kulkarni. Protective effect of rutin, a polyphenolic flavonoid against haloperidol-induced orofacial dyskinesia and associated behavioural, biochemical and neurochemical changes. Funda & Clin Pharmacol **2007**; 1:521–529.
47. S. Nikam, P. Nikam, SK. Ahaley and AV. Sontakke. Oxidative stress in Parkinson's disease. Ind J Clin Biochem **2009**;24:98-101.
48. K. Magalingam, A. Radhakrishnan and N. Haleagrahara. Rutin, a bioflavonoid antioxidant protects rat pheochromocytoma (PC-12) cells against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity. Int J Mol Med **2013**;32:235-240.
49. MM. Khana, A. Ahmada, T. Ishratb, G. Khuwajaa, P. Srivastawaa, MB. Khana, SS. Razaa, HJ. Vaibhava, A. Khana, F. Islama. Rutin protects the neural damage induced by transient focal ischemia in rats. Brain Res **2009**; 1292:123-135.
50. K. Linde, L. Knüppel. Large-scale observational studies of hypericum extracts inpatients with depressive disorders a systematic review. Phytomedicine **2005**;12:148–157.
51. DG. Machado, LEB. Bettio, MP. Cunha, ARS. Santos, MG. Pizzolatti, MC. Brighente, ALS. Rodrigues. Antidepressant-like effect of rutin isolated from the ethanolic extract from Schinus molle L. in mice: Evidence for the involvement of the serotonergic and noradrenergic systems. Eur J Pharmacol **2008**;587:163–168.
52. FR. Lapa, KC. Soares, YD. Rattmann, et al. Vasorelaxant and hypotensive effects of the extract and the isolated flavonoid rutin obtained from polygala paniculata L. J Pharm Pharmacol **2011**;63:875-81.
53. J. Guerrero, M. Quinones. Inhibition of angiotensin-converting enzyme activity by flavonoids: structure-activity relationship studies. Plos One **2012**;7:1-11.
54. Xia ML, Zhou XM, Yao H, et al. Rutin-induced endothelium-dependent vasorelaxation in rat aortic Rings and the underlying mechanism. Conf Proc IEEE Eng Med Biol Soc **2005**;6:5595-7.
55. P. Stanely, M. Prince, M. Karthick. Preventive effect of rutin on lipids,lipoproteins, and ATPases in normal and isoproterenol-induced myocardial infarction in rats. J Biochem Mol Toxicol **2007**;21:1-6.
56. K. Sattanathan, CK. Dhanapal, R. Manavalan. LDL lowering properties of rutin in diabetic patients. Int J Pharm Bio Sci **2010**;4:467-73.
57. Kamalakkannan N, Stanely Mainzen PrinceP. The antihyperglycaemic and antioxidant effect of rutin, a polyphenolic flavonoid, in streptozotocin-induced diabetic Wistar rats. Basic Clin Pharmacol Toxicol **2006**;98:97–103.
58. Chakravarthy BK, Gupta S, Gambhir SS, Gode KD. Pancreatic beta-cell regeneration a novel antidiabetic mechanism of Pterocarpus marsupium Roxb. Ind J Pharmacol **1980**;12:123–127.
59. Chakravarthy BK, Gupta S, Gode KD. Functional β-cell regeneration in the islets of pancreas in alloxan induced diabetic rats by (−)-epicatechin. Life Sci **1983**;31:2693–2697.
60. Coskun O, Kanter M, Korkmaz A, Oter S. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and cell damage in rat pancreas. Pharmacol Res **2005**;1:117–123.
61. Tiedge M, Lortz S, Drinkgern J, Lenzen S. Relation between antioxidant enzyme gene expression and antioxidant defense status of insulin-producing cells. Diabetes **1997**;46:1733–1742.
62. Cook NC, Samman S. Flavonoids chemistry, metabolism,cardioprotective effects, and dietary sources. J Nutr Biochem **1996**;7:66–76.
63. Newgard CN, McGarry JD. Metabolic coupling factors in pancreatic beta-cell signal transduction. Annu Rev Biochem **1995**;64:689–719.
64. Webster RP. and Bhattacharya RK. Activity of some nuclear enzymes associated with DNA repair following bepatocarcinogen administration to rats. J Biochem Toxicol **1995**;10:33-40.
65. Sestili P, Spadoni G, Balsamini C, Scovassi I, Catlaberi F, Devanti E, Cantoni O, Higgins D. and Thompson C. Structural requirements for inhibitors of poly(ADPribose) polymerase. J Cancer Res.Clin Oncol **1990**;116:615-622.
66. Smulson ME, Stark P, Gazzoti M. and Roberts J. Release of template restriction for DNA synthesis by polyR. (ADP-ribose) polytnerase during the HeLa cell cycle. Exp Cell Res **1975**;90:175-182.
67. Starvic B. and Matula TI, Whish WID, Davis M. and Shall S. Stimulation of poly (ADP-ribose) polymerase activity by antitumor antibiotic streptozotocin. Biochim Biophys Res Commun **1975**;65:722-730.
68. AR. Silva, AM. Pinheiro, CS. Souza, SRVB. Freitas, V. Vasconcellos, SM. Freire, ES. Velozo, M. Tardy, RS. El Bachá, MFD. Costa, SL. Costa. The flavonoid rutin induces astrocyte and microglia activation and regulates TNF-α lpha and NO release in primary glial cell cultures. Cell Biol Toxicol **2008**;24:75–86.
69. C. Fiocchi. Intestinal inflammation: a complex interplay of immune and nonimmune cell interactions. Am J Physiol **1997**;273: G769-G775.
70. MF. Neurath, C. Becker and K. Barbulescu. Role of NFkappaB in immune and inflammatory responses in the gut. Gut 43(6):856Y860 (1998). H. Ogata and T. Hibi. Cytokine and anti-cytokine therapies for inflammatory bowel disease. Curr Pharm **2003**;9(14):1107-1113.
71. CK. Weber, S. Liptay, T. Wirth, G. Adler, and RM. Schmid. Suppression of NF-kappaB activity by sulfasalazine is mediated by direct inhibition of IkappaB kinases alpha and beta. Gastroenterol **2001**;119(5):1209-1218.
72. SY. Cho, SJ. Park, MJ. Kwon, TS. Jeong, SH. Bok, WY. Choi, WI. Jeong, SY. Ryu, SH. Do, CS. Lee, JC. Song and KS. Jeong. Quercetin suppresses proinflammatory cytokines production through MAP kinases and NF-kappaB pathway in lipopolysaccharide-stimulated macrophage. Mol Cell Biochem **2003**;243 153-160.
73. MM. Mu, D. Chakravortty, T. Sugiyama, N. Koide, K. Takahashi, I. Mori, T. Yoshida and T. Yokochi. The inhibitory action of quercetin on lipopolysaccharide-induced nitric oxide production in RAW 264.7 macrophage cells. J Endotoxin Res **2001**;7(6):431-438.

74. AJ. Garcia-Pineres, V. Castro, G. Mora, TJ. Schmidt, E. Strunck, HL. Pahl and I. Merfort. Cysteine 38 in p65/NF-kappaB plays a crucial role in DNA binding inhibition by sesquiterpene lactones. J Biol Chem **2001**;276(43):39713-39720.
75. Heejung Kim, Hyesik Kong, Boim Choi,Youngwook Yang, Youngmi Kim, Mi Jung Lim,Len Neckersand Yunjin Jung. Metabolic and Pharmacological Properties of Rutin, a Dietary Quercetin Glycoside, for Treatment of Inflammatory Bowel Disease. Pharm Res **2005**;22(9):1499-1509.
76. Brown JR, DuBois RN. COX-2: a molecular target for colorectal cancer prevention. J Clin Oncol Offi J the Am Soci Clin Oncol **2005**;23:2840–2855.
77. Subbaramaiah K, Dannenberg AJ. Cyclooxygenase 2: a molecular target for cancer prevention and treatment. Trends in Pharmacolog Sci **2003**;24:96 -102.
78. Lee JL, Mukhtar H, Bickers DR, Kopelovich L, Athar M. Cyclooxygenases in the skin: pharmacological and toxicological implications. Toxicol and Appl Pharmacol **2003**;192:294–306.
79. Lu H, Li J, Zhang D, Stoner GD, Huang C. Molecular mechanisms involved in chemoprevention of black raspberry extracts: from transcription factors to their target genes. Nutrition and Cancer **2006**;54:69–78.
80. Divya CS, Pillai MR. Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. Mol Carcinog **2006**;45:320–332.
81. Xiong HQ. Molecular targeting therapy for pancreatic cancer. Cancer Chemoth and Pharmacol **2004**;54(1): 69–77.
82. Matsuura H, Sakaue M, Subbaramaiah K, Kamitani H, Eling TE, Dannenberg AJ, et al. Regulation of cyclooxygenase-2 by interferon gamma and transforming growth factor alpha in normal human epidermal keratinocytes and squamous carcinoma cells. Role of mitogen-activated protein kinases. The J Biol Chem **1999**;274:29138–29148.
83. Ouyang W, Ma Q, Li J, Zhang D, Ding J, Huang Y, et al. Benzo[a]pyrene diolepoxide (B[a]PDE) upregulates COX-2 expression through MAPKs/AP-1 and IKKbeta/NF-kappaB in mouse epidermal Cl41 cells. Mol Carcinog **2007**;46:32-41.
84. Normanno N, De Luca A, Bianco C, Strizzi L, Mancino M, Maiello MR, et al.Epidermal growth factor receptor (EGFR) signaling in cancer. Gene **2006**;366:2–16.
85. Heuckmann JM, Rauh D, Thomas RK. Epidermal growth factor receptor (EGFR) signaling and covalent EGFR inhibition in lung cancer. J Clin Oncol Offi J the Am Soci Clin Oncol **2012**;30:3417-3420.
86. Amann J, Kalyankrishna S, Massion PP, Ohm JE, Girard L, Shigematsu H, et al.Aberrant epidermal growth factor receptor signaling and enhanced sensitivity to EGFR inhibitors in lung cancer. Cancer Res **2005**;65:226–235.
87. Filardo EJ. Epidermal growth factor receptor (EGFR) transactivation by estrogen via the G-protein-coupled receptor, GPR30: a novel signaling pathway with potential significance for breast cancer. The J Steroid Biochem and Mol Biol **2002**;80:231–238.
88. Seunghwan Choi, Tae-Gyu Lim, Mun Kyung Hwang, Yoon-A Kim, Jiyoung Kim, Nam Joo Kang, Tae Su Jang, Jun-Seong Park, Myeong Hun Yeom, Ki Won Lee Rutin inhibits B[a]PDE-induced cyclooxygenase-2 expression by targeting EGFR kinase activity. Biochem Pharmacol **2013**;86:1468–1475.
89. Jader Nones & Ana Paula Costa & Rodrigo Bainy Leal & Flávia Carvalho Alcantara Gomes &Andréa Gonçalves Trentin The flavonoids hesperidin and rutin promote neural crest cell survival. Cell Tissue Res **2012**;350:305–315.
90. Lambert PJ, Shahrier AZ, Whitman AG, Dyson OF, Reber AJ, McCubrey JA, Akula SM. Targeting the PI3K and MAPK pathways to treat Kaposi's sarcoma-associated herpes virus infection and pathogenesis. Expert Opinion on Therapeutic Targets **2007**;11:589–599.
91. Agullo G, Gamet-Payrastre L, Manenti S, Viala C, Rémésy C, Chap H, Payrastre B. Relationship between flavonoid structure and inhibition of phosphatidylinositol 3-kinase: a comparison with tyrosine kinase and protein kinase C inhibition. Biochem Pharmacol **1997**;53:1649–1657.
92. Hagiwara M, Inoue S, Tanaka T, Nunoki K, Ito M, Hidaka H.Differential effects of flavonoids as inhibitors of tyrosine protein kinases and serine/threonine protein kinases. Biochem Pharmacol **1998**;37:2987–2992.
93. Schroeter H, Boyd C, Spencer JP,Williams RJ, Cadenas E, Rice-Evans C. MAPK signaling in neurodegeneration: influences of flavonoids and of nitric oxide. Neurobiol Aging **2002**;23:861–880.
94. JS. Choi, SW. Kang, J. Li, JL. Kim, JY. Bae, DS. Kim, SY. Shin, JG. Jun, MH. Wang, YH. Kang. Blockade of Oxidized LDL-Triggered Endothelial Apoptosis by Quercetin and Rutin through Differential Signaling Pathways Involving JAK2. J Agric Food Chem **2009**;57:2079–2086.
95. Collins T, Cybulsky MI. NF-kappaB: pivotal mediator or innocent bystander in atherogenesis? J Clin Invest **2001**;107:255– 264.
96. Brand K, Page S, Walli AK, Neumeier D, Baeuerle PA. Role of nuclear factor-kappa B in atherogenesis. Exp Physiol **1997**;82:297–304.
97. Boring L, Gosling J, Cleary M, Charo IF. Decreased lesion formation in CCR2-/- mice reveals a role for chemokines in the initiation of atherosclerosis. Nature **1998**;394:894–897 83.
98. Cybulsky MI, Gimbrone MAJ. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. Sci **1991**;251:788–791.
99. Poynter ME, Irvin CG, Janssen-Heininger YM. Rapid activation of nuclear factor-kappaB in airway epithelium in a murine model of allergic airway inflammation. Am J Pathol **2002**;160:1325–1334.
100. Hart LA, Krishnan VL, Adcock IM, Barnes PJ, Chung KF. Activation and localization of transcription factor, nuclear factor-kappaB, in asthma. Am J Respir Crit Care Med **1998**;158:1585–1592.
101. Bureau F, Bonizzi G, Kirschvink N, Delhalle S, Desmecht D, Merville M-P, Bours V, Lekeux P. Correlation between nuclear factor-B activity in bronchial brushing samples and lung dysfunction in an animal model of asthma. J Respir Crit Care Med **2000**;161:1314–1321.
102. Bureau F, Delhalle S, Bonizzi G, Fievez L, Dogne S, Kirschvink N, Vanderplasschen A, Merville MP, Bours V, Lekeux P. Mechanisms of persistent NF-kappa B activity in the bronchi of an animal model of asthma. J Immunol **2000**;165:5822–5833.
103. Henderson WRJ, Chi EY, Eo JL, Guyen C, Ahn M. A small molecule inhibitor of redox-regulated NF-kappa B and activator protein-1 transcription blocks allergic airway inflammation in a mouse asthma model. J Immunol **2002**;169:5294–5299.
104. Nabel G, Baltimore D. An inducible transcription factor activates expression of human immunodeficiency virus in T cells. Nature **1987**;326:711–713.
105. Hiscott J, Kwon H, Genin P. Hostile takeovers: viral appropriation of the NF-kappaB pathway. J Clin Invest **2001**;107:143–151.
106. Surabhi RM, Gaynor RB. RNA interference directed against viral and cellular targets inhibits human immunodeficiency virus type 1 replication. J Virol **2002**;76:12963–12973.
107. Quinto I, Mallardo M, Baldassarre F, Scala G, Englund G, Jeang KT. Potent and stable attenuation of live-HIV-1 by gain of a proteolysis-resistant inhibitor of NF-kappaB (IkappaB-alphaS32/36A) and the implications for vaccine development. J Biol Chem **1999**;274:17567–17572.
108. Kwon H, Pelletier N, DeLuca C, Genin P, Cisternas S, Lin R, Wainberg MA, Hiscott J. Inducible expression of IkappaBalpha repressor mutants interferes with NF-kappaB activity and HIV-1 replication in Jurkat T cells. J Biol Chem **1998**;273:7431–7440.
109. Spencer MJ, Montecino-Rodriguez E, Dorshkind K, Tidball JG. Helper (CD4 (+)) and cytotoxic (CD8 (+)) T cells promote the pathology of dystrophin-deficient muscle. Clin Immunol **2001**;98:235–243.
110. Spencer MJ, Tidball JG. Do immune cells promote the pathology of dystrophin-deficient myopathies? Neuromuscul Disord **2001**;11:556–564.
111. Spencer MJ, Walsh CM, Dorshkind KA, Rodriguez EM, Tidball JG. Myonuclear apoptosis in dystrophic mdx muscle occurs by perforin-mediated cytotoxicity. J Clin Invest **1997**;99:2745.

112. Porter JD, Merriam AP, Leahy P, Gong B, Khanna S. Dissection of temporal gene expression signatures of affected and spared muscle groups in dystrophin-deficient (mdx) mice. Hum Mol Genet **2003**;12:1813–1821.
113. Porter JD, Khanna S, Kaminski HJ, Rao JS, Merriam AP, Richmonds CR, Leahy P, Li J, Guo W, Andrade FH. A chronic inflammatory response dominates the skeletal muscle molecular signature in dystrophin-deficient mdx mice. Hum Mol Genet **2002**;11:263–272.
114. Smahi A, Courtois G, Rabia SH, Doffinger R, Israel A. The NF-kappaB signalling pathway in human diseases: from incontinentia pigmenti to ectodermal dysplasias and immunedeficiency syndromes. Hum Mol Genet **2002**;11:2371–2375.
115. Aradhya S, Nelson DL. NF-kappaB signaling and human disease. Curr Opin Genet Dev **2001**;11:300–306 162.
116. Landy SJ, Donnai D. Incontinentia pigmenti (BlochSulzberger syndrome). J Med Genet **1993**;30:53–59
117. Smahi A, Courtois G. Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. Nature **2000**;405:466–472.
118. Bonetti B, Stegagno C, Cannella B, Rizzuto N, Moretto G, Raine CS. Activation of NF-kappaB and c-jun transcription factors in multiple sclerosis lesions. Implications for oligodendrocyte pathology. Am J Pathol **1999**;155:1433–1438.
119. Gveric D, Kaltschmidt C, Cuzner ML, Newcombe J. Transcription factor NF-kappaB and inhibitor I kappaBalpha are localized in macrophages in active multiple sclerosis lesions. J Neuropathol Exp Neurol **1998**;57:168–178.
120. Selmaj KW, Raine CS. Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. Ann Neurol **1998**;23:339–346.
121. Li QQ, Bever CT, Burt DR, Judge SI, Trisler G. Induction of RANTES chemokine expression in human astrocytic cells is dependent upon activation of NF-kappaB transcription factor. Int J Mol Med **2001**;7:533.
122. Abu-Amer Y, Tondravi MM. NF-kappaB and bone: the breaking point. Nat Med **1997**;3:1189–1190.
123. Xing L, Carlson L, Story B, Tai Z, Keng P, Siebenlist U, Boyce BF. Expression of either NF-kappaB p50 or p52 in osteoclast precursors is required for IL-1-induced bone resorption. J Bone Miner Res **2003**;18:260–269.
124. Toraldo G, Roggia C, Qian WP, Pacifici R, Weitzmann MN. IL-7 induces bone loss in vivo by induction of receptor activator of nuclear factor kappa B ligand and tumor necrosis factor alpha from T cells. Proc Natl Acad Sci USA **2003**;100:125– 130.
125. Juji T, Hertz M, Aoki K, Horie D, Ohya K, Gautam A, Mouritsen S, Oda H, Nakamura K, Tanaka S. A novel therapeutic vaccine approach, targeting RANKL, prevents bone destruction in bone-related disorders. J Bone Miner Metab2002; 20:266–268.
126. Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. Nat Rev Immunol **2003**;3:745–756.
127. Dinchuk JE, Car BD, Focht RJ, Johnston JJ, Jaffee BD, Covington MB, Contel NR, Eng VM, Collins RJ, Czerniak PM, Gorry SA. and Trzaskos JM. Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase II. Nature (London) **1995**;378:406–409.
128. Morham SG, Langenbach R, Loftin CD, Tiano HF, Vouloumanos N, Jennette JC, Mahler JF, Kluckman KD, Ledford A, Lee CA. and Smithies O. Prostaglandin synthase-2 gene disruption causes severe renal pathology in the mouse. Cell **1995**;83:473–482.
129. Yang ZM, Das SK, Wang J, Sugimoto Y, Ichikawa A. and Dey SK. Potential sites of prostaglandin actions in the periimplantation mouse uterus: differential expression and regulation of prostaglandin receptor genes. Biol Reprod **1997**;56:368–379.
130. Lim H. and Dey SK. Prostaglandin E-2 receptor subtype EP2 gene expression in the mouse uterus coincides with differentiation of the luminal epithelium for implantation. Endocrinol **1997**;138:4599–4606.
131. Lim H, Paria BC, Das SK, Dinchuk JE, Langenbach R, Trzaskos JM. and Dey SK. Multiple female reproductive failures in cyclooxygenase-2 deficient mice. Cell **1997**;91:197–208.



**How to cite this article:**

Haidarali M. Shaikh et al. RUTIN: A PHARMACOLOGICAL REVIEW. J Pharm Res 2018;7(2):23-30. **DOI: https://doi.org/10.5281/zenodo.1188425**

**Conflict of interest:** The authors have declared that no conflict of interest exists.

**Source of support: Nil**