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Chapter- 14

Exploration of The Therapeutic Effects of a Dietary Flavonoid Rutin

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Abstract:

Phytochemicals, which are also known as phytonutrients, are secondary metabolites and natural bioactive compounds found in a wide variety of plants. They are abundantly present in foods like fruits, nuts, vegetables, whole grains and even in various parts of plants. There are different kinds of phytochemicals, namely, carotenoids, isoprenoids, polyphenols, phytosterols, saponins, dietary fibres, polysaccharides etc. Rutin is one of a such kinds of flavonoids that are widely found in asparagus, buckwheat, apples, figs, tea etc. Researchers report many therapeutic properties of rutin. Rutin has been reported to have a beneficial role in controlling various diseases such as cancer, hypertension, arteriosclerosis, diabetes, anti-inflammatory, cardiac diseases and obesity. In this chapter, we demonstrate a comprehensive study of various therapeutics activities of rutin.

Introduction:

India is cradle for a vast array of medicinal plants which are enriched with enormous phytochemicals. From ancient times, these medicinal plant-derived phytochemicals have served man and mankind to deal with different diseases and physiological challenges (Kar et al., 2022; Pawar et al., 2023; Thangavel et al., 2023). Flavonoids are a subset of the dietary phytochemicals present in fruits and vegetables of our daily consumption. Amongst various bioactive phytochemicals, Rutin is an important flavonol present in apples, citrus fruits, tea, grapes etc. (Figure 1). The main source of this polyphenolic flavonoid is buckwheat plant (Ganeshpurkar and Saluja, 2016). The name rutin comes from the plant *Ruta graveolens* L., which is a major source of rutin phytochemical. Another names of rutin are quercetin-3-O-rutinoside, rutoside, vitamin P and sophorin (Farha et al., 2020). The combination of flavonol

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quercetin and the disaccharide rutinose forms Rutin. It is mentioned that near about 130 therapeutic drugs existed in the market containing rutin in their composition (Satari et al., 2021). Rutin is well known with its various pharmacological attributes. It has antioxidant, anti-cancer, anti-inflammatory, anti-diabetic, anti-microbial, and anti-arthritic properties. The neuroprotective, cardioprotective, hepatoprotective characteristics of rutin are also well-known (Negahdari et al., 2020). Due to its pharmacological activity rutin is used in many therapeutic and medicinal preparations such as cardiovascular protective remedies, gastric lesion therapies, nephropathic treatments, as anti-inflammatories (Dong et al., 2020). The chemopreventive and chemotherapeutic effects of rutin make it a suitable anti-cancer agent to treat various kinds of carcinomas. Rutin exerts its anti-carcinogenic effects by suppressing cell proliferation, induction of autophagy and/or apoptosis and it also prevents metastasis and angiogenesis in a variety of cancers. (Farha et al., 2020). Rutin can also modify PI3K/Akt, Janus kinase/signal transducers and transcription-activators, NF-κB, mitogen-activated protein kinase (MAPK) and Wnt/β-catenin signalling in cancer (Imani et al., 2020). Reports also suggest that rutin can also be used in combination with conventional anticancer drugs for cancer treatment *in vitro* (Satari et al., 2021). In the following section, we have highlighted the chemical structure and multiple pharmacological features of dietary polyphenol rutin.

Chemical nature of rutin:

Rutin is non-toxic in nature and a glycosylated version of rhamnose-glucose disaccharide and quercetin. The molecular weight of rutin is 610.53 Dalton (Farha et al., 2020). Its chemical name is (2-(3,4-dihydroxyphenyl)-4,5-dihydroxy-3-[3,4,5trihydroxy-6-[(3,4,5-trihydroxy-6 methyl-oxan-2-yl)oxymethyl]oxan-2-yl] oxy-chromen-7-one (Figure 1). This lipophilic phytochemical is poorly water soluble but highly soluble in organic solvents such as methanol, ethanol, pyridine etc. Rutin has low stability and low bioavailability due to its low solubility in water (Negahdari et al., 2020).

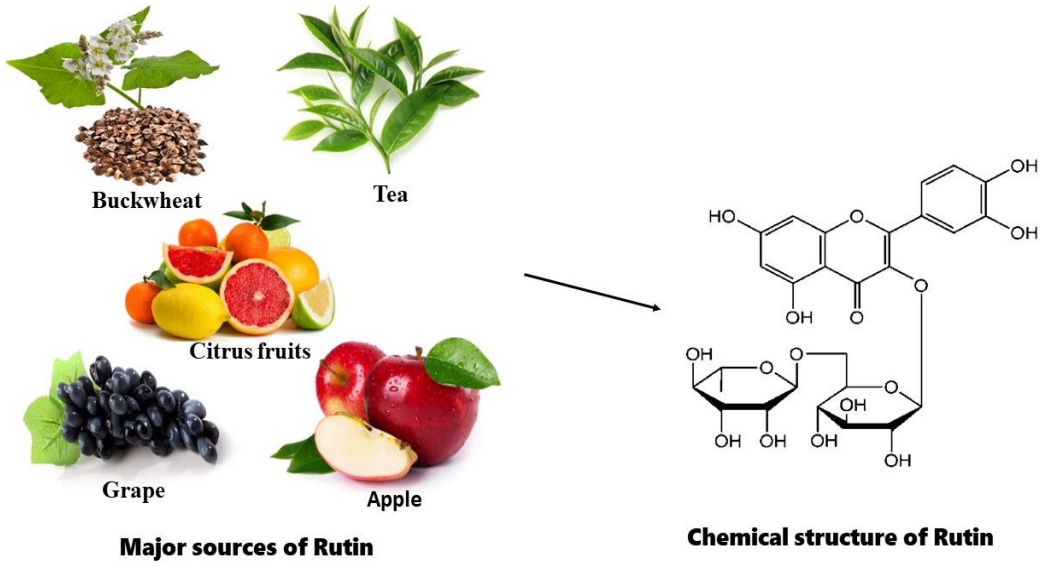

Figure 1. Major sources and chemical structure of Rutin

Anti-carcinogenic effect of rutin:

Rutin can detoxify different carcinogenic agents. It is a potent chemopreventive and radio protective agent. As per reports, rutin can act against Benzo (α) pyrene-7, 8-diol-9, 10-epoxide, which is a potent carcinogen. It can prevent oxidative DNA damage by different mutagens like, mitomycin C, benzo (α) pyrene, methyl-methanesulfonate, hydrogen peroxide, 4-(methylnitrosamino)-1-(3-pyridyl)-1- butanone (NNK) and 13-hydroperoxyoctadecadienoic acid. Owing to its radio protective effect, rutin can reduce UV irradiation induced inflammation. The solution of rutin and DMSO can protect UV-B irradiated cells from being degradation (Farha et al., 2020).

Therapeutic efficacies of Rutin in the treatment of cancer and other diseases:

Anti-cancer properties of rutin:

Evidences from different studies indicate that rutin has the capability to inhibit different types of cancer cell proliferation. According to various study reports, rutin can be used to treat breast, pancreas, glioma, colon, skin, lung, ovarian, cervical, prostate, liver cancer and as well as neuroblastoma (Imani et al., 2020; Mehta et al., 2023). The effectiveness of rutin is extended from different types of cancers to carcinogenic agents. Various anti-cancer properties and associated signalling pathways of rutin have been summarized in Figure 2.

Inhibition of cell cycle progression:

Rutin can target cell cycle pathways during cancer treatment. It promotes cell cycle arrest at different cell cycle check points like, G1, S, G2/M. It can successfully alter the cell cycle regulatory proteins i.e., cyclins, cyclin-dependant kinases (CDKs) and also the CDK inhibitors (CKIs). According to recent researchers, it can also increase the expression of cell cycle-related genes, CDK1 and p21 and reduce Cyclin B expression during G2/M phase arrest. It can inhibit the phosphorylation of GSK-3b and promote apoptosis in cancer cells. In Glioma GL-15 cells rutin promote G2 phase cell cycle arrest and apoptosis (Farha et al., 2020).

Induction of apoptosis and autophagy in cancer cells:

Rutin can modulate both the intrinsic or mitochondria-mediated pathways and extrinsic or death receptor-mediated pathways of apoptosis in cancer cells. In the case of neuroblastoma (LAN-5), rutin targets intrinsic apoptotic pathway by reducing the ratio of B-cell lymphoma 2 (Bcl2) protein and Bcl-2-associated X protein (Bax) in cellular level. In colon cancer cells (HT-29) rutin can trigger both the apoptotic pathway by increasing Bax, caspase-3, 8 and 9 expression and decreasing Bcl-2 expression. In another colon cancer cell line HCT 116, rutin activate caspase-3 expression (Farha et al., 2020). TNF-α accompanied by rutin can trigger the apoptosis of (A549) human lung cancer cells by GSK-3β modulation. In leukaemia (K562 cell line) rutin can promote intrinsic apoptotic pathways for cancer prevention (Imani et al., 2020). In human breast cancer cells (MCF-7), rutin can induce the expression of tumour suppressor gene p53, phosphatase and tensin homologue (PTEN) and promote cancer cell apoptosis. In

pancreatic cancer cells (PANC-1), prostate cancer cells (LNCaP) and ovarian cancer cell (OVCAR-3), rutin downregulates cancer cell proliferation and upregulates cellular apoptosis (Farha et al., 2020).

Rutin can also mediate autophagy in CA9-22 (oral cancer cell line), A549 and THP-1 (human leukemia) cell lines by reducing TNF-α production, Beclin-1 upregulation and NF-κβ suppression respectively. It can also target LC3-II activation and ATG5/12 upregulation (Park et al., 2016).

Inhibition of angiogenesis:

Angiogenesis is an important phenomenon in tumour development and progression. Rutin bears anti-angiogenic property. It can significantly decrease the development and tube formation of endothelial cells by lowering the generation of angiogenesis inducers like TNF- α, IL-1β and VEGF. *In vivo* experiments have indicated that rutin obstructs the angiogenesis process. Rutin can also reduce VEGF expression, which implies to its anti-angiogenic characteristics (Farha et al., 2020).

Increase of Reactive Oxygen Species (ROS):

ROS sustains an equilibrium in the aggregation and degradation of normal cells. In cancer cells the balance is disrupted, which in turn increases ROS accumulation and enhances the oxidative stress. At a certain level, oxidative stress can initiate cellular apoptosis and check cancer development. As per research studies, C33A (cervical cancer cell), HepG2, MCF-7 cell lines have shown ROS-mediated apoptosis after rutin treatment. It can also increase ROS production in melanocyte cells to destroy those cells (Farha et al., 2020; Dey & Guha, 2020). In fibroblast cells, rutin exerts cytoprotective effect and also inhibits the ROS accumulation triggered by UV irradiation (Gegotek et al., 2017).

DNA damage regulation:

Rutin is a potent DNA damage inducing agent in cancer (Thangavel et al., 2023). Doxorubicin mediated DNA damage is managed by rutin treatment in hepatocellular carcinoma cell line (HepG2) (Imani et al., 2020). In BRCA mutant cells, this polyphenol can initiate DNA abrasion (Maeda et al., 2014). But there is a lack of information about rutin mediated DNA damage related signalling pathways. Therefore, we can focus on that particular site of research in the near future.

Inhibition of metastasis:

Metastasis is a crucial process for tumour progression in different parts of the body. Rutin plays a vital role in inhibition of tumour metastasis. It can obstruct the formation of lung tumour nodule and its metastasis in B16-Fl0 melanoma bearing mice model (Swiss mice and C57BL/6 mice). Rutin is also a potent matrix metalloproteinase inhibitor. Metastatic cell invasion and migration is also modulated by rutin treatment in HT-29 and A549 cancer cells (Imani et al., 2020; Selvaraj et al., 2016).

Anti-inflammatory activity:

Enzymes associated with inflammation and inflammatory responses are protein kinase C, cyclooxygenase, phosphoinositide 3-kinase (PI 3-kinase) and lipoxygenase. Prostaglandins and leukotrienes are important inflammatory mediators. Rutin can modulate these agents negatively by exerting an anti-inflammatory activity upon cells. It can downregulate the pro-inflammatory cytokines like, IL-1β, TNF-α, and IL-6 and also the NF-κB to reduce inflammation (Negahdari et al., 2020; Pandey et al., 2020; Bee et al., 2023).

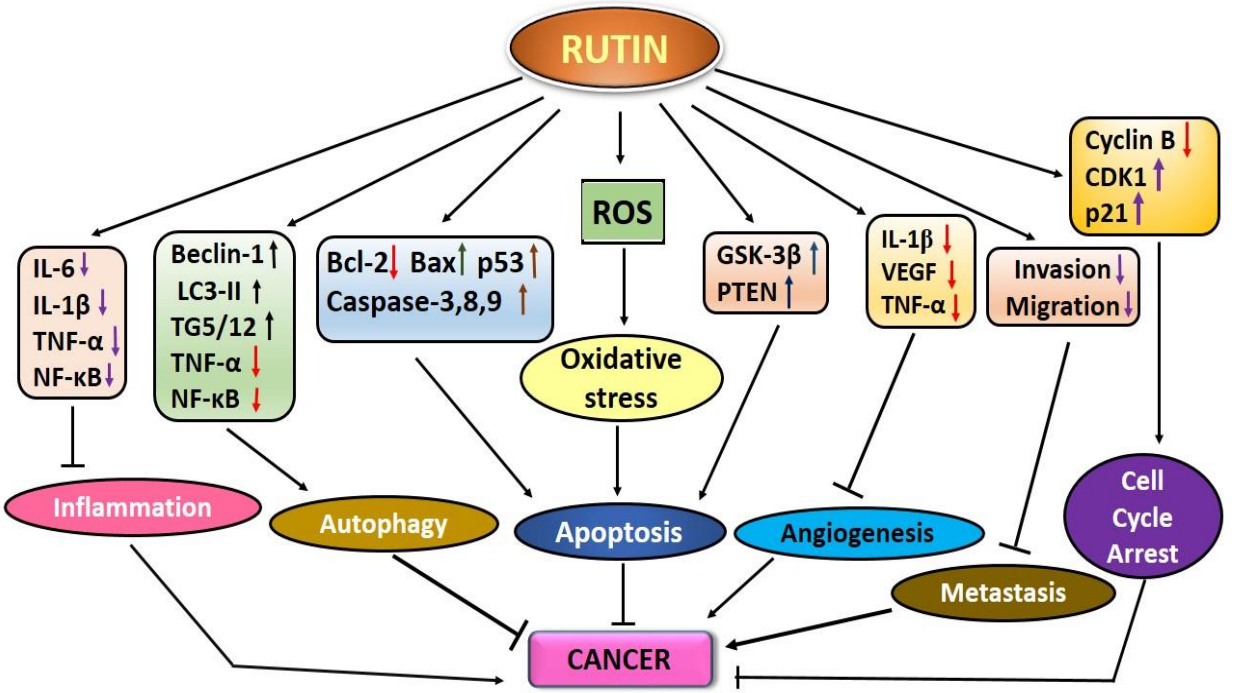

Figure 2. A schematic representation of different signalling pathways and signalling molecules involved with the anti-cancer properties of rutin

Neuroprotective properties of rutin in treating central nervous system disorders:

Rutin has strong neuroprotective activity against ischemia induced neural apoptosis. It can significantly decrease lipid peroxidation by enhancing the level of different endogenous antioxidant enzymes. Study reported that administration of rutin at 10mg/kg can improve memory retrieval in rat model. Daily administration of rutin also reverses the trimethyltin associated hippocampal -pyramidal neuron damage and spatial memory loss (Patel and patel, 2019). Rutin acts as anti-convulsant flavonol and positively regulate the action of GABA (Gamma-aminobutyric acid) receptor complex, so, it is useful in epileptic convulsions. Neural crest, an important progenitor cells could become neurons and other mesenchymal cells. Research demonstrated that treatment with rutin can protect trunk neural crest cells viability via modulating the PI3K/ERK2 axis, but it doesn't alter or block cell proliferation and differentiation activity (Ganeshpurkar and Saluja, 2016).

Alzheimer's disease:

Alzheimer's disease (AD) is the most frequent progressive neurological disorder that causes progressive neuronal loss due to accumulation of amyloid plaques and neurofibrillary tangles (Dumon et al., 2011). In human AD model, oxidative stress occurs before the formation of amyloid plaques in the brain (Cheignon et al., 2018). Rutin has free radical scavenging property and it can highly reduce Aβ25–35 fibril formation related neurotoxicity. Multifunctional rutin can decrease the Aβ aggregation by enhancing the level of several antioxidant enzymes such as superoxide dismutase, catalase, glutathione, glutathione peroxidase etc. along with significantly decrease in production of ROS, nitric oxide, nitric oxide synthase (Enogieru et al., 2018). Xu et al. reported that when rutin is orally administrated (100mg/kg) for 6 weeks, it can effectively decrease the oligomeric form of Aβ, IL-1 and IL-6 level. By this way, it can supress astrocytosis and microgliosis in transgenic mice brain. Another study shows that rutin can improve both memory and cognition deficits in Aβ25–35 treated mice (Enogieru et al., 2018).

Parkinson's disease:

Parkinson's disease (PD) is the second most frequent progressive neurodegenerative disorder and is characterized by loss of dopaminergic (DA) neurons (Weng et al., 2018; Haloi et al., 2023). 6-hydroxydopamine (6-OHDA) has been used as an *in vitro* model of PD. In this study, pretreated rutin can reduce the toxicity of 6-OHDA in dose-dependent manner and also exhibit the cytoprotective activity in 6-OHDA treated PC12 cell line (Enogieru et al., 2018). In addition, pretreated rutin can decline the PD related genes expression including ubiquitin carboxyl-terminal esterase L1(UCHL1), PARK2 (Parkin gene), DJ-1 (deglycase-1) and proapoptotic genes like Caspase3, Caspase7 etc. in conjugation with a significantly enhanced expression of antiapoptotic genes like optic atrophy type1 (Opa1) and N-ethylmaleimide sensitive fusion protein (NSF). It also increased the tyrosine hydroxylase mediated dopamine production (Enogieru et al., 2018). In 6-OHDA administrated Wistar rat model, the application of rutin can improve impaired motor coordination and locomotion activity (Enogieru et al., 2018). In another study rotenone treated SH-SY5Y cells were used as a PD *in vitro* model to investigate the effect of rutin on PD. Here, rutin inhibits the rotenone mediated cell cytotoxicity by inhibition of ROS production and or downregulation of JNK/p38 MAPK cascade. It also regulated the mitochondrial membrane potential and supress the apoptosis pathway related different gene (Bax, Bcl-2, caspase-9 and caspase-3) expression (Enogieru et al., 2018).

Huntington's disease:

Huntington's disease (HD) is an inherited (autosomal dominant) neurodegenerative disorder which is characterized by dysregulation of cognitive, motor and behavioural abnormality. In case of HD destruction of neurons mainly located in striatum. In 3-Nitropropionic administrated Huntington's disease rat model rutin at the dose of 25-50mg/kg can prevent neural degeneration by upregulating antioxidant enzymes defence system, reduce protein peroxidation and recover behavioural alterations (Enogieru et al., 2018).

Stroke:

Stroke is known as death of brain tissue, which is characterized by inadequate flow of blood or oxygen to the brain due to presence of artery blockage (Crack and Taylo, 2005). According to the World Health Organisation reports, large number of world population are suffering from stroke. According to research reports, it is considered that high level of ROS production is associated with stroke-induced brain injury (Allen and Bayraktutan, 2009). Rutin can considerably protect brain from focal cortical ischemia which is caused by thermocoagulation of motor and somatosensory blood vessels, as well as restoring the normal function of sensorimotor (Ganeshpurkar and Saluja, 2016).

Cardiovascular disease:

Ischemia-reperfusion **(**I/R**)** injury is a well-known deleterious effect commonly seen after myocardial infarction when the blood flow resumes in previously ischaemic or O_2 deprived tissue. In ischemia-reperfusion injury, oxidative stress is mainly responsible for cell death by increasing the lipids and protein oxidization (Briegera et al., 2012; Madhual et al., 2023). *In vivo* experimental study shows that rutin (5, 10mg/kg doses) has a strong cardioprotective effect against ischemia–reperfusion induced myocardial infarction. Application of rutin can significantly decrease the oxidative stress-mediated lipid peroxidation due its antioxidative properties (Patel and Patel, 2019). The higher expression of TGβ1 is responsible for dilated cardiomyopathy, hypertrophic cardiomyopathy and interstitial fibrosis. In coronary heart disease *in-vivo* model application of rutin can decrease the TGβ1 expression along with increased expression of p-ERK1/2 and p-Akt. The expression of ERK/ Akt is very important for normal cardiac function. This report also demonstrates that the administration of rutin (45mg/kg) in CHD (congenital heart defects) pig model has an ability to reduce the systolic internal diameter or infract size of the myocardium (Lv et al., 2018). Application of rutin restores the production of different cardiac marker enzymes such as aspartate transaminase, alanine transaminase, creatine kinase, acetate dehydrogenase etc. (Ganeshpurkar and Saluja, 2016). Rutin also exhibits its cardioprotective effect by reducing heart homogenate protein nitration (Patel and Patel, 2019).

Hepatoprotective activity:

Cirrhosis is known as liver tissue scar or damage of hepatocytes which ultimately result in death of hepatocytes or impaired liver function. Several research shows that application of antioxidant agents may reduce oxidative stress induced liver cirrhosis. Recently, several research investigates the hepatoprotective activity of rutin in hepatic injury. Among these experiments one of them experiment demonstrates that treatment with rutin can effectively reduce carbon tetrachloride induced hepatic injury in *in vivo* system; in serum, it can decline the production of aspartate aminotransferase, alkaline phosphatase and alanine aminotransferase which is induced by carbon tetrachloride (Ganeshpurkar and Saluja, 2016).

Anti-diabetic property:

Diabetes, a lifelong metabolic illness which is associated with hyperglycaemia (Sur et al., 2023; Biswas et al., 2023; Biswas et al., 2023). Insulin resistance or low production of insulin from pancreatic islets is main cause of hyperglycaemia (Ganeshpurkar and Saluja, 2016; Sarkar et al., 2023). Research have shown that long-term administration of streptozotocin in rats results in excessive superoxide production in pancreatic beta cells, increased plasma glucose level and reduced insulin production. In this study, the administration of rutin can restore normal insulin level and it also helps in refunctioning of the glycolytic enzymes in streptozotocin-treated diabetic rat. In addition, regeneration of pancreatic islets and reduction of fatty acid infiltration in diabetic rats were found after rutin treatment. According to another study report, rutin also elevates the activity of insulin receptor kinase and by this way it can stimulates insulin signaling pathway. Upregulation of insulin signaling pathway can enhance GLUT4 mediated glucose uptake (Ganeshpurkar and Saluja, 2016).

Rheumatoid arthritis:

Rheumatoid arthritis (RA) is an autoimmune disease. Due to this, joints are affected where synovial inflammation causes cartilage and bone damage. In collagen-induced (CIA) *in vivo* model, administration of gold nanoparticles (NPs) loaded rutin (R-AuNPs) and without NPs conjugated rutin exhibits strong anti- rheumatic arthritis property by reducing the level of different oxidative stress markers/mediators including iNOS, NF-κB etc. (Gul et al., 2018; Singh & Sharma, 2023). Sun et al. reported that rutin at 15 mg/kg dose can significantly decline the proinflammatory cytokines (TNF- α, IL-1 β) production and NF-κB p65 expression in arthritis rat model. Histopathological experiment of above study demonstrated that the synovial hyperplasia, infiltration of inflammatory cells and erosion of bone/cartilage was reduced after rutin administration (Sun et al., 2017).

Nephropathy:

Nephropathy is one of the lethal disease responsible for high death rate throughout the world. Research investigation suggested that rutin intake may lead the way-out of oxonate-stimulated renal dysregulation and hyperuricemia. Administration of rutin can significantly reduce the level of blood urea nitrogen, serum urate and kidney uromodulin (Ganeshpurkar and Saluja, 2016).

Anti-microbial activity:

Rutin has shown antibacterial, antiviral, antifungal activity against different pathogens or microorganisms. Rutin exhibits antibacterial effects on *Klebsiella sp.*, *Shigella sp.*, and *Proteus vulgaris* (Ganeshpurkar and Saluja, 2016). Rutin is an effective antiviral phytochemical compound that significantly kill avian influenza strain H5N1, in this experiment antiviral property of rutin is determined in the ‘Madin-Darby canine kidney’ by plaque inhibition assay (Ibrahim et al., 2013). Another study demonstrated that only 60 µg/ml of concentrated rutin can

exhibit strong antifungal activity against *Candida gattii* (fungus). Application of rutin can successfully reduce the *C. albicans* induced septic arthritis (Ganeshpurkar and Saluja, 2016).

Reproductive disease:

It has been reported that rutin can reduce lipid peroxidation in sperm. In type1 diabetes mellitus patients, administration of rutin can reduce oxidative stress mediated testicular tissue damage and improve reproductive health (Moretti et al., 2012; Ganeshpurkar and Saluja, 2016).

Discussion & Conclusion:

Rutin is a natural bioactive compound with multiple pharmacological attributes. A plant derived dietary polyphenol rutin has significant metabolic effects (Farha et al., 2020; Sarkar et al., 2021; Satari et al., 2021; Ghosh et al., 2022). It is a potent phytomedicine that can be used to treat multiple health issues like neuronal disorder, cardiac diseases, arthritis, cancer, diabetes, liver disease and reproductive problems. Being a potent free radicle scavenger, it can act against body's oxidative stress and can detoxify carcinogens. We have focused more on the anti-cancer properties exerted by rutin. Different signalling pathways and different signalling molecules are employed in the treatment of breast, brain, ovarian, cervical, oral, liver, lung and other cancers. Apart from that other therapeutics aspects of rutin have been described in this chapter. Both the *in vivo* and *in vitro* trials with different modifications of rutin are ongoing to find its maximum potencies. *In vivo* information are lacking in this regard, therefore further investigations are needed to prepare a human safety profile with different therapeutic benefits of rutin.

Conflict of Interest:

The authors declare no conflict of interest.

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