

Original Research Article

Therapeutic Effects of Quercetin in the Management of Age-Related Diseases and Disorders

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Abstract: Quercetin is a polyphenol derived from many fruits and vegetables which is known for its antioxidant, anti-hypertensive and anti-inflammatory properties. This comes under the class flavonoids. Polyphenols consists of many phenol structures in it and is not synthesized in the human body. These polyphenols exhibit its anti-oxidative effects by stimulating the anti-oxidant enzymes such as glutathione peroxidase and catalase. Quercetin is present in many plant based substances such as onion, apple, broccoli, hypericum, cherries, green tea and etc. Quercetin as many therapeutic effects such as anti-oxidant, anti-inflammatory and anti-aging. It also plays significant role in many diseases and disorders such as hypertension, type 2 diabetes mellitus, anxiety, depression, neurodegenerative disorders, Huntington's disease and cardiovascular diseases such as atherosclerosis, etc. Quercetin up regulates the enzyme Sirtuin 1, is an enzyme which is also present in many plant based substances. This Sirtuin 1 also plays a pivotal role in the many age-related diseases and disorders. The primary objective of this article is to study the therapeutic effects of quercetin and its role in controlling the major age-related diseases and disorders based on several studies. This article also highlights the potential bio enhancer property of quercetin in many class of drugs such as anti-viral, anti-hypertensive, anti-fungal, anti-tuberculosis and anti-cancer drugs.

Keywords: Quercetin, Sirtuin 1, Anti-Inflammatory, Anti-Oxidant, Anti-Aging, Diabetes Mellitus, Atherosclerosis, Bioenhancer.

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INTRODUCTION

Quercetin is a polyphenol derived from many citrus fruits and vegetables which is known for its antioxidant, anti-hypertensive and anti-inflammatory properties. This comes under the class flavonoids. Polyphenols consists of many phenol structures in it and is not synthesized in the human body. These polyphenols exhibit its anti-oxidative effects by stimulating the anti-oxidant enzymes such as glutathione peroxidase and catalase. These polyphenols helps in maintaining different cells and tissues in the human body including smooth muscle cells and endothelial cells from the inflammatory and oxidative effects from the external or internal factors (Marunaka Y *et al.*, 2017). They reduce the resistance towards the cells and tissues and maintain normal resistance. These polyphenols exhibit its anti-oxidative effects by stimulating the anti-oxidant enzymes such as glutathione peroxidase and catalase (Bai Y., 2016).

Polyphenols also play a vital role in the transport of ions between different channels to help in regulating homeostasis and they are soluble in water (Sun H., 2014). Homeostasis is the important mechanism which regulates various factors in the human body such as temperature, pressure, fluids, electrolytes and etc. These factors should not up regulate or down regulate and must present in normal range to retain all the body functions in the optimal level (Marunaka Y, 2014). Quercetin also as anti-proliferative, anti-viral, anti-carcinogenic and anti-diabetic properties. Quercetin is present in plant based products, mainly it is available in the high quantity in onion. They also present in the products derived from the plants such as coffee, tea, chocolate and red wine. These polyphenols presence in the plants and play a role in the defense mechanisms in plants as they are produced as secondary metabolites (Kim Y *et al.*, 2016; Deepika, Maurya PK., 2022). Quercetin also has a property of increasing the efficacy

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and bioavailability of co-administered drugs used to treat major diseases and disorders. So, quercetin is also considered as a potential bio enhancer. The various

sources of quercetin are listed in the Fig. 1 (Li Y., 2016).

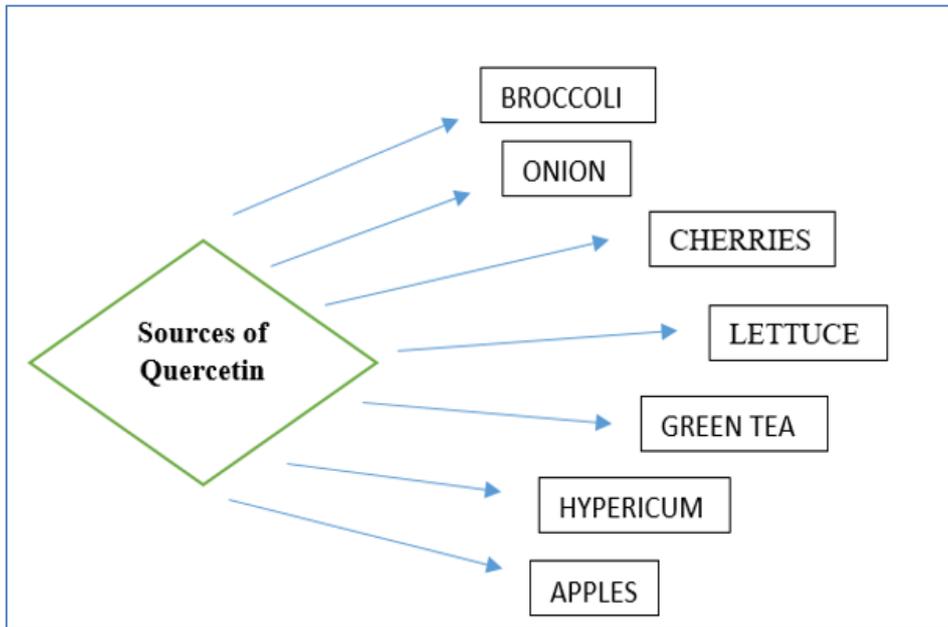


FIG. 1: SOURCES OF QUERCETIN

ABSORPTION OF QUERCETIN

Quercetin is available in various forms or metabolites such as quercetin aglycone quercetin glucoside, glucuronidated quercetin, sulfated quercetin and methylated quercetin. The absorption of quercetin into human body is shown in the Fig. 2 (Németh K *et*

al., 2003). Aglycone quercetin is lipophilic and is easily absorbed into the body tissues, whereas the glycosylated form of quercetin is non-lipophilic and is not easily absorbed into the body tissues. The mechanism of absorption of quercetin into the body is shown in the Fig. 3 (Suzuki T *et al.*, 2011).

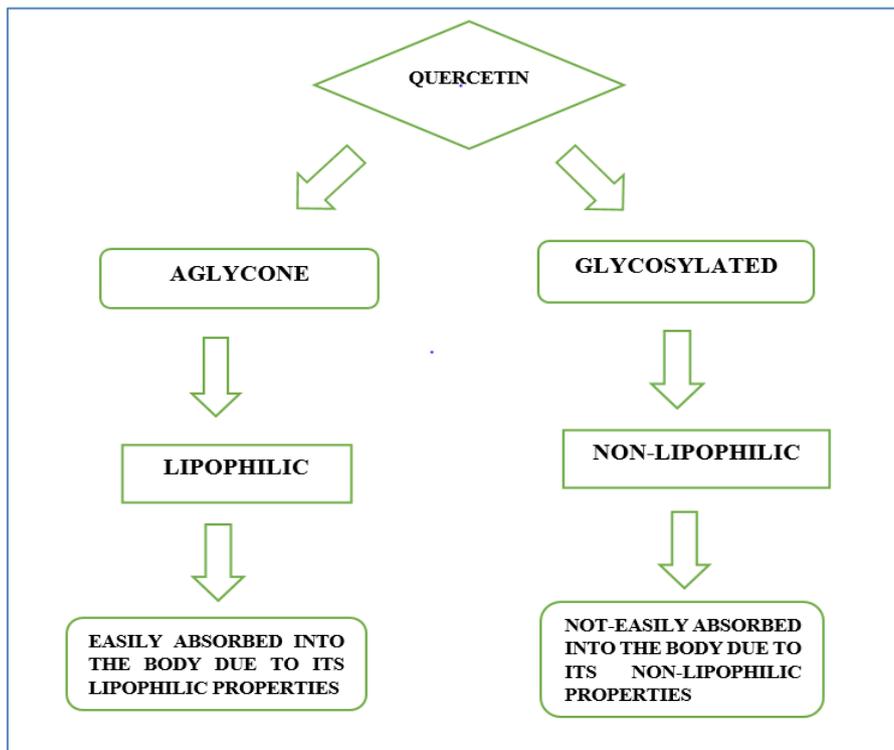


FIG. 2: AGLYCONE VS GLYCOSYLATED QUERCETIN.

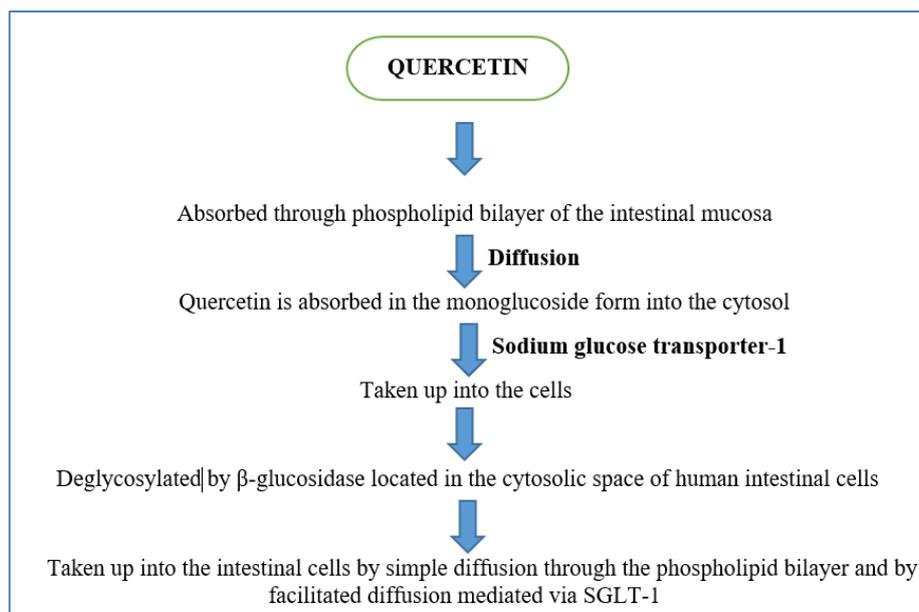


FIG. 3: MECHANISM OF ABSORPTION OF QUERCETIN INTO THE BODY.

Role of Quercetin on Hypertension

In the double-blind randomized placebo controlled study, it is shown that the dose of 730 mg of quercetin decreased the systolic and diastolic pressure in the patients diagnosed with stage-1 hypertension. The duration of this therapy was 4 weeks. But at the same time, this therapy does not work on the patients diagnosed with pre-hypertension (Edwards RL *et al.*, 2007). In the meta-analysis, conducted by Serban *et al.*, it is shown that the quercetin administration reduced the blood pressure when it is taken in the dosage of more than 500 mg, once a day for eight weeks but not had any effect on blood pressure when taken in the less dose (Serban MC., 2016).

In the double-blind randomized clinical trials, conducted with 72 female patients diagnosed with T2DM, the administration of 500 mg of quercetin reduced the systolic blood pressure but it has no effect on diastolic pressure. The course of this therapy was 10 weeks (Zahedi M., 2013). Quercetin shows its anti-hypertensive property by regulating the vascular resistance, blood volume, other body fluids, RAAS mechanism and nervous system (Marunaka Y., 2017).

Role of Quercetin as an Anti-Oxidant, Anti-Inflammatory and Anti-Aging

Cyclooxygenase helps in the production of prostaglandins which secreted at the site of inflammation. So, this quercetin exhibits its anti-inflammatory action by inhibiting the secretion of the cyclooxygenase enzyme (Lee KM *et al.*, 2010; Endale M *et al.*, 2013; Kim HP *et al.*, 1998). Quercetin shows its anti-oxidative property by interacting with the enzyme heme oxygenase-I. It also exhibit its oxidative property by its ability of removing a radical (Kro1 W *et al.*, 1990; Chow JM *et al.*, 2005). The quercetin shows anti-hypertensive effects by the mechanisms with

respect to its anti-oxidant and anti-inflammatory properties (Pfeuffer M *et al.*, 2013). Some studies have proven the anti-aging properties of the polyphenols but the exact mechanism involved in it is still unknown (Queen BL., 2010). In the study conducted by Maurya, P.K., it was shown that quercetin elevate the levels of membrane sulfhydryl and glutathione but it reduces the level of malondialdehyde (MDA). This proves that quercetin has the ability to reduce oxidative stress and prevent aging by acting as anti-aging agent (Maurya PK *et al.*, 2016). The anti-oxidant effect of quercetin is due to it inhibits the enzyme xanthine oxidase, thus preventing the formation of free radicals. The absorption of quercetin increases 60-80 % when it is hydrolyses to glycoside to aglycone form (Shi GJ *et al.*, 2019).

Role of Quercetin in Neurodegenerative Diseases

Quercetin helps in preventing neurodegenerative disease and it also proved in many studies. Quercetin downregulates NF-kB and iNOS, thus it suppress the neurodegenerative process. It also prevents the oxidation of the neurons by decreasing the lipid peroxidation (Khan H *et al.*, 2019). As the quercetin is lipophilic in nature, it can easily cross the BBB and act as neuroprotective (Ebrahimpour S *et al.*, 2020). Quercetin prevents the occurrence of Alzheimer's disease by down regulating the proteins responsible for this disease (Park S *et al.*, 2019). The important factor responsible for age-related neurodegenerative disease is oxidative stress. Quercetin helps in inhibiting the oxidative stress and prevents the occurrence of neurodegenerative disease (Grewal AK *et al.*, 2021).

Role of Quercetin on Diabetes Mellitus

It is shown in many studies that quercetin can reduce the blood glucose level and helps in the

treatment of T2DM by the conservation of islets cells, increasing the insulin level, improvement in dyslipidemia, and reduction in the oxidative stress (Zu G *et al.*, 2021). In the study conducted by using rats, it is shown that oral administration of quercetin, the testicular damage, sperm count and sexual activity which were affected by T2DM have improved by quercetin (Deepika *et al.*, 2022). Quercetin prevents the onset of diabetic nephropathy by improving the shape of the kidney and pathological changes occurring in the renal system caused due to diabetes (Roth G *et al.*, 2000). The important factors responsible for diabetic retinopathy are inflammation, oxidative stress, and retinal damage. Quercetin helps in preventing this factors and avoids diabetic retinopathy by also reducing blood glucose level (Elbe H *et al.*, 2015).

Role of Quercetin on Arthritis

Arthritis is a joint inflammation and may cause redness, swelling, pain and stiffness in the joints. They are usually treated by steroids, NSAIDS, and surgeries. The type of arthritis includes osteoarthritis, rheumatoid arthritis, psoriatic arthritis and gout. The factors responsible for causing arthritis include environmental, genetic and hormonal factors (Cobelli N *et al.*, 2011). In a study conducted using mice, it is reported that quercetin helped in reducing pain and inflammation caused due to arthritis. It also reduced edema and tenderness. It is also shown that quercetin in combination with methotrexate is more effective in treating arthritis than treating alone with quercetin (Haleagrahara N *et al.*, 2017; Salehi B *et al.*, 2020).

Role of Quercetin on Mitochondrial Function

Mitochondria is responsible for homeostasis, production of ATP and regulation of calcium. The dysfunction of mitochondria is one of the important factor in the age-related Alzheimer's disease. In a study, it is shown that quercetin helps in preventing the age-related progression of Alzheimer's disease. The mechanism involved in it is the quercetin activated the production of AMP activated protein by preventing the dysfunction of the mitochondria (Wang DM *et al.*, 2014). By this mechanism, it also involved in improvement of memory in case of Alzheimer's disease in older mice and prevents the memory deterioration in the initial stages of AD.

Role of Quercetin on Huntington's disease

Huntington's disease is a progressive neurodegenerative disorder, characterized by the loss of dopaminergic neurons in the substantia nigra. The symptoms associated with this disorder are memory loss, weight loss, dystonia, chorea, mood related disturbances (Choudhary S *et al.*, 2013). Sirtuin 1 is an enzyme which is present in plant based substances such as fruits and vegetables. It is largely up regulated by quercetin. This Sirtuin 1 enzyme up regulation tend to increase the survival of mice affected by Huntington's disorder in a study (Jiang M *et al.*, 2011).

Role of Quercetin on Depression

The most common mental disorders include anxiety and depression. The medications used to treat these disorders are more expensive, has limited efficacy with adverse effects. These disorders may be caused due to lack of sleep, environmental factors, personal factors or drug induced anxiety and depression (Masse C *et al.*, 2021; Anacker C *et al.*, 2017). Quercetin plays a major role in controlling anxiety induced by doxorubicin. The mechanism carried over here is reducing the oxidative stress. Quercetin also possesses anti-depressant activity by its anti-oxidant and anti-inflammatory properties (Khan K *et al.*, 2018). It also increases 5-HT levels. Another mechanism for quercetin's anti-depressant property is it signals the Sirtuin 1 enzyme to reverse the effects of anxiety and depression. In a study performed using rats, it is shown that 40 mg per kg of quercetin for a period of 8 weeks, the depression induced by LPS was shown to be alleviated (Fang K *et al.*, 2020).

Role of Quercetin on Atherosclerosis

Atherosclerosis is a common cardiovascular disease caused by formation of plaques in the arteries carrying blood. It is mostly due to accumulation of high cholesterol and fats. Quercetin prevents or reduces the accumulation of cholesterol in the arteries, thus reducing the incidence of atherosclerosis (Cao H *et al.*, 2019). It also increases the anti-oxidant properties of the cells and inhibits oxidative damage caused by oxidized low density lipoprotein by activating Sirtuin 1 enzyme (Mirsafaei L *et al.*, 2020; Mirsafaei L *et al.*, 2015). Quercetin inhibits the formation of plaque in atherosclerosis by activation of NF- κ B and TNF- α and 3 (Lu XL *et al.*, 2017). Quercetin helps in the alleviation of atherosclerosis by prevention of the endothelial damage of cells through Sirtuin 1 mediated inflammatory response and oxidative stress (Jiang YH *et al.*, 2020).

Role of Quercetin on Osteoporosis

Osteoporosis is one of the major age-related disease which causes weakness and brittleness in bones. Quercetin promotes the bone cell differentiation and proliferation, thus preventing the occurrence of osteoporosis through the up regulation of Sirtuin 1 by inducing its oxidative properties (Wang N *et al.*, 2021). Quercetin prevents the incidence of age-related osteoporosis by inhibiting apoptosis, inflammation and autophagy of osteoblasts through Sirtuin 1 (Vakili S *et al.*, 2021). In an in vitro study, it was found that quercetin inhibits the differentiation of osteoclasts (Wong SK *et al.*, 2020; Cui Z ET A., 2022).

Role of Quercetin as Bioenhancer

Bioenhancers are the agents which do not possess pharmacological activity on their own but when

co-administered with other active ingredients, it increases the efficacy and bioavailability of the drugs or active ingredients. There are many bio-enhancers available naturally, they are quercetin, curcumin, piperine, naringin, genistein, glycyrrhizin and sinomenine. In this article, we can see the detailed effect of quercetin as bio enhancers. The bio enhancers helps in stimulating the bioavailability and bio efficacy of many class of drugs at their low doses which are used to treat the major diseases such as anti-viral, anti-tuberculosis, anti-cancer, anti-fungal and anti-hypertensive drugs. The importance of bio enhancers in the treatment of diseases includes reduction in the dosage of administered drug, reduction in the duration of the therapy, prevent or reduce adverse drug reactions or drug toxicity, prevent drug resistance and reduce the cost of drugs (Ajazuddin *et al.*, 2014). The bioenhancer activity of quercetin is due to inhibition of P-gp (Hayeshi R *et al.*, 2006).

In a study conducted using rabbits, when quercetin is administered in a dosage of 15 mg/kg before the administration of 10 mg/kg of verapamil, the bioavailability of verapamil has increased than the verapamil alone treated group in rabbits (Choi JS *et al.*, 2004). It is also shown in a study that the oral bioavailability of diltiazem has increased when quercetin is administered before the verapamil administration in rabbits (Choi JS *et al.*, 2005).

Quercetin also increases the absorption of epigallocatechin. This is observed in a study that the absorption of epigallocatechin was increased with red onion supplements, which is rich in quercetin. The AUC of quercetin was increased from 1323 to 1814 ngh/mL, for a period of 6 hours when it is concomitantly administered with quercetin (Kale A *et al.*, 2010).

CONCLUSION

In this study, it is elaborately shown that quercetin has a potential to cure or prevent the age-related diseases and disorders. It has a positive effect on Hypertension, Diabetes mellitus, Osteoporosis, Alzheimer's disease, Huntington's disease, atherosclerosis, depression, mitochondrial dysfunction and arthritis. It also has a property of anti-inflammatory, anti-oxidant, anti-proliferative, anti-microbial and anti-aging. Apart from this, quercetin also act as an excellent bioenhancer. It helps to increase the absorption and bioavailability of several drugs used in the treatment of major diseases and disorders when used as pre-treatment or using concomitantly with the major drugs. It helps to decrease the dose and duration of the therapy. It also paves the way to treat or cure the disease with the low cost in the poor or developing countries. As we are using low dose of drug, it is also possible to prevent the drug toxicity due to drug over dosage and adverse drug reactions.

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