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Quercetin: A Potential Flavonol with Multiple Health Benefits

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Abstract

Flavonoids are naturally occurring polyphenolic parts of phytonutrients (plant chemicals) existing in fruits, vegetables, stems, roots, bark, grains, flower, wine, and tea. These are widely known for their beneficial effects on mammalian health and to support homeostasis. The findings obtained from some *in vitro* and pre-clinical trials have evidenced effectiveness of quercetin (a polyphenol) in sustaining mammalian physiology under both stressed and non-stressed conditions against inflammation, oxidative stress, bacterial, viral or fungal invasion etc. In addition to this, some *in silico* studies have also confirmed the efficacy of quercetin in curtailing SARS-COV-2 viral load by exhibiting inhibitory effects major viral peptides of the virus. Therefore, the present review focuses on the consolidated physicochemical properties of quercetin and also emphasizes on the clinical investigations to be carried out by using quercetin in order to explore its other nutritional aspects contributing to boost immunity & improve human survival.

Keywords: Quercetin, dietary sources, physicochemical attributes significance.

Introduction

Flavonoids are popularly known as the secondary metabolites of plants and plant products with a polyphenolic structure [1,2]. They are reported to be an essential clusters of naturally occurring, bioactive phyto-phenolics which exists ubiquitously in all plants and associated products such as- fruits, nuts, vegetables, medicinal plants, and several beverages namely- tea, coffee, cocoa, wine etc., [3]. As per the literature, these flavonoids belong to the class of low molecular weight heterocyclic compounds with indispensable health-promoting effects along with several medicinal attributes synthesized from the amino-acid residues of Shikimate pathway [4]. Apart from this, they have also been associated with carrying out numerous biological activities in plants and animals such as- imparting colour and fragrance to the flowers, preventing the plants from biotic and abiotic stress, serves as an effective anti-oxidants and anti-inflammatory molecules as a part of animals and human's diet, an effective regulators of cell cycle progression etc., [5]. Broadly these flavonoids are classified into six distinct subgroups, based on their C ring carbon associated with B rings, degree of unsaturation, and oxidation of C ring [6] (Figure 1).

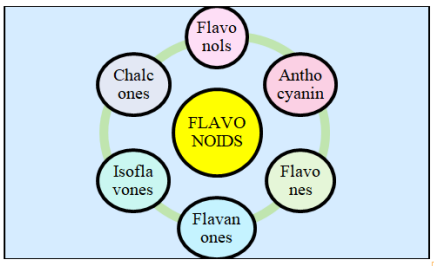

Figure 1: Classes of flavonoids.

Current research and trends on flavonoids have largely focussed on the health related and biological aspects of quercetin in maintaining the homoeostasis under both

stressed and unsaturated conditions [7]. This name quercetin has been derived from a latin encryption Quercetum which means "oak forest" [8]. Quercetin (a flavonol) is known to be the most abundant flavanoid or polyphenolic bioflavonoid, which cannot be synthesized naturally in the mammalian system is known for its free radicals scavenging potential [9]. Literature has also referred it as a phytoestrogens [10]. Some of the recent studies have also come-up with its unique biological characteristic of subsiding infection risk along with improving physical/mental performance [11].This attributes to the potential benefits to total health and disease resistance properties especially- anti-oxidants, anti-inflammatory, anti-carcinogenic, anti-viral, psycho-stimulant behaviour, platelet aggregation, and a potent nitric oxide (NO) inducer [11].

General Chemistry of Quercetin

Quercetin is a brilliant ($C_{15}H_{10}O_7$) yellow needle crystal with a molecular weight of 302.24 gm consists of 5 hydroxyl (-OH) groups at 3,5,7,3, and 4' carbons due to which it has assigned with an IUPAC name of 3,3',4',5,7-pentahydroxy-2-phenylchromen-4-one or 3,3',4',5,7-pentahydroxyflavonone [11] (Figure 2). It is also referred to as a building block of remaining flavonoids [11].

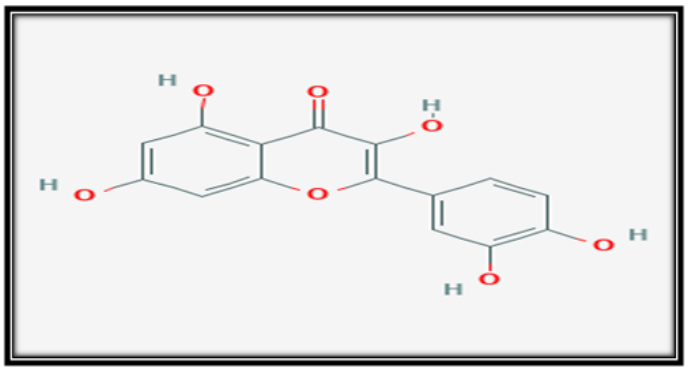

Figure 2: Pictorial representation of naive form of quercetin (quercetin aglycone).

Physicochemical properties of quercetin

In general quercetin in its native form exists as aglycone i.e., devoid of any sugar moiety in the food items, which later wards by acid hydrolysis turns to rhamnose and quercetin [12]. Quercetin due to its high molecular weight (302.24 gms), melting point of 316.5ºC, and complex chemical structure (i.e., having 5-OH groups) is insoluble in cold water, slightly soluble in warm water and entirely soluble in lipids and alcohol which makes it a lipophilic molecule [13]. Apart from aglycone form, quercetin is found to exist in four other distinct forms- (i) Quercetin glycoside, formed by substituting one –OH group on quercetin with a glycosyl residue (a sugar moiety such as- rutinose or rhamnose) (Figure 3(a)); (ii) Quercetin sulphate, produced by replacing –OH group with a sulphate group at 3rd position on quercetin (Figure 3(b));(iii) Quercetin glucuronide is formed by attaching a beta-D-glucuronopyranosyl moiety at position 3 via glycosidic linkage as a replacement to –OH group on quercetin (Figure 3(c)); (iv) Methylated quercetin, by substituting –OH group with a methyl group (Figure 3(d)) [11, 13].

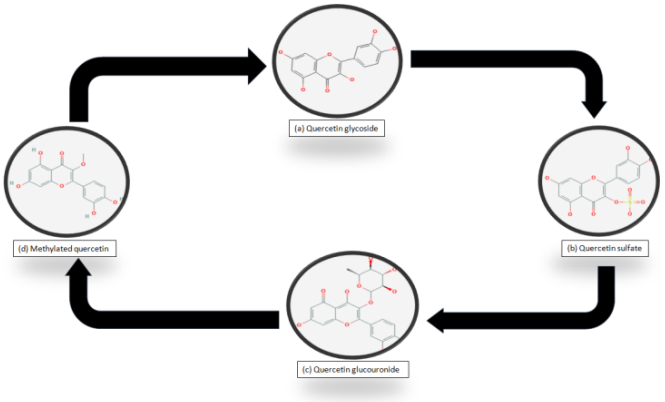

Figure 3: Forms of quercetin.

3a. Quercetin glycoside (synonyms: Meletin; Xanthaurine); 3b. Quercetin sulphate; 3c. Quercetin glucouronide; 3d. Methylquercetin

Dietary intake and sources of quercetin

Quercetin (especially the quercein glycosides) is the abundant most among all the flavonols, which is reported to be distributed widely in plants and variety of food stuffs such as- onions, apple, grapes, berries, tomatoes, tea, coffee, shallots, brassica, broccoli, cherries, citrus fruit, nuts as well as in seeds, barks, flowers, and leaves of plants and trees [11]. In addition to this, quercetin is also sought to exist in medicinal botanicals such as- Hypericum perforatum, Ginkgo biloba, Sambucus canadiensis, and Ocimum sanctum [14-16]. A very recent study has also indicated the occurrence of different proportions of quercetin in honey from different sources [17] (Table 1).

Table: Sources of quercetin.

S. No.	Quercetin sources	Quercetin (mg/100g)
1	Caper	234
2	Dill	79
3	Fennel leaves	46.8
4	Onion	45
5	Oregano, fresh	42
6	Chilli pepper	32.6
7	Spinach	27.2
8	Cranberry	25
9	Kale	22.6
10	Bee pollen	20.95
11	Cocoa powder, unsweetened	20.1
12	Cherry	17.4
13	Lettuce	14.7
14	Blueberry	14.6
15	Asparagus	14
16	Broccoli	13.7
17	Apple	4.42
18	Green tea	2.69
19	Red wine	3.19
20	Black tea	1.99

Depending on the daily consumption of vegetables, fruits, and beverages such as- tea, coffee or wine, the estimated intake of quercetin has been reported to range from 10 to 800 mg/day, which varies dramatically from nation to nation for example- In Japan, the quercetin intake has been found to be recommended up to nearly 16 mg/day, in USA it is around 16.4 mg/day, in Spain approximately 18.48mg/day etc. [11, 18-20].

Clinical and Physiological Significances of Quercetin

Anti-oxidant behaviour

Anti-oxidants are the molecules synthesized in the plants and mammalian system against the environmental stresses, which acts by inhibiting free radicals generation [21]. They can be both natural and synthetic supplements namely- vitamin- A, C& E, generally called as dietary anti-oxidants, plays role in maintaining general homeostasis by improving the free radical induced pathological conditions [22].

Indeed, most of the flavonoids (the phenolic substances) areknown to exhibit anti-oxidant behaviour especially the quercetin [23]. The literature reveals that, the plant derived aglycone form of quercetin has profoundly been used as a nutraceutical or nutritional supplement all over the globe against oxidative injuries either due to anthropogenic activities such as- smoking, pollution etc. or due to environmental stress such- low pO_2 in the atmosphere [24]. In corroboration to this, quercetin prophylaxis has shown to exhibit a significant protection against accumulating reactive oxygen species followed by protein oxidation and lipid peroxidation in the lungs of animals exposed to hypobaric hypoxia [25]. According to literature quercetin induces reduced glutathione (GSH) production within the cells in order to counter the effects of increased generation of free radicals within the body as consequence of some stress exposure or injury. This quercetin-mediated synthesis of GSH along with super-oxide dismutases plays a crucial role in capturing the oxygen free radicals (O^{2-}), transforming into H_2O_2 and catalyzing their decomposition into non-toxic H_2O [26,27]. Chen et al. (2017) have evidenced the role of quercetin in regulating in considerably elevating the levels of other endogenous anti-oxidants namely- catalase (CAT), Cu/Zn-SOD, Mn-SOD, etc. in hippocampal CA1 pyramidal neurons of the rodents suffering from ischemic injury [28]. Besides this, the hydroxyl groups (-OH) attached to the phenyl rings in quercetin are known to impart an inhibitory effects on two key enzymes- acetylcholinestrase (AChE) and butylcholinesterase (BChE) associated with oxidative attributes [29].There's a bunch of data documenting the anti-oxidant behaviour of quercetin based on various *in vitro, in vivo, and in silico* analysis such as- effectiveness of quercetin in abating paraquat-induced oxidant injuries in A549 cells, on the other hand, quercetin administration has demonstrated a dramatic alleviation in oxidative stress counts by modulating the levels of anti-oxidant-related genes in lung epithelial cell lines (A549), apart from this quercetin supplementation has also proven to be an effective treatment for gastric epithelial injury caused by oxidative stress in gastric epithelial cells (GES-1), etc. [30, 31]. Even the data mounted from the various nutrionists has clearly

evidenced the effectiveness of quercetin in scavenging free radicals and countering oxidant injury within the mammalian system and thereby regulates homeostasis [22].

Anti-inflammatory property

Inflammation is a biological response or a self-protecting mechanism of the body's immune system which aims at eliminating the damaged cells or pathogens affecting the body due to its exposure to any harmful or irritating stimuli [32]. Among the flavonoids, quercetin intake has effectively demonstrated a significant attenuation in the catalytic actions of two remarkable inflammatory enzymes- cyclooxygenase (COX) and lipooxygenase, which has further shown to down-regulate the count inflammatory mediators such as- leukotrines and prostaglandins [33,34].

In fact a team of nutritional scientists from Michigan state university has also elucidatedthe role of quercetin as an effective anti-inflammatory agents [35]. Moreover, the data from certain *in vitro* studies has explored the potential of quercetin in significantly lowering down the levels of some major inflammatory mediators such as- COX-2, C Reactive Protein (CRP), and NO syntheses in human hepatocyte derived cell lines [36]. Apart from targeting COX-2, lipooxygenases, and CRP, quercetin has also found targeting High Mobility Group Box Protein-1 (HMGB1), receptor for advanced glycation end product (RAGE), toll-like receptors (TLR 2 & 4), and extracellular signal-regulated kinase (ERK 1/2) signalling cascades affecting chronic inflammation and associated pathologies namely- sepsis, psoriasis, Atopic Dermatitis (AD), arthritis, etc. [37]. As per the literature, interaction of RAGE, TLR 2 & 4 with HMGB1 activates NFκB pathway to stimulate cytokine activity contributing to inflammation and oxidative stress [38]. Not only this, a study in rats supplemented with quercetin (80 mg/Kg BW dose) has elicited a dramatic decrease in both acute and chronic inflammation along with a significant reduction in arthritis levels in humans [39]. In addition to this, one of the recent findings has also revealed the biphasic, modulating, and regulatory behaviour of quercetin on inflammation and immunity [40]. Further, quercetin has also exhibited the stabilization of mast cells and gastrointestinal cytoprotective roles in human as well as animal model according to certain recent studies [41].

Anti-viral response

Literature has elucidated the anti-viral responses of quercetin not only against the enveloped viruses such as- parainfluenza type III, herpes simplex type I, pseudorabies, respiratory syncytial, and sindbis but also against cardioviruses has gained general acceptance in public domain nowadays [42]. This anti-viral activity of quercetin is mainly due to its capability to associate itself with the viral coat protein, polymerases, and to the damaged DNA within the host [43]. Quercetin was also evidenced to have elevated antiviral tendencies when associated with the agents like- ascorbate, 5ºethyl-2'-deoxyuridine, and interferon [43].

Neurological activity

An *in vivo* studyon rat brain has indicated the application of quercetin in combination with fish oil has exhibited favourable effects against neurodegenerative ailment especially Alzeimer's Disease (AD) [44]. In corroboration to this, quercetin has also displayed the inhibitory effects against acetylcholinestrases production [45]. In another study, quercetin treatment to the rats in an *in vivo* study exhibited a significant reduction in 6-hydroxydopamine mediated oxidative stress in the neurons of rats' brain striatum [46]. The mounting data on quercetin made it evident that quercetin comprises of tremendous neuroprotective activities followed by preventing of multiple age-related neurodegenerations when administered as recommended [47].

Effects on cardiovascular disorders

The diet is said to play a major role in the occurrence of cardiovascular diseases, which are known to cause maximum morbities in number of countries [48]. The data collected from meta-analyses studies presented an inverse relation between bioflavonoid intake and onset of stroke [49]. It has been noted that intake of quercetin prevents the platelet aggregation leading to improvise the endothelial functioning [50]. Besides this, it also provides protection against Coronary Heart Diseases (CHD), which later minimizes the mortalility chances arising, due to low-

density lipoproteins [51]. In addition to that, quercetin consumption has also reported to elicit vasorelaxant behaviour on isolated arteries responsible for lowering blood pressure, inhibits fat accumulation in maturing fat cells, and prevents the onset of cardiac hypertrophy [51].

Anti-carcinogenic activity

The flavonoids derived from the fruits and vegetables have been marked-up positively against cancer onset and progression [43]. Even the epidemiological survey has revealed that diet rich in fruits and vegetables offer protection against different types of cancer [52]. Among all the flavonoids, quercetin has gained maximum attention of the researchers and dieticians in acting as an anti-cancerous nutraceutical, which offers anti-proliferative, antioxidant, and growth factor suppression properties [53]. Besides this, findings from an *in vitro*study have also explored the anti-carcinogenic behaviour of quercetin, where it was observed that quercetin supplementation hinders the growth of cancer cells and fosters the apoptosis mechanism [52]. It is reported to subside the progression of tumour specifically in colon, liver, brain, and in some other tissues as well [53-54]. Apart from this, quercetin administration has also demonstrated the benefits against prostate cancer [55].

Allergic intervention

Quercetin ($C_{15}H_{10}O_7$) has been reported to employ anti-allergic effects by impeding the secretion of histamine from mast cells and hence acts as a "natural anti-histamine" agent [56]. The dietary intake of quercetin has also been associated with relieving the pathologies of asthma especially mucus and collagen production, eosinophil and neutrophil enrolment, bronchial epithelial cell activation and airways hyperactivity [43].

Significance of quercetin in High Altitude Illnesses (HAI)

The commendable anti-inflammatory and anti-oxidative attributes of quercetin makes it highly beneficial candidate to not only to minimize but to prevent major manifestations of exposure to low PO_2conditions [25,27]. Besides curtailing the hypoxia-mediated increase in free radicals production, oxidant injury, and excess inflammation, the supplementation of quercetin in recommended dosage has also demonstratedasignificant restoration of mammalian lung physiology by retaining the regulation of major signalling cascades like NFκB, GPCR, and NO- signalling which are known to regulate body's cellular and physiological processes essentially- cell division, proliferation, differentiation, apoptosis, strengthening immunological support, vasodilatation etc. to normal [58,59]. In addition to this, quercetin has also proven its efficiency in stabilizing the mammalian haematological and blood gas compositions to normal, which usually gets impaired upon rapid ascent to high altitude conditions [60].

Quercetin: a possible remedy to Severe Acute Respiratory Syndromes (SARS)

Since a decade, quercetin supplements have been a prime recommendation by naturopathic doctors to support monitored inflammatory and healthy immune responses [61,62]. Additionally, due its incredible contribution in regulating the expressions of cytokine producing genes, quercetin has gained a general acceptance and preference over the other nutraceuticals in inhibiting the progression of influenza a strains (H1N1, H3N2) and inhibition of H5N1 entry [63]. Recently researchers have also identified the relevance of quercetin uptake in the cure of SARS [62,64]. SARS is a contagious and often fatal respiratory severityemerged from China (Nov 2002) to worldwide [64]. It usually begins with the symptoms like flu, cold, fever, etc. and if left undiagnosed then may lead to death [64]. However, as per the recent stats, the corona strain or SARS-COV-2 has infected nearly 80,133,093 people across the globe and has resulted into approximately 1,755,653 deaths worldwide; as a result World Health Organization (WHO) has declared the situation as "a public health emergency of international concern" on January 30, 2020 [65]. Yet, no guided medication or therapy has come into the consideration.Based on the previous studies on antiviral compounds; the foremost thing is to obtain knowledge about target viral protein. In case of SARS-COV-2, the viral load is mainly because of 3-chymotrypsin-like proteases (3-CLpro), papain-like proteases (PLpro), RNA polymerases, and spike (S) proteins [64]. Interestingly, quercetin has found to impart an inhibitory effect on 3-CLpro and PLpro with -6.25 and -4.62 kcal/mol of docking binding energy

[64]. Therefore, based on these aforementioned attributes, quercetin can be considered to have theoretical but considerable potential to interfere SARS-COV-2 replication. Hence on the ground of this quercetin has been considered as the fifth-best compound out of 18 candidates selected for COVID-19 inhibitors [64].

The overall effect of quercetin on mammalian health has been represented pictorially in figure 4.

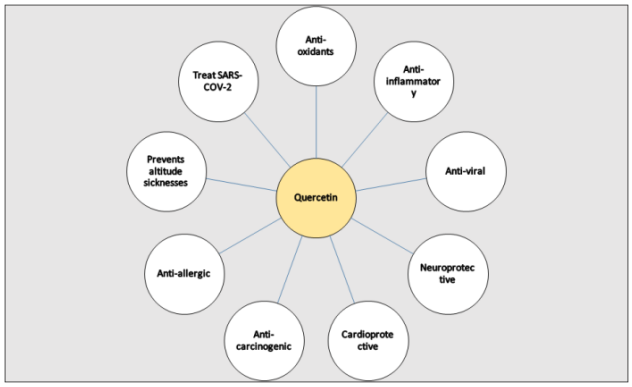

Figure 4: Pleitropic effects of quercetin on mammalian health.

Conclusion

This multifaceted molecule quercetin has potential to exert protective effects on mammalian health by exhibiting tremendous anti-oxidant, anti-inflammatory, anti-viral, anti-carcinogenic, and anti-allergic activities along with subsiding the cardiovascular and neurologic risk. In addition to this, the quercetin pre-conditioning prior to hypoxia exposure has also confirmed the relief from the complications of different forms of High Altitude Injuries (HAIs) varying from mild (AMS) to severe (HAPE & HACE) once. Interestingly, the reports on efficiency of quercetin to interfere SARS-COV-2 replication & progression strongly support its consideration for further clinical trials against the existing viral strains as well. Therefore, the conclusion drawn from these findings validates the intake of quercetin endowed diet to be safer and effective in maintaining the homeostasis under both stressed and non-stressed conditions.

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Author's Contributions: SKS has conceived the idea. AT has prepared the manuscript, graphs, and figures. SS and RV performed final analysis.

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