REVIEW

An Insight into the Potentially Old-Wonder Molecule—Quercetin: the Perspectives in Foresee

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ABSTRACT Use of phyto-medicine and digitalization of phyto-compounds has been fallen enthralling field of science in recent years. Quercetin, a flavonoid with brilliant citron yellow pigment, is typically found in fruits and leafy vegetables in reasonable amount. Quercetin's potentials as an antioxidant, immune-modulator, anti-inflammatory, anti-cancer, and others have been the subject of interest in this review. Although, profiling the insights in to the molecular characterization of quercetin with various targets provided the loop-holes in understanding the knowledge for the aforementioned mechanisms, still necessitates research globally to unearth it completely. Thus, the available science on the synthesis and significant role played by the old molecule - quercetin which does wonders even now have been vividly explained in the present review to benefit the scientific community.

KEYWORDS quercetin, antioxidant, flavonoids, mechanism of action, molecular characterization

In recent years, the values of synthetic drugs have almost lost due to its significant side effects and most of them have been withdrawn from the market because of their high toxicity. In fact, researchers have realized the potentials of herbs, which have been very well documented even before thousands of years. Generally, synthetic drugs are synthesized by pure ingredients, while herbal medicines are made up of complex ingredients. Those different ingredients in one or many herbs may balance each other, or in other words buffer each other, and act synergistically to make the systemic effect more potent. Moreover, some synthetic drugs may target only one molecule and therefore, its effect on other molecules in the pathways or systems are unknown and this often could lead to severe side effects. However, in contrast to this, herbs act on multiple targets, for example, one formulation may have effects on major diseases such as anti-inflammatory, anti-allergic,[1] anti-oxidant, anti-toxic, including improvement of cardiovascular functions, anti-cancererous,[2] anti-diabetic,[3] and anti-osteoporotic.[4]

Generally, bioflavonoids are a large group of non-nitrogenous class of plant secondary metabolites that provide pigmentation to flower and protect from ultraviolet light, microbes, and insects, apart from imparting flavors to the fruits and vegetables of the plants.[5] They are identified as a good alternative to the synthetic drugs. One of the most valuable bioflavonoid is quercetin, which needs to be explored to a larger extent as it is reported to be the highly competitive and potential component in drug formulations.[6] Therefore, the present review was written to emphasize the information on quercetin's structure, synthesis, metabolism, medicinal value, proteomic, and genomic information, which in turn may provide evidence about its role as a therapeutic and outlines gap in the available data that need to be filled in order to determine the quercetin's appreciable role in future disease therapy.

Classification of Bioflavonoids

Bioflavonoid shares a common flavones backbone; three ringed with hydroxyl [OH] groups. According to the international union of pure and applied chemistry (3-hydroxy-2-phenylchromen-4-one: IUPAC) nomenclature, bioflavonoids are classified into flavonoid, isoflavonoid, and neo-flavonoid (Figure 1). The flavonoids are further grouped in to flavanones, flavones, flavonols, flavans, and anthocyanins, based on the position of functional groups. However, among them flavonols that enrolls the 3-hydroxyflavone backbone plays a vital role in imparting taste, flower color and flavor to fruits and green leafy vegetables.[7] Many different flavonols such as kaempferol, morin, spirenoside, fisetin, quercetin, and Galanginetc, have been identified in a wide variety of

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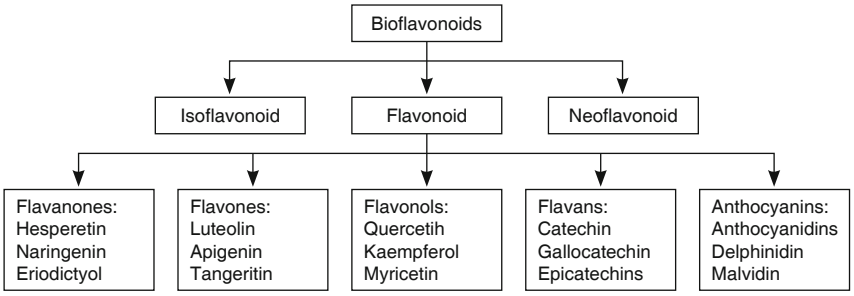

Figure 1. IUPAC Classification of Bioflavonoids

plants and are reported to exhibit the difference by the position of their functional group (Table 1).

Table 1. Position of the Functional Group in Flavonols

Examples	Position of functional group in carbon chain						
	3	5	7	2'	3'	4'	5'
Kaempferol	OH	OH	OH	H	H	OH	H
Morin	OH	OH	OH	OH	H	OH	H
Rutin	O-R	OH	OH	H	OH	OH	H
Myricetin	OH	OH	OH	H	OH	OH	OH
Quercetin	OH	OH	OH	H	OH	OH	H
Quercetrin	O-R'[a]	OH	OH	H	OH	OH	H
Myricitrin	O-R'	OH	OH	H	OH	OH	OH
Spirenoside	OH	OH	OH	H	OH	O-Gluc	H
Galangin	OH	OH	OH	H	H	H	H
Robinin	O-R	OH	OH	H	H	OH	H
Kaempferide	OH	OH	OH	H	H	O-Me	H
Fisetin	OH	H	OH	H	OH	OH	H
Rhamnetin	OH	OH	O-Meb	H	OH	OH	H

Notes: a-O-R' = alkoxy; b-O-Me = methoxy; c-O-Glu = glucosyl

Structural Organization and Implications of Quercetin

Quercetin (molecular formula $C_{15}H_{10}O_7$; molecular weight of 302.236 g/mol) is a heterocyclic pyrone ring (aromatic trimeric heterocyclic) with two benzene rings. According to IUPAC, quercetin is a 3,3',4',5,7-pentahydroxyflavanone (synonym 3,3',4',5,7-pentahydroxy-2-phenylchromen-4-one), a compound with five hydroxyl groups attached in the ring structure at the position 3, 5, 7, 3', and 4' (Figure 2), giving it a status of amphipathic, i.e., both lipophilic and hydrophilic in nature. Those quercetin derivatives which have O-methyl, C-methyl, and prenyl derivatives are lipophilic and are reported in glands located on the surface of the leaves, flowers, or fruits in members of Labiatae or Compositae families.[7] Basically, it is a brilliant citron yellow color compound which is often found in plant as either glycosides [with attached

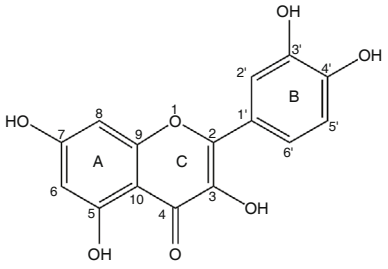

Figure 2. Molecular Structure of Quercetin

sugars (glycosyl groups)] or as aglycones (without attached sugars). The hydroxyl group at the C-3 carbon is easily glycosylated to form quercetin glycosides. The monosaccharides such as glucose, galactose, rhamnose, or xylose are attached with quercetin at C-3 carbon and form quercetin 3-O-glycosides,[8] as found in sage (*Salvia officinalis*) and mango fruit (*Mangifera indica*),[9,10] while quercetin 3-O-rhamnoside is found in olive (*Olea europaea*) oil,[11] peppers (*Piper nigrum*),[12] and spinach (*Spinacia oleracea*).[13] During glycosylation of the hydroxyl group (commonly at position 3), quercetin derivatives undergo a change from lipophilic to hydrophilic to form glycosylated quercetin, which is cytosol-soluble and could be easily transported to various parts of the plant.[14,7] In general the physical and chemical properties (such as absorption, solubility, and *in-vivo* effects) of the glycosylated quercetin differ from aglycosylated quercetin.[15,16] Disaccharides are also found to be attached with quercetin molecule such as rutin3-O-rhamnosylglucoside as in tea (*Camellia sinensis*),[17] spinach,[13] chokeberries (*Aronia arbutifolia*),[18] and buckwheat (*Fagopyrum esculentum*).[19] Another glycosylation site (hydroxyl group) is observed at C-7 as 3-O-rhamnoside-7-O-glucoside as seen in peppers[12] and quercetin 7-O-glucoside in beans[20] respectively. Perhaps, C-glycosides and sulphate derivatives of quercetin such as 3, 4, 7, 3', 4'-pentahydroxy-6-glucose flavon and quercetin 3-O-glucoside-3'-sulfate were also found in *Ageratina calophylla*[21] and cornflower (*Centaurea cyanus*)[22] respectively, but these compounds occur relatively rare in nature.

Metabolism of Quercetin

Quercetin is consumed daily by millions of people as a dietary source due to its presence in vegetables and fruits such as beans, onions, grapes, apple, green tea, berries, vegetables, nuts either in the fruits, flowers, barks, and leaves (Figure 3). Digestion of quercetin begins from oral cavity by cleavage of glycosides molecule by β-glycosidases, while aglycosylated molecule become more lipophilic and could be absorbed into the epithelial cell of the colon.[23] Generally, absorbed quercetins are metabolized in liver and unabsorbed in intestine involving four processes namely, glucuronidation, methylation, hydroxylation, and sulfonylation.

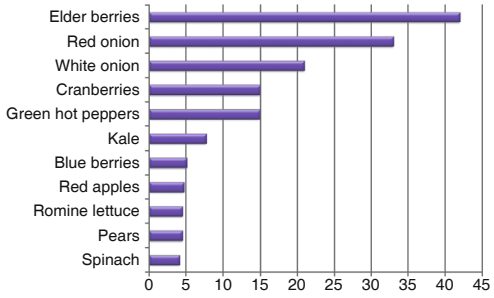

Figure 3. Amount of Quercetin (mg/100 g edible portion) in Food

Glucuronidation is one of the detoxifying mechanisms in liver which play a major role in metabolism of xenobiotic compound with the help of uridine 5'-diphospho (UDP)-glucuronosyltransferase enzyme.[24] Quercetin is reported to be glucoronidized during passage across the epithelium in the liver by UDP-glucuronosyl transferase[25,26] and further conjugates with glucose transporter receptor in small intestine.[27] For instance, a study on a rat's small intestine revealed the uptake of quercetin conjugate that interacted with intestinal hexose transport pathway through glucose transporter receptor and competitively inhibited the uptake of galactose, due to the presence of quercetin-3-glucoside in the mucosal medium, indicating its interaction with the sodium-dependent glucose transporter pathway (SGLT1).[28] However, several observations suggested that quercetin could be absorbed by two ways; as stated above, one in the small intestine by SGLT1 with subsequent deglycosylation within the enterocyte by cytosolic β-glucosidase, or luminal hydrolysis of the glucoside by lactase phlorizin hydrolase (LPH); and the other is absorption by passive diffusion of the released aglycone.[29] However, the first hypothesis was evaluated with the use of phlorizin (the inhibitor of SGLT1) and N-(n-butyl)-deoxy galactonojirimycin (as an inhibitor of the lactase domain of LPH) in a rat everted-jejunal sac model.[30] Quercetin-3-glucuronides and quercetin-7-glucuronides, the major product of quercetin metabolism in the intestine are further absorbed or excreted by two pathways: (i) methylation of both quercetin-3-glucuronides and quercetin-7-glucuronides by methyltransferases, and (ii) hydroxylation of endogenous β-glucuronidase followed by sulfonylation to quercetin-3'-sulfate.[31,32] Quercetin agylocones were found in human plasma as main circulating metabolite in an un-conjugated form, which resulted in deconjugation of quercetin glucuronides by the enzyme β-glucuronidase.[33] Nevertheless, an alternate mechanism for quercetin absorption was also revealed in small intestinal tract of human, where the flavonoid degrading strict anaerobic microorganism *Eubacterium ramulus* resides and cleaves quercetin ring structure into 3, 4-dihydroxy phenyl acetic acid.[34]

Pharmaceutical Accomplishment of Quercetin in Human Diseases

Mainly, by the fact that the quercetin has all the right structural features for free radical scavenging activity, they exert beneficial health effects such as anti-inflammatory, anti-allergic, anti-oxidant, anti-toxic, and anti-viral against reverse transcriptase of human immuno deficiency virus (HIV) and other retroviruses including *Herpes simplex* virus type 1, polio-virus type 1, parainfluenza virus type 3, respiratory syncytial virus (RSV), and HIV-1 integrase.[35] Additionally, it is also reported to interact with cyclin-dependent kinases such as CDK6, CDK5, and CDK1,[36] fatty acid synthesizing enzyme (enoyl-acyl carrier protein reductase),[37] and G protein-coupled receptor[38] to label a few. Moreover, it has remarkably proven to improve the cardiovascular functions, reducing the risk for cancer. Although potential benefits are extraneous, it is not possible to highlight all of them individually and therefore, with much care, effort has been undertaken to cover at most under the four major headings.

Effects on Allergy

An immune response produces effector molecules that act to remove antigen by various mechanisms. Generally these effector molecules induce a subclinical and localized inflammatory response that eliminates antigen without extensively damaging the host tissue. An allergy is a hypersensitivity disorder of the immune system. An excessive activation of white blood cells, mast cells and basophils, through the immunoglobulin

E antibody (IgE) is a symptom of allergic reaction. Quercetin exerts many effects on anti-allergic response; to inhibit histamine release in rat connective tissue mast cells, mucosal mast cells,[39] human lung, and intestinal mast cells.[40] In fact, quercetin isolated from *Gingko biloba* is reported to inhibit the lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β transcription by inhibiting the activation of ERK1/2 and p38 MAPK in macrophages.[41] The pathologic role of TNF-α and IL-4, which are involved in the onset of various allergic diseases including atopic dermatitis, atopic rhinitis, and asthma, were arrested even at the lower (100 μmol/L) concentration of quercetin, when applied on human umbilical cord blood-derived cultured mast cells (hCBMCs).[42] In another study, IgE or phorbol-12-myristate 13-acetate and calcium ionophore A23187 (PMACI)-mediated histamine release were blocked by quercetin in RBL-2H3 cells and also it inhibited the elevation of intracellular calcium as well as gene expression and production of all the pro-inflammatory cytokines.[43] In an experiment, quercetin also inhibited the expression of CD63 and CD203c and the histamine release by the basophils that were activated with anti-IgE.[44] Yet another investigation reported that quercetin inhibited the process of degranulation and suppressed the CD23 mRNA expression in RBL-2H3 cells at 10 μmol/L concentration.[45]

Likewise, when FcεRI- anti-IgE activated model was treated with 1.8–20 μmol/L quercetin, it interacted with catalytic pocket of the enzyme and inhibited P13K, consequently leading to the loss of phosphorylation of kinases (such as Bruton's tyrosine kinase)[46] which otherwise would phosphorylate phosphoinositide phospholipase C-γ (PLCγ) and lead to the production of inositol trisphosphate (IP3) and diacylglycerol (DAG) that may be responsible for the activation of membrane markers up-regulation and histamine production.[47] Moreover, quercetin is also reported to be effective on N-formyl-methionine-leucine-phenylalanine (fMLP) triggered basophil function, which activate the P13Kγ and G-coupled receptor kinase (GRK) that are basically responsible for degranulation event by IP3-calcium signaling or by the activation of diacylglycerol-protein kinase C-PKC pathway. The calcium ionophore A23187 induced the expression of CD63 and CD203c and these markers promote the activation of Ca^{2+}/calmodulin pathway, which is inhibited by quercetin.[48] Thus collectively, quercetin acts as a strong inhibitor of components those involved in allergic reaction and found to be functional even at the micromolar concentrations and thereby arising as a novel alternative for allergic treatments.

Effect on Inflammation

Inflammation is a mechanism of innate immunity which act as a first response from immune system against harmful stimuli, such as injury caused by pathogens, damaged cells, and irritation.[49] It is characterized by increased blood flow to the tissue, raise in temperature, redness, swelling, and pain. It may involve in developing various diseases such as allergy, asthma, arthritis, atherosclerosis, cancer, aging, etc.[50] Inflammation is a complex response which is caused by numerous biological factors such as LPS (major component of the Gram-negative bacteria cell wall),[51] enzymes [cyclooxygenase (COX) and lipoxygenase (LOX)],[52] nitric oxide production, and nitric oxide synthase (NOS) expression.[53]

LPS is one of the major factor for inflammation which is recognized by Toll-like receptor (TLR4) receptors that is found on the immune cells, including macrophages.[54] When LPS bind with specific TLR4 receptor, it can trigger signaling pathways and activate nuclear factor (NF)-κB.[55] Under normal conditions, NF-κB occurs in cytoplasm in an inactive state, bound to the inhibitory κB (IκB) proteins. The NF-κB is activated by IκB kinase (IKK) complex, that are composed of Ser/Thr kinases IKKα and IKKβ associated with other signal transducers IKKγ and IKAP. Signal components activate Ser/Thr kinases in IKK complex and activated IKK complex phosphorylates IκB and then followed by proteasome-mediated degradation of IκB.[56,57] After IκB degradation NF-κB enters into the nucleus and bind to the promoter regions of immune genes including IL-6 for transcriptional activation.[58] IL-6 is a pleiotropic interleukin that acts as both pro-inflammatory and anti-inflammatory cytokine. It is produced by T cells and macrophages as well as varieties of other cell types including adipocytes and microglial cell.[59] However, the effect of quercetin 3-O-β-(2"-galloyl)-glucopyranoside (QG-32) from *Persicaria lapathifolia* (polygonacease) was realized when it inhibited reactive superoxide (ROS) production in human monocytes.[60] Perhaps, studies showed that ROS could increases the LPS-induced IL-6 expression at the transcription level. In spite of ROS's independent production, it could still amplify TLR4-mediated

inflammatory responsiveness.[61] When endotoxin LPS-activated macrophages RAW 264.7 were treated with various concentrations (10–100 μmol/L) of QG-32 or pyrrolidine dithiocarbamate (PDTC) within 24 h, it inhibited the production of IL-6 as well as down-regulated the LPS-induced IL-6 expression at the transcription level.[62] Similarly, NF-κB, a transcription factor that is involved in proteolytic degradation of IκB was also inhibited by the administration of quercetin.[62] In fact, quercetin inhibits cyclooxygenase and lipoxygenase at concentration of 10–20 μmol/L, which is an important mediator in inflammation and tumor promotion.[52] The NOS expression is also found to suppressed by administration of 100 μmol/L quercetin, resulting in inhibition of nitric oxide (a pro-inflammatory mediator) production.[53] Hence these factors may attribute a major role in numerous chronic diseases such as allergy,[50] diabetes,[63] atherosclerosis,[64] depression,[65] Alzheimer's disease,[66] systemic lupus erythematosus,[67] prostate cancer,[68] and rheumatoid arthritis.[69] Since these studies have given lots of pharmacological potential of quercetin in the inflammatory disorders, the action of quercetin against numerous inflammatory factors may provide a better option to cure above mentioned diseases in the future.

Quercetin as an Antioxidant

The antioxidant activity of a compound is determined by the presence of free hydroxyl groups as well as position of double bond[14] that can donate electron through resonance to stabilize the free radicals.[70] The radical scavenging property defends the body against oxidative stress, reduces heart disease, prevents cancer, and slows the aging process in cells.[71] Lipid peroxidation is an oxidative degradation of lipid in which unsaturated fatty acids are converted to free radicals via the abstraction of hydrogen and further these free radicals are oxidized by molecular oxygen to create lipid peroxy radicals.

Quercetin shows inhibitory effect against human lipoxygenase (hLO) isozymes[71] that catalyzes the dioxygenation of polyunsaturated fatty acids to their hydroperoxy acids that have been implicated in several diseases including inflammation, immune disorders, and various types of cancers.[72] The low-density lipoprotein (LDL) is another reason for cardiovascular disease. While, studies have shown the ability of quercetin to inhibit LDL oxidation,[73] it not only stops the lipid peroxidation but also increases the glutathione (GSH) level,[74] which is a tripeptide that acts as an antioxidant in our body and neutralizes the free radicals by regulating the nitric oxide cycle [75] and other biochemical reactions involved in DNA synthesis and repair, protein synthesis, prostaglandin synthesis, amino acid transport, and enzyme activation.

Administration of quercetin-3'-glucuronidequercetin is also reported to inhibit xanthine oxidase,[76] which catalyzes the oxidation of hypoxanthine and xanthine to uric acid and superoxide radicals. The former plays a crucial role in gout, while the latter is involved in oxidative stress including inflammation, atherosclerosis, cancer, and aging. So, an increase in xanthine oxidase influences the rate of hepatitis and the degree of brain edema and its control by derivative of quercetin could accomplish a good measure for treating hepatitis, brain edema and also reduce the oxidative stress.[77,78]

In view of the number of studies, it is clear that quercetin possesses the structure that act as an effective and powerful antioxidants and since it is playing a major role in preventing the above mentioned diseases, and hence quercetin could be a subject of interest to control them naturally.

Quercetin as an Anti-cancer Agent

Oxidative DNA damage by oxygen species superoxide, hydroxyl, peroxyl, and alkoxyl, and reactive nitrogen species play a key role in human cancer development. The hydroxyl groups of quercetin have electron accepting capacity, while the catechol group chelate with metal ions.[23] *In-vitro* studies indicate that quercetin plays an important role in cancer treatment with the ability to act as potential antioxidants and there by inducing numerous molecular pathways such as apoptotic pathway, down-regulation of mutant P53 protein, G_1-phase arrest, inhibition of tyrosine kinase, inhibition of heat shock proteins, inhibition of ras protein expression, and estrogen receptor binding capacity.

Quercetin is reported to induce cell death by apoptosis in leukemia, lung, hepatoma, oral, and colon cancer cell lines.[79] For instance, administration of 40–50 μmol/L of quercetin induced the mitochondrial apoptotic pathway through initiating Bcl-2-associated X protein (Bax) and/or Bcl-2 homologous antagonist/killer (Bak) proteins. These proteins are involved in increasing the size of outer mitochondrial membrane pore and cytochrome C leakage into

the cytoplasm which further activates the apoptotic protease activating-factor 1 (APAF-1) and produces apoptosome.[80] The P53 is another important tumor suppression protein which activates the Bax and initiate cell death. When human hepatocellular carcinoma cell was treated with 40–120 μmol/L of quercetin, p53 expression was increased, while down-regulating the anti-apoptotic protein survivin that regulates the caspase activation and Bcl-2 that prevents mitochondrial mediated apoptosis.[81]

TNF-α-related apoptosis-inducing ligand (TRAIL or Apo2L) that belongs to the TNF cytokine family is produced by the activated macrophages and it is responsible for inducing inflammation, apoptotic cell death, and inhibiting tumorogenesis through enhancing the transcription of Bcl-2.[82] TRAIL, however, binds with the death receptors DR4/DR5, which further interact with the adaptor protein Fas-associated death domain (FADD) and procaspase-8 and form the death-inducing signaling complex (DISC). Procaspase-8 activation and DISC lead to cleavage of procaspase-3 and engagement of the cellular machinery associated with the type Ⅰ extrinsic apoptotic pathway. However, evidence claim that these attributes by the TRAIL proves futile under glioma cells and many cancer cell lines became more or less resistant to the apoptotic effect.[83] Thus the administration of quercetin especially 250 μmol/L was revealed to reducing the viability of U251, LN229, U87-MG, MDA-MD-231 and A172 glioma cells and also affecting the estrogen receptor α (ER-α) by inducing cytotoxicity in some cancer cell lines.[84] Moreover, quercetin is also reported to prevent the ROS production in the human cervix epithelial carcinoma cell line (HeLa) and stimulate the activation of p38/MAPK,[85] which are responsible for proapoptotic caspase-3 activation and mediate poly (adenosine diphosphate-ribose) polymerase (PARP) cleavage. In another study quercetin (50 μmol/L) in combination with ascorbate bound to the estrogen receptor (ER-β) and induced apoptosis of breast cancer (T47D-ER-α) and osteosarcoma (U2OS-ER-α and -ER-β) by increasing the intracellular pH through the modulation of the cells Na^+/H^+ exchanger.[86]

Quercetin reportedly evidenced the inhibition of malfunction of protein chaperons that are basically responsible for protein folding and maintenance of protein structure in our body. The disturbed chaperons are unable to perform their function and eventually result is death. Moreover, the heat shock proteins (HSP) such as HSP90, HER2, and IGFBP-2 allowed tumor cells to bypass normal mechanisms of cell cycle and allowed survival of cancer cell in unfavorable condition viz., hypoxic condition, low circulation, high temperature etc. However, these conditions were reported to be suppressed by quercetin (1–100 μmol/L) in several malignant cell lines namely colon cancer,[87,88] breast cancer, and prostate cancer.[89] Thus, the ability of quercetin to interact with electrons even at lesser concentrations plays a central role in its mechanism of action, mainly by the activation of proteins and DNA damage, leading to the induction of many downstream pathways of the cancer.

Thus quercetin is the subject of intense research on the basis of its anti-inflammatory, anti-allergic, antioxidant, and anti-cancer activities, as well as many therapeutic targets to cure different kinds of diseases such as Alzheimer's disease, diabetes, malaria, Chagas' disease, Schizophrenia etc. Apart from this, studies also suggested that quercetin is effective against antibiotic resistance bacteria. For instance, the antibacterial activities of quercetin has been tested on anti-methicillin resistant *Staphylococcus aureus* (MRSA), which uncovered the unique antibacterial properties of quercetin against *Staphylococcus aureus* (*S. aureus*).[90] The study was further substantiated by in-silico approach, which showed a strong interaction of quercetin and kaempferol with multidrug resistant β lactamase of *S. aureus*.[91] Thus, collectively, one could say that the quercetin has risen as a novel alternate to the synthetic molecules as evidenced by the enlisted literature presented in Table 2.

Biosynthesis

Realizing the potentials, it has become essential to know about the synthesis of quercetin, which involves in multiple enzymatic processes in the cytoplasm and associated with endoplasmic reticulum[137] via phenyl propanoid pathway (Figure 4). The first step of this pathway is deamination of phenylalanine by the enzyme L-phenylalanine ammonia-lyase (PAL),[138] which acts as a precursor molecule to synthesize 4-coumarate that further acts as a substrate for formation of 4-coumaroyl coenzyme (CoA) with the help of 4-coumarate-CoA ligase using 1 ATP molecule. The 4-coumaroyl CoA also participates in 6'-deoxychalcone metabolism and in isoflavonoid biosynthesis Ⅰ, in addition to the synthesis of naringenin chalcone, which involves in the precipitation of bioflavonoid or may form many

Table 2. Responses of Quercetin against Identified Vulnerable Diseases Targets

Target	Kia (nmol/L) value	IC_{50} (nmol/L) value	Tested on[c]	Effect of the target	References
Dopamine D4 receptor	7.8	–	*Homo sapiens*	Schizophrenia and antipsychotic action	(38)
Enoyl-acyl-carrier protein reductase, 3-oxoacyl-acyl-carrier protein reductase	22.0	–	*Plasmodium falciparum*	Fatty acid synthesis	(92,37)
Cytochrome P450 1A1, Cytochrome P450 1B1 (CYP1B1), Cytochrome 1A2, Cytochrome P450 2C9	23.0	–	*Homo sapiens*	Metabolism of xenobiotics	(93,94,95)
Casein kinase Ⅱ	1180.0	–	*Homo sapiens*	Wnt signaling pathway (96)	(97)
Xanthine dehydrogenase	1200.0	–	*Bos taurus*	Purine catabolism	(77,98)
Multidrug resistance-associated protein 1	2400.0	–	*Homo sapiens*	Multidrug resistance in tumor cells	(99)
Adenosine A1, A2A, A3 receptor	2470.0	–	*Rattus norvegicus*		(100)
Carbonic anhydrase Ⅰ, Ⅱ, Ⅲ, Ⅳ, Ⅵ, Ⅶ, Ⅷ, Ⅸ, Ⅻ, ⅩⅣ, VA, VB, 1 (CA Ⅰ), 2 (CA Ⅱ)	2540.0	–	*Homo sapiens*	Maintain acid-base balance in blood and other tissues	(101,102)
beta-Secretase (BACE-1)	–	10820.0	*Homo sapiens*	Alzheimer's disease	(103)
Cyclin-Dependent Kinase1 (CDK1), 5 (CDK5), 6 (CDK6), CDK4/Cyclin D1	–	>20000.0	*Homo sapiens*	Cell-cycle progression & cellular proliferation	(104,36,105)
Glycogen synthase kinase-3, beta	–	2100.0	*Rattus norvegicus*	It is implicated in Type 2 diabetes, Alzheimer's disease, inflammation, cancer, and bipolar disorder	(36)
Phosphoinositide 3-kinase (PI3K), alpha Chain A/beta Chain A/beta chain B/delta Chain A/gamma Chain A,	–	3800.0	*Homo sapiens*	involved in cell growth, proliferation, differentiation, motility, survival and intracellular trafficking	(106,107)
Alpha-Amylase	–	21400.0	*Homo sapiens*	Playing role in carbohydrate digestion	(108)
PIM-1 kinase		1100.0	*Homo sapiens*	Involved in cell cycle progression, apoptosis and transcriptional activation	(109)
Aldose reductase	–	50100.0	*Sus scrofa*	Polyol pathway	(110,111)
Arachidonate 5-lipoxygenase, arachidonate 12-lipoxygenase, arachidonate 15-lipoxygenase, arachidonate 15-lipoxygenase, type Ⅱ	–	37000.0	*Oryctolagus cuniculus*	Participates in arachidonic acid metabolism	(112,113,71)
Cyclooxygenase-1/Cyclooxygenase-2	–	50000.0	*Rattus norvegicus*	Formation of prostaglandins, prostacyclin and thromboxane	(112,114,113)
Tyrosine-protein kinase LCK, Tyrosine-protein kinase SRC, EGF-R Tyrosine Kinase	–	15000.0	*Homo sapiens*	phosphorylation of tyrosine residues in proteins	(115,116)
HIV-1 integrase	–	13600.0	Human immunodeficiency virus 1	Key component in the retroviral pre-integration complex	(35)
Trypsin	–	7100.0	*Homo sapiens*	Cleaves peptide chains	(117)
Chymotrypsin, Beta-chymotrypsin	–	100000.0	*Homo sapiens*	Digestive enzyme component of pancreatic juice	(118)
Protein-tyrosine phosphatase 1B (PTP1B)	–	23300.0	*Homo sapiens*	Therapeutic target in treating type 2 diabetes	(119)

(To Be Continued)

(Continued)

Target	Kia (nmol/L) value	IC_{50} (nmol/L) value	Tested on[c]	Effect of the target	References
Sorbitol dehydrogenase	–	177000.0	*Homo sapiens*	Carbohydrate metabolism	(120)
Aldehyde reductase	–	38400.0	*Sus scrofa*	Catalyzing the reduction of glucose to sorbitol	(120)
Malate dehydrogenase	–	6000.0	*Thermus thermophilus*	Reversibly catalyzes the oxidation of malate to oxaloacetate	(107)
Beta-lactamase/Penicillin-binding protein ampH	–	4000.0	*Escherichia coli*	Responsible for resistance to beta-lactam antibiotics	(107)
Beta-lactamase	–	–	*Staphylococcus aureus*	Responsible for resistance to beta-lactam antibiotics	
Serine beta-lactamase-like protein	–	4000.0	*Homo sapiens*	Responsible for the β-lactamase activity	(107)
Glutathione reductase	–	218000.0	*Homo sapiens*	Targets for aldose reductase inhibitor action	(121,120)
Cell division protein kinase 5	–	–	*Rattus norvegicus*	Inhibit cell cycle progression	(122)
Fatty acid synthase	–	1500.0	*Plasmodium falciparum*	Fatty acid biosynthesis	(92)
Serotonin receptor 1A	–	–	*Homo sapiens*	Target of antidepressants, antipsychotics, anorectics, anti-emetics, gastroprokinetic agents, anti-migraine agents, hallucinogens, and entactogens (123)	(124)
Glyoxalase I	–	3200.0	*Homo sapiens*	Target for anticancer drug	(125)
Dipeptidyl peptidase Ⅳ (DPP-Ⅳ)	–	130000.0	*Homo sapiens*	–	(125)
17-beta-hydroxysteroid dehydrogenase 2 (17-beta-HSD2)	–	1540.0	*Homo sapiens*	Target for anti-breast cancer therapy	(126)
Sialidase (Neuraminidase)	–	1700.0	*Clostridium perfringens*	Involved in the release of *Progeny* influenza virus from infected cells	(78)
Glyceraldehyde-3-phosphate dehydrogenase, glycosomal	–	142000.0	*Trypanosomacruzi*	Target for Chagas' disease	(127)
Replicasepolyprotein 1ab	–	>50000.0	Human SARS coronavirus	Target for human SARS coronavirus	(128)
Monoamine oxidase type A (MAO-A), monoamine oxidase B, amine oxidase, monoamine oxidase A	–	2800.0	*Homo sapiens*	Central role in the metabolism of monoamine neurotransmitters	(129,130)
Hypoxia-inducible factor 1-alpha inhibitor	–	10200.0	*Homo sapiens*	Target for treating anemia	(131)
Aromatase (CYP19)	–	12.0	*Homo sapiens*	Target for anti-breast cancer therapy	(132)
NADPH oxidase 4	–	680.0	*Homo sapiens*	Contributes in oxidative damage related diseases	(133)
Calmodulin	–	12970.0	*Homo sapiens*	Target for antihypertensive agents	(134)
ATP-Binding cassette transporter ABCG2	–	6900.0	*Homo sapiens*	Target for anti-breast cancer therapy	(135)
Mitogen-activated protein kinase p38 alpha, c-Jun N-terminal kinase 3 (JNK3)	–	3450.0	*Homo sapiens*	Involved in cellular proliferation, differentiation, transcription	(136)

Notes: [a]Ki- inhibitor constants; [b]IC_{50}- half maximal inhibitory concentration; [c]Toxicity tested in the mentioned organism cell line or culture; SARS: severe acute respiratory syndrome; NADPH: nicotinamide adenine dinucleotide phosphate

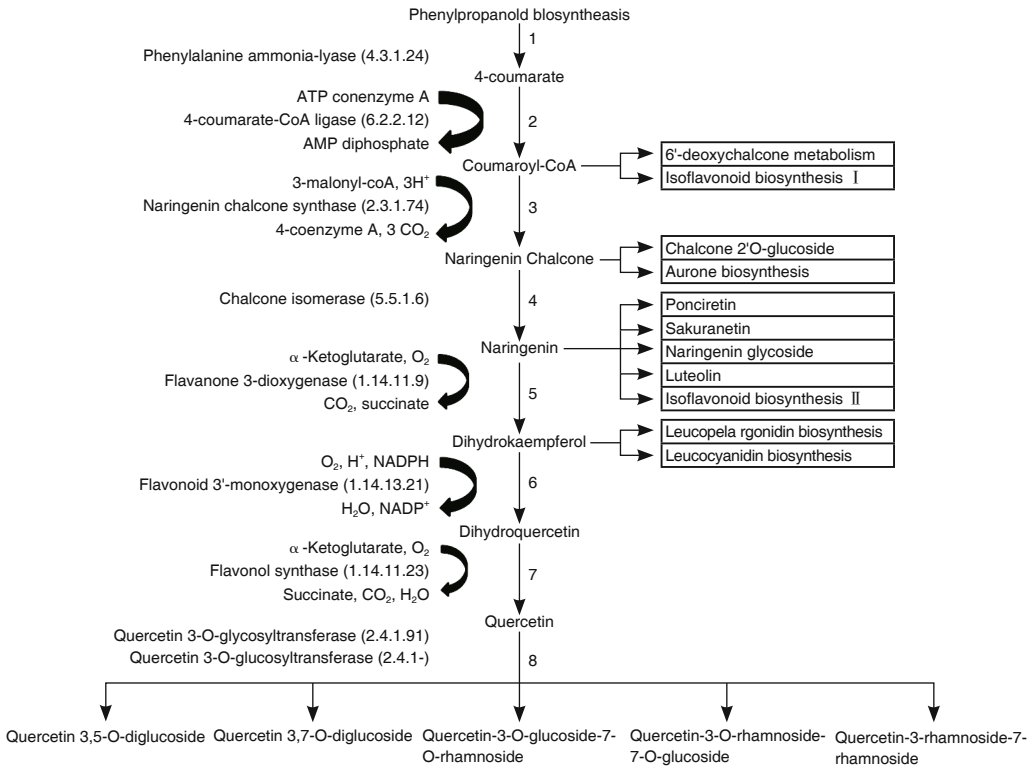

Figure 4. Quercetin Glucoside Biosynthesis Pathway in *Arabidopsis thaliana*
Notes: Compiled from Plant Metabolic Pathway Databases; http://www.plantcyc.org/

derivatives of quercetin through a series of reactions. Meanwhile, naringenin chalcone may take part in aurone biosynthesis and chalcone 2'-O-glucoside biosynthesis, where the former is important for synthesizing derivatives of auronem that imparts yellow color to flowers,[139] while the later is involved in synthesizing chalcone 2'-O-glucoside. The most stereochemically important reaction of flavonoid biosynthesis is conversion of naringenin chalcone to naringenin (2S-flavanones) using chalcone isomerase (CHI, 4th step) or chalcone-flavanone isomerase.[140] Precisely, the synthesized naringenin acts as an intermediate for formation of flavones, flavonols, flavan-4-ols, anthocyanins, and isoflavonoids. Thus, naringenin is involved in five different pathways that include ponciretin biosynthesis, sakuranetin biosynthesis, naringenin glycoside biosynthesis, luteolin biosynthesis, and isoflavonoid biosynthesis Ⅱ, which synthesizes ponciretin, 2S-sakuranetin, naringenin, luteolin, and pratensein respectively. In the meanwhile as a 5th step dihydrokaempferol is synthesized using naringenin 3-dioxygenase, which leads to the leucopelargonidin, leucocyanidin and kaempferolglucoside biosynthesis apart from quercetin/flavonol biosynthesis. Further, dihydrokaempferol in the presence of flavonoid 3'-monoxygenase is converted to dihydroquercetin.

Thus it is evident from the step 7 that the synthesis of quercetin is dependent on 2-oxoglutarate-dependent dioxygenases flavonol synthase (FLS), which is an enzyme that belongs to oxidoreductases family and shows a broad substrate and product selectivity.[141,142] Since FLS is an enzyme that catalyzes the formation of quercetin, it is considered to be vital in the quercetin biosynthetic pathway. Eventually the synthesis of glycosylated quercetin from aglycosylated quercetin is catalyzed by the quercetin 3-O-glucosyltransferase and quercetin 3-O-rhamnosyltransferase enzyme (8th and 9th step)[143] by the transfer of a glucosyl group from UDP-glucose to the 3'-hydroxy group (of a quercetin molecule). Thus, the glycosylation of aglycosylated quercetin is responsible for the modification of stability, solubility, or localization, and the biological properties of the quercetin glycosides.[143]

Molecular Investigations and Digitalization

Taking into account the importance of each enzyme or the intermediary products formed during the process of secondary metabolite (quercetin) synthesis, it has become necessary to know about the genes involved in the system. With this perception, the literary surfing earmarked the remarkable quantity of work done on this segment. In fact, the genes

responsible for almost all the enzymes involved in the pathway has been studied and very well documented (Table 3). However, when observed keenly, one could realize that the plant systems, that has been explored is very limited (http://medicinalplantgenomics.msu.edu/; http://www.plantcyc.org/). When the medicinal plants find application in pharmaceutical, cosmetic, agricultural, and food industry right from the prehistoric era and that when the plant diversity is rich in the world,[144] why there is scarce research on the molecular investigation of this vital compound in the herbal systems? Digital inventory has a significant role in the pharmaceutical market as many drug interaction studies use these databases for either virtual screening of ligand based on plant origin or proteins, which are of clinical importance (Table 4).[91] Although many plant databases are available (many are licensed/commercialized), most of them reveals less information on the important secondary metabolites, which once again give us a scope in the future for extending research in this frontier area.

Conclusion

Quercetin derivatives are available not only in dietary vegetables; also it is present in plants that are non-dietary such as *Ginkgo biloba* and *Hypericum perforatum*. Quercetin derivatives are generally nontoxic and manifest a diverse range of beneficial biological activities which are abundantly present in the human diet, as evidenced through the ongoing epidemiological studies, promotion as an effective anti-oxidative agent with scavenging (chelating) capacities and interaction with diverse range of therapeutic target. Therefore, this compound is being intensively investigated, which indicated its role as anti-inflammatory, anti-allergic, antioxidant, anti-cancerous, etc. This has proportionally increased the demand for quercetin from the pharma-industry as an alternate for the synthetic molecules and has given scope for two important concepts to be concentrated in the future. One, in spite of the diverse

Table 3. Details of the Genes Involved for the Biosynthesis of Quercetin

Serial No.	Enzyme involved in the biosynthesis of quercetin	Source organism	Gene (mRNA) sequence length (bp)	Gene bank ID
1	phenylalanine ammonia-lyase	*Arabidopsis thaliana*	2530	30687012
		Arabidopsis lyrata	2436	297827210
		Isatis tinctoria	2490	95020528
		Parrya nudicaulis	2113	323709173
		Brassica rapa	2476	282182892
		Brassica oleracea	2145	269313497
		Thellungiella halophila	2477	312281768
2	4-coumarate-CoA ligase	*Arabidopsis thaliana*	1648	145336963
		Arabidopsis lyrata	1631	9322511
3	Naringenin chalcone synthase	*Arabidopsis thaliana*	1491	145357993
		Arabidopsis lyrata	1490	297807414
		Arabidopsis arenosa	1422	333448902
		Arabidopsis halleri	2427	56797558
4	Chalcone isomerase	*Arabidopsis thaliana*	930	42565949
5	Flavonone/Naringenine 3-dioxygenase	*Arabidopsis thaliana*	1508	334185877
		Arabidopsis lyrata	1494	297816383
6	Flavonoid 3'-monoxygenase	*Arabidopsis thaliana*	1835	30682179
		Arabidopsis lyrata	1796	297806828
		Matthiola incana	1748	12231885
		Brassica napus	3038	84380740
7	Flavonol synthase	*Arabidopsis thaliana*	1323	334187529
		Arabidopsis lyrata	1241	297806938
8	Quercetin 3-O-glucosyltransferase	*Arabidopsis thaliana*	1672	42569054
		Arabidopsis lyrata	1446	297832031
9	flavonol-3-O-rhamnosyltransferase	*Arabidopsis thaliana*	1829	42562413

Table 4. Role of Secondary Metabolites as A Therapeutic Agent for Deadly Diseases

Name of the herb	Major metabolites
Atropa belladonna	Atropine, scopolamine, calystegine A3, calystegine B2
Camptotheca acuminata	Camptothecin, 10-hydroxycamptothecin, 9-methoxycamptothecin, strictosidine, secologanin, strictosamide
Cannabis sativa	D9-tetrahydrocannabinol, cannabidiol, cannabichromene, cannabigerol, cannabinol
Catharanthus roseus	Vincristine, vinblastine, ajmalicine, serpentine, yohimbine, catharanthine tabersonine, vindoline, strictosidine, secologanin
Digitalis purpurea	Digitoxin, digoxin, gitoxigenin, gitoxin
Dioscorea villosa	Diosgenin, dioscin, prosapogenin α
Echinacea purpurea	Cichoric acid, echinacoside undeca-2E/Z-en 8, 10-diyonic acid, dodeca-2E,4E, 8Z, 10E/Z-tetraenoic acid isobutylamide, dodeca-2E, 4E, 8E, 10E-tetraenenoic acid isobutylamide, trideca-2E, 7Z-diene-10,12-diynoic acid isobutylamide, tetradeca-8Z-ene-11,13-diyn-2-one, pentadeca-8Z,11E,13Z-trien-2-one
Ginkgo biloba	Ginkgolide A, B, C, J, M, bilobalide, quercetin 3-methylquercetin, kaempferol, narcissin flavonol
Hoodia gordonii	P57AS3, hoodigoside A-Z, hodigogenin A, hoodistanaloside A, hoodistanaloside B, gordonoside D, F, G, J
Hypericum perforatum	Hypericin, hyperforin, pseudohypericin amentoflavone, euxanthone
Panax quinquefolius	Ginsenosides Rb1, Rb2, Rb3, Rc, Rd, Re, Rf, Rg1, Rg2, Rh1, Rh2, 20(S)-ginsenoside Rg3 pseudo-ginsenoside F11
Rauvolfia serpentina	Betulinic acid, carnosic acid carnosol, oleanolic acid rosmarinic acid, ursolic acid
Rosmarinus officinalis	Betulinic acid, carnosic acid carnosol, oleanolic acid rosmarinic acid, ursolic acid
Valeriana officinalis	Acevaltrate, actinidine hesperidin, isovaleramide linarin, pinoresinol-4,4'-di-O-beta-D-glucoside, valeric acid

medicinal properties upholded by quercetin, the lack of experiments in testing quercetin's efficiency on various diseases clinically has necessitated the need to clarify the nature of the impact and interactions between quercetin on different types of targets; and the other concept probably would be a mechanism to determine how efficient and practical it would be to increase the production of quercetin using the available proteomic and genomic details, as the role of quercetin is limitless.

Conflicts of Interest

Nidhi Rani, Lakshmi Palanisamy Thanga Velan, Saravanan Vijaykumar and Annamalai Arunachalam declare that they have no conflict of interest.

Author Contribution

Nidhi Rani made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and participated in drafting the article. Lakshmi Palanisamy Thanga Velan takes the overall responsibility in supervising the designed work and involved in revising the article critically for the intellectual content. Saravanan Vijayakumar made substantial contributions to data collection and integration and participated in drafting and critical revision of the article. Annamalai Arunachalam contributed to the literary resources and enabled for the technical drafting of the article.

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