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Quercetin, a health promising phytoadditive for poultry production: Trends & advances

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Abstract
Plants sources are densely rich with the polyphenolic compound. Among that flavonoid is the major group found and due to their immense availability have rising a great interest for its multidimensional properties. Quercetin, the most plentiful flavonoid has combined properties of growth promoter, antioxidant, anti-inflammatory, anti-lypolytic, potent hepatoprotective, immune boosting and gut health enhancing potential. Their strong antioxidant activity was due to presence of the central C-ring along with high number of hydroxyl groups and conjugated π orbitals in its chemical structure. A substantial amount of literature on different animal studies with positive effects on growth, antioxidant status, hepatoprotection, immunomodulation, gut morphology, gut microbiota with ultimate improvement in gut health and birds health status. Current trends have been focused to find a natural phytoadditive with having a multidimensional action and potentially health promoting effects in animals and birds by nutritionist. Therefore, the aim of this review is to explore the biological actions of quercetin, aware the medicinal importance and highlighting that it can be a safe and excellent phytoadditive for the fast-growing poultry industry as an alternative of banned synthetic growth promoting agents for the welfare of birds.

Keywords: Antioxidant, flavonoid, hepatoprotectant, poultry, quercetin

Introduction

Supplementation of antibiotic growth promoter has banned by the European union (EU) in poultry industry (El-Hack *et al.*, 2016) [14]. The possible toxic effect of synthetic feed additive has enhanced the interest of poultry nutritionist to seek alternative originated from plant sources. Currently inclination to improve growth, feed utilization, meat and egg quality, immune system, gut environment and health of avian species including Turkeys, broilers and layers (Salah *et al.*, 2015; Orayaga *et al.*, 2016; Aguihe *et al.*, 2017) [59, 48, 5] through natural feed additives. Antioxidants are the agents, essential for poultry production as they decrease lipid peroxidation, improve the organoleptic characteristics, nutritional value of eggs, meat and can extend shelf life (Fellenberg and Speisky, 2006) [18]. More emphasis has been given to herbal source of additive having combine property of antioxidant, lipolysis, and gut modulating and immunomodulatory activity.

Flavonoids have aroused enormous interest in the preceding decades, due to its multidimensional health promoting effects on human, animals and omnipresence in plant king dome. They are known to as “functional ingredients” and “health promoting biomolecules” (Nijveldt *et al.*, 2001; Kamboh *et al.*, 2015) [46, 29]. Quercetin is a major concern when studies about flavonoids, Quercetin (3,3",4",5,7-pentahydroxyflavone) is polyphenolic flavonoid compounds found almost ubiquitous in plants and plant foods sources having strong antioxidant property as free radical terminators (Sikder *et al.*, 2014) [63]. Presence of central C-ring along with high number of hydroxyl groups and conjugated π orbitals makes the compound strong reducing agents (Rice - Evans *et al.*, 1996) [57]. It is found in various foods such as vegetables, tea, fruits, wine apples and onions, tomatoes and is known to exert positive effect on poultry production and health (Saeed *et al.*, 2017) [58]. Being a powerful free radical scavenger, it ameliorates the organ damage, inhibit effect of oxidative stress (Yi *et al.*, 2011 and Sikder *et al.*, 2014) [73, 63] possess immunomodulatory and anti-inflammatory properties (Serafini *et al.*, 2010) [61]. Thus, the aim of this review is to highlighting the beneficiary potential and effects of quercetin as a phytoadditive in poultry health and production.

Chemical Structure

The chemical name of quercetin is 2-(3, 4-dihydroxyphenyl)-3, 5, 7-trihydroxy-4 Hchromen-4-one (Quercetin, $C_{15}H_{10}O_7$) and its derivatives structure are shown in Figure 1. The different alternative names for quercetin are sophoretin, meletin, quercetine, xanthaurine, quercetol, quercitin, quertine and flavinmeletin (Saeed *et al*., 2017) [58]. Quercetin as a natural antioxidant, polyphenol and is highly lipophilic and slightly hydrophilic properties. It is yellow colored in powder form practically insoluble in water, but soluble in aqueous alkaline solutions. The melting point of quercetin is 316 °C or 601°F and its molar mass is 302.23 g/mol (Ades, 2009) [3]. Presence of central C-ring along with high number of hydroxyl groups and conjugated π orbitals makes the compound strong reducing agents (Rice-Evans *et al*., 1996) [57]. Quercetin and its glycosidic metabolites possess cell signaling pathways and having high reducing power, effectively neutralized the ROS reduction thereby oxidative DNA damage (Wilms *et al*., 2005) [72]. Therefore, all consequent ROS mediated events like hepatic inflammation and subsequent liver damage were efficiently inhibited by quercetin.

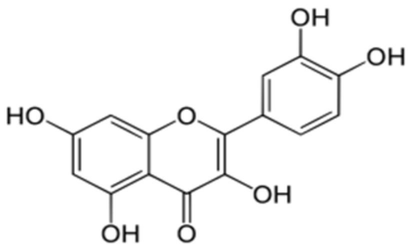

Fig 1: Molecular structure of Quercetin

Sources of Quercetin

Quercetin is a common flavonoid polyphenol compound enriched in most of vegetables and fruits in the form of glycosides (Alrawaiq and Abdullah, 2014) [7]. Synthetic production of flavonoids has not been practiced yet hence plants are the only major source of quercetin (Abdelmoaty *et al*., 2010) [1]. It is widely distributed in plant sources such as onions, moringa, tomatoes, garlic, ginger, broccoli, barries, tea, citrus fruits, brassica, cocoa, capers, apples, grapes, olive oil, flowers, nuts and leaves etc. (Saeed *et al*., 2017) [58] as describe in Table 1.

Absorption and Metabolism of Quercetin

Quercetin is a glycosides, after oral ingestion efficiently hydrolyzed in the small intestine by beta-glucosidases to the aglycone form and much of which is then absorbed (Scholz *et al*., 2007) [60]. Once it absorbed, further processed in epithelial cells of the stomach and intestines by phase II enzymes (Alrawaiq and Abdullah, 2014) [7]. Quercetin and its derivatives are very stable against gastric acid in the gastrointestinal tract but evidences suggest its absorption site in the upper small intestine (Saeed *et al*., 2017) [58]. Its absorption is influenced by differences in its glycosylation, the food sources from which it is ingested and dietary components such as fiber and fat (Guo *et al*., 2013) [24]. After absorption, it will be got metabolized in different organs including the small intestine, colon, liver and kidney (Li *et al*., 2016) [35]. The biotransformation enzymes generate different metabolites of quercetin includes the methylated, phenolic acid, sulfo-substituted and glucuronidated forms in the small intestine and liver (Day *et al*., 2000) [12]. Studies suggest the highest accumulation of these metabolites lung, liver and kidneys in different animal models (Li *et al*., 2016) [35]. These metabolites acted as an antioxidant through the resistance low-density lipoprotein (LDL) oxidation (Manach *et al*., 1997) [39]. Quercetin metabolites concentrations were in the liver were lower than those in plasma, and the methylated (90%-95%) form were highest in hepatic metabolites (Manach *et al*., 1999) [41]. Accumulation of quercetin is rising over continuous ingestion of quercetin rich sources which was highly correlated with dietary contents. Final, excretion of it, is being done by kidney (Li *et al*., 2016) [35].

Biological Effects of Quercetin

Quercetin as a Growth Enhancer

Supplementation of quercetin in poultry ration has a better growth promoting and feed utilizing effect in birds as reported in previous studies. Liu *et al*. (2014) [37] had found improvement in feed conversion ratio with level of 0.367 to 0.369 g quercetin/kg of feed in laying hens, also found quadratic correlation with the level of quercetin (P=0.05) in laying rate and it was maximized by the supplementation level of 0.2 g/kg of diet. In same trend, quercetin @ 100, 200 and 300 mg/kg feed in combination with α-tocopherol feed imparted significant effect on gain in weight and feed conversion efficiency in broilers (Sohaib *et al*., 2015) [64]. Similarly, Ramamneh, (2017) [54] noted improved chicken performance with high (P<0.001) weight gain, better feed conversion ratio with onion extract inclusion in broilers. That is attributed to a sulphur-containing organic compound known as Allicin, which characterized by antimicrobial activity that could be responsible for the growth promoting effect of onion (Ramamneh, 2017) [54]. Consistence better growth

Table 1: Various food sources and Quercetin contents (mg/100g).

Food sources			
Vegetables	**Quercetin content**	**Fruits**	**Quercetin content**
Ancho pepper	27.61	Unsweetened apple sauce	2.01
Raw broccoli	3.22	Raw apple with skin	4.43
Cooked broccoli	1.07	Raw apricot	2.54
Red raw onion	19.94	Raw bilberry	3.05
Boiled onions	19.37	Black grapes	2.56
Loose-leaf lettuce	1.94	Frozen blueberry	3.94
Raw kale	7.72	Raw blueberry	3.12
Canned kale	4.51	Raw cherry	1.24
Chilli	16.8	Raw cowberry	21.01
Iceberg lettuce	2.48	Canned sweet cherry	3.21
Hot wax raw yellow pepper	50.62	Cherry raw tomato	2.78
Hot green raw chili pepper	16.81	Raw cranberry	14.01

Raw green beans	2.74	Raw cranberry juice	16.42
Green tea	2.00	Frozen chokeberry	8.91
Capers	234	Raw lemon without peel	2.3

(**Source:** Muhammad *et al*., 2017) [45]

Performance and improvement in feed conversion efficiency was observed by Hassan *et al*. (2018) [25] with of rutin (i.e., rutoside, vitamin P, quercetin-3-rutinoside or sophorin) as a flavonolglycoside supplementation in broilers. These improved growth performance, likely due to favorable effect of flavonoids on gut morphology and the functional architecture of the small intestine (Awad *et al.*, 2011 [9]; Viveros *et al*., 2011 [71]). Moreover, flavones up-regulate the combination of the growth hormone and the hepatic growth hormone receptor, which increases insulin-like growth factor 1 concentrations, thereby promoting animal growth (Ouyang *et al*., 2016) [49]. In general, dietary flavonoid supplementation has been reported to improve the growth performance of broiler chickens (Starcevic, 2015) [65].

Quercetin as a Potent Antioxidant/Anti-Stressor

Health enhancing properties of polyphenol were directly related to their antioxidant (i) an ortho-dihydroxy or catechol group in the B-ring, (ii) a 2, 3, double bond, and (iii) hydroxyl substitution at position 3 and 5 in their chemical structure (Ozgen *et al.*, 2016) [50]. Experimental studies suggested enhanced endogenous antioxidant enzyme activities by quercetin and possible damages to the vital organs in diabetic rat (Elik *et al.*, 2007) [15]. Alike to that Zou *et al*. (2015) [75] reported free radical scavenging resultant oxidative stress preventing and anti-inflammatory effect of quercetin against the perfluorooctanoic acid induced liver damage. The free radical generating ROS (reactive oxygen species) is the major etiological factors responsible for many metabolic disorders (David *et al.*, 2017) [11]. Flavonoid supplementation also have protective mechanism in terms of decreased liver MDA (melondialdehyde) due to down regulation of the expression of TNF-α (tumor necrosis factor) and NF- kB (necrosis factor) thereby the increased antioxidant capacity and mitigate the inflammation (Zengpeng *et al.*, 2018; Abu Hafsa and Ibrahim, 2018) [74, 2]. Similarly, either quercetin or β-sisterol reflect improved antioxidant status and protective effect in dietary induced dyslipidemic and hepatotoxic mice noticed by Marcolin *et al.* (2013) [42], Sikder *et al.* (2014) [63] and Iskender and Yenice, (2016) [28]. They suggested that quercetin (0.5 g/kg diet) being superioriourly decreased MDA concentration and increased (gluatathione peroxidnase) GSH-Px, GR (glutathione reductase), GST (glutathiones S-transferase), and SOD (super oxidedismutase) activities and GSH (glutathione reduced) level in laying hens. Further, Oleiveira *et al*. (2014) [47] reported that quercetin (50 mg/kg BW) reduce the LPO (lipid peroxidation) and SOD concentration and increased the GpX level in polychlorinated phenyl induced liver injury in Wister rat. Hassan *et al*. (2018) [25] observed that a high concentration of rutin (0.5 and 1 g/kg) supplementation in broilers, significantly reduced malondialdehyde (MDA) concentrations (P=0.001), with increased superoxide dismutase (SOD), catalase and glutathione peroxidase (GpX) activity and ameliorate the oxidative stress in broiler chickens. As in poultry birds are so sensitive to various stresses that ultimately causing various health alteration, being a strong antioxidant potential of quercetin seems to be effective ameliorating agents as phytoadditive in the poultry sector.

Quercetin as a Potent Hepatoprotective Agent

Numerous experiments have been reported the hepatoprotective activity of quercetin in liver damages (Table 2). Quercetin administration significantly decreased liver triglycerides, liver and serum total cholesterol, serum low-density lipoprotein cholesterol, and serum high density lipoprotein cholesterol (HDL-C) along with reduced (P<0.05) the elevated activity of serum alanine aminotransferase, aspartate aminotransferase and γ-glutamyltranspeptidase (G-GT) in hepatic lipemic-oxidative injury, in addition also ameliorate the steatohepatitis in rats fed with a high cholesterol diet (HCD) reported by Mariee *et al*. (2012) [43]. Consistently, Porras *et al*. (2017) [53] and Gedikli *et al*. (2017) [20] were noted reduction in higher plasma triglyceride and ALT levels and protective effect of quercetin with high fat diet induced liver damages with alleviate the histomorphological changes and inflammatory activities in liver in rats or mice models, respectively. Corroborated hepatoproetctive action was suggested by El-Faras *et al*. (2017) [13] in rats with paracetamol induced toxicity in rats. Overall the evidences suggesting anti-lypolytic and a potent hepatoprotective potential of quercetin due to the its chemical structure as strong free radical scavenger with reducing lipid peroxidation potential.

Quercetin as an Immunomodulators

As a resultant of oxidative stress, various metabolic processes generated wide range of the reactive species (RS) either reactive oxygen species (ROS) or reactive nitrogen species (RNS) in the body (Rehman *et al*., 2018) [55].The ROS play vital roles in the signaling pathways, cytokine transcription, immunomodulation, ion transport, and apoptosis (Gloire *et al*., 2006 [21] Rehman *et al*., 2018) [56]. Over production of ROS may causing damage to DNA, protein, and lipid structures, leading to the disruption of the cell functions (Markesbery *et al*., 2013) [44]. Non-specific response a stress, one of the most pesky issues in the modern poultry industry causing compromised immune status, health, growth and productive performance of poultry birds (Surai *et al*., 2016) [67]. Dietary polyphenol with having potent antioxidant potential not only stimulate immune response of birds additionally that also leads a modulation of detoxification enzymes, scavenging of oxidative agents and regulation of gene expression in cells (Kamboh *et al*., 2015) [29]. Flavonoids regulate mucosal and cellular immunity and modulate the endocrine and circulatory markers of health; dietary supplementation with flavonoids can be, therefore, used for improving immunity and health of broiler chickens (Kamboh *et al*., 2018) [30]. Numerous literatures suggested a immunostimulant activity of quercetin. In these concern, Huang *et al*. (2010) [26] reported quercetin effectively inhibited LPS (Lypopolysaccharides)-induced dendritic cells (DC) activation by reducing the production of proinflammatory cytokines/chemokines and the expression levels of MHC (Major histocompetability complex) class II and costimulatory molecules, additionally also abrogated the ability of LPS-stimulated DCs to induce Ag (Antigen)-specific T cell activation, both *in vitro* and *in vivo* study. Manach *et al*. (2004) [40] reported immune regulatory activity through enhancing Ig Y antibody titer, lymphoid

Table 2: Biological Activities of Quercetin/Flavonol.

Activities	Flavonol/Quercetin Compound	Reference
Hepatoprotective	Quercetin	Amalia *et al.*, 2007 [8]; Vieira *et al.*, 2011 [70]; Shizuma, 2014 [62]
Antilipid/Lypolytic	Quercetin	Ahn *et al.*, 2008 [6]; Lee *et al.*, 2011[33]
	Onion powder	Chandra *et* al., 2013 [10]; Emamat *et al.*, 2016 [16]
	Grape seed powder (Flavonol)	Adisakwattana *et al.*, 2010 [4]; Fawzia *et al.*, 2014 [17]; Abu Hafsa and Ibrahim, 2018 [2]
	Genistein	Park *et al.*, 2013 [52]; Zenpeng *et al.*, 2018 [75]
	Rutin	Liu *et al.*, 2017 [38]; Hassan *et al.*, 2018 [25].
Anti inflammatory	Quercetin	García-Mediavilla *et al.*, 2007 [19]; Stewart *et al.*, 2008 [66]; Panchal *et al.*, 2012 [51]

Organs weights and natural killer cells activity and resultant better performance of animals. Alike to that Konard *et al.* (2011) [32] noted a positive impact on immune parameters includes total blood leucocytes count and proinflammatory cytokines (IL-6, TNFα, GM-CSF, IFNγ, IL-1β, IL-2,IL-8 and IL-10) in humans fed with quercetin. Similarly, Liu *et al.* (2012) [36] confirmed the immunostimulant function of quercetin with better effect on IL-8, IL-1 and IL-1) level in rats. Further, enhancing the IgY level showing a promoting effect of quercetin on mucosal immunity in broilers (Hager-Theodorides *et al*., 2014) [25].

Quercetin as a Gut Modulator

Dietary bioactive constituents directly or indirectly purported to act on continuously interacting elements that define gut ecology such as gut microbiota composition and metabolic activity, gut integrity and inflammatory status (Suzuki and Hara, 2011; Lee *et al*., 2017) [69, 34]. The status of the gut and its microscopic structure are good indicators of the stress and nutrient response of the intestinal tract (Viveros *et al*., 2011) [71]. The increased villus surface area (height or width) is an indication of increasing the absorption capacity of mucosa for the available nutrients which regulates the nutritional status and ultimate health of birds (Kamboh *et al.*, 2015) [29]. As the crypt is known to be a villus factory, a large crypt depth suggesting a rapid tissue turnover and a high demand for generation of new tissues. The intestinal epithelial cells originate at the base of crypts as immature proliferative cells, differentiate and migrate along the villus surface upward to the villus tip and are finally extruded into the intestinal lumen (Hu and Guo, 2007) [27].

Few literatures are available for gut modulatory activity of quercetin. Although, Zou *et al.* (2016) [76] reported a positive effect on intestinal morphology with increased jejunal villus height in pigs with stressful condition. In the ceacal digesta, birds fed grape pomace concentrate and grape seed extract diets had higher populations of Escherichia coli, Lactobacillus, Enterococcus, and Clostridium than birds in any other treatment group. Viveros *et al.* (2011) [71] noted a higher microbial count such as Escherichia coli, Lactobacillus, Enterococcus, and Clostridium and modulatory effect on gut morphology in broilers fed with grapes polyphenols. In same line, Kamboh and Zhu, (2014) [31] suggest a flavonoid such as genistein and hesperidin was promoted intestinal morphology and absorptive functions of growing broilers. This gut modulating activity is not exactly known for quercetin but it might be due to the polyphenolic structure and strong antioxidant potential of quercetin. Thus, these seems to proves that quercetin can be a very good flavonol with improving gut morphology and microbiota, thereby gut health and performance of poultry birds.

Conclusions

The current evidences suggesting that, among the various phytochemical flavonoids, quercetin could be very effective ROS scavengers due to its chemical structural characters in poultry birds. This quercetin possesses multifarious biological actions including growth enhancer, antioxidant, anti-inflammatory, anti-lypotropic, potent hepatoprotective, immunomodulating and gut modulating activities. These positive actions and the present scientific findings supports that quercetin can be an excellent natural phytoadditive and would be a promising in modern poultry industry to alleviates the sparking issues of this sector, the stress by improvement in health, production and welfare of chickens. However, further studies is needed to decide incorporation level in poultry ration and found an ideal practical techniques for extraction additionally to find economically feasible sources of quercetin to reach up by the farmers as well as distributed it at a commercial level in poultry production.

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