Review Article

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Quercetin: A Versatile Flavonoid Antioxidant

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Summery

Quercetin which belongs to the class flavonols, one of the five subclass of flavonoid compounds. Flavonoid observed in vegetables, fruits, tea, and wine. Quercetin is ubiquitously present in foods such as onions, berries, nuts, tea, cauliflower, and cabbage. Flavonoids occur in foods primarily as glycosides or aglyconesform which breaks down to various extents in thedigestive column. Quercetin is usually found in the in the glycoside form. Quercetin act as a potent antioxidant molecule and may exerts beneficial effects on its free radical scavenging function which prevent the formation of stabilized phenoxyl radicals. Quercetin plays important role in improvement of cancer disease, heart-related disease, diabetes, asthma and allergy and much more. Quercetin metabolism occurred in the small intestine, the kidney and the liver which sufficiently reduce plasma oxidant status. Quercetin and its compound based on the flavan nucleus and positions, numbers and type of substitutions affect radical scavenging activity.

Keyword: Aglyconesform; Quercetin; Antioxidant.

Introduction

The main sources of the production of free radicals are radiation process, the action of pesticides, pollution, and smoking. Free radicals are found in the normal metabolism and respiration process of the human body. These are very unstable molecules as it contains one electron and reacts easily with our body macromolecules such as protein, lipid, and nucleic acids. Each material consists of the atom which can be linked to form large molecules. Proton and electrons are responsible for the formation of one single atom. These single atoms are in search of the other atoms for the formation of molecules by donating or receiving electrons from other sources. Chemical structure of any material changed by donating an electron to another molecule by free radicals and affect the destruction of the cell. To neutralise the activity of free radicals in the material antioxidants are used. Antioxidants are chemicals which give their electron to the free radical and protect the cellular damage. Now a day, the risk of

cancer and heart disease spread quickly due to the action of free radicals. Control of these free radicals can be achieved by the use of natural antioxidant obtained from plant and vegetable sources such as quercetin (Baghel et al., 2012)

Free Radical forms

Free radicals formed with help of oxygen atoms and called reactive Oxygen Species (ROS) such as hydrogen peroxide, hydroxyl radical, superoxide ion and singular oxygen.

Superoxide Ion

Superoxide ionconsists of oxygen molecules with one or more electron. This is responsible for damage to brain and DNA. Superoxide ionsneutralise with the help of superoxide dismutase antioxidant.

Hydroxyl Radical

The main effect of hydroxyl radical on thedamage of DNA, protein, lipids and carbohydrate. Hydroxyl radical formed with reduction of oxygen molecules in the electron chain. These are very active with short life and react the molecules within the vicinity. Hydroxyl radical cannot be destroyed by the action of anenzyme, unlike the superoxide ion.

Singlet Oxygen

Oxidation of lipid is caused Singular oxygen and is available in our immune system.

Hydrogen Peroxide

Hydrogen peroxide is not a free radical but it is available in the production of many reactive oxygen species. Hydrogen peroxide is a byproduct of oxygen metabolism and is neutralized by peroxidases enzyme.

Reactive Nitrogen Species (RNS)

Unpaired electrons are found in the metals such as iron and copper and can act as free radicals. An example of reactive oxygen molecules is nitric acid. These free radicals can easily donate or accept the electron from another molecule.

Oxidative Damage:

Free radicals mainly attack damage of DNA and alter the DNA base structure. Lipids are easily attracting to the free radicals to form the oxidative damage which is also called lipid peroxidation. The main reason behind the outbreaks of cancer disease is mutation form due to the action of free radicals and DNA. Also. Free radicals are responsible for the Parkinson's, atherosclerosis and Alzheimer's disease (Kaneda et al., 2002).

Quercetin

In human body production of reactive oxygen species(ROS) and reactive nitrogen species (RNS) occurred that showed different physiological functions, such as muscle relaxation, xenobiotics mechanism, and the respiratory burst to kill invading micro-organisms (Moncada et al., 1991). Quercetin is a member of bioflavonoid family. Name came from latin word 'quercetum' which means 'oak forest', 'quercus oak'. Flavonoids are part of the natural substances and found in the vegetable, fruits, flowers, tea and wine (Middleton, 1998). Quercetin has the ability to produce the free radical scavenger activity and plays an important role in the control of diseases outbreaks (Valls-Pedret et al., 2012). However, there is a limitation for application of quercetin as free radical scavengers alone due to its low bioavailability and capacity to absorb phenolic compounds (Sharma et al., 2015). Even though, quercetin has the capacity to scavenge the free radicals directly and exert the antioxidant effect through several mechanisms. These mechanisms consist of development of endogenous antioxidant enzyme which helps to reduce the development of reactive nitrogen and oxygen species (Halder et al., 2008). Antioxidant mechanisms of the quercetin are mostly occurring in the mitochondrial part. For the production of superoxide anion free radical, the mitochondria aresuitable place and effective against oxidative stress (Han et al., 2001; De Olivera, et al. 2016).Due to the hydrophilic characteristics of quercetin i.e glycosides help to utilise in the gastrointestinal track by apassive mechanism (Griffiths, 1982). However, Hollman et el. (1995) reported that not only quercetin glucosides but also aglycone absorbed in the small intestine.

Structure and Properties of Quercetin

Quercetin is available in many of the food and consumed almost daily. It comes under flavonols group of flavonoids which have a common flavone nucleus consist of two benzene rings combine together with a heterocyclic pyrone (Fig. 1). The chemical formula of the quercetin is 3, 3, 4, 5, 7- pentahyroxyflavone and its structure is given below.

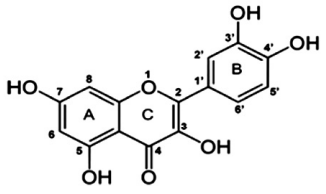

Fig. 1: Molecular structure of Quercetin.

Generally, quercetin available in the form of glycosides (sugar derivatives) such as rutin in which the hydrogen of the four hydroxyl atom is changed by disaccharide. Quercetin is also called aglycone or sugarless form of rutin. It is found in the yellow colour with crystalline solid and has abitter taste. Quercetin is soluble in glacial acetic acid and alkaline solution while insoluble in water. Animals are incapable to synthesis flavones nucleus as compared to that of the plant. Because of this reason quercetin is exclusively found in the vegetables and fruits (Lakhanpal & Rai, 2007).

Table 1: The functional properties of quercetin.

Density	1.799 g/cm3
Colour	Yellow
Boiling point	Sublimes
Melting point	316.5 0C
Solubility	In water: 60 mg/mL at 16 °C Very soluble in methanol, ether; Soluble in pyridine, ethanol, acetone.
Decomposition	During heatingit emits acrid smoke and irritating fumes.

(Source: National Library of Medicine, United States, 2009)

Quercetin Source

Quercetin is obtained from various vegetables and fruits sources includes, apricots, cauliflower, onions, grapes andchili peppers (Table 2). Quercetin is available in the form of glycosidic in the plant. The amplesttypes are rutin (quercetin-3-rutinoside), isoquercitrin, (quercetin-3-glucoside) and quercetin-3, 4-diglucoside. Olive oil, cherries, blue berries and clack berries are also anabundant source of quercetin (De Olivera et al., 2016).

Table 2: Quercetin sources from the plant and their contents.

Plant name	Common name	Tissue	Concentration (g/kg)	Reference
	Onion	Bulb	0.347	Hertog et al., (1992)
			0.221	Lombard et al., (2005)
Allium cepa	Patrik onion	Bulb	3.830	Caridi et al., (2007)
	Red onion	Bulb	0.307	Lombard et al., (2002)
Brassica oleracea	Broccoli		0.030	Hertog et al., (1992)
Brassica oleracea	Cauliflower	Vegetable	0.219	Miean and Mohamed (2001)
Brassica oleracea	Kale		0.110	Hertog et al. (1992)
Allium fistulosum	Welsh onion	Leaves	1.498	Miean and Mohamed, (2001)
Aloe barbadensis	Aloevera	Leaves	0.095	Sultana and Anwar, (2008)
Arontiamitschurinii	Chokeberry	Fruit	0.089	Häkkinen et al., (1999)
Calamus scipronum	Semambu	Leaves	1.188	Miean and Mohamed (2001)
Capsicum annuum	Red chili	Fruit	0.800	
Euphorbia helioscopia	-	Plant	3.570	Liu et al. (2011)
Euphorbia wallichii	-		1.460	Taskeen et al., (2009)
Ficus religiosa	Peepal	Fruit	0.256	Sultana and Anwar, (2008)
Helichrysum chionophyllum	-	Aerial parts	0.015	Albayrak et al., (2010)
Helichrysum compactum	Apple	Leafy	0.006	Suzgeç et al. (2005)
Malus pumila	Apple	Pomace	0.036	Hertog et al., (1992)
	Mango		0.067	Schieber et al., (2001)
Mangifera indica	Sohanjana	Fruit peel	0.469	Ribeiro et al., (2008)
Moringa oleifera	Mulberry	Leaves	0.281	Sultana and Anwar, (2008)
Morus alba	Bean	Fruit	0.359	
Phaseolus vulgaris	Apricot	Vegetable	0.039	Hertog et al., (1992)
Prunus armeniaca	Cherry (sweet)		0.322	Sultana and Anwar, (2008)
Prunus avium Hartland	Cherry (sour)	Fruit	0.028	Kim et al., (2005)
Prunus cerasus Schattenmorelle	Black currant		0.025	
Ribes nigrum ojebyn	Apple		0.044	Hakkinen et al., (1999)

Antioxidant Properties of quercetin

Quercetin is the potential flavonoids which prevent the human body from anattack of free radical such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), developed in the normal respiration process. Quercetin acts as a potent antioxidant property due to its ability to capture free radicals by donating hydrogen atom. Lipid peroxidation is inhibited by use of quercetin. Lipid peroxidation processes in which the unsaturated fatty acids are converted to free radicals by adetachment of hydrogen (Young & MzEneny, 2001). Lipid peroxidation in the

body create the detrimental effects includes cardiovascular and neurodegenerative disease which can be prevented by the use of quercetin antioxidant. Inflammation can also control by scavenging free radical quercetin(Shoskes et al. 199). Furthermore, During the smoking process, most dangerous environmental cause free radical developed is scavenged by thequercetin and protect the body. Begum & Terao (2002) described that damage of erythrocytes during the smoking could protect by the quercetin and their metabolites. Quercetin prevents the development of oxidative stress by athlete's exercise.

Mechanism of action

Antioxidative action

Lipid peroxidation leading to the cell death by interfering the cellular mechanism in the body. To avoid this cell death and protect the body from theformation of reactive oxygen species there is aneed to developed antioxidant defence mechanism in the living organisms. This includes enzymatic and non-enzymatic antioxidants that control the outbreak of reactive oxygen species.The first defence mechanism by enzymes result into the neutralization of ROS and consist of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase. The second defence mechanism is achieved by the development of free radical scavenging antioxidants such as quercetin which impede the oxidation process and retard the propagation phenomenon (Bahorun et al., 2006).

Direct radical scavenging action

In animal cells, thefree radical formation is common practice and development of free radical result into the outbreaks of many human diseases. Quercetin act as free radical scavengers and help to protect the tissue damage. Quercetin has the ability to scavenge the free radicals directly and inhibit the LDV oxidation process (Bhagel et al., 2012)

Nitric oxide syntheses inhibitory action

Reduction of ischemia-reperfusion injury in thehuman body is prevented by intake of quercetin. Quercetin has the potential to perform nitric oxide synthase activity which is responsible for the occurrence of . Different types of cells produced nitric oxide including endothelial cells and macrophages (Huk et al., 1998). Regular supply of blood to the bold vessel in human body depend on the production of nitric oxide by the nitric oxide synthase activity. The higher concentration of nitric oxide developed by inducible nitric oxide synthase in macrophages resultsin oxidative damage. This leads to the production of nitric oxide and free radical as superoxide anion. Nitric oxide reacts with free radicals and producing high damaging peroxynitrite. Peroxynitrite can directly oxidize LDL resulting into damage of cell. Quercetin prevents the action superoxide anion to the nitric oxide by scavenging and prevent the cell death (Van Acker et al., 1995).

Bioavailability of Quercetin

Bioavailability is the ratio between thequantity of quercetin orally ingested in the body and amount which is metabolised or absorbed in theintestine and then available for physiologic function (Jackson, 1997). Quercetin is entering in the diet in the form of glycoside conjugates. Direct absorption of glycoside in the body is not possible due to its high molecular weight and hydrophilic properties (Formica & Regelson, 1995). For the absorption of quercetin in the body, quercetin is hydrolysed to glycoside and available of the lipophilic aglycone. The effects on the bioavailability of quercetin glycoside are observed in the small intestine by hydrolysis of isoquercitrin, (quercetin-3-glucoside) and quercetin-3,4-diglucoside with intestinal ß-glucosidases enzyme (Reinboth et al., 2010). While unhydrolysed quercetin glycoside in the small intestine enters into the large intestine and hydrolyzed by gut microflora hydrolyses. However, rhamnosides, quercetin rutinosides, andgalactosidesare not effectively hydrolysed in the gastrointestinal tract. In the large intestine plenty of enterobacteria available for the hydrolysis of quercetin and their metabolites.The majority of the quercetin undergoes bacterial fission and only small portion of the quercetin are absorbed. (Graefe et al., 2001). The hydrolysed quercetin glycoside (aglycone) in the small intestine found soluble with the help of surrounding liquid and help to transfer into the enterocytes. These takes part into phase-II metabolism which includes methylation, sulfation, and glucuronidation (Day et al., 2000). In liver part, quercetin and its factionendure phase-I reaction. Quercetin undergoes different reactions such as hydrolysis, oxidation, and reduction and makes it suitable for phase-ii metabolism. Kidney removed the water-soluble metabolites of quercetin. Quercetin conjugated metabolites are passed in the serum albumin and circulate in the blood stream. In humans, quercetin-3-glucoside (isoquercitrin) and quercetin-4-diglucoside were absorbed rapidly after 1 hrs ingestion. In plasma, only quercetin glucuronides could be observed and showed antioxidant (Manach et al., 1998). Fiorani et al. (2010) worked on the effect of quercetin on the mitochondrialproperties of human lymphoblast cells. They found that quercetin accumulates in the mitochondrial cell at a concentration

of 35 mM when cells were treated at 50 µM quercetin for 10 min.

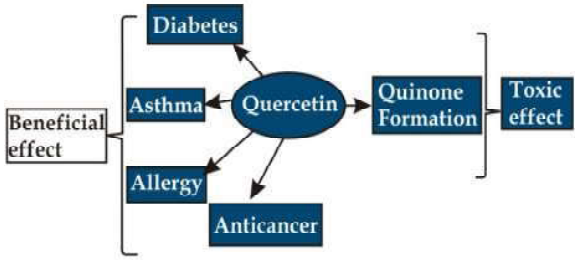

Fig. 2: **Beneficial and toxic effect of quercetin**

Allergies, fever, and hives

Quercetin has the capacity to stabilize the cell membrane and mast cell to inhibit the outbreak of histamine and other allergic metabolites which help in the fever and hives like allergies (Lombard, 2005). Environmental and emotional stress is controlled by mast cell and observed in different neuropathological processes. The neurodegenerative process caused by protease tryptase product of mast cell in thebrain. Like histamine, quercetin inhibits the growth of malignant cells and acts as anticancer properties. Quercetin blocks the metabolites produced in the allergies and ultimately reduce the production of tryptase, IL-6 and MCP-1 and histidine decarboxylase (HDC) from mast cell lines (ShaiK et al., 2006)

Anti-Cancer

Free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) responsible for the outbreak of the cancer disease. ROS have been shown to be carcinogenic effect by causing damage to DNA and also altering cell signaling pathways and gene expression. It has been observed that 7-31 % of cancer could be reduced by consumption of fruits and vegetable in the daily diet (Muhammad et al., 2006). Quercetin consists of antioxidant property block the production of ROS and RON induces DNA damage and leading to mutational changes. Caltagirone et al. (2000) studied therelationship between quercetin intake and incidence of lung cancer. They found that quercetin inhibits the growth of melanoma cell. Quercetin also having the capacity to inhibit the protein kinases which is responsible for cell growth in cancer (Russo et al., 2014). Reiter et al. (2009) worked on antioxidant effects of quercetin and coenzyme in mini organ cultures of human nasal mucosa cells. They described damage of nucleic acid (DNA) due to the oxidative stress is a risk factor for neck and head cancer. Quercetin available in the red wine and tea play a significant role to prevent the formation of oxidative stress by reactive oxygen species (ROS). Quercetin concentration 5 µM and 50µM found best after 24 h incubation for the control of human nasal mucosa cancer.Effective action of quercetin mostly observed in the lung, brain, blood and salivary gland cancer. Quercetin effect on the melanoma of having high cytotoxic activity and observed higher in aggressive cells than those of slow growing cells (Sak, 2014).

Diabetes:

Jeong et al. (2012) worked on theeffect of antioxidant, hypoglycemic and hypolipidemic properties quercetin on the melitus (type 2 diabetes) in animal tissue. Diet was prepared with 0.04% quercetin and fed for 6 weeks to the animals. Insulin, plasma glucose, adiponectin, lipid, and lipid peroxidation of the liver were investigated. Plasma levels reduced in the diet fed with quercetin than that of thecontrol group. Also, 0.08 % quercetin increased in plasma adiponectin, decreased plasma cholesterol. Formation of diabetic cataracts due to the conversion of glucose to sorbitol in the eye by aldose reductase enzyme. It has been reported that quercetin has the ability to inhibit aldose reductase and efficiently prevent polyol accumulation in rat lenses (Lai et al., 2012). Quercetin prevents the diabetic action by uptake of glucose through insulin process which consists of monophosphate-activated protein kinase leads to the glucose replacement to the plasma membrane (Eid et al., 2015).

Asthma:

Many researchers reported that worked on the relationship between quercetin intake and its effect on asthma (Knekt et al., 2002).Hirano et al. (2009) studied the effect of an enzymatically altered isoquercitrinon allergic symptoms. They reported that feeding of isoquercitrinon at the rate of 100-00 mg/day for eight weeks showed relief of ocular symptoms but not significantly relief of nasal symptoms caused by pollen.

Toxic effect:

In vitro study revealed that quercetin has agenotoxic effect. In bacterial cell mutagenic effect of quercetin mostly observed and are suggested to form quinone formation as mediators (Silva et al., 2000). Quercetin has the capacity to induce DNA and subsequent mutation in theanimal cell. In contrast, intake of quercetin in mice or rats with aorta restriction could protect against DNA damage.This help to protect against the development of lung cancer and to attenuate cardiac hypertrophy (Jin et al., 2006)

Conclusion

Quercetin has the potential to act as powerful antioxidant activities.Quercetin could be effective against several chronic diseases. Quercetin has versatile biological effects which include health benefit, the growth of physical and mental activity, and other physiological functions. Bioavailability of quercetin and its metabolites is essential to understand theeffect on the metabolism and help to prevent the outbreak of various diseases. In vitro experiments by the use of cell culture and in vivo trial in the animal model were showed that quercetin could be effective in thetreatment of various types cancer, asthma, diabetes and allergies.

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