5. Rutin: A bioactive flavonoid

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Abstract. Since, Plants have been used for curing or preventing diseases from centuries so continuous efforts are being made to study the bioactive compounds present in these plants consequently, research in this area is growing every year. Till now, many bioactive compounds have been identified in various medicinal plants. Flavonoids are major active nutraceutical ingredients in plants, which represent a large family of polyphenolic secondary metabolites. Flavonoids occur naturally in fruit, vegetables, and beverages such as tea and wine. Research in the field of flavonoids has increased, as it possesses anti-oxidant, anti-inflammatory, anti-allergic, hepato-protective, anti-thrombotic, antiviral, and anti-carcinogenic activities. Several other potential beneficial properties of flavonoids have since been ascertained. In this review we summarized the putative biological actions of rutin (a bioactive flavonoid), in order to obtain a further understanding of the reported beneficial health effects of flavonoids (rutin).

Introduction

Flavonoids are major active nutraceutical ingredients in plants which represent a large family of low molecular weight polyphenolic secondary metabolites that are widespread throughout the plant kingdom, ranging from
mosses to angiosperms [1, 2]. Research on flavonoids received an added impulse with the discovery of the French paradox, i.e., the low cardiovascular mortality rate observed in Mediterranean populations in association with red wine consumption and a high saturated fat intake. The flavonoids in red wine are responsible, at least in part, for this effect [3]. An important effect of flavonoids is the scavenging of oxygen-derived free radicals. In vitro experimental systems also showed that flavonoids possess anti-inflammatory, anti-allergic, antiviral, and anti-carcinogenic properties [4]. Flavonoids promote physiological survival of plant by protecting it from pathogenic microorganisms and UV radiations. In addition, flavonoids are involved in pigmentation for flowers, fruits and seeds to attract pollinators and seed dispersers, morphogenesis, sex-determination, and in plant-microbe interactions [1, 5, 6]. They also contribute to nutraceutical qualities of fruits and vegetables and have long been recognized to possess anti-oxidant, anti-inflammatory, anti-allergic, hepatoprotective, anti-thrombotic, antiviral, and anti-carcinogenic activities [2, 5]. The health-promoting effects of flavonoids may relate to interactions with key enzymes, signaling cascades involving cytokines and transcription factors, or antioxidant systems [7].

Over 6,000 flavonoids have been identified, and categorized, according to chemical structure, into flavonols, flavones, flavanones, isoflavones, catechins, anthocyanidins, dihydroflavonol and chalcones [6, 8]. The flavonoid rutin (quercetin 3-O rutinoside), is a flavonol glycoside comprised of the flavonol quercetin and the disaccharide rutinose (Figure 1). Its name comes from the name of Ruta graveolens, a plant that also contains rutin.

Figure 1. Chemical structure of rutin (http://en.wikipedia.org/wiki/File:Rutin_structure.svg).
Rutin in plant species

Rutin is a citrus flavonoid glycoside found in many plants such as *Viola tricolor* (3.36%), *Cappris spinosa* (0.28%), Apple (0.17%), *Lycopersicon esculentum* (0.002%-0.009%) and many more [9, 10]. Tartary buckwheat seeds have been found to contain more rutin (about 0.8-1.7% dry weight) than common buckwheat seeds (0.01% dry weight). Analysis of rutin content in leaves and flowers of 50 medicinal plants of rue, buckwheat, rose, sage, clove, rose etc. showed that content was highest in leaves of rue (8.6%), followed by flowers (5.3%) and leaves (2.0%) of buckwheat, flowers of pansy (3.35%) and flowers of rose (1.0%) while others contained less than 0.05% of rutin content [11]. Musallam et al. [12] also reported variation in rutin content in *Capris spinosa* with 2.76% in leaves, 1.8% in flower buds and 0.28% in fruits. Rutin is one of the primary flavonols found in 'clingstone' peaches.

Biosynthesis of flavonoids (rutin)

The precursors of the synthesis of most flavonoids are malonyl-CoA and p-coumaroyl-CoA, which are derived from carbohydrate metabolism and

![Rutin Biosynthetic pathway](image-url)
phenylpropanoid pathway, respectively [13]. The biosynthesis of flavonoids is initiated by the enzymatic step catalysed by chalcone synthase (CHS), resulting in the yellow coloured chalcone. In the majority of plants chalcones are not the end-products, but the pathway proceeds with several enzymatic steps to other classes of flavonoids, such as flavanones, dihydroflavonols and finally to the anthocyanins, the major water soluble pigments in flowers and fruits. Other flavonoid classes (i.e. isoflavones, aurones, flavones, proanthocyanidins and flavonols) are derived from intermediates in anthocyanin formation (Figure 2).

Factors affecting biosynthesis and accumulation of rutin in different plant species

The flavonoid biosynthetic pathway is under tight developmental control, and multiple environmental conditions of light and hormones affect the expression of flavonoid biosynthetic genes. Indeed, a decrease of flavonoid biosynthesis was observed when either endogenous (e.g. plant hormones), or exogenous factors (e.g. water and temperature stress, light, fertilizer, etc.) are limiting or excessive. UV-radiations stimulated the activity of enzymes of phenylpropanoid pathway and therefore, influenced rutin content in plants. The comparison of different UV-B treatments in buckwheat revealed that under ambient light conditions 97% more rutin content accumulated in leaves in comparison to leaves grown under reduced UV-B radiations [14]. Under stress conditions like drought, salinity etc. rutin content increased in seedlings of Dimorphandra mollis, suggesting their role in protecting tissues against oxidative damage [15]. Environmental factors that increase plant vigour (e.g. excessive fertilizer) are reported to negatively influence flavonoid content in grape berry. Methyl jasmonate showed an inhibitory effect on rutin content in Cucurbita and Buckwheat [16, 17]. Also, the accumulation of rutin increases with increased in sucrose content in Arabidopsis, buckwheat seedlings along with the expression of flavonoid genes [18, 19].

Medicinal importance of rutin

Many in-vitro studies have been carried out to understand the medicinal importance of rutin. Rutin has an ability to increase intracellular ascorbic acid levels, decreases capillary permeability and fragility, scavenge oxidants and free radicals, inhibits destruction of bones as well as lowers the risk of heart diseases [20, 21]. The use of rutin as medicinal agent has stimulated interest in this compound.
Rutin as an antioxidant:

Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. Oxidative stress has been linked to cancer, aging, atherosclerosis, ischemic injury, inflammation, and neurodegenerative diseases. Recent studies have demonstrated that flavonoids found in fruits and vegetables may also act as antioxidants. Rutin, a polyphenolic bioflavonoid has shown wide range of pharmacological applications due to its significant antioxidant properties. Few of them are mentioned in Table 1. Conventionally, it is used as antimicrobial, antifungal, and antiallergic agent.

Table 1. Medicinal importance of rutin.

<table>
<thead>
<tr>
<th>SNo</th>
<th>Effect of Rutin</th>
<th>References</th>
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<tbody>
<tr>
<td>1.</td>
<td>Anti-hyperglycaemic and antioxidant activity in streptozotocin induced diabetic rats.</td>
<td>[22]</td>
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<tr>
<td>2</td>
<td>Effective in Inhibition of lipid peroxidation</td>
<td>[23]</td>
</tr>
<tr>
<td>3</td>
<td>Inhibits oxiloplatin induced chronic painful peripheral neuropathy by reducing induced nitric oxide synthase and nitrotyrosine in spinal cord</td>
<td>[24]</td>
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<tr>
<td>4</td>
<td>Reversed hepatotoxicity induced by HCD by reducing oxidative stress and inflammation in liver</td>
<td>[25]</td>
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<td>5</td>
<td>Inhibits osteoclast formation in bone marrow derived macrophages by inhibiting activation of NF-kappaB</td>
<td>[26]</td>
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<tr>
<td>6</td>
<td>Improves spatial memory in Alzheimer’s disease because of its anti-oxidant and anti-inflammatory activity</td>
<td>[27]</td>
</tr>
<tr>
<td>7</td>
<td>Treatment of Type 2 Diabetes by inducing the insulin signaling pathway causing increased GLUT4 translocation and increased glucose uptake.</td>
<td>[28]</td>
</tr>
<tr>
<td>8</td>
<td>Prevents stroke, hearth attack, cardiovascular disease</td>
<td>[29, 30]</td>
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<tr>
<td>9</td>
<td>Anti-inflammatory effect on arthritis</td>
<td>[31]</td>
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<tr>
<td>10</td>
<td>Anti-fungal effect</td>
<td>[32]</td>
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<td>11</td>
<td>Suppresses atopic dermatitis and allergic contact dermatitis.</td>
<td>[33]</td>
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<td>12</td>
<td>Inhibits leukemia</td>
<td>[34]</td>
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<tr>
<td>13</td>
<td>Strengthens blood vessels</td>
<td>[35]</td>
</tr>
<tr>
<td>14</td>
<td>Anti-cancerous effect</td>
<td>[36]</td>
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Global market of rutin

As the number of countries around the world suffering from thrombosis on the rise, to prevent drug rutin increase in demand. China is a big country in production and export of rutin. According to statistics, China produces 1200 tons rutin, accounting for about 1/3 of the total output of the
world of rutin. Rutin (rutin) amount of medicinal began in the 60's of last century, since the 80's of the last century; rutin has become China's important export of medicinal plant extracts of raw materials products. The United States FDA has approved the rutin as level GRAS (i.e. "generally recognized as safe") products, can be used for medicine, health food or cosmetics products. China is one of the world's leading producers and exporter of rutin. (http://www.yunkce.com/en/industry/28.html)

Conclusion

Most of the studies related to rutin have been performed on experimental animals or cultured tissues. Fewer studies have been carried out in humans. Comprehensive clinical studies in humans are needed to develop pharmaceutics related to bioactive compound rutin.

References

Rutin: A bioactive flavonoid

29. Prescott, B. 2012, Flavonoid compound can prevent blood clots