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### CLINICAL EFFECTS OF FLAVONOIDS IN DENTISTRY - AN UPDATE

*Nishanthana Murali<sup>1</sup>, Anitha Roy<sup>2</sup>*

<sup>1</sup>Saveetha dental college and Hospitals, Saveetha Institute of Medical And Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

<sup>2</sup>Department of Pharmacology, Saveetha dental college and Hospitals, Saveetha Institute of Medical And Technical Sciences Chennai, Tamil Nadu, India.

<sup>1</sup>151701004.sdc@saveetha.com, <sup>2</sup>anitharoy@saveetha.com

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#### **ABSTRACT**

Flavonoids are naturally occurring organic compounds. Flavonoids play an assortment of natural functions in plants, and other beings including microscopic organisms. In plants, flavonoids have for some time been known to be orchestrated specifically locales and are liable for the pigmentation and fragrance of blossoms, and in fruits to draw in pollinators and thus facilitate its scattering to help in seed and spore germination, and the development and improvement of seedlings. Flavonoids have been attributed beneficial outcomes on human wellbeing and the ebb and flow intrigue is for infection treatment and chemoprevention. As of now there are around 6000 flavonoids that add to the brilliant shades of natural products, herbs, vegetables and therapeutic plants. The antimicrobial properties of flavonoids were proposed for both the improvement of new food additives and advancement of treatments. It is utilized for the treatment of different microbial diseases, thinking about the expansion in microbial obstruction against anti-toxin treatment. These days, about 70% of the microscopic organisms that cause diseases in emergency clinics are impervious to at any rate one of the medications most generally utilized for treatment. They have anti-inflammatory, anti-allergic, anti-bacterial, anti-cancer and many other properties and are one of the organic sources of medication. They have various applications used for the health promotion of human beings and this includes the branch of dentistry as will this review endeavors to examine the ebb and flow patterns of innovative work on the effects of flavonoids and their clinical applications in dentistry.

## INTRODUCTION

Plants are important in the sense that common phytochemicals secluded from plants utilized in customary medication are considered as acceptable options in contrast to engineered synthetics, plant products are likewise being progressively utilized as narcotics, or plaque decrease and solid gums. Many other plants like *Caralluma fimbriata* also have antihyperglycemic (Anitha and Ashwini, 2017) and anti cancer properties (Ashwini, Ezhilarasan and Anitha, 2017) while plants like *Azadirachta indica* have dental uses as well. (Lakshmi *et al.*, 2015). Some of the other plants include *Acacia catechu* (Devaraj and Lakshmi, 2017) with anti cancer properties, *Mangifera indica* (Rajeshkumar, Venkat Kumar, *et al.*, 2018), *Garcinia mangostana* Bark (Karthiga, Rajeshkumar and Annadurai, 2018) *Brassica oleracea* (Rajeshkumar, Agarwal, *et al.*, 2018). Certain nanoparticles synthesised like selenium (Menon *et al.*, 2018) have therapeutic potential and are present in various plants. Some of the other topics of interest and future scope include antioxidant property (Gheena and Ezhilarasan, 2019) (Ezhilarasan, 2018), anti cancer with drug therapy (Perumalsamy *et al.*, 2018) (Sharma *et al.*, 2019) and chronic inflammation (Mehta *et al.*, 2019), cell specific therapy (Ezhilarasan, Sokal and Najimi, 2018) and the ability of naturally obtained drugs to treat these conditions effectively. The compounds of plants being useful as potential alternative medicine include flavonoids as well. Around 100 articles were collected in various bibliographic databases, and 61 articles related to the title were selected and explored to combine this review article titled clinical effects of flavonoids in dentistry.

Flavonoids are a collection of common substances with variable phenolic structures (Panche, Diwan and Chandra, 2016). These are notable for their impact on health and wellbeing and endeavors are being made to extract them for potential applications. They are considered as an irreplaceable segment in an assortment of restorative, pharmaceutical nutraceutical applications. This is ascribed to their wide range of properties (Kozłowska and Szostak-Węgierek, 2019) that will be further discussed in this article. They have protective roles against diseases especially the fact that they are not present in only one part of the plant but in many parts of different plants they have several subdivisions in classification and each one has a unique major source that is currently in use (Manach *et al.*, 2004). They have a variety of pharmacological actions and help prevent the acquisition of certain diseases to an extent due to daily usage of flavonoids in the natural source form (Justesen and Knuthsen, 2001). Flavonoids intake in human diet is estimated to be 20-200MG/d on a normal scale while tea drinkers may range up to  $\geq 1000$ MG/d (Corcoran, McKay and Blumberg, 2012). There is no establishment of an upper limit in the consumption of flavonoids in the dietary form and is hence not a concern for a case of toxicity (Crozier, Jaganath and Clifford, 2009).

The flavonoids occupy a valuable place in the management of certain diseases. Among the dietary sources of flavonoids there are vegetables, nuts, seeds and so on. Utilization of these substances as part of the diet has been known to have some effect in the prevention process and hence is accordingly legitimate to consume flavonoids as part of the diet (Liu, 2013).

## PHARMACOLOGICAL PROFILE OF FLAVONOIDS

Flavonoids seem to have a variety of pharmacological actions and show major protective effects in case of chronic and fatal diseases if ingested in the daily diet.

### *Cardiovascular Effects*

Flavonoids seem to have an effect on the cardiovascular disease mortality rate by reducing it. Though they may not have a significant effect in the prevention they have an indicative effect in reducing the mortality rate (Peterson *et al.*, 2012). It seems to have a preventative effect on the progression of coronary heart disease and the study suggest that flavonoids may increase tolerance to cardiac injury and reduces the risk or procurement of the disease to an extent as well (Li *et al.*, 2010)

### *Biochemical, Antioxidant Effects*

Flavonoids like quercetin have large potential to inhibit the production of reactive oxygen species (ROS) and also to reduce the levels once they are formed. (Agati *et al.*, 2012). Most ingested flavonoids are broadly debased to different phenolic acids, some of which despite everything have a radical-scavenging capacity. Both the ingested flavonoids and their metabolites may show some in vivo cell reinforcement action (Pietta, 2000).

### *Anti Cholinesterase Activity*

Flavonoids are a topic of interest in the treatment of Alzheimer's disease and their anticholinesterase activity is what is indicative for the symptomatic treatment of Alzheimer's disease (Uriarte-Pueyo and Calvo, 2011). Quercetin is the only compound that exhibited significant inhibitory activity of 76.2% against AChE (Orhan *et al.*, 2007). From the basic action relationship, it is inferred that the greatest AChEI movement of the greater part of flavonoids is because of the nearness and position of hydroxyl (OH) bunch at ring A and ring B, and because of the unsaturation of ring C. Studies demonstrated that the most extreme AChEI action of baicalein is because of the nearness of OH group at position 5, 6 and 7 of ring A. In this way, the evacuation or change of the situation of OH group in ring A makes the inhibitor more vulnerable or totally inert (Khan *et al.*, 2018).

### *Immunomodulatory Effects*

*They have specific immunomodulatory effects and hence* help in the autoimmune branch of disorders and also among several different types of cancer. They are able to induce the TCD4 + regulatory cells and hence have a promise of future research. (Hosseinzade *et al.*, 2019). The flavonoids could essentially decrease the articulation and arrival of TNF- $\alpha$  in LPS-activated RAW 264.7 cells in asubordinate way. Besides, the consequences of p65 and P-p65 proposed that flavonoids hinders aggravation related factor articulation by stifling the NF- $\kappa$ B signal pathway (Shi *et al.*, 2017).

### *Antibacterial Effect*

Flavonoids, particularly chatones groups showed an increase in the antibacterial activities up to 6 times more than the drugs designed for this

purpose. Some of its derivatives that are artificially synthesized seem to have 20-80 times the activity shown by the original drugs against multidrug resistant bacteria, both gram negative and gram positive (Farhadi *et al.*, 2019). The suggested mechanisms of flavonoids action against bacteria include, nucleic acid synthesis inhibition, cytoplasm membrane function inhibition and also inhibition of energy metabolism, cell attachment formation, porins on the cell membrane as well as affecting the permeability of the membrane (Xie *et al.*, 2014)

#### ***Anti Inflammatory Effect***

***There is an inverse proportional relationship*** between intake of flavonoids and the risk of procurement of chronic disease due to its anti-inflammatory effect. It involves the inhibition of inflammatory mediators such as eicosanoids, C-reactive protein, cytokines, adhesion molecules and soon. (Serafini, Peluso and Raguzzini, 2010) It has a valuable effect on the chronic inflammatory conditions and is hence very promising in the controlling of acute conditions turning chronic (Pan, Lai and Ho, 2010) They seem to have promising results in the category as they also show results in clinical studies as well as molecular studies (Matias *et al.*, 2014)

#### ***Antitumor Effects***

***These seems to be a proportional increase*** in the intake of flavonoids by cancer diagnosed patients in nature of its properties and antitumor effect (Grosso *et al.*, 2017). There have been numerous suggestions that quercetin, a very popular flavonoid that is most abundant in its presence in fruits and vegetables has a positive effect in controlling cancers like human metastatic ovarian cancer cells owing to its down regulating effect of anti-apoptotic factors (Teekaraman *et al.*, 2019) and also breast cancer (Wu *et al.*, 2018). It also has significant effects in case of oral cancer as well as the pathogenesis of all cancers are similar in respect to its hallmarks.

#### ***Anti Osteoporotic Effect***

Tea consumption can significantly reduce osteoporosis but only in case of females. Tea contains flavonoids and is hence related to the antiosteoporotic effect it has (Sun *et al.*, 2017) Nutritional adjustments can help in the long run of prevention of osteoporosis and can improve bone microstructure, mineral density and also strength to an extent. (Shen *et al.*, 2011) The nutritional adjustments include flavonoid intake. Flavonoids inhibit osteoclast differentiation, especially luteolin, a flavonoid present in tea and also protects against OVX induced bone loss according to studies (Kim *et al.*, 2011)

### **FLAVONOIDS IN DENTISTRY**

Some of the flavonoids most used in dentistry are Quercetin, Naringenin and proanthocyanidins and are also said to have maximum effect in the oral cavity.

#### ***Quercetin***

It is the most abundant flavonoid and is found in vegetables like role, red onion and some amount is even present in honey and is known for its antiatherosclerotic (Somerset and Johannot, 2008), anti-obesity properties along with its vasodilator effects (Parasuraman, David and Arulmoli, 2016)

But the property that is most pronounced in quercetin is the anti-inflammatory effect and it has clinical applications that are currently in use (Qureshi, Khan and Mahjabeen, 2012). It is known to have both most all stabilizing property as well as a modulating biphasic regulatory action over inflammatory process (Chirumbolo, 2010). It also has beneficial effect on oral health in conditions like periodontal disease, oral lesions, tooth decay and so on owing to its wide range of actions in the human body.

### ***Naringenin***

Naringenin is present in some fruits and vegetables mainly of the citrus family (Mbaveng, Zhao and Kuete, 2014) also tomatoes and other fruits can serve as a source of the principle considering its bioavailability and protective action on the cardiovascular system. Its capacity to improve endothelial function is very much known but further research on its physical and chemical properties is very much essential to use the full potential of naringenin. To overcome its limited production, attempts have also been made to extract naringenin from micro-organism sources like *E. coli* and so on (Wu *et al.*, 2015). It has an effect on the biofilm formation over the teeth and is a potential anti-caries agent (Yue *et al.*, 2018).

### ***Proanthocyanidins***

It is an important group of flavonoids that are often overlooked. It is known for its antioxidant properties. The bioavailability and metabolic processes are not yet studied so as to provide values but there are indications in studies that smaller chains are absorbed. Thus, they also seem to have a role in apoptosis, gene expression processes which are crucial anti-cancer properties (Cos *et al.*, 2004). They are suggested to have an effect on the demineralization of artificial carious lesions in both enamel and dentin and their effect ranges based on their structure (Silva *et al.*, 2015).

### ***Apigenin***

It is one of the most widespread flavonoids that are present in plants like asteraceae, Artemisia, and so on (Ornano *et al.*, 2016). It has many effects such as a positive effect in reducing depression and insomnia (Salehi *et al.*, 2019). The antidiabetic potential of apigenin is also of considerable value (Pamunuwa, Nedra Karunaratne and Waisundara, 2016). Apigenin also seems to affect dental pulp cells which are a promising future for regeneration of dental tissue and apigenin seems to help in maintaining them in an undifferentiated phase to inhibit differentiation (Liu *et al.*, 2015).

## **DENTAL APPLICATION OF FLAVONOIDS**

### **Remineralisation of Artificial Root Caries**

In a study which compared the effect of quercetin, naringenin and proanthocyanidin on the remineralization of artificial root caries, all three flavonoids showed measurably greater hardness than that of fluoride without the flavonoids (Epasinghe, Yiu and Burrow, 2016). The remineralization of dentine occurs in a demineralized collagen matrix (Pavan *et al.*, 2011) and hence it is necessary to research and validate other methods for the remineralization of dentin as the deeper parts of the lesions are left out of this process.

### ***Inhibition of Plaque Formation***

Naringenin, quercetin and many other flavonoids aid in the inhibition of bacterial and fungal growth which is vital for plaque formation on the teeth. (Gutiérrez-Venegas *et al.*, 2019). Proanthocyanidins may also help in inhibition of dental caries formation by inhibiting organic acids synthesis by *S. mutans* and *S. sobrinus* (Feng *et al.*, 2013). Apigenin also has antibacterial effect and helps in the inhibition of plaque formation by increasing the proton permeability and inhibiting acid synthesis of the membrane and *S. mutans* respectively (Koo, 2003).

### ***Effect on Mechanical Properties of Dentin***

In a study that compared the effect of quercetin, naringenin and proanthocyanidin on the modulus of elasticity and ultimate tensile strength which are mechanical properties of demineralised dentine it was seen that both of the properties were affected by the flavonoids and proanthocyanidins was more effective than quercetin and naringenin in improving the mechanical properties (Epasinghe *et al.*, 2014) Proanthocyanidin rich collagen cross-linkers aid in increasing the mechanical properties and stability of dental matrix. Short term resin dentin bonds can also be improved by treatment with proanthocyanidin (Castellan *et al.*, 2010)

## **CONCLUSION**

This review article highlights the clinical uses of flavonoids particularly in dentistry. Some of the flavonoids most used in dentistry include quercetin, naringenin and proanthocyanidins and are also said to have maximum effect in the oral cavity. The importance of this study lies with the properties of flavonoids and that it is of natural origin and not chemically synthesized. There are many health benefits and long term preventive effects of consuming flavonoids in their natural form as well.

## **AUTHOR CONTRIBUTION**

Data collection and Manuscript writing: Nishanthana Murali  
Critical revision and final approval of the version to be submitted : Dr .Anitha Roy

## **CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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