

APIGENIN IN DENTISTRY - A NARRATIVE REVIEW

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ABSTRACT:

Apigenin, is a nutraceutical agent which belongs to the flavanoid group. It has antioxidant, anti-inflammatory, antiviral properties. Owing to its properties its healing potential has been researched in medical field for diabetes, cancer, Alzheimer's diseases, amnesia, depression, insomnia, knee osteoarthritis, anxiety disorders, multiple sclerosis. The role of apigenin in dentistry has been studied regarding its effect on *S.mutans* (*Streptococcus mutans*), reparative dentin formation, remineralization of dentin, use of apigenin along with fluoride, dental adhesives and composite, proliferation of osteoblasts, regeneration of pulpodentinal complex, effect on periodontal ligament, and anticancer properties.

Keywords: Apigenin, dentistry, flavonoid, *S.mutans*, reparative dentin.

INTRODUCTION:

Apigenin is a natural bioactive substance and it is from the flavonoid group.^[1] Apigenin has developed interest in recent years as it promotes health with minimal toxicity.^[27]

Source of apigenin:

Apigenin is in glycosylated form in vegetables such as onions, parsley, celery and fruits such as oranges, herbs such as chamomile, thyme, oregano, basil, and plant-based beverages such as tea, beer, and wine.^[1]

Properties of apigenin:

Apigenin has nutraceutical properties. Nutraceutical agent is a substance present in food that provides medicinal benefits, including prevention and treatment of diseases.^[2] Apigenin acts as remover of free radicals exhibiting antioxidant, anti-mutagenic, anti-inflammatory and antiviral properties. The flavanoids inhibit cell cycle thereby producing anticancer properties, reduces oxidative stress, improving detoxification enzymes, stimulates apoptosis, and improves the immune system^[1] (Fig 1).

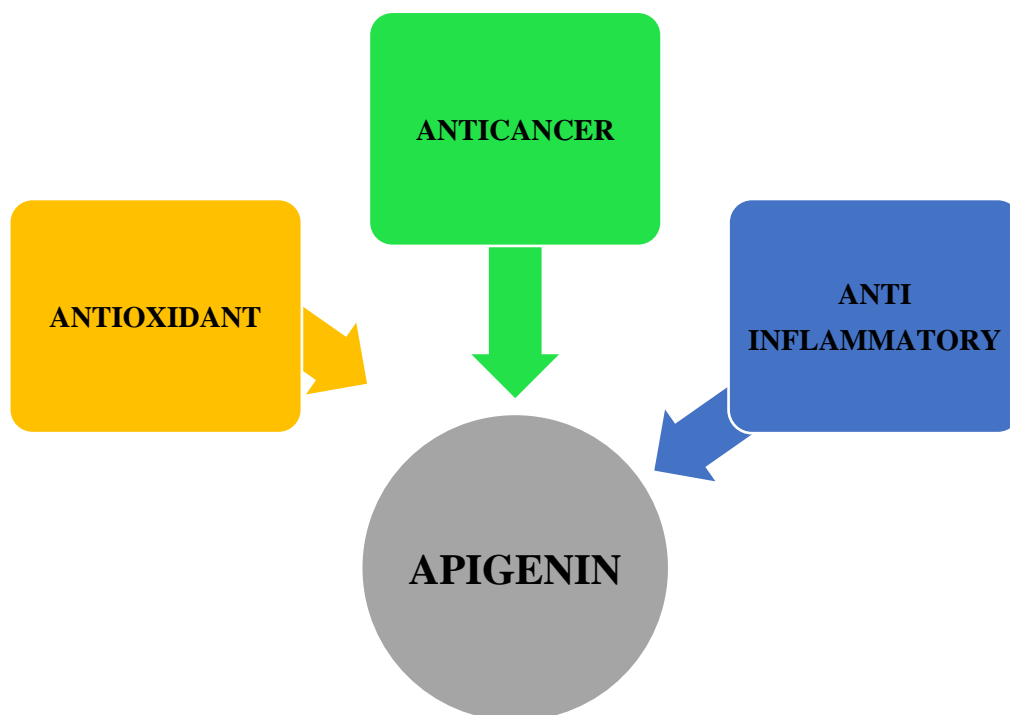


Fig 1: Properties of Apigenin

Medicinal use of apigenin:

The healing properties of apigenin has been studied in animal models for the treatment of diabetes^[1], cancer^[3], alzheimer's diseases^[4], amnesia, depression^[1]. Clinical trials have been conducted for alzheimer's disease, insomnia^[5], knee osteoarthritis^[6], anxiety disorders^[1] (Fig 2). As apigenin has anti-inflammatory

properties it has been considered as an agent for treatment of inflammation of CNS for diseases like multiple sclerosis.^[1]



Fig 2: Medicinal Uses of Apigenin

Rationale:

As dentistry is mainly concerned with materials used in treatment, more research is being carried out to use materials with less side effects. As apigenin is a naturally derived substance and has properties such as antioxidant, antiinflammatory, antiviral, reduces the virulence of S.mutans, anticancer ,this review was carried out to acknowledge its potential use in the field of dentistry.

METHODS:

This review includes the studies which has researched about Apigenin, and its various application in the field of dentistry because of its antinflammatory, antioxidant, antiviral, anticancer, immunomodulation properties. An online search was conducted using the database from Pubmed, Scopus, Google scholar to find articles related to the same. This review includes articles from 2011 to 2022.

RESULTS:

30 articles were included and analysed for review.

DISCUSSION:**Apigenin In Conservative Dentistry And Endodontics:**

The role of Apigenin in Conservative dentistry and endodontics are effect of apigenin on *S.mutans*,^{[9][12][13]} biofilm, ^{[16][18][19]} formation of reparative dentin,^[15] remineralization of dentin,^[25] use of apigenin along with fluoride,^{[7][17]} dental adhesives and composite,^[10] proliferation of osteoblasts,^[8] effect on dental pulp cells for regeneration of dental tissue and maintains it in an undifferentiated phase.^[11]

Use Of Apigenin In Other Branches Of Dentistry (Fig 3):

The other uses of apigenin in dentistry includes anti-inflammatory effects of apigenin in periodontal ligament,^{[14][20]} bone formation after extraction,^[21] role of apigenin in oral cancer^[22].

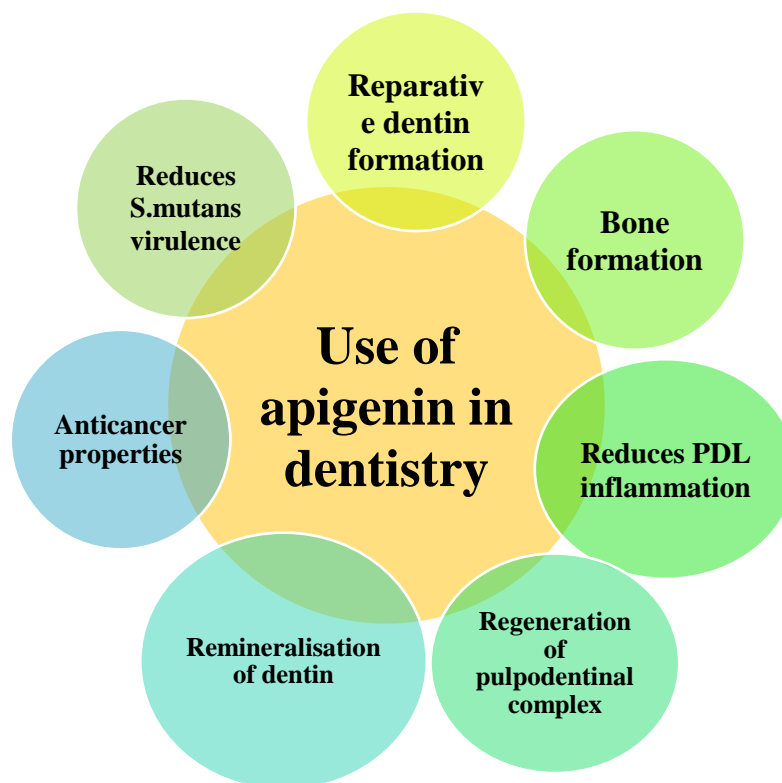


Fig 3: Uses of Apigenin in dentistry

Effect of Apigenin on *S.mutans*:

Mutans streptococci are the organisms which widely causes caries as they are very acidogenic, producing short-chain carboxylic acids which decalcify hard tissues is enamel and dentine. The two species of mutans streptococci commonly identified from tooth samples are *S. mutans* and *S. sobrinus*.^[23] Hence studies have been conducted to reduce the cariogenicity of mutans Streptococcus.

H. Koo et al have studied the combined effect of apigenin, tt-farnesol with fluoride on *S.mutans* biofilm and dental caries. This combination affected the formation of insoluble glucans which is essential for bacterial colonisation as they provide binding

site, interruption of acid formation which leads to reduced pH, and prevents accumulation of intracellular polysaccharides essential for biofilm formation. The combination of apigenin, tt-farnesol with fluoride decreased the virulence of *S. mutans* and this combination displayed maximum therapeutic effect in vitro.^[7]

Hyun Koo et al studied the effect of apigenin on *gtf* gene expression in *S. mutans* UA159. Apigenin inhibits glucosyltransferase activity. Apigenin reduced the insoluble glucans in biofilm and increased the levels of soluble glucans. Apigenin affected the enzymes-*gtfB*, *gtfC*, *gtfD* which is required for the expression of glucosyltransferase. *gtfB*, *gtfC* expresses the formation of insoluble glucans, whereas *gtfD* expresses the formation of soluble glucan.^[9]

Yinchen LIU et al in 2019, studied the role of apigenin in surface-associated characteristics and adherence of *S. mutans*. With apigenin only the virulence of *S. mutans* is affected and not the overall count, hence the equilibrium of microflora is maintained. Apigenin's effect was seen on hydrophobicity and cellular aggregation and on gene expression of *pac* and *gbpC* of *S. mutans*. The *pac* gene codes for protein antigen which functions as an adhesin, *gbpC* codes for glucan binding protein C (GbpC).^[13]

Using apigenin for reparative dentin formation:

Reparative dentin is a type of tertiary dentin, which is formed by the pulpal progenitor cells in reaction to external stimulation such as caries, noxious agents, wear. The prevailing disadvantages in available pulp capping materials has led to the search of newer materials which aid in healing pulp.^[24]

Yam Prasad Aryal et al in 2021 have studied the local delivery of apigenin for the formation of reparative dentin. Pulpal necrosis follows inflammation. Hence to modulate the inflammation, apigenin is used as it is a potent anti-inflammatory agent. Apigenin has the ability to modulate inflammation by reducing the levels of TNF, MPO, cytokines and helps in formation of dentin bridge.^[15]

Dental tissue regeneration:

Lu Liu et al in 2015 have studied the outcome of Luteolin and apigenin on the development of Oct-4, Sox-2, and c-Myc gene markers in pulp cells in vitro. They found that apigenin along with luteolin helped the dental pulp stem cells to stay in undifferentiated state by increasing telomerase activity, and caused the development of markers Oct-4, Sox-2 and c-Myc by cadherin which are essential for pluripotency and reprogramming property.^[11]

Role of apigenin in dentin remineralisation

Bengao Zhu et al have studied apigenin loaded along with phosphorylated polyamide for remineralisation of dentin. In their study, in artificial saliva they have found that the dendrimer helps in dentinal tubules occlusion by mineralisation, and with

antibacterial properties of apigenin it prevents further erosion of dentin from bacteria.^[25]

Incorporation of apigenin in dental composite:

Carolina Bosso André et al have studied the effect of apigenin along with tt-farnesol in resin-based composite and cement material. In their study they have found that adding apigenin and tt-farnesol decreased the polysaccharide count of *S.mutans* by reducing the virulence of *S.mutans* without killing them. But apigenin increased the yellow shade of composite.^[10]

Incorporation of apigenin in dental adhesives:

Carolina Bosso André et al in 2017 have studied the virulence of *S.mutans* by addition of anticaries agent -apigenin -1mM , farnesol -5mM. Apigenin, farnesol were added separately and in combination in clear fill S₃ bond plus, optibond. In their study they have found that when apigenin, farnesol separately and in combination, reduced the formation of insoluble polysaccharide in biofilm. This reduced the virulence of *S.mutans* without formation of antimicrobial resistance. This prevents the formation of secondary caries.^[26]

Effect of apigenin on periodontal ligament:

Lu Liu et al in 2015 have studied the effect of Luteolin and apigenin in activation of Oct-4/Sox2 signal via NFATc1 in human periodontal ligament cells. Apigenin and luteolin which belong to bioactive flavanoids help to enhance the reprogramming efficiency and increase the expression of Oct-4 /Sox2/ c-Myc. Human periodontal ligament cells are a source of progenitor cells for osteogenesis. Luteolin and apigenin causes restrained cell proliferation, increased apoptosis, and arrests periodontal ligament cells in G₂/M and S phase.^[14]

Gil-Saeng Jeong et al in 2009 have studied the anti-inflammatory properties of apigenin on nicotine and lipopolysaccharide stimulated human periodontal ligament cells via hemoxygenase 1. In their study they found that apigenin downregulates nitric oxide, prostaglandin E₂, proinflammatory cytokines responses in periodontopathogen and nicotine stimulated PDL cell model and hemoxygenase 1 pathway. Hence it can be used as an adjunct for the treatment of periodontitis due to biofilm and smoking.^[20]

Effect of apigenin on bone:

José Luis Calvo-Guirado et al in 2020 have studied the influence of Apigenin k and melatonin in the salvage of socket as bone stimulators as an experimental study in beagle dogs. Apigenin was found to accelerate the process of mineralisation of bone matrix. Less resorption of post extraction socket can be seen with the topical use of apigenin K.^[27]

Jose Luis Calvo-Guirado et al studied the histological evaluation of new bone in post extraction socket induced by melatonin and apigenin and they found early cellular differentiation increased bone matrix formation and mineralization.^[21]

Emira D'Amico et al in 2022 studied the role of apigenin on human osteoblasts and found that apigenin induces bone-forming osteoblasts through stimulating proliferative and mineralization activities and up-regulating osteogenic markers such as alkaline phosphatase, osteocalcin and collagen I.^[8]

Role of apigenin in oral cancer:

Muhammad Imran et al in 2020 have reviewed the literature for role of apigenin in cancer. They have found it efficient against breast, stomach, colon, cervical, prostate, pancreatic, oral, leukemia, skin, lung, bone, ovarian, liver, brain cancer. As its role was evaluated in vitro the dosage and efficiency against cancer cell lines are not comparable with living system due to the presence of immune system and enzymes in the latter.^[28]

Daniele Maggioni et al in 2013 have studied the effect of apigenin in oral cancer. They found that apigenin was able to arrest cell cycle progression in different phases.^[29]

CONCLUSION:

From the various articles reported here, it is understood that apigenin, which belongs to the flavonoid group has a great potential to be used as therapeutic agent in regard to its effect on *S.mutans*, reparative dentin formation, effect on bone and as an adjunct to treatment in case of effect on periodontal ligament, it is capable of increasing the effectiveness of treatment when used along with composite, dental adhesives, and fluoride. It has the capability of regenerating the pulpodentinal complex. More in vivo studies will help in calculating the dosage to be used and its effectiveness in human being.

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