



## ORIGINAL RESEARCH PAPER

## Oral Pathology

### APIGENIN A BOON OR BANE?-NARRATIVE REVIEW

**KEY WORDS:** Apigenin, antioxidant, neuroprotective, anti-cancer, organic

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#### ABSTRACT

Apigenin, a flavonoid constituent present in various plants such as chamomile, parsley, and celery has proven to possess immense pharmacological benefits. The compound demonstrates exceptional antioxidant qualities while simultaneously reducing inflammation making it an excellent alternative for treating several medical conditions such as diabetes that require low toxicity levels with added neuroprotective medical properties. Moreover, apigenin exhibits promising results regarding the alleviation of mental health disorders by providing anxiety reduction or depression relief treatments alongside its potential anti-cancer attributes thereby proving versatile across different healthcare sectors without risking severe side effects; our analysis highlights extensive medicinal uses displaying therapeutic abilities linked to this organic chemical agent.

#### INTRODUCTION:

Fruits and vegetables contain apigenin, a flavonoid that is very commonly found in plant products including chamomile tea, wine, and orange grapes as well as in vegetables and fruits. (1) It possesses antiviral, antioxidant, and anti-inflammatory properties and to test apigenin's anti-proliferative effectiveness, melanoma was treated with it. (2) It works against cancerous cells and it is especially important for gastrointestinal disorders like colon cancer. (4) Additionally, apigenin is used to treat Alzheimer's disease and Parkinson's illness. A yellow crystalline substance called apigenin is used to dye linen. (5) The neuroprotein properties of apigenin also protect against brain ischemia, subarachnoid hematoma, epilepsy, and melancholy. (6)

#### ROLE OF APIGENIN:

TNF-alpha is a target of apigenin, which either inhibits it or suppresses its synthesis. (7) It encourages osteogenic differentiation and quickens the formation of in vivo bones. Maximizing the amount of available bone for the insertion of implants in the maxilla is essential in dentistry then the beneficial effects of apigenin on metabolic processes, including diabetes, are also well-known. (8) Low-density lipoprotein levels in the bloodstream and cell cycle are both reduced by flavonoids. (9). Apigenin has nutritional advantages. A food ingredient known as a nutraceutical agent has medicinal properties that can be used to treat and prevent illness. (10) Through the NF-B signaling cascade, apigenin prevents the transition of the epithelium to the mesenchyme in hepatocellular carcinoma. Investigation shows that the STAT3-NF-B pathway is influenced by apigenin to produce anti-IBD and anti-CAC effects. (11) To maintain endogenous antioxidants, restore cardiac and left ventricular function, histologically preserve myofibrils, attenuate apoptosis, and lessen lipid peroxidation in the myocardial tissues are all part of apigenin's cardioprotective impact. Additionally, apigenin improved PPAR-γ expression. (12)

#### Bioavailability of APIGENIN:

Common fruits like grapefruit, beverages made from plants, and veggies like parsley, onions, oranges, tea etc and some seasonings all contain a lot of apigenin. Peppers (*Piper nigrum*) and parsley (*Petroselinum crispum*) are two significant sources of flavones, with 13.526 mg and 4.98 mg per 100 grams, respectively. An excellent source of apigenin is also celery, which contains 108 mg of it per kilogram. The

dried flowers of the chamomile plant, *Matricaria chamomilla*, are one of the most popular forms of apigenin used in herbal teas. (5)

#### METABOLISM OF APIGENIN

Two flavonoids, apigenin and genistein, undergo faster intestinal metabolism than hepatic metabolism. In yeast cells, this was demonstrated using the rat-isolated UGT1A variant. Apigenin intestinal excretion was found to be higher in Gunn rats (which are defective in UGT1A) than in Wistar rats, suggesting that UGT isoforms are up-regulated in Gunn rats. Flavonoids are efficiently metabolized by UGT1A deficient, restricting their bioavailability and enhancing disposition, due to compensatory up-regulation of intestinal UGT2B and hepatic anion efflux transporters. (5)

#### Uses:

##### APIGENIN IN ENDODONTICS:

Dental tissue regeneration about streptococcus mutans, biofilm development, reparative dentin remineralization, fluoride use, and dental tissue regeneration (10)

##### REPARATIVE DENTIN FORMATION:

By pulpal progenitor cells in response to external stimuli like caries and wear, tertiary dentin is produced. Consequently, apigenin, a strong anti-inflammatory agent, is used to regulate inflammation. By lowering the levels of TNF, MPO, and cytokines, apigenin can regulate inflammation and aid in the formation of the dentin bridge. (10)

##### APIGENIN IN BONE FORMATION:

APIGENIN in having a role in bone formation after the extraction of a tooth and in the formation of oral bone in humans. Apigenin exhibits a stimulating impact on cell growth when 5-APG is used at 48 hours, and it should be kept in a dark room at -20°C. Apigenin's protective effect against osteoporosis progression suggests that it plays a function in the skeletal system. APG was among the natural substances that demonstrated beneficial effects on bone metabolism; it was also discovered to enhance new bone production and speed up fracture healing in living organisms. (8)

##### EFFECT OF APIGENIN ON BIOFILM ACCUMULATION:

APIGENIN negatively impacts the accumulation and growth of new biofilms. The development of fresh approaches that target the virulence factors involved in the pathogenesis of

this widespread mouth disease is necessary to continue the progress toward the eliminating action of dental caries. The manifestation of *S. mutans* virulence depends heavily on the glucans that GTFs produce. (9)

### APIGENIN IN HEMOSTASIS

In platelet-rich plasma and cleansed platelets, APIGENIN inhibits collagen and ADP-induced aggregation by about 80-97%. By suppressing the cyclooxygenase pathway, APIGENIN prevents platelet clumping. By suppressing the cyclooxygenase pathway, antioxidants prevented platelet aggregation. Adenylyl cyclase inhibit also served to lessen the platelet cyclic AMP reaction to PGI<sub>2</sub>. (5)

### ANTIVIRAL ACTIVITY:

APIGENIN, a compound found in the medicinal plants *Kummerowia striata* and *Chrysanthemum morifolium*, stimulates anti-HIV action in MT 4 cells and T cells transfected with HIV-1 and HIV-1 (III B). The bulk of viral infections can be largely inhibited by modifying cellular c-reactive protein (CRP) levels and preventing viral IRES-mediated translational activity. How to activate jun N-terminal kinase (JNK). (5)

### AUTOIMMUNE DISORDER:

The capacity of lupus B cells to produce autoantibodies is suppressed by APIGENIN, according to studies using a mouse model of the disease. Apigenin also decreased the levels of COX-2 and cellular FLICE-like inhibiting protein (c-FLIP), which led to immune cells going into death. T cell resilience to activation-induced cell death is associated with autoimmune disease and lymphocyte proliferation. (AICD). Apigenin inhibited NF- $\kappa$ B translocation after leukemic Jurkat T-cell lines' T-cell receptors (TCRs) were stimulated and revived peripheral blood CD4 T-cells. (5)

### APIGENIN IN DIABETES:

Apigenin's anti-diabetic properties may be ascribed to its ability to stop glucosidase activity, increase insulin secretion, interact with and equalize reactive oxygen species (ROS) in the cell, and increase insulin uptake, all of which help to avoid diabetic complications. Additionally, apigenin has demonstrated the capacity to moderately feed endothelial cells with nitric oxide (NO), reducing the risk of endothelial cell dysfunction and injury due to hyperglycemia. (9)

### APIGENIN inhibits colon damage:

In the colon tissue of rodents with chronic UC, there were localized mucosal hyperemia and edema, granulated internal mucosa, and superficial ulcer development. These kinds of colonic damage were improved by APIGENIN, and the amount of colon macroscopic damage decreased. Apigenin was a successful therapy for long-term UC. MPO, COX-2, and inflammatory mediators were all decreased by apigenin. Compared to colon tissues from untreated animals, inflammatory cell infiltration. CAC risk is increased by long-term IBD. Inflammatory mediators help create a microenvironment that supports tumor growth in IBD patients. (11)

### APIGENIN IN HEAD AND NECK CARCINOMA :

Cell survival is 20% lessened by APIGENIN. The difference between the underlying intracellular pathway of the combination therapy and the APG and 5-fluorouracil's oxidative impact on the SCC 25 cell line has been described. Even though the authors claimed that this co-treatment might be an effective novel approach to treating HNSCC, they failed to consider the molecular basis for its effectiveness. (15)

### NEUROPROTEIN EFFECT OF APIGENIN ON BODY WEIGHT OF Me-Hg INDUCED NEUROTOXICITY IN ADULT RAT:

In rats, APIGENIN 80mg/kg raised an effective weight. Comparatively to the MeHg-treated group, reduced body weight was effectively regained on days 35 and 42 of the post-

treatment with a continuous dose of APG 40 mg/kg and APG 80 mg/kg. (6)

### OTHER USES OF APIGENIN:

Apoptosis is induced by APIGENIN, which also alters the shape of melanoma cells and impairs their ability to migrate. (2) Melanoma tumor cells that are exposed to APIGENIN undergo apoptosis and undergo histopathological alterations. (2)

By restoring NO bioavailability and Eliminating oxidative stress, APIGENIN enhances endothelial function in elderly mice. (3)

Age-related arterial inflammation is reduced by apigenin. (3) 2.5 mg of APIGENIN is marginally beneficial for daytime performance and inconsistently beneficial for the sleep journal measure. (9)

### Challenges and Opportunities in the Therapeutic Use of Apigenin:

Utilizing apigenin supplements with purified apigenin in capsule form allows for the achievement of physiologically meaningful plasma concentrations that have the potential to affect cellular behaviors. Coming from the healing Perspective The delivery and following metabolism of the bioactive molecule are complicated by flavonoid structure, despite the fact that the body handles it well as a natural product. Due to their molecular makeup, apigenin and similar flavones have a low solubility, medium permeability, and chemical instability. (13)

### FUTURE DEVELOPMENTS :

Despite apigenin's poor water solubility and lack of toxicity, it is still regarded as safe even at large dosages. A number of micro- and When used as drug delivery systems, nano-encapsulated APG products have shown better stability, bioavailability, and sustained release at much lower doses against a variety of diseases. Apigenin acting as a helpful factor in high risk breast cancer. (16)

### CONCLUSION:

Since Apigenin can cause cell cycle arrest and apoptosis in OSCC cells, it indicates that it should be further researched as a possible agent for both prevention and treatment of oral cancer. Since Apigenin can cause a double cell cycle arrest in various phases, it also appears to be a very hopeful cell cycle regulator (1). APIGENIN normalizes age-related increases in arterial ROS generation, oxidative stress, and expression of antioxidant and oxidant enzymes, reverses age-associated aortic intrinsic mechanical wall stiffness, and adversely remodels the extracellular matrix. (3). Apigenin serves to repair demyelination brought on by long-term MeHg administration, and it was also noted to improve rat brain tissue. (6) To create a therapeutic plan for use in clinical practice, apigenin may be taken into consideration as a possible active phytochemical compound. Osteoblasts are stimulated, and osteogenic indicators are upregulated. (8) Although apigenin has low cytotoxicity and anti-inflammatory and anti-tumor activities in a variety of cancer cells, the mechanisms underpinning these effects are still unknown. (11). Despite mounting evidence that the capacity of these organisms to synthesize glucans might be more significant than their population in the mouth, most chemotherapeutic strategies are focused on reducing the levels of cariogenic bacteria by using antimicrobials (which are not selective). (14) It is crucial to newly emerging worldwide health issues. (9) When administered alone by advised human physiological doses, apigenin also demonstrates a modest anticancer activity. (15)

### REFERENCES:

- 1) Apigenin impairs oral squamous cell carcinoma growth in vitro inducing cell cycle arrest and apoptosis Authors: Daniele Maggioni Werner Garavello Roberta Rigolio Lorenzo Pignataro Renato Gaini Gabriella Nicolini

- 2) Apigenin induces apoptosis by regulating Akt and MAPK pathways in human melanoma cell A375SM Authors: Joong-Seok Woo Gang-Sik Choo Eun-Seon Yoo Sung-Hyun Kim Jae-Han Lee So-Hee Han Hyeong-Jin Kim Soo-Hyun Jung Young-Seok Park Byeong-Soo Kim Sang-Ki Kim Byung-Kwon Park Sung-Dae Cho Jeong-Seok Nam Chang-Sun Choi Jeong-Hwan Che Ji-Youn Jung
- 3) Apigenin restores endothelial function by ameliorating oxidative stress, reverses aortic stiffening, and mitigates vascular inflammation with aging Authors: Zachary S. Clayton, David A. Hutton, [...], and Douglas R. Seals
- 4) Does Oral Apigenin Have Real Potential for a Therapeutic Effect in the Context of Human Gastrointestinal and Other Cancers? Authors: Eva F. DeRango-Adem and Jonathan Blay
- 5) Health functionality of apigenin: A review Authors: Fahad Ali, Rahul, Falaq Naz, Smita Jyoti & Yasir Hasan Siddique
- 6) Protective effects of apigenin on Methylmercury-induced behavioral/Neurochemical abnormalities and Neurotoxicity in rats Authors: Rajeshwar Kumar Yadav, Sidharth Mehan, Rakesh Sahu, Sumit Kumar, Andleeb Khan, Hafiz Antar Makeen and Mohammed Al Bratty
- 7) Apigenin Exerts Anti-inflammatory Effects in an Experimental Model of Acute Pancreatitis by Down-regulating TNF- Authors: ALEXANDROS CHARRALABOPOULOS, SPYRIDON DAVAKIS, MARIA LAMBROPOULOU, APOSTOLOS PAPALOIS, CONSTANTINOS SIMOPOULOS and ALEXANDRA TSAROUCHA
- 8) Apigenin Promotes Proliferation and Mineralization of Human Osteoblasts and Up-Regulates Osteogenic Markers Authors: Emira D'Amico , Tania Vanessa Pierfelice , Giovanna Iezzi, Natalia Di Pietro, Stefania Lepore, Felice Lorusso , Antonio Scarano , Assunta Pandolfi , Adriano Piattelli and Morena Petrini
- 9) The Therapeutic Potential of Apigenin Authors: Bahare Salehi , Alessandro Venditti , Mehdi Sharifi-Rad , Dorota Kręgiel, Javad Sharifi-Rad , Alessandra Durazzo , Massimo Lucarini , Antonello Santini , Eliana B. Souto , Ettore Novellino , Hubert Antolak , Elena Azzini , William N. Setzer and Natália Martins
- 10) APIGENIN IN DENTISTRY – A NARRATIVE REVIEW AUTHORS: Dr. Srinidhi P, Dr. Janani Karunakaran, Dr. Sreelakshmi P.S, Dr. Kaavya B, Dr. Kokila Sivakumar, Dr. Yashini Thanikachalam.
- 11) Apigenin inhibits colonic inflammation and tumorigenesis by Suppressing STAT3-NF- $\kappa$ B signaling Authors: Xiao-Yu Ai, Yuan Qin, Hui-Jua Liu, Zhan-Hong Cui, Meng Li, Jia-Huan Yang, Wei-Long Zhong, Yan-Rong Liu, Shuang Chen, Tao Sun, Hong-Gang Zhou and Cheng Yang
- 12) The Protective Effect of Apigenin on Myocardial Injury in Diabetic Rats mediating Activation of the PPAR- $\gamma$  Pathway Authors: Umesh B. Mahajan , Govind Chandrayan , Chandragouda R. Patil , Dharamvir Singh Arya , Kapil Suchal, Yogeeta O. Agrawal, Shreesh Ojha , and Sameer N. Goyal
- 13) Does Oral Apigenin Have Real Potential for a Therapeutic Effect in The Context of Human Gastrointestinal And Other Cancers? Authors: Eva F. DeRango-Adem and Jonathan Blay
- 14) Inhibition of Streptococcus mutans biofilm accumulation and Polysaccharide production by apigenin and  $\alpha$ -farnesol Authors: H. Koo, M. F. Hayacibara, B. D. Schobel, J. A. Cury, P. L. Rosalen, Y. K. Park, A. M. Vacca-Smith and W. H. Bowen
- 15) Chemoprotective and chemosensitizing Effects of apigenin on cancer therapy AUTHORS: Zahra Nozhat, Shabnam Heydarzadeh , Zahra Memariani and Amirhossein Ahmadi
- 16) Probing into Therapeutic Anti-Cancer Potential of Apigenin: Recent Trends and Future Directions Authors: Ajay Sharma, Abdul Ghani, Katrin Sak, Hardeep S. Tuli, Anil K. Sharma, William N. Setzer, Sanjeev Sharma And Amit K. Das