



## **RESVERATROL AND GREEN COFFEE EXTRACT GEL AS ANTICARIES AGENT**

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### ABSTRACT

#### Keywords:

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**Introduction:** There prevalence of dental caries ranges from 49% to 83% worldwide which is affected by various factors like socioeconomic status, access to dental care and diet. Several treatment modalities have been employed to prevent the initiation and progression of dental caries. The efficacy of resveratrol and green coffee extracts against *Streptococcus mutans* has been investigated previously.

**Hypothesis:** Resveratrol and Green Coffee Extract in the form of a gel with methyl cellulose as a carrier medium applied topically on the tooth surface can help by providing an antibacterial effect to prevent bacterial colonization and dental caries.

**Testing the Hypothesis:** A gel containing Resveratrol and green coffee extract in methyl cellulose carrier will be formulated and its pharmacokinetics and drug release profile will be assessed. Evaluation of the anticaries and remineralization potential of the gel should be performed on artificially created dental caries lesions in-vitro on human natural permanent teeth like premolars that are caries free and extracted for orthodontic reasons. After the in-vitro analysis, clinical trial with a randomized double-blinded design with a placebo and test gel containing resveratrol and green coffee extracts must be done.

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## Introduction

Dental Caries is the most commonly encountered dental problem globally. It is well known that dental caries results due to the interaction between substrate (fermentable carbohydrates), the host (tooth surface and saliva) and acid producing microorganisms<sup>[1,2,3]</sup> It can occur in childhood as a rapidly progressing aggressive rampant caries affecting the primary dentition of infants<sup>[4]</sup> The prevalence of dental caries ranges from 49% to 83% worldwide which is affected by various factors like socioeconomic status, access to dental care and diet<sup>[5]</sup> In the development of caries; acidogenic bacteria play a pivotal role especially *Streptococcus mutans*, *Streptococcus sobrinus* and *Lactobacilli* which in the presence of fermentable sugars like sucrose cause demineralization of enamel. A retentive niche is formed by *Streptococcus mutans* which aids in the colonization of *Lactobacilli*.<sup>[6]</sup> The initial caries lesions on the enamel surface appear as white spots of demineralization that results when the pH of the tooth surface is lowered by the acidogenic bacteria.<sup>[7]</sup> The acid ions enter through the prism sheath porosities on the enamel causing demineralization of the subsurface as the superficial surface of the

enamel is remineralized due the high levels of Calcium and Hydrogen phosphate and fluoride ions in the saliva that acts as a buffering agent by constantly bathing the tooth surface<sup>[7]</sup> Matrix metalloproteinases (MMPs) have been suggested to play an significant role in the destruction of dentin organic matrix subsequent to demineralization of enamel by acids from the bacteria and in the control or progression of dental caries. Caries causing bacteria present in the tooth cavity release acids such as lactic acid that reduce the pH of the environment locally. The resulting acidic environment demineralizes the dentin matrix and induces the activation of host MMPs derived from dentin or saliva. Once the local pH is neutralized by salivary buffer systems, activated MMPs degrade the demineralized dentin matrix. Several treatment modalities have been employed to prevent the initiation of dental caries such as application of various forms of fluoride, pit and fissure sealants<sup>[8]</sup>

## Resveratrol

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) is a natural compound present in many plant extracts, including grapes skin, peanuts and cranberries. It belongs to the stilbene family like viniferins and pterostilbene (trans-3,5-



dimethoxy-40-hydroxystilbene). Resveratrol possesses multiple biological functions such as antimicrobial activity, antiviral, antioxidant, anti-inflammatory, and anticancer<sup>[9,10]</sup> The effect of resveratrol on *S.mutans* has been studied where in it is known to have an inhibitory effect on *S. mutans* virulence properties which makes it a potential anticariogenic molecule. Resveratrol in its minimum inhibitory concentration significantly decreases acid production tolerance, inhibited synthesis of water-soluble polysaccharide and water-insoluble polysaccharide by *S.mutans*. Furthermore, resveratrol has anti extracellular matrix metalloproteinase inducer (EMMPRIN) effect<sup>[11]</sup> and is a natural polyphenol antioxidant that has been shown to facilitate osteogenic differentiation [12].

### Green Coffee

The efficacy of green coffee extract as an anticaries mouth rinse has been investigated previously<sup>[13]</sup> Green coffee bean extract, apart from caffeine, it is composed of chlorogenic acids which forms about 5–12 gm/100 grams of the extract and caffeic acids, which act as antibacterial agents.<sup>[14]</sup> Esterification of cinnamic acids leads to the formation of chlorogenic acids which gives it an

antibacterial activity.<sup>[15]</sup>The minimum inhibitory concentration of green coffee extract against dental caries causing bacteria like *Streptococcus mutans* and *Lactobacilli* was found to be 2.5%.<sup>[13]</sup> The antibacterial activity of green coffee extract against *Streptococcus mutans* was comparable to chlorhexidene.<sup>[13]</sup> Chlorogenic acids, cause irreversible damage to the bacterial cell membrane, causing cells to lose the ability to maintain membrane potential and leakage of cytoplasm macromolecules including nucleotide.<sup>[16]</sup>

### Hypothesis

Resveratrol and Green Coffee Extract in the form of a gel with methyl cellulose as a carrier medium applied topically on the tooth surface can help by providing an antibacterial effect to prevent bacterial colonization and dental caries. It has been documented that both resveratrol and green coffee extract have antimicrobial effects hence a synergism could result if they are coupled together. It is also noteworthy that resveratrol has anti MMP effects through inhibition of a key molecule EMMPRIN. Since dental caries is a lesion initially caused by bacterial production of acids which cause demineralization of enamel, dentinal spread of the lesion and destruction



occurs predominantly by MMP mediated mechanisms. Hence, it could be reiterated at this point that the combination of resveratrol and green coffee would not only attack the microbial challenge but also would control host MMP mediated dental caries progression. In an in-vitro model on cancer cell lines the actions of resveratrol in mediating apoptosis have been found to occur at an acidic pH which seems to be the ambient condition for the action of this molecule. This ambient environment will be recreated if green coffee extract is combined with resveratrol as chlorogenic acids in green coffee extract would confer an acidic pH to the combination. Since both Resveratrol and Green Coffee extract are natural products minimal or no toxic effects are anticipated when used in a local drug delivery form. Its benefits could be of immense use especially for children who are susceptible to dental caries and have poor compliance with oral hygiene methods or children with special needs or to the geriatric population and institutionalized patients who cannot perform regular oral hygiene procedures. This gel can be used as an adjunctive tool to maintain good oral health.

### Testing the Hypothesis

The first step would be to formulate a gel containing resveratrol and green coffee extract in methyl cellulose carrier for application on tooth surface. Then, the in-vitro pharmacokinetic and drug release profile of the gel formulation must be assessed. Evaluation of the anticaries and remineralization potential of the gel should be performed on artificially created dental caries lesions in-vitro on human natural permanent teeth like premolars that are caries free and extracted for orthodontic reasons. After the in-vitro analysis, clinical trial with a randomized double-blinded design with a placebo and test gel containing Resveratrol and Green Coffee Extract must be done. Briefly, the participants who are age and gender-matched will be recruited into the study after obtaining their informed consent. The participants will be screened for dental caries with a standardized index system for recruitment into the study. After randomization, one group of participants will receive a test gel to be applied topically twice a day throughout the treatment phase while the other group will receive a placebo gel. Clinical examination will be done to assess dental caries using standardized clinical indices at baseline and post intervention.



Statistical analysis of the results obtained in the placebo and test groups will be estimated. It is anticipated that the gel formulations made in the study will have a significant positive impact on the caries lesions due to its anti - S.Mutans effect and anti - EMMPRIN effect. If the experiment produces positive results the combination of resveratrol extract and green coffee extract could be employed in mouthwashes, tooth varnishes and remineralization creams to aid in the bio chemoprevention of dental caries.

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