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Role of Nutraceuticals from an Orthodontic Perspective - A Review

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ABSTRACT:
With the everyday rising standards of beauty, cosmetic surgeries as well as dentistry are gaining immense popularity. Orthodontic treatment being one of the most common procedures to improve smile esthetics has seen a rising demand not only in adolescents but in adults as well. Adults with their oral and periodontal diseases present as a new challenge. Orthodontic treatment creates physiologic and psychological stresses which levy additional requirements already hiked by the stresses, activities and growth of the adolescent and young adult life. Most of the adults nowadays are aware of the side effects of prolonged use of medication/pharmaceutical drugs. Nutraceuticals are plant derived food and their derivatives that have preventive as well as therapeutic effects. They can be used to speed up the orthodontic movement without any adverse effects as well as prevent relapse and bone or root resorption, and improve overall oral health. The aim of this review is to provide the latest and thoughtful perspective on the relationship of nutraceuticals with various aspects of orthodontic tooth movement and related quality of life to help in obtaining a modern diagnostic–therapeutic approach.

Keywords:
Nutraceuticals, Dietary supplements, Orthodontic, Tooth movement, Relapse, Resorption, Curcumin, Vitamins.

Introduction

The health benefits associated with the consumption of plant food has been established. Nutraceuticals are pharmaceutical systems (powders, pills, capsules, etc.) that contain natural bioactive compounds as active components. [Espín JC et al., 2007].

"Nutraceuticals" are foods or their derivatives that have therapeutic or protective effects and without any adverse effects so that they can be incorporated into diet. As a result there is no controversy based on culture or religious beliefs of people. [Asefi et al., 2018].

The term "nutraceutical" was coined in 1989 by Stephen De Felice, founder and chairman of the Foundation for Innovation in Medicine, an American association which promotes medical research. He described nutraceuticals as "food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease"[Bull E et al., 2000].

There is an increased demand for cosmetic dentistry in today's world and orthodontics is one of the most important procedures to attain proper occlusion and harmonious soft tissue profile. The increase in the number of adult patients requiring orthodontic treatment presents as a new challenge [Suparwitri et al., 2016].

Orthodontic treatment generates physical, physiologic and psychological stresses, which levy

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additional requirements already hiked by the stresses, activities and growth during adolescence. Certain agents cause an increase or decrease in tooth movement, prevent chances of relapse, improvement of oral health, and bone or root resorption.
This review paper highlights the significance and status of research in regards to such agents also known as Nutraceuticals and their varied applications in the field of orthodontics.Figure 1 depicts the major nutraceuticals of importance during orthodontic treatment.

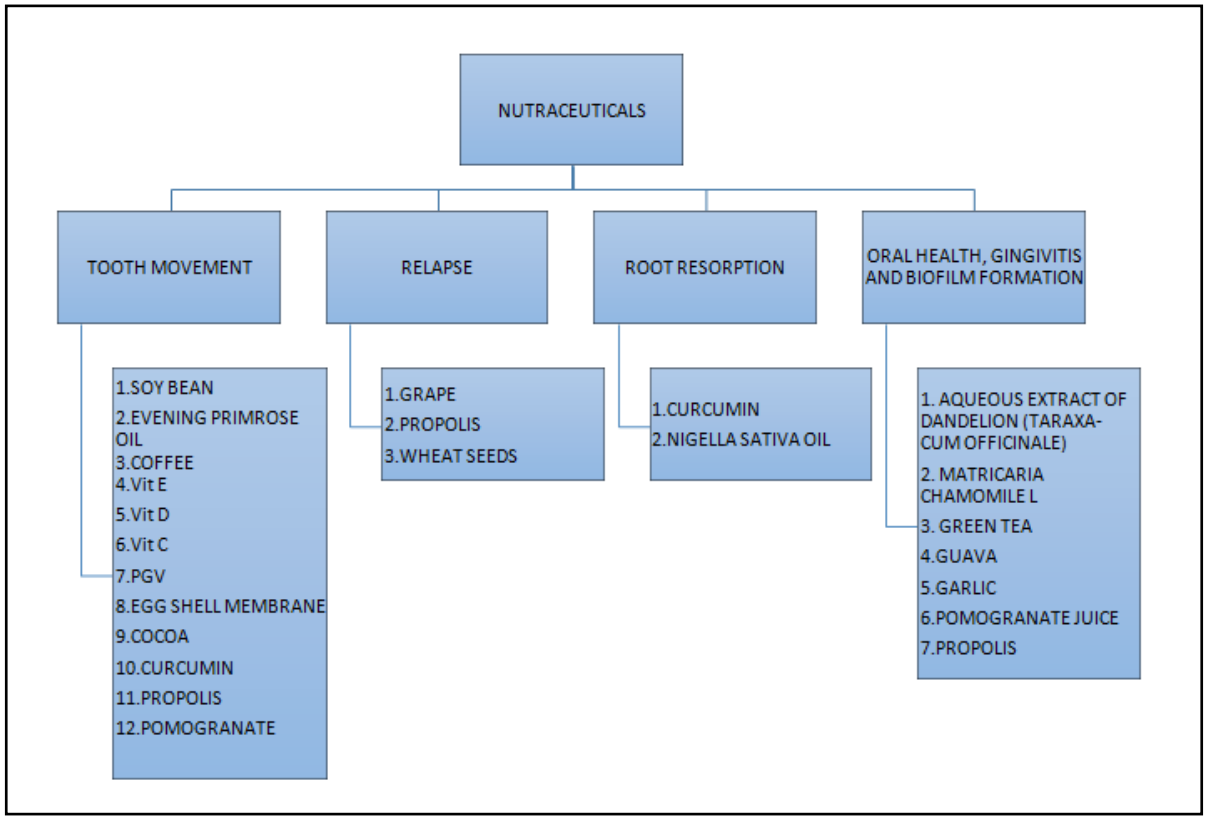

Figure 1: Major Nutraceuticalsof Importance during Orthodontic Treatment

Objectives of the study

1. To review the existing literature on nutraceuticals.
2. To review the role of nutraceuticals in oral health and orthodontic procedures.
3. To review the advantages and disadvantages of nutraceuticals based on existing literature.

Methodology

The study is descriptive in nature and is based on secondary data. The data are collected from various reports and research papers from Indexed databases, Google Scholar and internet sources.

Orthodontic tooth movement

Orthodontic tooth movement takes place as a result of bone remodelling in response to force application. This is mediated by osteoblasts and osteoclasts that help in bone apposition and resorption respectively [Suparwitri et al., 2019].

Soybean:

The rate of bone deposition and resorption is balanced in children and adolescents. However in adult patients, especially women after menopause, there is a fall in the oestrogenlevel which is associated with an increased incidence of osteoporosis. Since it can also affect the tooth movement, it is important to address this systemic condition to improve the treatment outcome

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[Boskey& Coleman, 2010; Gambacciani&Levancini, 2014].

Hughes et al [1996] demonstrated that replacement of the hormone estrogen reduces the lifespan of osteoclasts and promotes apoptosis, thereby, inhibiting bone resorption.

According to Dole et al [2017], estrogen increases Transforming Growth Factor Beta (TGF-β1) synthesis within the blastic cells which help in bone apposition.

A recent study by Suparwitri et al [2016] showed that soybean contains isoflavonegenistein. This phytoestrogen mimics innate oestrogen in their physiological functions. It is shown to maintain bone apposition rates in rats after ovariectomy-induced osteoporosis. These isoflavones present in soybeans improve the remodelling process by inducing TGF-β1 within osteoblasts.

Wheat seeds:

Wheat seeds contain plant oestrogens, which are non-steroidal products that imitate native estrogen [Hunsel et al., 2015].

Suparwitri et al [2019] observed a reduction in the rate of tooth movement in the study group which received a daily dose of wheat. It was associated with an increase in the Osteoprotegerin (OPG) levels and a reduction in Receptor activator of nuclear factor kappa-B ligand (RANKL) levels.

Thus, wheat seeds administration post orthodontic treatment might help in maintaining the teeth in their corrected position.

Evening primrose oil:

The popularity of oils containing evening primrose oil (EPO), γ-linolenic acid (GLA), borage oiland blackcurrant seed oil have increased as health supplements. GLA, is an 18 carbon polyunsaturated fatty acid, is a metabolite of linoleic acid (LA), from which dihomo- γ -linolenic acid and ProstglandinE_1 are synthesized. Since PGE_1 is known to accelerate orthodontic tooth movement, it is expected that administration of EPO during the course of orthodontic treatment could enhance bone remodelling and fasten the treatment [Fan and Chapkin, 1998].

Taweechaisupaponget al [2005] administered EPO rich in γ-linolenic acid intraorally on rats and found that there was an upsurge in the osteoclasts formation which was maximum on the third day, after which it progressively diminished. This was in consistent with the study conducted by Lee [1990] who inspected the outcome of Prostaglandin administration on the rate of orthodontic tooth movement.

Thus we should be aware that supplementation of diets with GLA-containing oils can enhance the number of osteoclasts thereby accelerating the orthodontic tooth movement.

Coffee:

Coffee today has become one of the most popular beverages in the world. Robusta coffee containing caffeine increases osteoclastogenesis through enhancement of RANKL [Pullman-Mooar et al., 1990].

Administration of caffeine at high dose along with orthodontic force application demonstrated an upsurge in the number of osteoclasts on the pressure side [Devchand et al., 1996].

Chlorogenic acid and caffeic acid are the two main components of Robusta coffee that have antioxidant properties, and may reduce oxidative stress on osteoblast [Katzhendler E, Steigman S, 1999].

It is also found that Chlorogenic acid encouragesbone apposition [Stanfeld J, 1986 and Yamaguchi, 2009].

Caffeine increases RANKL levelswhich in turn binds to adenosine receptors and modulates numerous other receptors expressed in osteoprogenitor cells (OPG) and promotes osteoblast differentiation[Schelling et al., 1980]

Caffeine rises OPG levels also. But this is less than that of coffee brew as it contains caffeic acid also in addition to caffeine.[Yamaguchi M, 2009].

Caffeine also reduces the bone density by interrupting the Ca^{2+} ion balance, thereby accelerating the rate of orthodontic tooth movement. [Zhang et al., 2012 and Shirazi et al., 2017]

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Vitamin C (Vit C):
Vitamin C (Ascorbic acid) plays an important role in osteoclast stimulation and has been confirmed by Otsuka et al [2000] and Tsuneto et al [2005].
Deficiency of Vit C can affect periodontal ligament organization as well as osteogenesis [Iwami et al.,1999]. Vit C is required for the stem cell differentiation into osteoblasts, collagen synthesis, stimulating protein-kinase pathway and phosphorylation of osteoblast-specific transcription factors [Ishikawa et al., 2004].
Litton [1974] and Hickory, Nanda [1982] have shown that Vit C deficiency during orthodontic treatment reduces the tooth movement by inhibiting the collagen turnover which is important for orthodontic tooth movement.
According to Ragab et al [1998] Vit C also increases the longevity and proliferation of osteoclasts and their progenitor cells.
Cheraskin E, Ringsdorf [1969] found that Blood levels of Vit C in orthodontic patients is 17% to 75% lower than the desired level.
Greater tooth movement and osteoclast lacunae were observed in the experimental group who received oral Vit C for 17 days [Miresmaeili et al., 2015].

Vitamin D (Vit D):
Vitamin D stimulated stem cell differentiation into osteoclasts and increased the function of existing osteoclasts, thereby, increasing bone resorption [Castillo et al., 1975; Reynolds et al., 1973 and Weisbrode et al., 1978].
Collins and Sinclair [1988] confirmed that Vit D metabolites given as intra-ligamentary injections increased the number of osteoclasts. This increased the rate of bone resorption and accelerated the tooth movement.
Kale et al [2004] found that administration of prostaglandin and 1,25-dihydroxy cholecalciferol (1,25 DHCC), which is the active form of Vitamin D accelerated tooth movement significantly. It was associated with an enhancement in the capillaries and Howships lacunae on the pressure side. When compared to Prostaglandin group, the number of osteoblasts were greater in 1,25 DHCC group which suggests that tooth movement could be slower in individuals with Vit D deficiency.
Kawakami and Takano [2002] and Boyce and Weisbrode [1985] found that calcitriol injections following orthodontic force application increased the mineral appositional rate on alveolar bone. This suggests that Vit D can help in re-establishing supporting tissue around the teeth following treatment enhancing the post treatment stability.

Curcumin:
Curcumin is the active component in turmeric. It inhibits osteoclasts formation by suppressing the nuclear factor kappa-light-chain-enhancer of B cell pathway. Sustained release formulations of curcumin are available as 10% w/v gelatin and 4% w/v chitosan for local application [Asefi et al., 2018].
Bharti et al [2004] showed that curcumin exerts its action by suppressing Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB) pathway which halts the osteoclast synthesis and subsequent bone remodelling.
According to Ozaki et al. [2000] the action of curcumin on clast cell apoptosis was dependent on dose and time.
French et al [2008] and Kim et al [2011] observed that curcumin has a bone protective effect and advocates it's use in osteoporosis following menopause or ovariectomy.
According to Cho et al [2013], Curcumin can be used for anchorage augmentation or to enhance the post treatment stability as it has a synergic effect on the bisphosphonates to reduce bone resorption.
Moran et al. [2012] found that curcumin can hinder Nitric oxide (NO) production by inhibiting the expression of enzyme Nitric Oxide Synthase expression. NO is known to regulate

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osteoblastogenesis. As a result, curcumin is expected to reduce bone apposition.
In contrast, Gu et al. [2012] found that curcumin had stimulatory effect on the rats' stem cell differentiation to bone forming cells along with an enhancement in the activity of enzyme alkaline phosphatase, suggesting it has bone formative effect as well. Since orthodontic tooth movement is associated with bone apposition as well as resorption, the exact role of curcumin cannot be identified.
According to Henrotinetal[2013], curcumin reduces root resorption by suppressing the inflammatory mediators like Interleukin-1 (IL-1)

Pentagamavunone (PGV-0):
Pentagamavunone-0(2,5-bis-(4'-hydroxy-3'- methoxybenzylidinecyclopentanone) (PGV-0) is one of the curcumin analogues and active molecule of the curry spice turmeric. This analogue is known to have a higher analgesic effect than paracetamol without causing adverse effects. [Reksohadiprodjo et al., 2003]
Karras et al [2007] found that PGV-0 does not inhibit tooth movement in rats and it is possible to develop PGV-0 as an alternative analgesic during orthodontic therapy.

Egg shell membrane (ESM):
In a study by Hiroki and Kouki [2020], Egg Shell Membrane have shown to upregulate the expression of collagen types I and III and enhanced bone remodelling when administered along with Vit C, thereby suggesting a potential role in promoting tooth movement. It can also protect the periodontium from force-related damage during the treatment. The clinical application of ESM along with Vit C may shorten orthodontic treatment time.

Cocoa:
Caffeine acts by decreasing vitamin D receptor protein (VDR) expression and alkaline phosphatase activity in human osteoblast cells [Rapuri et al., 2007]. A reduction in VDR expression supress the osteoblastic activity which, in turn, can result in a diminution of bone density. Thus, administration of cocoa can accelerate the rate of tooth movement, reducing the treatment duration.
Chocolate (*Theobroma cacao*) is a processed cocoa product that has a diverse mixture of chemical compounds. Chocolate generally contains 55% fat, 17% carbohydrates, 11% protein, and the rest are tannins. The amount of caffeine in chocolate varies by the percentage of cocoa it contains.
Liu et al [2011] studied the effect of the dose and the duration of caffeine consumption in chocolate on the mineral density, the right compressed side of alveolar mandibular bone showed a decrease in calcium levels in the bones in the control group starting from day 1 to day 14. This indicates that there has been remodelling of the alveolar bone that was dominated by bone resorption.
The effect of caffeine on bones also depends on the concentration of the caffeine metabolite, namely paraxanthine. The concentration of caffeine consumed is relatively the same as the amount of paraxanthine concentration in the body, so with a low dose of caffeine the concentration of paraxanthine is also low [Fahmi, 2016 and Wolg et al., 2006].

Vitamin E (Vit E):
Vitamin E has a stimulatory effect on bone formation. Sufarnap et al [2020] have shown that there is an increase in the number of osteoblast cells in the Vit E supplemented group.
According to Uysal T et al [2009], Vit E has antioxidant and anti-inflammatory properties and they suppress the harmful effects of oxygen free radicals during bone apposition.
In this regard,Esenliket al.[2012] and Liu et al. [2011]suggest thatVitEcan modify cytokine production and it's supplementationpreserves normal bone remodelling in animals and improves bone mass by reducing the free radicals concentration which inhibits osteogenesis.

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Norazlinaet al. [2007] observed that Vit E supplementation can enhance trabecular bone formation and halt bone calcium loss by decreasing the pro-inflammatory cytokines.
Feresinet al. [2013] found that when a Vit E diet was given to rats, there was an increase in the bone volume by 65% compared to the control group.This shows that Vit E diet was able to enhance osteoblast mediated bone mineralisation.
According to Jiang Q [2014] et al, Vit E can reduce the pain associated with orthodontic tooth movement because of anti- inflammatory effect.
Propolis:
Propolis is a bee product consisting of resin substances collected from flowers, buds, and exudates of various plant sources. Bees mix these substances with enzymes excreted from their mandibular gland. According to Toreti VC et al [2013], propolis is an antioxidant, anti-inflammatory,antibacterial,immunomodulatory, antitumor substance and has analgesic and anesthetic properties.
Orthodontic tooth movement can increase oxidative stress. According to Aydin et al [2018] and Bereket et al [2014], propolis has been shown to reduce the levels of Malondialdehyde (MDA), a marker of oxidative stress. Propolis plays an important role in the regulation of bone remodelling, possibly through angiogenesis.
Wiwekowati et al [2020] showed that local propolis from Indonesia contains flavonoids, quercetin, rutin, and gallic acid. Flavonoids play an important role in eliminating oxidative stress in various ways, including the direct scavenging of reactive oxygen species, to protect the lipophilic antioxidants, and increase enzymatic antioxidants.
According to Hyunchu et al [2007], application of antioxidants like quercetin plays a role in angiogenesis to increase Vascular Endothelial Growth Factor(VEGF).

Pomegranate juice:
According to Yami EA [1999], consumption of pomegranate extract accelerate bone formation. It inhibits bone resorption and retards Orthodontic Tooth Movement (OTM).

Relapse prevention
The success of a treatment depends on its long term stability. According to Alhasyimi et al [2018], uncompleted alveolar bone remodeling caused by a prolonged and unstable treatment mechanics is one of the main causative factors for relapse. It is associated with an elevation of RANKL levels and reduction in OPG levels.
Al Yami et al [1999] evaluated the stability of orthodontic treatment 10 years post retention and found that relapse could still occur following retainer discharge and also heavily rely on patient cooperation. Using pharmacological methods like Bisphosphonates can have adverse effects like osteonecrosis of the jaw bone [Kennel KA & Drake MT, 2009]. Thus, using Neutraceuticals as biological retainers following orthodontic therapy for long term stability could greatly improve the treatment results.

Grape seed:
Grape seeds contain proanthocyanidinswhich forms a complex known cyanidin-3-glucoside (C3G). It is proven that C3G has the potential to inhibit stem cell differentiation into osteoclast [Ananto et al., 2019].
High doses of Cyanidin (>10 μg/mL) suppresses RANKL-induced osteoclastogenesis and increases the OPG levels, which in turn, prevents orthodontic relapse. It is also associated with osteoblastogenesis which subsequently increases bone apposition and reducing the relapse tendencies [Dou et al., 2016].
Flavonoids present within grape seeds have antioxidant and anti-inflammatory properties and were found to accelerate bone remodelling process [Vislocky LM & Fernandez, 2010].

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Propolis:
Handayaniet al [2018] showed that administrating 5% of propolis is the most effective in increasing the number of osteoblast and, accordingly, the amount of new bone formation in tension side of alveolar bone in relapse after orthodontic treatment.
Altan et al [2013] systemic administration of 100 mg/kg of propolis has shown to promote bone formation and prevent relapse following the orthodontic procedure.

Wheat seeds:
According to Suparwitri et al [2019], wheat seeds hinder osteoclast production by the upregulation OPG and suppression of RANKL, which inversely affects the tooth movement. This suggests that it can be used during the retention phase to prevent relapse.

Root resorption
Root resorption is an undesirable complication during orthodontic treatment that results in permanent loss of root structure. Cementoclasts are the root resorbing cells. Their morphology and functions are similar to osteoclast and mediate cementum resorption via acidization/degradation-associated pathway [MatsumotoY, 1994].

Curcumin:
According to Henrotin et al [2013], curcumin's potential to suppress inflammatory mediators, especially IL1 is responsible for its protective mechanism against root resorption.
Cho et al [2013] showed that curcumin has not only decreased root resorption but also bone resorption by decreasing the number of osteoclasts in the site.
Nigella sativa oil:
Extracts fromnatural products Curcumin and Nigella sativa oil may be systemically used for enhancing bone response around orthodontic implant as the serum calcium levels were lower than the control group [Mustafa al Sultan & Ali R AL Khatib, 2016].

Oral health, gingivitis and biofilm formation
According to Balenseifen JW and Madonia [1970], orthodontic appliance increases plaque retentive sites which make it difficult to maintain oral hygiene. It is associated with an increase in the harmful microbial load leading to gingival inflammation characterized by oedema, erythema, and bleeding upon probing.
Mattingly et al [1984] showed that there was an increase in the *Streptococcus mutans* colonization in individuals with orthodontic appliance.
The use of plant extracts like *Azadirachtaindica, Ocimum sanctum, Murrayakoenigii L., Acacianilotica, Eucalyptus camaldulensis, Hibiscus sabdariffa, Mangiferaindica, Psidiumguajava, Rosa indica, and Aloe barbadensis* Miller were used to kill microorganism that harmful for oral health [Shekar et al., 2015].

Aqueous extract of dandelion (*Taraxacumofficinale*):
Taraxacumofficinale, is flowering plant, commonly known as Dandelion.
According to Han et al [2011], Kenny et al [2015], Diaz et al [2018], Chu Q et al [2006], Dandelion has antimicrobial, anti-inflammatory and antiviral properties.
Smullen et al [2007] recommends gargling with aqueous extract of Dandelion because of its antiplaque and anti *Streptococcusmutans* effects mediated by the polyphenol content of Dandelion.
These studies suggest that Dandelion extract can be incorporated into dental supplies for augmenting their antimicrobial properties.

*Matricaria chamomile L.**:***

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*Matricariachamomilla*L. (MTC), also known as chamomile (family Asteraceae), is a medicinal plant.
According to McKAy et al [2006], the plant contains several phenolic compounds like flavonoids apigenin, quercetin, patuletin, and luteolin which have antioxidant and anti inflammatory properties.

1% MTC mouthwash significantly reduced the plaque and improved periodontal status in individuals with fixed appliance. This is possibly because of its anti-inflammatory and antimicrobial properties [Paula et al 2016].
A studyby Albuquerque et al [2010] observed that Matricaria inhibited synthesis of glucan thereby preventing the adherence of micro-organisms.
Pomegranate juice:
Pomegranate (*PunicagranatumL.*) is native to the Mediterranean region. Pomegranate juice has potential anti-atherogenic effects and is rich in antioxidants.
Its antioxidant activity is three times greater than those of red wine and green tea. Pomegranate juice contains calcium, phosphorus and fluoride which is beneficial to dental and periodontal health. [Haryono& Kimberly, 2012].
Pomegranate mouth rinse was very effective to reduce dental plaque compared to chlorhexidine and distilled water in fixed orthodontic patients Menezes et al [2006].
Vahabi et al [2011] showed that *P. granatum* have shown strong antimicrobial properties against Gram positive and Gram-negative non-oral microorganisms.
According to Alsaimary et al [2009], pomegranate extracts supresses the ability of *S.mutans, S.mitis and S.sanguis*to adhere to the surface of the tooth.
Punicagranatum L. water extract had significant antibacterial properties against oral bacteria and prevented orthodontic wire bacterial biofilm formation[Elahe et al 2014].
Garlic:
Garlic (*Allium sativum*), is an essential component of food, which is known to have antimicrobial effects. Allicin, produced when garlic is crushed is responsible for this property. As a result, it effective against methicillin-resistant *Staphylococcus aureus* (MRSA)and oral pathogens like *P.gingivalis, S.mutans*[Ankri S, Mirelman D 1999, Cutler RR, Wilson P 2004, Bakri IM, Douglas CW 2005], Escherichia, Salmonella, Klebsiella, *Clostridium Proteus*, and Helicobacter species[Uchida et al., 1975 and Cellini et al., 1996].
According to Groppoet al [2002], as streptococci are found sensitive to garlic, mouthwash containing extracts from garlic can be used to reduce oral bacterial load.
Shuford et al. [2005] confirmed that garlic extracts suppressed *Candida albicans* growth in both sessile and planktonic phases.
In contrast, Lee et al [2011] found that garlic extracts upregulates glucosyltransferase expression in *S.mutans*, thereby, enhancing biofilm formation on orthodontic wire in spite of its antibacterial action.
Green tea:
Gong et al [2006] reported that green tea contains catechin and fluoride, which exerts anti-cariogenic property by inhibiting adhesion of the *S.mutans* to enamel and suppressing their enzymes glucosyltransferase and amylase.
According to Tehrani et al [2011], catechin present in green tea is responsible for in plaque reduction by inhibiting glucosyltransferase enzyme.
Rosy et al [2014] found that Green tea mouth wash proved to be equally effective compared to chlorhexidine which is considered as gold standard.

Guava:
It is known that Guava is effective against both Gram-negative and positive bacteria [Ushimaru et al., 2007].

According to Kocak et al [2009] Guava extract suppress plaque bacteria by interfering with their growth, adherence and co-aggregation. It doesn't disrupt the oral homeostasis as well. So it can be used as an adjunct to the periodontal treatment.

Propolis:

Koo et al. [2000] found that propolis mouthwash improved the dental plaque index and reduced the Papillary Bleeding Index significantly. It was found to be more effective in younger ones than elders [Anauate-Neotto et al., 2014].

According to Tanasiewiczet al. [2012], toothpaste and gel that contains 3% Propolis effectively removed plaque and improved the periodontal health.

Dehghani et al [2019] observed an improvement in plaque index, gingival index and community periodontal index in subjects who were given propolis mouthwash and its effect was found to be similar to chlorhexidine.

Santos et al [2005] found that topical application of a propolis extract on oral *Candida albicans* lesions resulted in remission within three weeks and treatment efficacy was comparable to treatment with nystatin, the standard antifungal product used to treat these infections.

A significant reduction in dental plaque and Gram-positive rods and improvement in gingival health was found in children with cleft lip and palate after using propolis toothpaste. This confirms anti-inflammatory, antibacterial and regenerative properties of propolis. [Agnieszka et al., 2013]

Conclusions

- Nutraceuticals are currently receiving recognition due to their potential nutritional, safety and therapeutic effects.
- They are beneficial in optimising the orthodontic tooth movement, reducing the relapse tendencies and also improving the periodontal health.
- Since most of these products are components of regular diet, they are more convenient, economical and can be used for alternative treatment strategies in conjunction with mechanical orthodontic therapy.

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