

# Chlorhexidine: The Gold Standard Antiplaque Agent

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## Abstract

Chlorhexidine is one of the most widely and commonly used antiplaque and antigingivitis agent. The properties and mechanism of action of chlorhexidine must be understood in order to be put into maximum use. Chlorhexidine was used as a broad spectrum antiseptic since the 1950's. Its antibacterial action is due to the disruption of the bacterial cell membrane by the chlorhexidine molecules, increasing the permeability and resulting in cell lysis. It can be either bacteriostatic or bactericidal depending on the dose. It is available in different formulations. However it does have some side effects like permanent staining of teeth and dysgeusia. This article discusses the various clinical applications, properties and adverse effects of chlorhexidine.

## Keywords:

Chlorhexidine, mouthrinse, chemical plaque control

## INTRODUCTION

Chlorhexidine is a gold standard against which other antiplaque and antigingivitis agents are measured. Understanding the properties and limitations of the molecule can ensure that the efficacy of the agent is maximized and the side effects are minimized allowing it to rightly remain the gold standard.

### Dental plaque

Dental plaque clinically is a structured resilient, grayish-yellow substance that tenaciously adheres to the intraoral hard surfaces including removable and fixed restorations<sup>[1]</sup>.

### Plaque control

It is the removal of microbial plaque and the prevention of its accumulation on the tooth and adjacent gingival tissues to prevent calculus formation. Plaque control can be of two types

- Mechanical plaque control
- Chemical plaque control

### Mechanical plaque control

Dental plaque is one of the most important etiological factors in the onset of periodontal disease. Dental plaque mineralizes to form dental calculus. Calculus formation is significantly reduced by proper plaque control. Bacterial plaque can be removed effectively by mechanical means. It is safe and effective. The various methods include:

- Toothbrushes
- Interdental cleaning aids
- Dental floss
- Toothpick
- Interdental brush and swab
- Dentifrices

### Chemical plaque control

#### Terminology

Antimicrobial agents: Chemicals that have a bacteriostatic or bactericidal effect in vitro that alone cannot be extrapolated to a proven efficacy in vivo against plaque.

Plaque reducing/inhibitory agents: Chemicals that have only been shown to reduce the quantity and/or affect quality of plaque which may or may not be sufficient to influence gingivitis and/or caries.

Anti-plaque agents: Chemicals that have an effect on plaque sufficient to benefit gingivitis and/or caries.

Antigingivitis agents: Chemicals which reduce gingival inflammation without necessarily influencing bacterial plaque (includes anti-inflammatory agents).

### Chemical plaque control agents<sup>[2]</sup>

The various chemical plaque control agents are listed in Table 1.

Commercial mouthwashes can be classified into based on their substantivity, range of antibacterial activity against various plaque bacteria, possible anti-inflammatory effect, acceptable taste, ability to promote fresh mouth sensation. They can also be classified as group A, B and C as follows,

- **Group A agents-** antiplaque
- Chlorhexidine, acidified sodium chlorate, salifluor and delmopinol
- **Group B agents-** plaque inhibitory
- cetyl pyridinium chloride,
- essential oil and triclosan rinses
- used as adjuncts to mechanical cleaning
- **Group C agents-** Have a low to moderate activity and are used for cosmetic purposes like breath freshening
- Sanguinarine, oxygenating agents, saturated pyrimidine, hexetidine

Table 1- Chemical plaque control agents

COMPOUNDS	AGENTS
Enzymes	Protease, Lipase, Nuclease, Dextranase, Mutanase, Glucoseoxidase, Amyloglucosidase
Bisbiguanides	Chlorhexidine, Alexidine, Octenidine
Quaternary Ammonium Compounds	Cetyl pyridinium chloride, Benzalconium Chloride
Phenolic compounds	Thymol, 4-Hexylresorcinol, 2-Phenylphenol Eucalyptol, Listerene
Fluorides	Sodium fluoride, Sodium monofluorophosphate Stannous fluoride, Amine fluoride
Metal ions	Copper, Zinc, Tin
Oxygenating agents	Peroxides
Other Antiseptics	Iodine, Povidone iodine, Chloramine-T Sodium hypochlorite, Hexetidine, Triclosan Salifluor, Delmopinol

### Bisbiguanide antiseptics

Bisbiguanide compounds are a group of chemical plaque control agents and comprises of the following agents

- Chlorhexidine
- Alexidine
- Octenidine

From a therapeutic point of view, the most obvious benefit of using mouth rinses is the potential to reduce plaque and gingivitis and particularly in youngsters where mechanical plaque control is not optimal in maintaining gingival health. The ADA council for scientific affairs has proposed a program for acceptance of plaque control agents. These include that the patients be evaluated in placebo control trials of 6 months or longer and demonstrate significantly improved gingival health compared with controls<sup>[3]</sup>.

To date the ADA has accepted 2 agents for treatment of gingivitis which include prescription solution of chlorhexidine digluconate oral rinse and non prescription essential oil rinse.

### CHLORHEXIDINE

#### History

Chlorhexidine was developed by Imperial Chemical Industries in England during 1940's. It was marketed as a general antiseptic in the year 1950. In 1957 chlorhexidine was introduced for human use in Britain as an antiseptic for skin. Later it was widely used in medicine and surgery. Plaque inhibition first investigated by Schroeder in 1969<sup>[4]</sup>. A definitive study for caries inhibition by inhibition of dental plaque was done by Loe and Schiott 1972<sup>[5]</sup>.

#### Forms

Chlorhexidine is available in various forms such as digluconate, acetate and hydrochloride salts which are sparingly soluble in water.

#### Structure

Chlorhexidine is a symmetrical molecule. It has four chlorophenyl rings and two biguanide groups connected by a central hexamethylene bridge. (figure 1)

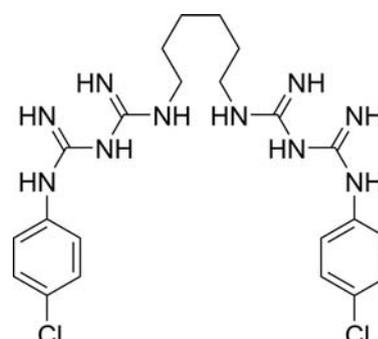


Figure 1- Structure of chlorhexidine

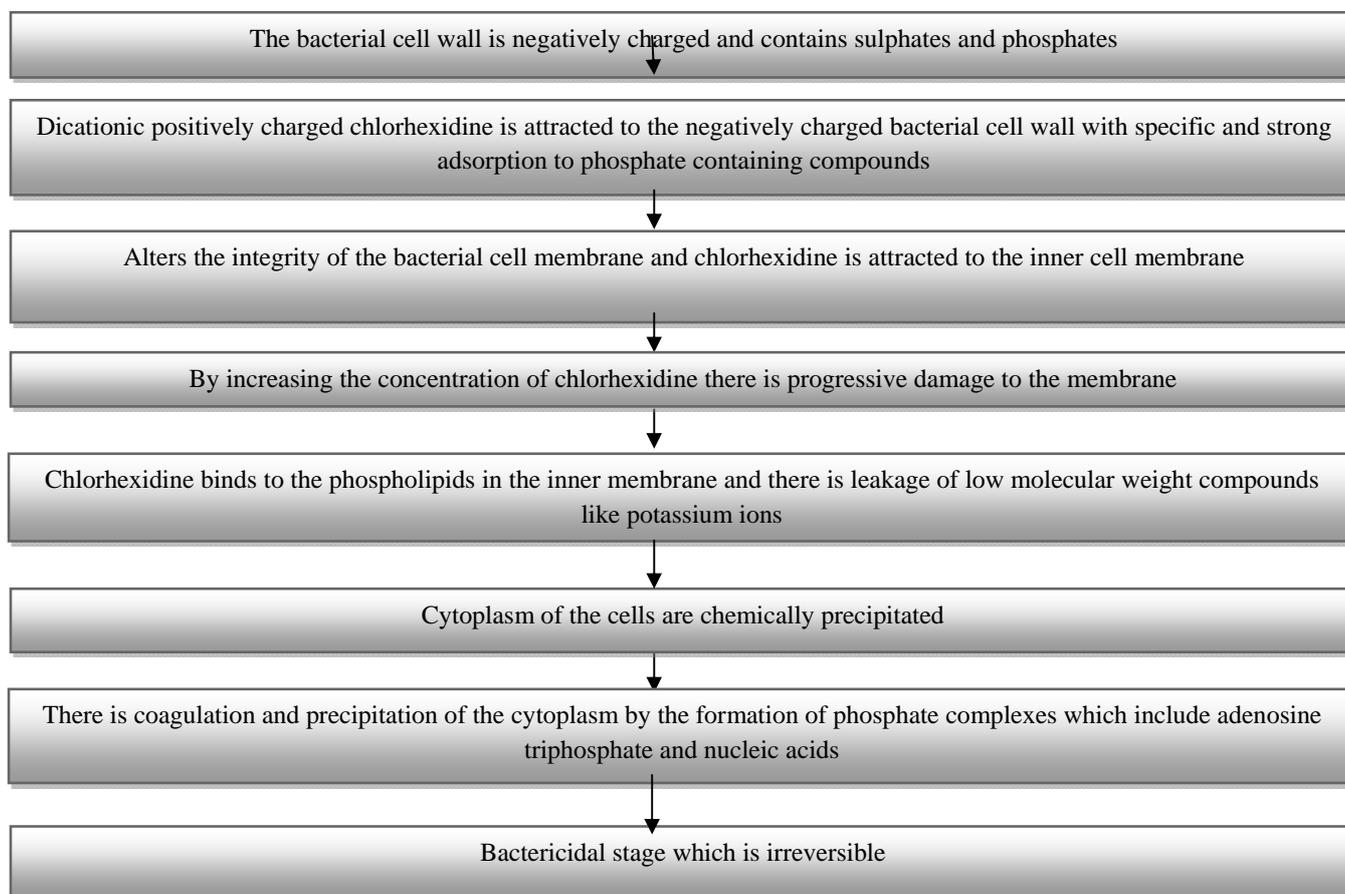
### Characteristics

Chlorhexidine is an antimicrobial agent. It acts on the inner cytoplasmic membrane hence it is a membrane active type of substance. It is dicationic at pH levels above 3.5. It prevents plaque accumulation, hence it is a antiplaque and antigingivitis agent<sup>[6]</sup> and reduces the adherence of Porphyromonas gingivalis to epithelial cells<sup>[7]</sup>. It can be bacteriostatic or bactericidal depending on the dose. It acts against a wide array of bacteria including Gram positive and Gram negative bacteria, dermatophytes and lipolytic viruses. It also acts against fungi, yeasts and some viruses including Hepatitis B virus and Human Immunodeficiency Virus. It acts against Streptococcus mutants making it anticariogenic in nature. Studies have also shown that chlorhexidine has the ability to neutralize pathogenic agents such as Streptococcus aureus, Porphyromans gingivalis and Prevotella intermedia.<sup>[8]</sup> Another most important unique property of chlorhexidine is its substantivity. Substantivity refers to the oral retentiveness. It depends upon various factors such as concentration, pH, temperature and time of contact of the solution with oral structures.<sup>[9]</sup>

### Mechanism of action of chlorhexidine:

The mechanism of action of chlorhexidine is outlined in table 2.

Table 2- Mechanism of action of chlorhexidine



### CHLORHEXIDINE FORMULATIONS

#### Mouthrinses

Chlorhexidine mouth rinses are available in the form of 0.2% and 0.12%. There is equal efficacy for 0.2% and 0.12% rinses when used at appropriate similar doses<sup>[10]</sup>. The time of rinsing is 30 or 60 seconds depending on the adsorption rate of antiseptics to the oral surfaces (50% of chlorhexidine binds to receptors within 15 seconds) but this does vary from individual to individual. The plaque inhibiting effect of a 0.2% chlorhexidine with rinsing times of 15, 30 and 60 seconds following a 72 hour non brushing period showed no difference<sup>[11]</sup>. The ideal regimen is twice daily (morning and night) which will have a substantivity for 12 hours.

The addition of fluoride to chlorhexidine is considered questionable<sup>[12]</sup>. The concentration of 0.06% and sodium fluoride 0.2% and 0.055% of stannous fluoride was considered compatible with fluoride<sup>[13]</sup>. The chlorhexidine monofluorophosphate complexes was considered incompatible without fluorides<sup>[14]</sup>.

#### Gel

The different available concentrations of chlorhexidine gel are 1%, 0.2%, 0.12%. They are delivered in trays and toothbrushes. Chlorhexidine gel, that is applied once a day

has therapeutic effects, like reducing oral malodour and also reduces chlorhexidine staining<sup>[15]</sup>.

#### Toothpastes

0.12% of chlorhexidine with 1 parts per million of fluoride has antiplaque effects similar to chlorhexidine mouthwash. However there were difficulties in incorporating chlorhexidine into gels and toothpastes. 1% chlorhexidine used as slurries and rinsed twice per day for one minute causes significant reduction in the plaque and gingival scores but also causes stains. Chlorhexidine in dentifrices gained little attention due to its possible interaction with anionic ingredients contained in toothpaste and competition for oral retention sites<sup>[16]</sup>.

#### Sprays

0.1% and 0.2% sprays have similar plaque inhibition properties of 0.2% mouthwash. It is well received by physically and mentally handicapped patients<sup>[17]</sup>.

#### Varnishes

Chlorhexidine varnishes are used for prophylaxis against root caries<sup>[18]</sup>.

#### Sugar free chewing gum

Chlorhexidine remains unbound in this form. It contains 20mg of chlorhexidine diacetate. It is advised to chew 2

pieces twice per day for 10 minutes. This procedure is said to cause less stains. It is a good method of using chlorhexidine for a long period of time <sup>[19]</sup>.

#### CLINICAL APPLICATIONS OF CHLORHEXIDINE

It is used as an adjunct to oral hygiene and professional prophylaxis. It is used post oral surgery in periodontal surgery or root planing. Studies have shown that the daily use of mouthrinse combined with toothbrushing resulted in reduced interproximal plaque when compared with toothbrushing and daily flossing <sup>[20]</sup>. Chlorhexidine is of importance in the maintenance protocol in immediate function implants as there is a correlation between plaque and bleeding index revealed a good result for 0.2% chlorhexidine gel for daily implant self care at 6 months <sup>[21]</sup>. It is used in patients with intermaxillary fixation and in patients who are under high risk of caries. For those patients who are physically and mentally handicapped chlorhexidine sprays can be used <sup>[22]</sup>. It is used in medically compromised patients who are predisposed to oral candidiasis. Chlorhexidine is used to limit the bacteremia and operatory contamination by oral bacteria and as an adjunct to antibiotic prophylaxis. Other uses of chlorhexidine include sub gingival irrigation, management of denture stomatitis, hypersensitivity and for oral malodour. Full mouth disinfection has been introduced with scaling and root planing and the application of chlorhexidine into periodontal pockets with daily use of chlorhexidine rinses at home for 2 months <sup>[23]</sup>. Chlorhexidine formulations have well proven short to medium term application as adjuncts and even replacements for mechanical cleaning but it is still controversial <sup>[24]</sup>. Wound healing is enhanced when chlorhexidine rinses are used before extractions and after scaling and root planing or periodontal surgery <sup>[25]</sup>. Chlorhexidine is shown to induce changes to human gingival fibroblast collagen production and non collagen protein production <sup>[26]</sup>. There is 65% reduction in collagen production and a 75% reduction in non collagen protein production.

Halita is the name of a mouth rinse containing 0.05% of chlorhexidine, 0.05% cetyl pyridinium chloride and 0.14% of zinc lactate. It is used in the management of halitosis <sup>[27, 28]</sup>. Zinc is added as it has the ability to convert volatile sulfur compounds and it also acts synergistically with chlorhexidine. Other clinical benefits include its use as a root canal irrigant <sup>[29]</sup> and in atraumatic restorative treatment where chlorhexidine containing glass ionomer cement <sup>[30]</sup>. Chlorhexidine is also used for surgical skin preparation for the patient and the surgeon. Chlorhexidine is used as a local drug delivery system in the form of a bio-degradable chip to be used in the subgingival environment <sup>[31]</sup>. There is controlled delivery of chlorhexidine to the periodontal pocket. A slow sub-gingival release of 2.5mg of chlorhexidine is found to have an average drug concentration greater than 125 microgram per milliliter for 7 to 10 days. The concentration of the drug remains above the minimum inhibitory concentration for more than 99% of the

subgingival micro-organisms from the periodontal pockets. The results of several clinical trials have shown that the use of the chlorhexidine chip in conjunction with scaling and root planing is effective in reducing periodontitis, clinical attachment loss and bleeding on probing over a period of 6 to 9 months. The use of the controlled release of chlorhexidine delivery system during maintenance therapy allows greater improvement in clinical signs of periodontitis. In subgingival exudates, the serum proteins may effectively compete with the bacteria for the chlorhexidine, thus reducing the availability of the drug. This might account for the occasional lack of clinical effectiveness when the agent is administered subgingivally <sup>[32]</sup>.

#### Toxicology and side effects <sup>[33]</sup>

The side effects of chlorhexidine include brown discolouration of the teeth, restorative materials and dorsum of tongue. There is taste perturbation. There can be oral mucosal erosion which is an idiosyncratic reaction and is dose dependent. The bitter taste is difficult to mask.

#### Chlorhexidine staining

There is degradation of the chlorhexidine molecule to release parachloroaniline. Non enzymatic browning reactions take place called catalysis of Maillard. Protein denaturation and metal sulfide formation occurs and there is precipitation of anionic dietary chromogens <sup>[34]</sup>.

#### Metabolism of chlorhexidine

The chlorhexidine that is swallowed undergoes minimal metabolic changes. It has a half life of 4 days and it is excreted in faeces.

#### Safety of chlorhexidine

Chlorhexidine is poorly absorbed in the gut and displays very low toxicity. It does not cause any teratogenic alterations. There is no evidence of formation of carcinogenic substances.

#### Precautions

After the use of chlorhexidine mouthwash the intake of tea, coffee and red wine must be avoided. The usage is restricted in cases of anterior composite restorations and glass ionomer restorations. There should be a 30 minute lapse between the usage of a dentifrice and chlorhexidine mouth wash <sup>[35]</sup>. It is so advised because the toothpastes contain detergents which are predominantly anionic agents. Chlorhexidine molecule being dicationic tends to bind with the anionic agents leading to a reduction in the substantivity of chlorhexidine mouthrinse.

#### Comparative studies

Increasing the rinsing frequency of cetyl pyridinium chloride to four times a day has been suggested to produce efficacy equivalent to that of chlorhexidine <sup>[8]</sup>. Listerine has a moderate plaque inhibitory effect poor oral retention and some antigingivitis effects <sup>[36]</sup>. Substantivity of hexitidine is one to three hours and has some plaque inhibitory effects <sup>[37]</sup>. The effect of three commercial mouth rinses on cultured human gingival fibroblast, an in vitro study revealed that chlorhexidine, listerine and povidone iodine are capable of inducing a dose dependant reduction in cellular proliferation of fibroblasts <sup>[38]</sup>.

### CONCLUSIONS

Chronic periodontitis is always preceded by chronic gingivitis; chemicals that inhibit plaque may be expected to be of value in both the prevention and management of periodontal disease in some individuals. Thus, the use of a chemical plaque-inhibitory mouthwash as an adjunct to tooth brushing may have a major effect on improving the oral health of the individual. Chlorhexidine is one chemical plaque control agent which has various clinical applications in dentistry especially in Periodontics . Chlorhexidine in its various formulations has come to stay and it is appropriate to call it the gold standard chemical plaque control agent.

### REFERENCES:

- Beck JD, Koch GG, Rosier RG, Tudor GE; Prevalence and risk indicators for periodontal attachment loss in population of older community-dwelling blacks and whites, *J Periodontol* 1971;61:521
- Addy et al Chlorhexidine digluconate—an agent for chemical plaque control and prevention of gingival inflammation: *J Periodontol* 1986; 21:16 74-89.
- Rethman MP, Beltrán-Aguilar ED, Billings RJ, Hujoel PP, Katz BP, Milgrom P, Sohn W, Stamm JW, Watson G, Wolff M, Wright JT, Zero D, Aravamudan K, Frantsve-Hawley J, Meyer DM; American Dental Association Council on Scientific Affairs Expert Panel on Nonfluoride Caries-Preventive Agents. Nonfluoride caries-preventive agents: executive summary of evidence-based clinical recommendations. *J Am Dent Assoc.* 2011; 142(9):1065-1071.
- Schroeder H E. Formation and Inhibition of Dental Calculus. *Hans Huber, Berlin* 1969; 145-172.
- Löe H, Von der Fehr FR, Schiött CR. Inhibition of experimental caries by plaque prevention. The effect of chlorhexidine mouthrinses *Scand J Dent Res.* 1972;80(1):1-9
- Corbet EF, Tam JO, Zee KY, Wong MC, Lo EC, Mombelli AW. Therapeutic effects of supervised Chlorhexidine mouthrinses on untreated gingivitis. *Oral Dis.* 1997; 3:9-18.
- Grenier D. Effect of chlorhexidine on the adherence properties of *Porphyromonas gingivalis*, *J Clin Periodontol.* 1996 Feb; 23(2):140-2.
- Vianna ME, Gomes BP, Berber VB, Zaia AA, Ferraz CC, de Souza-Filho FJ. In vitro evaluation of the antimicrobial activity of chlorhexidine and sodium hypochlorite. *Oral Surg, Oral Med, Oral Pathol, Oral Radiol Endod.* Jan 97(1), 79-84.
- Bonesvoll P, Gjermo P. A comparison between chlorhexidine and some quaternary ammonium compounds with regard to retention, salivary concentration and plaque inhibiting effect in human mouth after mouth rinses. *Arch Oral Biol* 1978, 23; 289-294.
- Hoffmann, T., Bruhn, G., Richter, S., Netuschil, L. & Brex, M. clinical controlled study on plaque and gingivitis reduction under long term use of low dose chlorhexidine solutions in a population exhibiting good oral hygiene. *Clin Oral Invest* 2001, 5: 89-95.
- Van de weijden GA, Timmerman MF, Novtny GA, Rosema N, Verkerk A, Three different rinsing times and inhibition of plaque accumulation with chlorhexidine, *J Clin Periodontol* 2005, 32(1):89-92.
- Regolati, B.; Schmid, R.; and Muhlemann, H.R.: Combination of Chlorhexidine and Fluoride in Caries Prevention. An Animal Experiment, *Helv Odont Acta* 1974,18: 12-16.
- Lorenz K, Bruhn G, Heumann C, Netuschil L, Brex M, Hoffmann; Effect of two new chlorhexidine mouthrinses on the development of dental plaque, gingivitis, and discoloration. A randomized, investigator-blind, placebo-controlled, 3-week experimental gingivitis study, *J Clin Periodontol*, Aug 2006; 33(8):561-7
- Barkvoll, Marinho, Home use oral hygiene products: mouthrinses, *J Clin Periodontol*, Oct 2008,48 (1):42-53,
- Addy M, Moran JM, Clinical indications for the use of chemical adjuncts to plaque control, *Periodontol* 2000, 1997 Oct;15:52-54.
- Dolles, Gjermo, The effects of a chlorhexidine toothpaste on the development of plaque, gingivitis and tooth staining, *J Clin Periodontol*, January 1993, 20,59-62.
- Kalaga A, Addy M, Hunter B: The use of a 0.2% chlorhexidine spray as an adjunct to oral hygiene and gingival health in physically and mentally handicapped adults. *J Periodontol* 1989, 60; 381-385.
- Matthijs S, Adriaens P A, Chlorhexidine varnishes: a review, *J Periodontol*, 2002, 29:1-8.
- Ainamo J, Etemadzadeh H, Prevention of plaque growth with chewing gum containing chlorhexidine acetate, *J Clin Periodontol* 1987,14(9):524-7
- Zimmer, S., Kolbe, C., Kaiser, G., Krage, T., Ommerborn, M. & Barthel, C. Clinical efficiency of flossing versus use of antimicrobial rinses. *J Periodontol* 2006 Aug; 77(8):1380-5.
- De Araujo Nobre M, Cintra N, Malo P, Peri implant maintainance of immediate function implants:a pilot study comparing hyaluronic acid and chlorhexidine, *Int J Dent Hyg.* 2007 May;5(2):87-94.
- Roncati M, Polizzi E, Cingano L, Lucchese A, An oral health aid for disabled patients, *Dent Cadmos* 2013; 81(7):447-452
- Quirynen M, Mongradi, van steenberghe D, The effect of a one stage full mouth disinfection on oral malodour and microbial colonization of tongue in periodontitis, *J Periodontol* 1998,69(3): 374-82.
- Greenstein G, Berman C, Jaffin R, Chlorhexidine. An adjunct to periodontal therapy. *J Periodontol* 1986; 57 (6): 370-6.
- Sridhar V, Wali GG, Shyla HN, Evaluation of the Perioperative Use of 0.2% Chlorhexidine Gluconate for the Prevention of Alveolar Osteitis After the Extraction of Impacted Mandibular Third Molars: A Clinical Study. *J Maxillofac Oral Surg.* 2011 Jun;10(2):101-11
- Angelo J. Mariotti, Chlorhexidine-Induced Changes to Human Gingival Fibroblast Collagen and Non-Collagen Protein Production, *J Periodontol*, Dec 1999; 70(12):1443-1448
- Winkel EG, Roldán S, Van Winkelhoff AJ, Herrera D, Sanz M, Clinical effects of a new mouthrinse containing chlorhexidine, cetylpyridinium chloride and zinc-lactate on oral halitosis. A dual-center, double-blind placebo-controlled study, *J Clin Periodontol.* 2003 Apr;30(4):300-6
- van Steenberghe D, Avontroodt P, Peeters W, Pauwels M, Coucke W, Lijnen A, Quirynen M, Effect of different mouthrinses on morning breath, *J Periodontol*, 2001; 72(9):1183-1191.
- Ferguson JW, Hatton JF, Gillespie MJ, Effectiveness of intracanal irrigants and medications against the yeast *Candida albicans*. *J Endod* 2002; 28(2): 68-71.
- Takahashi Y, Turkun M, Ertugul, Ates M, Brugger S, Long term antibacterial effects and physical properties of chlorhexidine containing glass ionomer cement, *J Esthet Restor Dent.* 2008, 20(11):29-45.
- Soskolne WA, Heasma PA, Stabholz A, Smart GJ, Palmer M, Flashner M, Newman HN, Sustained local drug delivery of chlorhexidine in the treatment of periodontitis. *J Periodontol.* 1997 Jan;68(1):32-8
- Jan Lindhe. Clinical Periodontology and Implant Dentistry, Fifth edition. Blackwell Munksgard Publications, 2007.
- Flotra L, Gjermo P, Rolla G, Waerhaug J: Side effects of chlorhexidine mouthwashes. *Scand J Dent Res*, 1971; 79: 119-125.
- Erikson H M, Nordbo H, Kantanen H, Ellingsen J E: Chemical plaque control and extrinsic tooth discoloration. A review of possible mechanisms. *J Clin Periodontol*, 1985; 12: 345-350.
- Kolahi J, Soolari A, Rinsing with chlorhexidine gluconate solution after brushing and flossing teeth: a systematic review of effectiveness. *Quintessence Int.* 2006 Sep;37(8):605-12
- Gordon J M, Lamster I B, Sieger M C. Efficacy of Listerine antiseptic in inhibiting the development of plaque and gingivitis. *J Clin Periodontol* 1985; 12: 697-704.
- Harper P R, Milsom S, Wade W, Addy M, Moran J, Newcombe R G. An approach to efficacy screening of mouthrinses: studies on a group of French products (II) Inhibition of salivary bacteria and plaque in vivo. *J Clin Periodontol* 1995; 22: 723-727
- Flemingson , Emmadi P, Ambalavanan N, Ramakrishnan T, Vijayalakshmi R, Effect of three commercial mouth rinses on cultured human gingival fibroblast: an in vitro study, *Indian J Dent Res* 2008 Jan-Mar; 19(1) :29-35.