Survey of the public's knowledge and opinions: the therapeutic effects of current orally administered drugs for periodontal diseases

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I. Introduction

Periodontal disease is an inflammatory state with destruction of gingival connective tissue, alveolar bone and periodontal ligament. The pathogenesis of periodontal disease involves local factors, environmental factors and genetic factors.

The mechanical removal of dental plaque and calculus from tooth surfaces is considered the standard treatment for chronic periodontitis. It is sobering to reflect that, despite spectacular advances in medical sciences, treatment of periodontal diseases has changed very little, in principle, over the years. A large evidence base now exists to demonstrate the efficacy of non-surgical periodontal therapy¹, and despite debate relating to the merits of manual versus ultra-

sonic instrumentation or the degree of root surface smoothness/hardness to be achieved, scaling and root planing (SRP) remains the 'gold standard' treatment for periodontitis against which other treatments are compared.

Periodontal treatment through the ages has focussed on the reduction of bacterial infection by mechanical removal of infectious agents (i.e. SRP). However, recent research into the pathogenesis of periodontal diseases has led to an important paradigm shift in the way we view periodontal disease progression.

That is to say, it is now recognised that the major component of the soft and hard tissue destruction seen in periodontitis occurs as a result of activation of the host's immune-inflammatory defence mechanisms in response to the presence of bacterial pla-

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que². The precise nature of the host inflammatory response is still an area of intense research, but it is clear that host-derived pro-inflammatory mediators and cyto-kines, together with proteolytic enzymes such as matrix metalloproteinases (MMPs), play a significant role in the changes in connective tissue and bone metabolism that lead to the breakdown of periodontal ligament (PDL) and alveolar bone resorption. For example, studies have shown that the predominant MMPs found in inflamed human gingiva and gingival crevicular fluid (GCF) derive from human cells rather than bacteria³.

Scaling and root planing (SRP) are effective treatment modalities in slowing or arresting periodontal diseases⁴. However, SRP does not directly target the host response component of periodontal disease. Therefore, novel therapeutic approaches have changed the trend towards pharmacologic modulation of exaggerated host response in addition to microbial elimination. Research on potential host-modulatory benefits of various pharmacological agents such as tetracyclines (TCs), non-steroidal antiinflammatory drugs and bisphosphonates gave promising results⁵⁻¹⁰.

Extensive research on TCs and TC analogues has shown that this antibiotic family has non-antimicrobial properties that can modulate host-response by various mechanisms^{6,11-13}. Current evidence suggests that TCs are able to inhibit collagenolytic activity through the inhibition of MMPs^{5, 14-16}. Suppression of MMP-mediated events with TCs results in decreased connective tissue breakdown and bone resorption^{15,17}. It was shown that TCs sustained their MMP inhibitory effect even at doses below those needed for antimicrobial efficacy¹⁵. In this regard, specially formulated subantimicrobial dose doxycycline (SDD) was approved by Food and Drug Administration as an adjunct to non-surgical periodontal therapy¹⁸.

The importance of the host inflammatory response in periodontal pathogenesis presents the opportunity for exploiting new treatment strategies for periodontitis by means of host response modulation. Host modulatory therapy (HMT) can be combined with traditional periodontal therapies that reduce the bacterial burden (e.g. SRP) and also risk factor modification (e.g. smoking cessation therapy) to constitute a compre-

Table 1. Age and sex distributions of investigated persons

Sex	Male	Female	Subtotal
20 - 30	8	12	20
31 - 40	14	23	37
41 - 50	5	13	18
51 - 60	5	8	13
60+	8	4	12

hensive treatment strategy for periodontitis¹⁹.

To date, there is only one therapeutic drug, subantimicrobial dose doxycycline. However there is many drugs for periodontal diseases in the market, and many patients visiting dental clinics had experience of arbitrarily purchasing drugs for periodontal diseases without prescription. According to drug manufacturers, the market size of drugs for periodontal diseases was about 2003. In 40-billion wons in addition. 'Insadol' was administered to National Health Institute Corporation in 2004, but there is few cases of prescribing the drug because of dentists' ignorance of the fact.

The purpose of this study was to determine the level of knowledge and opinions on drugs for periodontal diseases through questionnaire and to search and review current orally administered drugs for periodontal diseases in Korea.

II. Materials and methods

The public's knowledge and opinions on periodontal drugs

A 10-item questionnaire was developed to determine the public's knowledge and opinions about the drugs for periodontal diseases (Appendix). The questionnaire was pretested with 10 dentists. After revisions, personal interview was conducted to the people who visited at department of industry medicine, Sacred Heart hospital of Hallym university for their periodic inspection.

The number of people who accepted the interview was 100. The 100 persons composed of 40 males and 60 females and their age ranged 20 to 75 years (Table 1).

Search for current orally administered drugs for periodontal diseases in Korea

For the search of drugs for periodontal disease administered to Ministry of Health and Welfare, the KIMS OnLine homepage (http://www.kimsonline.co.kr) was searched. In total drug search page, the additional condition of '231. dental-oral drugs' at classification of Ministry of Health and Welfare was used. From the search results, orally administered drugs for periodontal diseases were selected.

For related articles on the drugs, the Pubmed homepage from National Library of Medicine of US was searched. Search keywords were combinations of each constituent plus gingivitis, periodontitis and periodontal disease. In the search, written language were limited English only except Zea mays extracts. Zea mays extracts had no limitation of language in search of articles because it had developed in Europe and it had relatively few articles written in English.

III. Results

The public's knowledge and opinions on periodontal drugs

On question 1 about the level of knowledge on periodontal disease, 85 persons reported 'yes' and 15 reported 'no'. From

this, we can think many people have interest in their oral health, especially periodontal health (Table 2).

On question 2 about self-esteem of their periodontal health, 28 reported 'yes' and 72 reported 'no'. On question 3 about the experience of drug medication, 14 reported 'yes' and 86 reported 'no'. This results mean that self-esteem of their periodontal health was low but they did not take any action for periodontal health since the first step to im-

prove health in korea is purchasing any medication at pharmacy. The 14 persons who had experience of drug medication thought that their periodontal health was not good (Table 2).

The 14 persons who had experience of drug medication reported on question 4, 5, and 6, which means causes of drug medication, reasons of drug medication and influencing factors on drug choice, respectively.

Table 2. The level of knowledge on periodontal disease, self-esteem on periodontal status, experience of drug medication and intention of drug medication in the future

Question	Answer	Yes	No
Level of knowledge on periodontal disease		85	15
Self-esteem on their periodontal health		28	72
Experience of drug medication		14	86
Intention of drug medication in the future		63	37

Table 3. Causes of drug medication among 14 patients with experience of drug medication (results of multiple answering)

Causes	No. of answers	%
Toothache	2	14.3
Tooth mobility	2	14.3
Tooth elongation with gingival recession	1	7.1
Gingival bleeding	3	21.4
Tenderness of tooth	1	7.1
Cold sensitivity	7	50.0
Decayed tooth	5	35.7
Suppuration of gingiva	1	7.1
Oral malodor	5	35.7
Discomfort of gingiva	1	7.1
Itching sensation of gingiva	1	7.1
Etc.	0	0.0

Table 4. Reasons of drug medication among 14 patients with experience of drug medication

Reasons	No. of answers	%
No need of treatment	6	42.9
Treatment effect of medication	4	28.6
No time	1	7.1
Financial problem	0	0.0
Etc.	3	21.4

Table 5. Factors influencing on the choice of d

rug among 14 patients with experience of drug medication

Factors	No. of answers	%
Previous knowledge	0	0.0
Experience of family members / acquaintances	4	28.6
Pharmacists	9	64.3
Medical doctors	0	0.0
Dentists	0	0.0
Etc.	1	7.1

Table 6. Individuals' sources of information on drugs for periodontal diseases

Route	No. of answers	%
Newspaper / Magazine	9	9.0
Internet	0	0.0
Television	52	52.0
Family members / acquaintances	17	17.0
Lecture / meeting	0	0.0
Pharmacy	10	10.0
Dental clinic	12	12.0
Medical doctor	0	0.0
Etc.	0	0.0

Table 7. Individuals' opinion about effect of periodontal drugs

Effect	No. of answers	%
No effect	4	4.0
Preventive but not therapeutic	20	20.0
Somewhat therapeutic	35	35.0
As effective as dental treatment	0	0.0
More effective than dental treatment	0	0.0
No answer	41	41.0

Table 8. Methods of drug choice

Choice of drug by	No. of answers	%
Self-decision	14	14.0
Family members / acquaintances	6	6.0
Pharmacist	20	20.0
Medical doctor	24	24.0
Dentist	35	35.0
Etc.	1	1.0

Table 9. Current orally administered drugs for periodontal diseases in Korea

Constituents	No. of drugs	Px./OTC	Insurance
Ascorbic acid Lysozyme chloride Carbazochrome Tocopherol	38	0 Px. 38 OTC	0
Zea mays extracts (beta-sitosterol)	25	1 Px. 24 OTC	19
Subantimicrobial dose doxycycline	5	5 Px. 0 OTC	5
Avocado-soya unsaponifiables	1	0 Px. 1 OTC	1
Oriental medicine	1	0 Px. 1 OTC	0
Total	70	6 Px. 64 OTC	25

The causes of drug medication were cold sensitivity (50%), decayed tooth (35.7%), oral malodor (35.7%), gingival bleeding (21.4%), etc. (Table 3). 6 persons (42.9%) thought that they didn't need any treatment, and 4 persons (28.6%) thought that the drugs would do for their symptoms (Table 4).

On drug selection most people were influenced by pharmacist (64.3%) and family members/acquaintances (28.6%) (Table 5).

Majority of the people acquired the knowledge of drugs for periodontal diseases through advertisement (61%) from television (52%) and newspaper (9%). Only 12% of the people reported that they had got knowledge of drugs for periodontal diseases from dental clinic (Table 6).

On the effect of periodontal drugs, 35% of the people thought 'somewhat therapeutic' and 20% thought 'preventive but not therapeutic'. However, 41% of the people didn't reply to this question (Table 7).

63% of the people had intention of drug medication for their periodontal health (Table 2). And about half (59%) of the people reported they would ask to medical doctors or dentists for choice of drugs. 20% would ask to pharmacist and 14% would choice drugs by themselves (Table 8).

Search for current orally administered drugs for periodontal diseases in Korea 210 drugs were searched from KIMS OnLine homepage. Currently unavailable drugs were also included in 210 drugs, so currently available ones were 132 drugs. There were 70 drugs for oral administration for periodontal disease and the other drugs were

gargling agents, dentifrices, troche, paste and eundan. 70 drugs included 38 ascorbic acid and lysozyme chloride containing drugs, 25 Zea mays L. extract drugs, 5 subantimicrobial dose doxycyclines, 1 avocado-soya unsaponifiables, and one drugs from oriental medicine.

Prescription drugs were 6 (5 SDDs and 1 Zea mays extract drugs). 25 drugs (1 avocado-soya unsaponifiables, 5 SDDs, and 19 Zea mays extract drugs) were administered to National Health Institute Corporation (Table 9).

From the Pubmed homepage, 47 articles related with ascorbic acid and lysozyme containing drugs, 6 for Zea mays extract drugs, 26 for SDDs, and 2 for avocado-soya unsaponifiables were searched (Table 10).

IV. Discussion

The investigation of this study was performed to clarify the public's level of recognition about drugs for periodontal diseases. The subjects visited the hospital for their periodic inspection. So we can think that this population have interest on their health at least.

From table 2, the level of knowledge on periodontal diseases was high and self-esteem of one's oral health status was generally not good. However, only 14 persons of 72 persons (7.1%) who thought their oral health status not good had experience of taking medicine for periodontal diseases. This can be thought as a neglect. But 63% of people had intentions on medication for preventive/controlling measure of their pe-

riodontal health, which reflects the interest of people on the health.

From table 3, many persons medicated periodontal drugs for cold sensitivity, dental caries and oral malodor. But these symptoms are not in the indications of the drugs. So there should be more intense action of public relations on these drugs.

From table 4, many persons thought that medication could be an appropriate treatment method for their periodontal problem. However, these drugs can be used as an adjuvant treatment with conventional mechanical therapies.

From table 5, persons who have the most power in selecting drugs are pharmacist and

family members/ acquaintances. Furthermore, most people got information from advertisement of drugs from table 6. From these results, there should be an action which restores the role of dentists to public.

From table 7, about half of examinee did not have any idea on the treatment effect of drugs and the other half had weak belief.

From table 8, only 35% of people will ask dentists for their medication. On the contrary, 44% of people will consult pharmacists or medical doctors for their periodontal drugs. This means the discrepancy between public's recognition and those of dentists' on role of dentists is large.

From the overall results of the survey,

Table 10. Searched related articles from PubMed homepage

Qtitt		Searched articles	
Constituent	Experimental study	Clinical study	The others
Ascorbic acid		14	
Ascorbic acid	3	4	7
Lyzaryma ablavida		23	
Lysozyme chloride	6	0	17
Carbazochrome		0	
Carbazochrome	0	0	0
Tacanhaval		10	
Tocopherol	5	0	5
Zoo maya artwasta		6	
Zea mays extracts	3	2	1
Subantimicrobial dose		26	
doxycycline	0	21	5
Avocado-soya		2	
unsaponifiables	2	0	0
O-it-1 ii-i		0	
Oriental medicine	0	0	0

dentists should make an effort to restore their role on public.

From table 9, the number of products is 70 but they can be categorized to 5 groups – ascorbic acid based formula, Zea mays extracts, subantimicrobial dose doxycyclines, Avocado-soya unsaponifiables and oriental medicine based formula.

Ascorbic acid based formula contains ascorbic acid, lysozyme chloride, carbazochrome and tocopherol. Ascorbic acid is well-known for vitamin C and associated with collagen synthesis, which play an important role in the formation of extracellular matrix and blood vessel wall. If deficient, scurvy may occur. According to recent study, vitamin C deficiency is weakly associated with periodontal disease in elderly population²⁰. Lysozyme is muramidase and has antimicrobial effect against gram-positive microorganisms. Muramidase converts insoluble polysaccharides of gram-positive bacterial cell wall into soluble mucopolysaccharides²¹. Carbazochrome is an oxidative product of adrenalin and it is used as anticoagulant²². Tocopherol is well-known as vitamin E. It acts as an antioxidant and prevents superoxidation of unsaturated fatty acid in cell membrane.

Searched articles related with ascorbic acid based formula were 47 - 14 for ascorbic acid, 23 for lysozyme and 10 for tocopherol. Clinical studies of ascorbic acid are about investigations of association between vitamin C level in serum and clinical/histological periodontal status. However, there is no evidence about the association between vitamin C concentration in serum and in

GCF and saliva. So these clinical studies are interpreted with caution. In experimental studies, ascorbic acid has 2 roles – one with collagen synthesis and the other with antioxidant action. Experimental studies of lysozyme are about its cleavage action against bacterial cell wall and biological marker in GCF at the state of periodontal disease. Experimental studies of tocopherol are animal studies and histological studies about collagen degradation.

On ascorbic acid based formula, there is no study with the whole formula.

Zea mays extract is beta-sitosterol but its exact action mechanism on periodontal health or host response modification is unclear. There are 3 clinical and 3 experimental studies on the association between administration of Zea mays extracts and periodontal condition/treatment outcome. However, one study doubted its clinical effects²³.

Doxycycline possesses the ability (an ability shared by all members of the tetracycline family) to downregulate MMP activity. Doxycycline downregulates collagenolytic activity by several synergistic mechanisms. For example, doxycycline inhibits active MMPs directly by a mechanism that is dependent on its calcium- and zinc-binding properties¹². In addition, tetracyclines are known to scavenge for, and inhibit, the production of PMN-derived reactive oxygen meincluding hypochlorous tabolites. (HOCl)²⁴. This ability may further contribto the nonantimicrobial, flammatory properties of doxycycline by inhibiting HOCl from activating latent

pro-MMPs^{25,26}. Furthermore, HOCl oxidizes and inactivates host-derived proteinase inhibitors a1-PI and a2-macroglobulin (inhibitors of MMPs)²⁷. Thus, the ability of tetracyclines to directly inhibit MMP activity and also scavenge for, and inhibit, reactive oxygen metabolites such as HOCl. represents an important pathway for modulation of the destructive connective tissue events that occur in periodontitis. Additional mechanisms of MMP inhibition by tetracyclines were also identified. For example, tetracyclines inhibit osteoblast- and osteoclastderived MMPs, thereby inhibiting bone resorption²⁸. Doxycycline can inhibit production of epithelial cell-derived MMPs by inhibiting intracellular expression or synthesis of these enzymes^{29,30}. Doxycycline also contributes to decreased connective tissue breakdown by downregulating the expression of pro-inflammatory mediators and cytokines (including IL-1 and TNF-a)³¹, and increasing collagen production, osteoblast activity and bone formation¹². Tetracyclines have also been shown to normalize collagen formation in diabetic rats with previously suppressed collagen synthesis^{32,33}.

Searched articles related with SDD was 26 - 21 clinical studies and 5 reviews. SDD was used as an adjuvant after mechanical periodontal therapy in all 21 studies and showed satisfactory results. Experimental studies about SDD was not found because experimental studies on tetracyclines had been performed previously.

Avocado-soya unsaponifiables acts as an inhibitor of IL-1, which is a key cytokine in the destruction of cartilage matrix and joint,

thus delays progression of osteoarthritis. And it also promotes synthesis of TGF-β, which plays a role in activation, proliferation and cartilage matrix synthesis of chondrocytes^{34,35}. Although Avocado-soya unsaponifiables has been developed primarily for the treatment of osteoarthritis, it can be used in dental field because IL-1 and TGF-β also plays an important role in pathogenesis and progression of periodontal disease. However, there is no study about the feasibility of using this medicine to periodontal patients. So studies on this drug should be performed in the future.

V. Conclusions

This study aimed to determine the public's level of knowledge and opinions on drugs for periodontal diseases through questionnaire to the public and to search and review current orally administered drugs for periodontal diseases in Korea. The level of the public's knowledge and opinions were surveyed through interview with questionnaire and drugs for periodontal diseases were searched from a web site of drug index. The results are as follows:

- The level of the public's knowledge on drugs for periodontal diseases is relatively low. Dentists had minor influence on the public's knowledge and opinions.
- There were 70 products of orally administered drugs for periodontal diseases in Korea. These drugs can be categorized into 5 groups 3 major

- groups (ascorbic acid based formula, Zea mays extract, SDD) and 2 minor groups (Avocado-soya unsaponifiables and oriental medicine based formula).
- Zea mays extract and SDD were supported by clinical studies, to the contrary ascorbic acid based formula wasn't.
- 4. On the basis of scientific evidences, SDD and Zea mays extract can be used as an adjuvant to the periodontal mechanical therapy.

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Appendix. A 10-item questionnaire used in this study.

1. Have you	ever he	eard the	e word, periodo	ntal disease?			
1) Yes	()					
2) No	()					
2. Do you th	nink that	t you ha	ave healthy gur	m?			
1) Yes	()					
2) No	()					
3. Do you h	ave any	experie	ence of purchas	sing OTC drugs for	periodontal dis	ease	s at pharmacy?
1) Yes	()					
2) No	()					
4. What is t	he caus	se of pu	urchasing the d	rugs? (You may ha	ive two or more	ans	wers)
1) Toothach					()
2) Tooth me					()
		due to	gingival recessio	on	()
4) Gingival					()
5) Tenderne					()
6) Cold sen	sitivity				()
7) Decayed	tooth				()
8) Suppurat	tion of g	ingiva			()
9) Oral mal	.odor				()
10) Discomf	ort of gi	ingiva			()
11) Itching	sensatio	n of ging	giva		()
12) Etc.					()
5. Why did y	ou pura	chase th	ne drugs if any	?			
1) I though	t that tr	eatment	was not necessa	ary	()
2) I though	t that th	ne drugs	would do		()
3) I had no	t enough	n time to	go clinic		()
4) I though	t that th	ne treatm	ment fee was too	expensive	()
5) Etc.					()
6. What had	I the ma	ost influ	ence on select	ion of drugs?			
1) Previous					()
		_	mbers/acquaintar	nces	()
3) Pharmac					()
4) Prescript	ion of m	nedical d	loctor		()
5) Prescript	ion of d	entist			()
6) Etc					()

7. Where did you get informations for drugs for periodontal diseases	?	
1) Articles from newspapers or magazines	()
2) Ads from newspapers or magazines	()
3) Articles on Internet	()
4) Ads on Internet	()
5) Television programs	()
6) Television advertisements	()
7) From family members/acquaintances	()
8) Lectures/meetings on oral health	()
9) From pharmacist	()
10) From dental clinic	()
11) From medical clinic	()
12) Etc.	()
8. What is your opinion about effects of drugs for periodontal diseas	es?	
1) Neither preventive nor therapeutic	()
2) Preventive only	()
3) Somewhat therapeutic	()
4) therapeutic as effective as dental treatment	()
5) more therapeutic than dental treatment	()
9. Do you have any intention of medication of drugs for periodontal d	iseases fo	or prevention/control of
periodontal diseases?		
1) Yes ()		
2) No ()		
10. What will be your primary means of selecting drugs?		
1) Self-choice	()
2) Asking family members/acquaintances	()
3) Inquiry of pharmacists	()
4) Inquiry of medical doctors	()
5) Inquiry of dentists	()
6) Etc.	()

시판증인 경구 치주질환치료제의 효과에 대한 일반인의 인식도 조사

손강배, 양병근, 이철우, 김태일, 구영, 한수부

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목꺽: 이번 연구에서는 일반인의 치주질환 치료제에 대한 인식도를 설문을 통하여 알아보았고 현재 국내에서 시판중인 치주질환 치료제를 의약품 검색 사이트를 이용하여 조사하였다. 조사한 치료제의 효과를 해당 약품의 성분과 관련된 문헌을 고찰함으로써 알아보았다.

재료 및 방법: 일반인의 치주질환 치료제에 대한 인지도를 조사하기 위하여 열 개의 문항으로 구성된 설문을 실시하였다. 설문은 한림대학교 성심병원 산업의학과에 정기 건강검진을 위하여 내원한 사람들을 대상으로 하였다.

보건복지부에 등록된 치주질환 치료제를 조사하기 위하여 킴스 온라인 홈페이지를 이용하였다. 의약품 종합 검색 페이지에서 '추가조건 입력하기'의 '복지부 분류'란에 '231. 치과—구강용약'의 조건을 주어 검색하였다. 검색 결과로부터 경구 치주질환 치료제를 구별하여 정리하였다. 치주질환 치료제와 관련된 문헌을 조사하기 위하여 미국 국립도서관의 검색 서비스인 Pubmed 홈페이지를 이용하였다. 검색어는 각 치료제의 성분명과 치은 염, 치주열환의 조합어를 사용하였다.

결과: 설문에 참여한 사람은 100명이었다. 이 중 85%는 치주질환이라는 말을 들어본 적이 있었으며 72%는 자신의 치주건강상태가 좋지 않다고 생각하였다. 14%는 치주질환 치료제를 복용한 경험이 있었다. 61%는 치주질환 치료제에 관한 정보를 광고로부터 획득하였다. 향후 치주질환 치료제의 선택과 관련하여 35%는 치과의사에게, 24%는 의사에게 그리고 20%는 약사에게 문의하겠다고 대답하였다.

치주질환 치료제는 70개였다. 이 중 38개는 아스코르빈산 제제, 25개는 옥수수 불검화 추출물 제제, 5개는 저용량 독시싸이클린 제제였고 아보카도-콩 불검화물과 동양의학적 제제가 각각 한 개였다.

결론: 치주질환 치료제에 대한 일반인의 인지도는 비교적 낮았으며 정보를 획득하는 주요 경로는 광고였다. 일반인들이 치주질환 치료제를 선택하는 데 치과의사는 큰 역할을 하지 못하였다.

시판중인 치주질환 치료제는 70개였다. 치료제는 다섯 개의 군으로 분류할 수 있었으며, 아스코르빈산 제제, 옥수수 불검화 추출물 및 저용량 독시싸이클린이 대부분이었고 아보카도-콩 불검화물과 동양의학적 제제는 각 각 한 개였다. 옥수수 불검화 추출물과 저용량 독시싸이클린은 임상 연구에 의해 그 효과가 입증되었으나 아스 코르빈산 제제는 임상 연구가 없었으며 따라서 이상적인 제제라고 할 수 있다.

기존의 문헌에 기초하여 볼 때 옥수수 불검화 추출물과 저용량 독시싸이클린만이 전통적인 치주질환 치료법 (SRP)과 병행하여 치료제로 사용될 수 있다.

주요어: 숙주반응조절, 치주질환 치료제, 저용량 독시싸이클린, 옥수수 불검화 추출물, 이스코르빈산, 리소짐